2,6-Pyridinophanes and Related Heteromacrocycles.

James Michael Robinson
Louisiana State University and Agricultural & Mechanical College

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2,6-PYRIDINOPHANES AND RELATED HETEROMACROCYCLES

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy in The Department of Chemistry

by

J. Michael Robinson
B.S., Louisiana Polytechnic Institute, 1967
M.S., Louisiana Polytechnic Institute, 1969

December, 1973
For my wife, Mary
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ABSTRACT

The syntheses of 2,6-pyridinophanes and related heteromacrocycles are studied with particular interest focused on new efficient methods for cyclization.

Studies were initially directed toward utilization of classical condensation reactions to effect cyclization. Perkin and Knoevenagel condensations of phenylacetic acid or α-phenylacetophenone, respectively, with benzaldehyde are known to give as the major product an olefin with cis oriented phenyl rings. This stereochemistry is a result of the stereo electronic overlap control during the elimination of water from the initial adduct. However, these procedures, using the thermally stable ethyl 2-pyridylacetate, α-(2-pyridyl)acetophenone, and α-(4-nitrophenyl)acetophenone with benzaldehyde and 2-pyridine-carboxaldehyde led to an unexpected predominance of the trans isomer. Condensations via piperidine under a variety of conditions illustrated that the initially formed E-olefin (cis aromatic rings) is equilibrated by nucleophilic addition (Michael) and subsequent preferred elimination of piperidine to the Z-olefin (trans aromatic rings). Reactions with 2-pyridinecarboxaldehyde in non-protic medium (benzene) required an equivalent amount, rather than a catalytic quantity, of piperidine to successfully remove the theoretical amount of water; Michael addition occurred affording the piperidine adducts. Subsequent acid-catalyzed trans-elimination of piperidine from the Michael adducts afforded only the Z-olefins. Experiments with α-(4-nitrophenyl)acetophenone and benzaldehyde showed that incorporation of small amounts of acid (benzoic)
shifted the isomerization (equilibrium) of the E- to Z-isomer even more dramatically, as expected, by further enhancement of 1,4-addition to, as well as elimination from, the conjugated α,β-unsaturated carbonyl system of the E-isomer. Condensation via tertiary or hindered secondary amines exclusively afforded the intermediate alcohol; subsequent dehydration resulted in detection of only the corresponding trans isomer.

During the preparation of ethyl 2-pyridylacetate, the previously undetected 1-carbethoxy-2-hydroxy-3-(2-pyridyl)-4H-quinolizin-4-one was isolated and characterized (Appendix I).

Photoisomerization of trans to cis-(2-pyridyl)olefins has been performed. Diels-Alder reactions between α-pyrone and 6-substituted 2-pyridylacetylenes have been utilized to prepare similar cis oriented pyridyl systems. However, neither of these systems has been successfully cyclized.

A study of the Diels-Alder reactions of tetraarylcyclopentadieneones and diarylacetylenes, which both contain the 2-pyridyl group, has been initiated. (Appendix II).

A study of condensation reactions using 2-pyridyl anils has also been initiated.

Finally, a template reaction, i.e., coordination to a central metal ion, has easily effected cyclization to produce 2,6-pyridino macrocycles, 1,5,9,13-tetraoxa-7,15-di(2,6)pyrida-3,11-di(1,2)phenacyclohexadecane (221, n = 2), and 1,5,9,13,17,21-hexaoxa-7,15,23-tri(2,6)-pyrida-3,11,19-tri(1,2)phenacyclotetracosane (221, n = 3) in 40% and 9% yield, respectively. Utilization of an alkali metal cationic template
permits isolation of the free ligand which can be studied and subsequently complexed with the desired metal salt.

\[
\begin{align*}
\text{HO} & \quad 74 \\
\text{Br} & \quad 220 \\
\text{NaH} & \quad \text{DME} \\
\end{align*}
\]
INTRODUCTION

In recent years, there has been a considerable amount of research directed toward the synthesis of annulenes, cyclophanes, and in particular, macrocyclic compounds containing hetero-atoms. Variations in ring size, hetero-atoms, and inherent geometric functionality permit related studies of the macrocycles and the corresponding metal complexes with respect to aromaticity, coordination ability, and biological activity. However, studies of the physical and chemical properties have been long-range and/or secondary goals; the primary goal has been the synthesis of the desired macrocycles.

The purpose of this work is to find efficient synthetic procedures for construction of hetero-macrocyclic compounds specifically utilizing the 2,6-pyridino moiety. More specifically, the desired cyclic compounds should contain two or more pyridine rings, each interconnected by at least two other atoms. The simplest compound of this class is \( \lambda^1 \) \((n=1)\). Incorporation of other interconnecting sequences would afford \( \lambda^2, \lambda^3, \lambda^4, \) and \( \lambda^5 \), where \( X \) represents a hetero atom (0, S, or N). Of the above skeletal series, only \( \lambda^2, \lambda^3, \) and \( \lambda^5 \) were actively pursued.

Since pyridine chemistry has been thoroughly reviewed through 1964 in an elegant four-volume series,\(^1\) the introductory material is presented in two sections. Part I contains predominantly condensation reactions of the 2-pyridylmethyl group. Since these condensation reactions are mainly pertinent to synthetic routes toward \( \lambda^2 \), the requisite side chain functionalization reveals some of the intriguing properties of pyridine chemistry. In Part II, a brief review of 2,6-pyridinophanes and related hetero-macrocycles is presented.
PART I

Due to the electron-attracting inductive and resonance effects of the pyridine nitrogen atom, 2-pyridylmethyl (2-picoly) hydrogens are acidic and thus readily abstracted by strong bases. The acidity of side chain protons can be further increased by simple preparation of the corresponding pyridinium salt, or N-oxide. However, this type of functionalization has three major drawbacks: (1) adds additional steps to any synthetic scheme, (2) N-derivatives are difficult to remove, and (3) give rise to an ortho steric effect in subsequent reactions.¹

Alternatively, the acidity of the 2-picoly hydrogens is enhanced upon replacement of one or more of the protons with an electron-withdrawing substituent, such as -CO₂H, -CO₂R, -CN, and -COR. A brief review of the key side-chain functionalization routes in simple pyridyl systems is necessary.

Oparina² reported that 2-pyridylacetic acid undergoes easy decarboxylation at 50-60°. To circumvent this problem the more thermally stable ester was utilized. Oparina's method to alkyl 2-pyridylacetate is shown in Scheme I.³ Conversion of 2-phenacylpyridine (6) to the oxime derivative (7) and subsequent Beckmann rearrangement afforded 2-pyridylacetanilide (8). Solvolysis of 8 in alcohol gave the corresponding alkyl esters. Woodward and Kornfeld⁴ employed direct carboxylation of 2-lithiomethylpyridine (11) with carbon dioxide and after careful esterification of the resultant acid salt obtained ethyl 2-pyridylacetate (12) in 35-40% overall yield. Similarly, the corresponding sodio
organometallic has been reported to give only a 25% yield of \( \text{12} \). Ethyl 2-pyridylacetate (12) can be obtained in a good yield (79%) by solvolysis of 2-pyridylacetonitrile (13), which has been synthesized from 2-methylpyridine (10) in an overall 37% yield (Scheme II). Oxidation of 2-methylpyridine (10) to the acid \( \text{14} \) and subsequent esterification provided ethyl 2-pyridylcarboxylate (15). Reduction of \( \text{15} \) with lithium aluminum hydride afforded the alcohol \( \text{16} \), which was converted to the corresponding 2-chloromethylpyridinium chloride (17) upon treatment with thionylchloride. Potassium cyanide in an aqueous alcoholic medium effected the nucleophilic transformation of \( \text{17} \) to \( \text{13} \). Schulze improved the yield of this substitution reaction by using a nucleophilic enhancing solvent, such as dimethylsulfoxide.

Boekelheide and Linn\(^{11}\) effected a novel synthesis of 2-hydroxymethylpyridine as shown in Scheme III. Treatment of \( \text{10} \) with an \emph{in situ} generated peracid afforded the N-oxide derivative \( \text{18} \). Subsequent thermal rearrangement of \( \text{18} \) in the presence of acetic anhydride afforded a mixture of acetoxy substituted 2-methylpyridines, which has been shown to be predominantly 2-acetoxymethylpyridine (12).\(^{12}\)
Scheme II

\[
\text{PyCH}_3 \xrightarrow{\text{KMN}O_4/83\%} \text{PyCO}_2\text{H} \]

\[
\xrightarrow{88\% \text{ EtOH/H}^+} \]

\[
\text{PyOH} \xrightarrow{\text{LAH/70\%}} \text{PyCO}_2\text{Et} \]

\[
\xrightarrow{83\% \text{ SOCl}_2} \]

\[
\text{PyCl}^- \xrightarrow{\text{KCN/EtOH/79\%}} \text{PyCN} \xrightarrow{87\% \text{ NaCN/DMSO}} \]

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Hydrolysis of the acetoxy function furnished the desired carbinol \( \text{I}_5 \) (50% overall yield from \( \text{I}_3 \)).

2-Chloromethylpyridine (\( \text{I}_2 \)) can be made in one step by a similar treatment of the N-oxide with an arylsulfonyl chloride, followed by thermolysis of the intermediary salt.\(^{13,14}\) Recently, 2-chloromethylpyridine (\( \text{I}_2 \)) was prepared by direct halogenation of \( \text{I}_6 \) with chlorine gas.\(^{15}\) A mixture of \( \text{I}_6 \) and sodium carbonate was maintained at a temperature below 60° and treated with a slow stream of chlorine gas to afford \( \text{I}_2 \) (65%), along with traces (5%) of \( \text{I}_4 \).

Goldberg, \textit{et al.},\(^{16}\) prepared ethyl 2-pyridylacetate (\( \text{I}_7 \)) by direct carboethoxylation of \( \text{I}_6 \), upon inverse addition of the organo-

metallic reagent to diethyl carbonate. 2-Picolyl ketones, prepared by acylation of \( \text{I}_6 \), were initially reported by Koppenburg and Wibaut.\(^{17}\)
After the initial reaction of 10 with phenyllithium, rapid treatment with acetylchloride or acetic anhydride gave the ketone 23, whereas slow addition of the acyl reagent resulted in further reaction of the initially formed ketone 23 with 11 to give predominately alcohol 24.

\[
\begin{align*}
\text{11} & \xrightarrow{\text{AcCl or } \text{Ac}_2\text{O}} \text{23} + \text{24}
\end{align*}
\]

Similarly, addition of benzoylchloride to 11 afforded either the ketone 6 or an olefinic product (25), which resulted from dehydration of the intermediary alcohol. Treatment of 11 with benzoic anhydride gave the

\[
\begin{align*}
\text{11} & \xrightarrow{\text{Bz}_2\text{O}} 6 + 26
\end{align*}
\]
phenyl ketone along with a trace amount of 2-pyridyldibenzoylmethane. Goldberg, et al., made a considerable improvement on the preparations of 2-picolyl ketones by direct acylation of 11. Rapid addition of a limited amount of methyl ester to 11 afforded the ketone, e.g., with methyl benzoate, was isolated in 80% yield.

Activated 2-methylpyridines, where more than one of the picolyl hydrogens has been replaced by an electron withdrawing substituent, have been synthesized by a variety of methods. Gruber and Schlogl utilized the sodium salt of diethyl malonate (dry powder) to effect nucleophilic replacement of a halogen atom from the 2-position of a pyridine ring, i.e., 27 to 28. 2-Pyridy malononitrile (29) was prepared in 56% yield by reaction of 2-lithiomethylpyridine (11) with N-methyl-N-cyanoaniline (29). The disproportionation to the nitrile has been explained by

![Chemical diagram](image)

the fact that the methylene protons of the initially formed 2-pyridyl-acetonitrile are so much more reactive than picoline that a proton is immediately removed by 11. This anion then reacts with the second mole
of \( \mathcal{O} \) to give \( \mathcal{O} \). Beckett and Kerridge\(^2\) generated the sodium enolate of \( \mathcal{O} \) with sodium amide in toluene and obtained, by rapid addition of various benzoylchlorides or benzoic anhydride, a 70% yield of (only) C-acylated products (\( \mathcal{O} \)). However, a similar reaction of \( \mathcal{O} \) with acetic anhydride gave rise to a 75% yield of (only) O-acylated product.

\[
\begin{align*}
\text{Beckett, et al.,}^2 & \text{ improved the synthesis of } \mathcal{O} \text{ by utilization of sodium hydride as the necessary base. The work was also extended to include isolation of two distinct forms for each of the } 1,3- \\
\text{diketones prepared. When only one isomer was obtained, it was shown by infrared and ultraviolet spectral data to be } \mathcal{O} \text{ (one of two possible}
\end{align*}
\]

\[
\begin{align*}
\text{Beckett, et al.,}^2 & \text{ improved the synthesis of } \mathcal{O} \text{ by utilization of sodium hydride as the necessary base. The work was also extended to include isolation of two distinct forms for each of the } 1,3- \\
\text{diketones prepared. When only one isomer was obtained, it was shown by infrared and ultraviolet spectral data to be } \mathcal{O} \text{ (one of two possible}
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\]

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\text{diketones prepared. When only one isomer was obtained, it was shown by infrared and ultraviolet spectral data to be } \mathcal{O} \text{ (one of two possible}
\end{align*}
\]

reduction structures). However, in some cases recrystallization of \( \mathcal{O} \) from ethanol afforded a higher melting isomer which was shown to have the structure(s) \( \mathcal{O} \). Hamana and Yamazaki\(^2\) reacted ethyl cyanoacetate with pyridine N-oxide in the presence of acetic anhydride to obtain (26%) ethyl \( \alpha \)-cyano-2-pyridylacetate (\( \mathcal{O} \)). Douglass and Wesolosky\(^2\)

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argue that the compound exists as $3_{4a}$, and that if the tautomeric form $3_{4a}$ is present in an equilibrium that "its concentration is below the limits of detection by nmr spectroscopy". In a recent communication, Abramovitch, et al.,$^{26}$ reported a novel, direct alkylation of pyridine N-oxide ($3_5$) by reaction with phenylpropionitrile ($3_6$). The expected $3_7$ was obtained in "very low yield" and the major products were $3_8$ (56%) and $3_9$ (17%). Unfortunately, spectral data that would allow comparison to the tautomeric $3_{4a}$ were insufficient.

**Ylides constitute a unique type of double-activated 2-picolyl group.** Reaction of alkylphosphonates with $3_{20}$, and subsequent removal
of a proton by sodium or potassium metal has been utilized to prepare 2-pyridylmethyl ylides, \(^{40}\).\(^{27}\) Recently, ylid (\(^{42}\)) was prepared, although in apparently low yield, by reaction of two equivalents of methylenetriphenylphosphorane with 2-bromopyridine (\(^{41}\)).\(^{28}\)

\[
\text{Br}_2 \text{Py} + 2 \text{CH}_2\text{P(Ph)}_3 \rightarrow \text{Br}_2 \text{PyCH=P(Ph)}_3
\]

2-Methylpyridines have been condensed with aldehydes by various acidic reagents of which the most common is acetic anhydride. Under these conditions, 2-methylpyridine (\(^{10}\)) afforded trans-2-stibazoles (2-styrylpyridines) \(^{43}\), in good to excellent yields (51-94\%).\(^{29,30}\) Similarly, simple N-derivatives of 2-methylpyridines have

\[
\text{PyCH}_3 + \text{ArCHO} \xrightarrow{\text{Ac}_2\text{O} / \Delta} \text{PyCH=Ar}
\]
been condensed under very mild basic conditions. Methyl 2-methylpyridinium iodide (44) reacted with aromatic aldehydes in the presence of piperidine to afford 40-75% yields of the corresponding trans-2-stilbazole methiodides (45). 2-Methylpyridine N-oxide (18) reacted with p-dimethylaminobenzaldehyde to afford the corresponding trans-2-stilbazole N-oxide (46) in 57% yield.

Although many examples of condensation reactions of 2-methylpyridines and the simple N-derivatives are known, only a few cases of condensations with directly activated 2-picoly groups have been realized. Bragg and Wibberley condensed ethyl 2-pyridylacetate (12) with benzaldehyde utilizing piperidine catalysis; distillation of the crude product mixture afforded (46%)(47). The ester 12

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underwent quaternization and subsequent cyclocondensation upon treatment with ethyl bromopyruvate affording diethyl indolizine-1,2-dicarboxylate \(^\text{133}\). 2-Phenacylpyridine (6) reacted with 5-nitrofurfural in the presence of acetic anhydride to afford \(^\text{134}\) ylides of 2-methylpyridine have also been condensed with aldehydes and ketones,\(^\text{35}\) for example \(^\text{136}\) (R=ethyl) and benzaldehyde afforded \textit{trans}-2-stilbazole in 87% yield.

2,6-Dimethylpyridines with one activating substituent were prepared by utilization of the same reactions as previously described for 2-methylpyridine. However, diacylation or dialkylation presents additional unresolved problems. Kloppenburg and Wibaut\(^\text{17}\) treated 2,6-dimethylpyridine (60) with two equivalents of phenyllithium and subsequently...
added benzoic anhydride to obtain a dibenzoylated compound which was considered to be $\mathcal{J}$. DeJong and Wibaut$^{30}$ extended the work and reassigned the compound to be the enol benzoate $\mathcal{K}$. Goldberg and Levine$^{19}$

![Chemical structure](image)

1) 2 PhLi/Et$_2$O  
2) PhCO$_2$CH$_3$  
3) PhCOCl/2 hrs (16 hrs)

52 67% (28%)

50 treated the monolithium derivative of 50 with methyl benzoate to obtain a 95% yield of 52. However, if a solution of 50 and two equivalents of phenyllithium was treated successively with methyl benzoate and benzoyl chloride, the ketone 52 (yields varied with reflux time), the enol benzoate 53, and the lithio salt of the ketone 54 were found.$^{37}$ Bergmann and Pinchas$^{38}$ reported that 2,6-dimethylpyridine (52), after treatment with two equivalents of phenyllithium, reacted with added ethyl bromide to afford (69%) 2,6-dipropylpyridine (56). DeJong and Wibaut$^{36}$ argued against the proposed symmetrically metallated intermediate 55, since alkylation with benzyl chloride afforded 57 (25%), 58 (17%), and a trace amount of another dialkylated compound. Strong evidence supporting the structure 57 was obtained by comparison to other possible isomers, 59 and 60, which were synthesized by
unambiguous routes. A stepwise mechanism was presented, and substantiated by treatment of 50 with phenyllithium and then benzyl chloride to afford (25%) 57.\textsuperscript{38} Lochte and Cheavens,\textsuperscript{39} however, also succeeded in symmetrically alkylating 2,6-dimethylpyridine by two additions of methyl iodide to a solution of 50 in liquid ammonia with sodium amide.
The mono- and dialkylated derivatives, 61 and 62, were obtained in ca. 2:1 ratio. Recently, 50, phenyllithium, and 3-phenylpropyl bromide were reported to afford 63 (45%) and 64 (48%), whereas cinnamyl chloride gave 65 (48%). The existence of a dimetallated intermediate 55.
was unequivocally established by Hiltmann and Wollweber, who generated the mono- and dianions of 50 with phenylsodium. Carboxylation of the anion mixture and subsequent esterification afforded (40%) ethyl 2-(6-methylpyridyl)acetate (66) and 15% of diethyl 2,6-pyridinediacetate (67). Similar attempts with phenyllithium afforded only 66 and trace amounts of ketone 52.17,41 Action of potassium amide on 50 and rapid treatment with diethyl carbonate was reported to give 66 (59-75%).42

Other 2,6-dimethylpyridines, symmetrically substituted with activating substituents, have been prepared by multi-step routes. 2,6-Di(phenacyl)pyridine was prepared in overall 16% yield from 50 according to Scheme IV.3,41 The corresponding diacetates 67 (R=ethyl) and 72 (R=methyl) were obtained in 20% yield from the symmetrical ketone 50 by Beckmann rearrangement of the oxime derivative (71) and solvolysis of the resulting anilide 72.
Scheme IV

\[ \text{50} \xrightarrow{\text{PhCHO, Ac}_2\text{O/Δ}} \text{68} \]

90% \quad 1) 2 \text{Br}_2
62% \quad 2) \text{KOH/EtOH}

\[ \text{70} \xrightarrow{\text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{69} \]

89% \quad \text{NH}_2\text{OH}

\[ \text{71} \xrightarrow{\text{H}_2\text{SO}_4} \text{72} \]

\[ \text{73} \xrightarrow{\text{CH}_3\text{OH/HCl}} \]
2,6-Pyridinediacetonitrile (77) was synthesized by the action of cyanide ion on 75 or 76, each prepared from 2,6-di(hydroxymethyl)-pyridine (74) in ca. 63% yield. Compounds 75 and 76 were converted to 77 in 28% and 40%, respectively. Boekelheide and Linn\textsuperscript{11} prepared 74 (14% overall) by consecutive N-oxide rearrangements in acetic anhydride and hydrolysis of the

\[
\begin{align*}
\text{50} & \xrightarrow{1) \text{H}_2\text{O}_2/\text{HOAc}} \text{78} \\
& \xrightarrow{2) \text{Ac}_2\text{O}/\Delta} \text{79} \\
\text{74} & \xrightarrow{\text{HCl, } \text{H}_2\text{O}} \text{72}
\end{align*}
\]
symmetrical diacetoxy substituted pyridine 79. Utilizing this route, 76 was prepared directly from 79 by hydrolysis with 48% hydrobromic acid.44 In a convenient preparation of the symmetrical alcohol 74, sodium borohydride in methanol was reported to reduce 80 to afford 74 in a 73% yield.45,46 Lithium aluminum hydride reduction of 80 gave only 5% of 74,47 whereas from the di-n-butyl ester a 58% yield was realized.48 Recently, 2,6-di(hydroxymethyl)pyridine (74) and 2,6-di(chloromethyl)pyridine (75) have been prepared in ca. 90% yield by diazotization of 2,6-di(aminomethyl)pyridine (or the hydrogen chloride salt) in the presence of sulfuric acid or hydrogen chloride, respectively.49,50

Acid-catalyzed condensations of 2,6-dimethylpyridine have been utilized for many years. A typical example is the formation of 68 from 50 (see Scheme IV). Utilization of simple N-derivatives, as with 2-methylpyridines, enables employment of milder catalytic conditions, but in every case the trans-olefin predominates.1 An apparent synthesis of a cis,cis-diolefin 81 was reported; however, the compound

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was not completely characterized. 2,6-Pyridinediacetonitrile (II) was condensed with benzaldehyde to afford 82, although yield and isomer data were not presented. Under the same conditions, II reacted with terephthalaldehyde to afford polymer.44

\[
\text{NC} \begin{array}{c}
\text{Ph} \\
\text{NC}
\end{array} \\
\text{II} + \text{NaOEt or LiCl/DMF} \\
\text{PhCHO}
\]

\[
\text{PhCH=CN} \\
\text{CN}
\]

2-Pyridinecarboxaldehyde (83) has been prepared by numerous routes. Methods providing the best results were oxidation of 2-hydroxymethylpyridine (16) by selenium oxide (\(\sim 95\%\)) or lead tetracetate (65%). However, selenium oxide oxidation of 2,6-di(hydroxymethyl)pyridine (74) was reported to afford 6-hydroxymethyl-2-pyridinecarboxaldehyde (29%), although only one-half the theoretical amount of oxidant was utilized. 2,6-Pyridinedicarboxaldehyde (85), along with 6-methyl-2-pyridinecarboxaldehyde (84), was obtained from a continuous gas phase oxidation of 2,6-dimethylpyridine. Recently, activated manganese dioxide was shown to oxidize 16 to 83, and 74 to 85, in 68% and 54% yield, respectively. Queguiner and Pastour reported preparation of 85 in 69% yield by lithium aluminum hydride reduction of dimethyl 2,6-pyridinedicarboxylate at low temperature.


2-Pyridinecarboxaldehyde (83) has been condensed with a large variety of acyl compounds under diverse conditions to afford 3-(2-pyridyl)-2-propenones and propenoic acid derivatives, 86.1,56-59

Reactions with doubly activated methylenes also have been thoroughly studied.1,60,61 However, there are few examples where an aryl-substituted activated methylene has been condensed with 2-pyridinecarboxaldehydes.

Arylacetonitriles react with 83 or 84 in hot alcoholic medium with hydroxide, alkoxide, or piperidine catalysis to form the corresponding (2)-3-(2-pyridyl)arylacrylonitriles 87, as listed in Table I. However, 83 and phenylacetonitrile in cold alcoholic hydroxide solution has been reported to afford (75%) 2,4-diphenyl-3-(2-pyridyl)glutaronitrile.69 Seus and Wilson70 reported that reaction of 83 with the ylide 88 affords trans-2-styrylpyridine (82, Ar=Ph) in 75% yield.
TABLE I

(Z)-3-(2-PYRIDYL)ARYLACRYLONITRILES

\[
\begin{align*}
\text{CHO} + \text{ArCH}_2\text{CN} & \rightarrow \text{NC} \equiv \text{Ar} \\
\text{83 (R=H)} & \\
\text{84 (R=CH}_3\text{)}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td>C\text{\textsubscript{6}H\textsubscript{5}}</td>
<td>67</td>
<td>62-65</td>
</tr>
<tr>
<td>83</td>
<td>3,4-(\text{MeO})\text{\textsubscript{2}C\text{\textsubscript{6}H\textsubscript{3}}}</td>
<td>75</td>
<td>4</td>
</tr>
<tr>
<td>83</td>
<td>4-ClC\text{\textsubscript{6}H\textsubscript{4}}</td>
<td>91</td>
<td>64,68</td>
</tr>
<tr>
<td>83</td>
<td>4-Me\text{\textsubscript{2}NC\text{\textsubscript{6}H\textsubscript{4}}}</td>
<td>(70-100)</td>
<td>6</td>
</tr>
<tr>
<td>83</td>
<td>4-NO\text{\textsubscript{2}C\text{\textsubscript{6}H\textsubscript{4}}}</td>
<td>99</td>
<td>67,68</td>
</tr>
<tr>
<td>83</td>
<td>3,4-(\text{MeO})\text{\textsubscript{2}}-6-NO\text{\textsubscript{2}C\text{\textsubscript{6}H\textsubscript{4}}}</td>
<td>96</td>
<td>8</td>
</tr>
<tr>
<td>84</td>
<td>C\text{\textsubscript{6}H\textsubscript{5}}</td>
<td>--</td>
<td>62</td>
</tr>
<tr>
<td>84</td>
<td>2-(6-MeC\text{\textsubscript{5}H\textsubscript{3}N})</td>
<td>72</td>
<td>43</td>
</tr>
</tbody>
</table>

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In a unique oxidative condensation, 2-hydroxymethylpyridine (16) and 2-methylpyridine N-oxide (18) were heated over potassium hydroxide giving (44%) trans-1,2-dil(2-pyridyl)ethene (43, Ar=2pyr).\textsuperscript{71}

\[
\begin{align*}
\text{16} + \text{18} &\xrightarrow{\text{KOH} \ 165^\circ \ 3.5 \ hrs} \text{43} (\text{Ar=2-pyr}) \\
\end{align*}
\]

2,6-Pyridinedicarboxaldehyde (85) was condensed with 2,6-dimethylpyridine (50) to afford trans,trans-2,6-[2-(6-methyl-2-pyridyl)-vinyl]pyridine (89).\textsuperscript{43} The trans,trans configuration has been recently confirmed.\textsuperscript{72} The dialdehyde 85 was also reacted with malonic acid to give 78% of the trans,trans-diacid 90.

\[
\begin{align*}
\text{85} + \text{Ac}_2\text{O} &\xrightarrow{} \text{89} \\
\text{85} + \text{CH}_{2}(\text{CO}_2\text{H})_2 &\xrightarrow{\text{piperidine} \ \text{pyr}} \text{90} \\
\end{align*}
\]
PART II

The first 2,6-pyridinophanes,* muscopyridines (odoriferous constituents of natural musk from the musk deer) were synthesized by Biemann, Büchi, and Walker, as illustrated in Schemes V and VI. Stobbe's condensation of cyclododecanone (25) with diethyl succinate gave the α,β-unsaturated compound 26. Cyclization of 26 with polyphosphoric acid led to the bicyclic vinylogous β-ketoester 27 which on acid hydrolysis was converted smoothly to the bicyclic ketone 28. Wolff-Kishner reduction of 28 resulted in the formation of a mixture of bicyclic olefins 29 (≤ 30%) and 100 (≥ 70%). Thereafter, the olefin mixture was reacted with hydrazine acid and the labile olefin obtained immediately dehydrogenated to the more stable decamethylene-pyridines 101 and 102. Scheme VI illustrates the functionalizations of [10](2,6)-pyridinophane (102) to afford other pyridine macrocycles, and finally, muscopyridine 108. Utilization of the N-oxide rearrangement gave a mixture of acetates which were hydrolyzed to 103 and 104. Chromium trioxide oxidation converted 104 into the ketone 105. Methylation under various conditions provided either 107 or the monoalkylated ketone 106. These ketones were subjected to Wolff-Kishner reduction to afford 109 and the desired muscopyridine (racemic) 108.

Several [7](2,6)pyridinophanes were synthesized recently, as shown in Schemes VII and VIII. 9b-Boraperhydrophenalene (111) was prepared in 73% yield by heating a mixture of cyclodeca-1t,5t,9c-triene

* For classification, nomenclature, and a partial review of phanes, see Reference 93.
Scheme V

25 \[\text{CH}_2\text{CO}_2\text{Et}]_2 \rightarrow \text{KOTBu} \rightarrow 85\%

26

\(\begin{array}{c}
\text{H}_2\text{O}/\text{H}^+ \\
\end{array}\)

27

55\% \text{W.K.}

28

29

1) \(\text{HN}_3\)

2) \text{Pd}

100

101

102

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Scheme VI

1. \( \text{H}_2\text{O}_2/\text{AcOH} \)
2. \( \text{Ac}_2\text{O}/\Delta \)
3. \( \text{H}_2\text{O}/\text{H}^+ \)

\( \sim 102 \)

\( \sim 103 (3\%) \)

\( \sim 104 (49\%) \)

\( \text{CrO}_3 \)

93%

35-75%

\( \text{KOtBu} \)

\( \text{CH}_3\text{I} \)

\( \sim 105 \)

\( \sim 106 \)(R=H)

\( \sim 107 \)(R=CH\(_3\))

\( \sim 108 \)(R=H)

\( \sim 109 \)(R=CH\(_3\))
Scheme VIII

117

O₂  -75°

115

Pyr  CrO₃

118

1) CO₂

2) MeOH/H⁺

116

H⁺  HC(OMe)₃

119

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(110) with a trimethylamine-borane complex. Treatment of 111 with an equimolar amount of acetic acid (or deuterioacetic acid) and subsequent chromic acid oxidation afforded a 30% yield of the diketone 112. Hydroxylamine effected aromatization to [7](2,6)pyridinophane (114) in 44% yield. The N-oxide derivative of 114 could not be formed under conditions sufficient to convert 102 into the corresponding N-oxide. This was interpreted as a result of a greater steric hindrance introduced by the shorter methylene chain. However, a different route for functionalization of 114, as shown in Scheme VIII, was found equally effective. Treatment of 114 with n-butyllithium followed by carboxylation and esterification resulted in a 52% yield of the methyl ester 116.

Similarly, the lithium derivative 115 was treated with oxygen to furnish the corresponding alcohol 117 (65%). Cornforth oxidation of 117 gave (55%) [7](2,6)pyridinophane-1-one (118) and subsequent ketalization with methyl orthoformate afforded 119 in 86% yield.

Baker, et al., synthesized the first 2,6-pyridinophane with two aromatic rings, [2.2](2,6)pyridinophane (1, n=1) as shown in Scheme IX. Condensation of 2,6-dimethylpyridine (50) with 6-methyl-2-pyridine-carboxaldehyde (84) gives trans-1,2-di-2-(6-methylpyridyl)ethene (120). Treatment of 120 with dilute peracetic acid resulted in the formation of the di-N-oxide 121, which rearranged in the presence of acetic anhydride to give 1,2-di-2-(6-acetoxyethylpyridyl)ethene (122). After hydrolysis of 122 to 123, catalytic reduction of 123 over Adams' catalyst led to the saturated diol 124. Subsequent reaction of 124 with hydrogen bromide in acetic acid gave the unstable dibromide 125. The intramolecular cyclization of 125 to 1 (n=1) apparently could not be
Scheme IX

\[
\text{CH}_3\text{NCH}_3 + \text{CH}_3\text{NCHO} \xrightarrow{\text{Ac}_2\text{O}/\Delta} \text{50-73\% CH}_3\xrightarrow{\text{Ac}_2\text{O}/\Delta} \text{120}
\]

\[
74\% \xrightarrow{\text{H}_2\text{O} / \text{AcOH}} \text{120}
\]

\[
\text{AcO-N-}\xrightarrow{\text{Ac}_2\text{O}/\Delta} \xrightarrow{50\%} \text{122}
\]

\[
81\% \xrightarrow{\text{H}^+ / \text{H}_2\text{O}} \text{123}
\]

\[
\text{H}_2 / \text{PtO}_2 \xrightarrow{65\%} \text{124}
\]

\[
67\% \xrightarrow{\text{HBr} / \text{HOAc}} \text{125}
\]

\[
\text{n-ButLi} \xrightarrow{28\%} \text{125}
\]

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effected by a Wurtz reaction with sodium metal but was effected by using phenyllithium (3%) or n-butyllithium (28%). In a reinvestigation of this compound, Boekelheide and Lawson describe a more convenient preparation by reaction of 2,6-di(bromomethyl)pyridine (126) with phenyllithium to give 1 (n=1) in 25% yield. Similarly, [2]metacyclo[2][2,6]pyridinophane (127) was prepared by ring closure of the dibromo compound 126 with n-butyllithium. It has been shown that symmetrical 2-halomethylpyridines can undergo intra- and intermolecular cyclization with tetraphenylethylene disodium. Thus, 126 led to 1 (n=3, 5, and 6) in 4.2%, 2.1%, and < 1%, respectively. Cyclization of 126 in the same manner...
resulted in the formation of \( \underline{\text{1}} \) (n=3, and 4) in 4.2% and 1.3% yield, respectively, and a trace amount of \( \underline{\text{1}} \) (n=6), which was detected by mass spectrometry. Linear compounds as well as \( \underline{\text{1}} \) (n=5) were also isolated.\(^{35}\)

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
76 & \\
\text{TPE}: 2\text{Na} & \\
-75^\circ & \\
\downarrow & \\
\underline{\text{1}} (n=2) & \\
+ & \\
\underline{\text{1}} (n=3, 4, 8, 6) & \\
\end{align*}
\]

Kauffmann, et al.,\(^{83}\) have investigated the feasibility of cyclic coupling of carbon atoms via the corresponding organocopper compounds. Thus, selective metallation of 128 is effected with n-butyllithium at \(-70^\circ\) to afford the dilithio compound 130 (82%). After metal-exchange

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{CH}_3 \quad \text{CH}_3 & \\
129 & \\
\text{n-butLi} & \\
-70^\circ & \\
\rightarrow & \\
\text{N} & \quad \text{N} \\
\text{CH}_2\text{Li} \quad \text{CH}_2\text{Li} & \\
130 & \\
\text{Cu}_2\text{Cl}_2 & \\
\rightarrow & \\
\downarrow (n=18, 3) & \\
\end{align*}
\]

of 130 with cuprous chloride, cyclization to \( \underline{\text{1}} \) (n=1 and 3) occurs in 1% and 4% yield, respectively. Application of the high dilution technique\(^{84, 85}\) does not result in higher yields of the cyclic products.

[2.2](2,6)Pyridinophane-1,9-diene (\( \underline{\delta} \), n=1) was synthesized from dithia[3.3](2,6)pyridinophane (\( \underline{\delta} \), n=1, X=S) by utilization of the non-pyrolytic ring-contraction reaction sequence shown in Scheme X.\(^{76}\)

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Scheme X

76

$\text{Me-S}^+ \overset{\text{dilute 25\%}}{\longrightarrow} 5 \ (n=1, X=\text{S})$

$\text{Me}_3\text{O}^+\text{BF}_4^-$

131

$\overset{\text{KotBu 42\%}}{\longrightarrow} 132$

$\text{Me}_3\text{O}^+\text{BF}_4^-$ 100%

133

$\overset{\text{"base" 20\%}}{\longrightarrow} 3 \ (n=1)$
2,6-Di(bromomethyl)pyridine (76) reacted with sodium sulfide at high
dilution to afford a 25% yield of $\mathcal{Z}$ (n=1, X=S),"¹⁷ which gave $\mathcal{Z}$ on
treatment with Meerwein's reagent. Treatment of the crude methylation
product $\mathcal{Z}$ with potassium t-butoxide afforded the Stevens' rearrangement
product $\mathcal{Z}$ $\mathcal{Z}$ (42%). When the mixture of stereoisomers $\mathcal{Z}$ $\mathcal{Z}$ was treated
with Meerwein's reagent, $\mathcal{Z}$ $\mathcal{Z}$ was isolated in essentially quantitative
yield. After several bases failed to effect elimination of dimethyl-
sulfide from $\mathcal{Z}$ to give recognizable products, the hindered base 2,6-
di(t-butyl)phenoxide ion was found to afford $\mathcal{Z}$ (n=1) in a 20% yield.
Another ring-contracting rearrangement, the Ramberg-Backlund reaction,
has been utilized in an attempt to prepare $\mathcal{Z}$ (n=1), as illustrated in
Scheme XI. 2,6-Di(chloromethyl)pyridine (72) reacted with sodium sul-
fide at high dilution to afford $\mathcal{Z}$ (n=1 and 2, X=S) in 19% and 3% yield,
respectively, whereas the dibromo compound 76 is reported to afford only
$\mathcal{Z}$ (n=1, X=S)."⁸⁶, "⁸⁷ Oxidation of $\mathcal{Z}$ (n=1, X=S) with excess m-chloroperben-
zonic acid gave a quantitative conversion to $\mathcal{Z}^t$, which was selectively
reduced at the N-oxide groups by iron in refluxing trifluoroacetic acid
giving the desired sulfone $\mathcal{Z}$ in high yield. "⁸⁶ Application of the Meyers
modification"¹⁰⁹ of the Ramberg-Backlund reaction, the only conditions
found to effect the reaction with model systems, failed to give satis-
factory results due to the low solubility of $\mathcal{Z}$ and the apparent in-
stability of the expected product $\mathcal{Z}$ (n=1) to the vigorously basic (nucleo-
philic) conditions. "⁸⁶ Sulfur dioxide extrusion under pyrolytic conditions,
however, proceeded smoothly to the stable saturated-bridge pyridinophane
$\mathcal{Z}$ (n=1) in 46% yield.

The dithia(2,6)pyridinophanes listed in Tables II, III, and IV
have been synthesized by utilization of the "high dilution principle"¹⁸⁴,¹⁸⁵
with the appropriate dithiol and di(bromomethyl)aryl compounds in the
presence of sodium hydroxide.
TABLE II

DITHIA(2,6)PYRIDINOPHANES

<table>
<thead>
<tr>
<th>Compound</th>
<th>n</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>136</td>
<td>3</td>
<td>36</td>
<td>88</td>
</tr>
<tr>
<td>137</td>
<td>2</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
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<td>137</td>
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### TABLE III

**DITHIA[2.2](2,6)PYRIDINOPHANES**

<table>
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<tr>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
<th>Reference</th>
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<tr>
<td>138a</td>
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<td>28</td>
<td>90</td>
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<tr>
<td>138b</td>
<td>F</td>
<td>14</td>
<td>90</td>
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<tr>
<td>138c</td>
<td>Me</td>
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<tr>
<td>138d</td>
<td>OMe</td>
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<td>139</td>
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<td>29</td>
<td>90,92</td>
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<td>2 (n=1, X=S)</td>
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<td>30</td>
<td>90</td>
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TABLE IV
DITHIA[3.3](2,6)PYRIDINOPHANES

<table>
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<th>Reference</th>
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<tr>
<td>140a</td>
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<td>87</td>
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<tr>
<td>140b</td>
<td>F</td>
<td>15-20</td>
<td>87</td>
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<tr>
<td>5_ (n=1, X=S)</td>
<td>-</td>
<td>8-20</td>
<td>76,86,87</td>
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<td>141</td>
<td>-</td>
<td>13</td>
<td>89</td>
</tr>
<tr>
<td>142</td>
<td>-</td>
<td>48</td>
<td>95</td>
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</table>
The recently synthesized \( \text{142} \) was shown to undergo the novel photochemical sulfur extrusion reaction \(^{96}\) in the presence of trimethyl phosphite to give \([2,2](2,6)\text{pyridinometacyclophane (143).}\) \(^{135}\) The yield of \( \text{142} \) was not specified, but similar photochemical sulfur extrusions occurred in high yield (49-85\%).

![Diagram of \( \text{142} \) to \( \text{143} \)](image)

Only a few more complex macrocycles containing the 2,6-pyridino-moiety are known. Apparently, the first 2,6-pyridino macrocycle was synthesized by Elvidge and Linstead in 1952.\(^{87}\) As illustrated, condensation of 2,6-diaminopyridine with 1,3-diminoisoindoline gave \( \text{144} \) (21-46\%). Cyclization was proposed to occur

![Diagram of \( \text{H}_2N\text{N}-\text{N}\text{H}_2 + \text{butanol} \rightarrow \text{144} \)](image)
through a sequence of condensations of the primary amine with the imino-moiety. In each step the necessary syn configuration was largely favored by steric interactions of the aromatic rings of the anti configuration. Several metal complexes, as well as the monohydrate, of \( \text{144} \) have been studied. \(^{37,38} \) Analogs of \( \text{144} \), which contain various substituents and/or replacement of one pyridine ring with other groups, are also known. \(^{93,100} \) Stotz and Stoufer \(^{101} \) obtained \( \text{146} \) the ligand \( \text{147} \) from the acid-catalyzed Schiff base condensation of 2,6-diacetylpyridine \( \text{145} \) with o-phenylenediamine \( \text{146} \) under dilute conditions.

\[
\begin{align*}
\text{CH}_3\text{CONCH}_3 & \quad \text{145} \\
\text{NH}_2\text{NH}_2 & \quad \text{146} \\
\rightarrow & \\
\text{N} & \quad \text{147}
\end{align*}
\]

Undheim, et al. \(^{102} \) in a preliminary communication, reported a unique synthesis of the 2,6-pyridino macrocycle \( \text{148} \), for which only X-ray information was given.

\[
\begin{align*}
\text{Cl} & \quad \text{147} \\
\rightarrow & \\
\text{N} & \quad \text{148}
\end{align*}
\]
In a special class are the 2,6-pyridino macrocyclic ligands synthesized by metal ion mediation during the cyclization. The presence of transition metal ions, although dramatically increasing the yield of cyclized products, precludes isolation of the macrocycles as a free ligand in most cases. Generally, this can be envisioned as the converse of normal sequestration, in which the ligand selectively removes a metal ion. In this case, the metal ion induces selective cyclization and removal of the macrocycle (as a complex) from competing reaction equilibria. Thus, numerous transition metal complexes of the ligands \(\textbf{149, 150, 151,}\) and \(\textbf{152}\) have been prepared \textit{in situ} and studied.\(^{103-109}\) The syntheses were performed by the slow addition of the appropriate polyethylenepolyamine to a previously formed (solution) complex of the desired metal salt with 2,6-diacetylpyridine (\(\textbf{145}\)).\(^{103}\) Similarly, this coordination template effect was employed to synthesize analogs of \(\textbf{146}\)^{100} and \(\textbf{147}\)^{101}.

It is not within the scope of this review to discuss the coordination ability or the conformation of pyridine macrocyclic complexes. However, general information concerning the design and synthesis of ligands\(^{110}\) and the complexes of macrocyclic ligands\(^{111}\) can be obtained in recent reviews.
EXPERIMENTAL

In all experiments described, the chemicals used were reagent grade, and unless otherwise indicated, no purification was considered necessary.

Melting points below 300° were taken in capillary tubes with a Thomas-Hoover Unimelt and are reported uncorrected. Melting points greater than 300° were obtained by a DuPont-900 Differential Thermal Analyzer (DTA) and were corrected with a thermocouple conversion chart. Boiling points were recorded uncorrected with reduced pressure specified in millimeters (mm) of mercury.

Nmr (60 MHz) spectra were recorded on either a Varian Associates A-60A or a Perkin-Elmer R12-B spectrometer. Where specified, 100 MHz and 220 MHz nmr spectra were determined on Varian Associates HA-100 and HA-220 spectrometers, respectively, by Dr. N. S. Bhacca. All chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as the internal standard.

Mass spectrograms were obtained in these laboratories on either a Varian M-66 mass spectrometer by Ms. Cheryl White, or on a Hitachi-Perkin-Elmer RMS-4 mass spectrometer by Ms. Paula Watts. Conditions were usually 70 eV and 80 μA. A fluorocarbon was used as a counting reference.

Infrared (IR) spectra were recorded on either a Perkin-Elmer 137 or a Perkin-Elmer 621 grating spectrophotometer.

Ultraviolet (UV) and visible (VIS) spectra were determined in absolute methanol on a Cary-14 recording spectrophotometer in matched...
1 cm quartz cells and were corrected by solvent blank. Absorbance values were reported in wavelength (nm) followed by molar extinction coefficient (ε).

Molecular weights were obtained with a Hewlett-Packard 302 Vapor Pressure Osmometer using benzene as solvent and benzil as reference.

Elemental analyses were performed by Mr. R. L. Seab in these laboratories, and by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Thin layer chromatography (tlc) were performed on 20 cm glass plates with a standard 0.25 mm coating of silica gel (Brinkmann HF-254+366). Frontal retention (Rf) values, albeit some error involved, are reported with solvent system specified. Preparative plate chromatography (plc) utilized silica gel thicknesses of either 2 mm (Brinkmann PF-254+366) or 5 mm (Brinkmann PF-254+15% CaSO4 binder). Multiple developed plates are reported as: number of elutions per solvent system. Column chromatography utilized either silica gel (Baker, 60-200 mesh) or florisil (60-100 mesh). Dry column chromatography utilized nylon tubing and Waters Associates Dry Column Grade, Activity III, absorbents (silica gel and alumina). Absorbents used for preliminary purification and initial decolorization were silica gel (Baker, 60-200 mesh), alumina (Alcoa F-20, 80-200 mesh), and charcoal (Nuchar C-190N).

Gas phase chromatography (glc) was performed with a Varian Aerograph 90-P using a 3.8" x 10' column packed with 20% SE 30 on 60/80 mesh chromosorb W.
Solvents

Benzene, ethyl ether, petroleum ether (A, bp 30-60°; B, bp 60-90°; C, bp 90-120°), toluene, and xylene were dried over sodium ribbon.

Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were distilled from lithium aluminum hydride and stored over activated molecular sieves (Linde Type 4A).

Dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), and hexamethylphosphoroustriamide (HMPA) were distilled from calcium hydride at reduced pressure and stored over activated molecular sieves (Linde Type 4A).

2-Hydroxymethyl-6-methylpyridine (153). In order to control the exothermic reaction as described by Boekelheide and Linn11,112 acetic anhydride (100 ml) was heated to 100° under nitrogen and 2,6-dimethylpyridine N-oxide (65.5 g, 0.532 mol) in 50 ml of DME was added dropwise over 2 hours. After the addition was complete, the mixture was refluxed an additional 1.4 hours, then concentrated in vacuo, poured into cold water, basified with solid sodium carbonate, and extracted with ether and chloroform. The combined extracts were dried with magnesium sulfate, concentrated, and the residual oil fractionally distilled to afford 70.7 g (80.6%) of crude 2-acetoxyethyl-6-methylpyridine: bp 105-115° (9-11 mm), [lit.11 bp 110-114° (15 mm)].

A portion of the crude acetoxy compound (16.5 g, 0.10 mol) was refluxed for 17 hours with 135 ml of concentrated hydrochloric acid. The solid residue, after concentration in vacuo, was suspended in chloroform and treated with saturated sodium carbonate solution until
slightly basic. Several extractions with ether were combined, dried over sodium sulfate, concentrated, and filtered to give 2.2 g (17.9%) of 3-hydroxy-2,6-dimethylpyridine (154): mp 209-211°, (lit.113 mp 210-212°); nmr (DMSO-d$_6$) δ 2.30 (pyr-CH$_3$, s, 6H), 3.38 (-OH, broad s, 1H), 6.8 (pyr-H, d, J = 8 Hz, 1H), 7.0 (pyr-H, d, J = 8 Hz, 1H); ir (nujol) 2500 (broad-OH), 1800 (broad), 1570, 1270 (C=O), 1250, 1160, 1125, 829, 793, and 710 cm$^{-1}$.

Anal. Calcd for C$_7$H$_9$NO: C, 68.27; H, 7.37; N, 11.38. Found: C, 68.36; H, 7.51; N, 11.29.

Fractional distillation of the filtrate afforded 7.6 g (61.8%) of 2-hydroxymethyl-6-methylpyridine (155): bp 107-116° (10 mm), [lit.43 bp 105-110° (14 mm)]; nmr (CDCl$_3$) δ 2.50 (6-pyr-CH$_3$, s, 3H), 4.71 (pyr-CH$_2$-O, s, 2H), 5.13 (-OH, s, 1H), and 6.85-7.75 (pyr-H, m, 3H); ir(neat) 3250 (broad-OH), 1595, 1575, 1455, 1075, and 783 cm$^{-1}$.

Trituration of the distillation residue with ether produced an additional 900 mg (7.3% of 155, mp 208-210°).

2-Acetoxymethyl-6-methylpyridine (158). This compound could be obtained pure in excellent yield by treatment of 2-hydroxymethyl-6-methylpyridine (155) with acetic anhydride at 80° for 15 minutes: bp 110-111° (10 mm), [lit.11 bp 110-114 (15 mm)]; nmr (CDCl$_3$) δ 2.05 (-O$_2$CH$_3$, s, 3H), 2.45 (6-pyr-CH$_3$, s, 3H), 5.19 (pyr-CH$_2$O, s, 2H), and 6.87-7.70 (pyr-H, m, 3H); ir(neat) 1740 (C=O, ester), 1585, 1570, 1225 (C=O), 1060, and 783 cm$^{-1}$.

2,6-Di(hydroxymethyl)pyridine (74) via N-Oxide Rearrangement. Crude 2-acetoxymethyl-6-methylpyridine (76 g, 0.46 mol) was heated under nitrogen at 70-80° for 2 hours with acetic acid (250 ml) and
a 30% hydrogen peroxide solution (50 ml). An additional 35 ml of hydrogen peroxide solution was introduced and the temperature was maintained at 80° for 9 hours. The mixture was concentrated to about one-third volume, diluted with an equal amount of water, and concentrated. The residual mixture was neutralized with a saturated sodium carbonate solution, extracted with chloroform, dried over magnesium sulfate, and concentrated at reduced pressure to afford the crude 2-acetoxymethyl-6-methylpyridine N-oxide. With no further purification, the N-oxide was dissolved in DME (50 ml) and added dropwise over a 3-hour period to a refluxing mixture of acetic anhydride (75 ml) and DME (50 ml) under nitrogen. After the addition was complete, reflux was continued for 6 hours. The mixture was concentrated in vacuo, poured into water, basified with sodium carbonate, and extracted with ether. The ether extract was dried over magnesium sulfate and evaporated. The residue was refluxed with 10% sodium hydroxide solution (250 ml) for 4 hours. The mixture was then extracted continuously with chloroform for 26 hours. Concentration of the chloroform extract afforded 2,6-di(hydroxymethyl)pyridine (74): 14.65 g (23%); mp 111-113.5° (lit.54 mp, 114.5-115°); nmr (CDCl₃) δ 2.5-2.8 (-OH, s, 2H), 4.77 (pyr-CH₂-0, s, 4H), 7.09-7.90 (pyr-H, m, 3H); ir(nujol) 3300 (sharp-OH), 3020 (broad-OH), 1590, 1570, 1155, 1100, 1080 (C-O), 1020, 976, 817, and 768 (broad) cm⁻¹.

2,6-Di(acetoxymethyl)pyridine (72). This compound was obtained in essentially quantitative yield by treatment of 2,6-di(hydroxymethyl)-pyridine (74) with acetic anhydride and a few drops of pyridine at 80° for 15 minutes: bp, 91-93° (0.7 mm) [lit.11 bp 135-139° (0.3 mm)];
nmr (CDCl₃) δ 2.10 (-O₂CH₃, s, 6H), 5.22 (pyr-CH₂-O, s, 1H), 7.18-7.90 (pyr-H, m, 3H); ir(neat) 1740 (C=O, ester), 1595, 1575, 1450, 1370, 1220, and 1060 cm⁻¹.

**Methyl 2,6-Pyridinedicarboxylate (155).** 2,6-Pyridinedicarboxylic acid (167.1 g, 1 mol) was suspended in anhydrous methanol (1.5 l) and saturated with anhydrous hydrochloric acid. After refluxing 2 days, the solvent was removed *in vacuo*. The residue was suspended in a 10% sodium carbonate solution and extracted with chloroform. The combined chloroform extracts were dried over sodium sulfate, and concentrated affording 191.7 g (98%) of methyl 2,6-pyridinedicarboxylate: mp 121-122.5° (lit.114 mp 124-125°); nmr (CDCl₃) δ 4.00 (-CO₂CH₃, s, 6H), 7.85-8.45 (pyr-H, m, 3H); ir (nujol) 1740 (C=O, ester), 1570, 1285, 1245, 1195, 1140, 995, 993, 813, 758, and 722 cm⁻¹.

**2,6-Di(hydroxymethyl)pyridine. Reduction of Methyl 2,6-Pyridinedicarboxylate. Method A. Sodium Bis(2-methoxyethoxy)aluminum Hydride.** Methyl 2,6-pyridinedicarboxylate (44.5 g, 0.228 mol) was refluxed in benzene (300 ml) and sodium bis(2-methoxyethoxy)aluminum hydride (70% solution in benzene, 73 ml, 0.282 mol) was added over 30 minutes. The mixture was stirred and cooled 30 minutes, then concentrated hydrochloric acid was introduced *carefully* until acidic. After stirring for 1 hour, the solution was made basic with a 40% sodium hydroxide solution and allowed to stand overnight. All solvents were removed *in vacuo*, and continuous extraction of the residual paste with benzene for 2-3 days afforded 14.8 g (75.5%) of crude 2,6-di(hydroxymethyl)pyridine. Recrystallization from benzene afforded 9.7 g (49.5%) of pure diol: mp 112-114°.
Method B. Sodium Borohydride. Similar to published methods, methyl 2,6-pyridinedicarboxylate (19.5 g, 0.10 mol) was stirred in anhydrous methanol while sodium borohydride (18.9 g, 0.50 mol) was added slowly via solid addition funnel. The temperature was maintained at $45 \pm 1^\circ$ with the intermittent aid of an ice bath. After the addition was complete, another 30 ml of methanol was introduced and the mixture was stirred for 30 minutes. Then the mixture was refluxed for 10 hours, cooled, and acetone (40 ml) was added. After evaporation to dryness, the solid residue was heated on the steam bath for 1.5 hours with 40 ml of 10% sodium carbonate solution and again taken to dryness in vacuo. Continuous extraction of the residue with chloroform for 10 hours gave 13.6 g (98%) of crude 2,6-di(hydroxymethyl)pyridine: mp 100-110$^\circ$. Recrystallization from methanol-ethyl acetate produced 9.7 g (70%) of the pure diol: mp 111.5-113$^\circ$.

2,6-Pyridinedicarboxaldehyde (85). Method A (via Reduction). Methyl 2,6-pyridinedicarboxylate (1.95 g, 10.0 mmol) was stirred under nitrogen in 40 ml anhydrous THF and cooled by ice-water bath to 12$^\circ$. Sodium bis(2-methoxyethoxy)aluminum hydride (70% solution in benzene, 3 ml, 10.0 mmol) was introduced by a syringe over 30 minutes. After the addition was complete, the mixture was allowed to stir at room temperature for 21 hours. A solution of acetic acid (5 ml) and water (5 ml) was added dropwise, stirred for 2 hours and poured into water (200 ml). Solid sodium carbonate was added until the solution was basic. Extractions with chloroform were dried over sodium sulfate and concentrated in vacuo. The solid residue was chromatographed on a florisil column with 25% ethyl acetate in petroleum ether-A to afford

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102 mg (7.6%) of 2,6-pyridinedicarboxaldehyde: mp 118-120° (lit. mp 121°); nmr (CDCl₃) δ 8.1-8.3 (pyr- H, m, 3H), 10.19 (-CHO, s, 2H); ir (nujol): 1710 (C=O), 1250, and 1205 (C-O), 910, 806, and 698 cm⁻¹.

**Method B (via Oxidation with Activated Manganese Dioxide).** The freshly prepared manganese dioxide¹¹⁵ (28 g) was activated by azeotropic distillation of water with benzene.¹¹⁶ The benzene was decanted from the active manganese dioxide (10 g, 115 mmol) and replaced by chloroform (100 ml). 2,6-Di(hydroxymethyl)pyridine (1.97 g, 14.2 mmol) was introduced and then refluxed ca. 4 hours. The mixture was filtered hot and the precipitate washed several times with hot chloroform. Removal of the solvent in vacuo gave a solid residue, which was chromatographed on a florisil column with 25% ethyl acetate in petroleum ether-A to give 290 mg (15.2%) of 2,6-pyridinedicarboxaldehyde: mp 120.5-122°.

**Method C (via Oxidation with Lead Tetraacetate).** A benzene solution of lead tetracetate (53.2 g, 0.120 mol) was brought to reflux. The heat was removed and 2,6-di(hydroxymethyl)pyridine (6.76 g, 0.049 mol) was added via solid addition funnel. The mixture was refluxed for 1 hour, cooled, and ca. 2 ml ethylene glycol was added. This solution was made basic with a 10% sodium carbonate solution, filtered, and washed with chloroform. The filtrate was extracted several more times with chloroform, dried with sodium sulfate, and concentrated in vacuo. Recrystallization from benzene-petroleum ether-A afforded 2.58 g (39.4%) of 2,6-pyridinedicarboxaldehyde (85): mp 119-121°. The mother liquor was concentrated and upon sublimation at 50-80° (2.5 mm) gave an additional 600 mg (9.1%): mp 119-121°.
trans,trans-2,6-Di[2-(2-(6-methylpyridyl))vinyl]pyridine (89). Acetic anhydride (1.27 g, 12.5 mmol), 2,6-pyridinedicarboxaldehyde (1.00 g, 7.41 mmol), and 2,6-dimethylpyridine (6.12 g, 57.3 mmol) were refluxed under nitrogen for 3 hours. The mixture was concentrated in vacuo and chromatographed on a florisil column with benzene to afford 861 mg (37%) of (89): mp 130-131.5° [lit. 43 mp 148-156° ("... falling to 129-133° on further crystallization from benzene...")43]; nmr (CDCl₃, 220 MHz) δ 2.57 (6-pyr-CH₃, s, 6H), 7.03 (H₅, d, J = 7.8 Hz, 2H), 7.30 and 7.305 (H₃, H₃', H₅', d, J = 7.8 Hz, 4H), 7.55 and 7.59 (H₄ and H₄', t, J = 7.8 Hz, 3H), 7.59 and 7.78 (vinyl-H, d, J = 16.5 Hz, 4H); ir(nujol) 1582, 1562, 1500, 985, 973, 805, and 740 cm⁻¹; uv(MeOH) 338 (28,090), 306 (32,800), and 266 nm (23,000).

Further elution with ethyl acetate gave 639 mg of a mixture of several unknown compounds.

Ethyl 2,6-Pyridinediacetate (67). An oil dispersion of sodium (26.2 g, 1.14 mol) in toluene (400 ml) was stirred under nitrogen. Chlorobenzene (57.5 g, 0.51 mol) was added dropwise over 30 minutes while the temperature was maintained at ≤ 35° via intermittent cooling. Stirring was continued for 45 minutes at this temperature.
2,6-Dimethylpyridine (58.5 g, 0.50 mol) in 50 ml of toluene was added dropwise over 1 hour and stirred for another 2 hours at 35°. The mixture was poured onto crushed solid-CO\textsubscript{2} with vigorous stirring and was allowed to warm slowly to room temperature. The solvent was removed \textit{in vacuo}. The residue was suspended in 400 ml of absolute ethanol, cooled, and treated with 82 ml of cold concentrated sulfuric acid. After refluxing for 10 hours, ethanol was removed \textit{in vacuo} and the residue poured onto ice. The aqueous solution was washed with ether, made slightly basic with sodium carbonate, and extracted with chloroform. The chloroform extract was dried over sodium sulfate, concentrated and fractionally distilled to give 17.9 g (20\%) of ethyl 2-(6-methylpyridyl)acetate (66): bp 132-134° (14 mm) [lit.\textsuperscript{5} bp 98-102° (5 mm)]; nmr (CDCl\textsubscript{3}) δ 1.26 (-CH\textsubscript{2}CH\textsubscript{3}, t, J = 7 Hz, 3H), 2.54 (pyr-CH\textsubscript{3}, s, 3H), 3.82 (pyr-CH\textsubscript{2}, s, 2H), 4.20 (CH\textsubscript{2}CH\textsubscript{2}-, q, J = 7 Hz, 2H), 6.90-7.75 (pyr-H, m, 3H); ir(neat) 1735 (C=O, ester), 1595, 1580, 1270, 1170 (C-O), 1030, and 766 cm\textsuperscript{-1}; ms (70 eV and 40 µA) m/e (relative intensity) 179 (12), 134 (22), 107 (100), 106 (72), 79 (20), and 77 (17); and 1.76 g (1.4\%) of crude ethyl 2,6-pyridinediacetate (67): bp 138-158° (6 mm) [lit.\textsuperscript{5} bp 158-160° (5 mm)]; nmr (CDCl\textsubscript{3}) δ 1.23 (-CH\textsubscript{2}CH\textsubscript{3}, t, J = 7 Hz, 6H), 3.82 (pyr-CH\textsubscript{2}, s, 4H), 4.27 (CH\textsubscript{2}CH\textsubscript{2}-, q, J = 7 Hz, 4H), and 7.05-7.80 (pyr-H, m, 3H).

\textbf{Reaction of 2,6-Dimethylpyridine Anions with Ethyl Chloroformate.}

2,6-Dimethylpyridine (0.550 g, 5.13 mmol) in 25 ml of THF was added dropwise with vigorous stirring over 15 minutes to a solution of t-butyllithium (1.12 g, 17.4 mmol) in 9 ml of hexane while the temperature was kept below -40°. The cooling bath was removed and the solution
allowed to warm to 6° during 30 minutes, transferred to an addition
funnel, and added over 10 minutes to ethyl chloroformate (11.35 g, 105 mmol) at 0°. After stirring 30 minutes the mixture was poured
into 100 ml of 10% sodium carbonate solution and stirred 10 minutes.
Then aqueous sodium hydroxide solution (10%, 25 ml) was added. The
solution was stirred 10 minutes and extracted with chloroform. The
chloroform extract was dried with sodium sulfate and concentrated in
vacuo to give 950 mg of a three-component mixture (determined by glc):
2,6-dimethylpyridine (34%), ethyl 2-(6-methylpyridyl)acetate (24%), and
ethyl 2-(6-methylpyridyl)carbonate (15%) (42%): nmr (CDCl3) δ 1.34
(-CH3CH3, t, J = 7 Hz, 3H), 2.57 (pyr-CH3, s, 3H), 4.38 (CH3CH2-0, q, J = 7 Hz, 2H), 5.27 (pyr-CH2-0, s, 2H), 6.95-7.75 (pyr-H, m, 3H);
ir(neat) 1750 (C=0, ester), 1595, 1580, 1255 (C-O), 1015, 875, and
792 cm⁻¹; ms (70 eV and 40 μA) m/e (relative intensity) 195 (4), 123
(13), 122 (100), 107 (31), and 106 (36).

An elemental analysis of 156 was not obtained since the sample
was inadvertently discarded.

Reaction of 2,6-Dimethylpyridine with Sodium Hydride and Diethyl-
Carbonate. Sodium hydride (4.2 g of a 50% mineral oil suspension,
100 mmol) was washed with petroleum ether and dried under nitrogen.
2,6-Dimethylpyridine (10.7 g, 100 mmol) in 50 ml of DME was introduced
and refluxed for 1 hour. Diethyl carbonate (35.4 g, 300 mmol) in 30 ml
DME was added and refluxed 3 days. The mixture was poured into ice
water and extracted with ether. The ether layer was extracted with
5% hydrochloric acid. This acidic solution was made basic with sodium
carbonate and extracted with ether. The ether was dried over sodium
sulfate and concentrated in vacuo. The residue was fractionally distilled affording 2.3 g of a yellow oil: bp 78-122° (0.2 mm).

Chromatography (pic, 2 mm, 5% ethyl acetate in chloroform) of this oil afforded 1.58 g (16.8%) of ethyl 2-(6-methylpyridyl)acetate ($R_f = .38$) and 714 mg (10.3%) of diethyl 2-(6-methylpyridyl)malonate ($R_f = .55$; bp 96-98° (0.8 mm); nmr (CDCl$_3$) δ 1.27 (-CH$_2$CH$_3$, t, $J = 7$ Hz, 3H), 2.57 (pyr-CH$_3$, s, 3H), 4.27 (CH$_2$CH$_2$-s, q, $J = 7$ Hz, 2H), 5.00 (pyr-CH, s, 1H), 7.0-8.0 (pyr-H, m, 3H); ir(neat) 1730 (C=O, ester), 1585, 1570, 1450, 1300, 1240, 1140, and 1030 cm$^{-1}$; ms (70 eV and 40 µA) m/e (relative intensity) 251 (10), 206 (41), 179 (100), 178 (34), 137 (69), 136 (20), 134 (21), 133 (17), 108 (81), 107 (78), 106 (74), and 77 (30).

Anal. Calcd for C$_{13}$H$_{17}$NO$_4$: C, 62.13; H, 6.82. Found: C, 62.17; H, 7.01.

**Reactions of 2,6-Dimethylpyridine Anion(s) with Methyl Iodide.**

2,6-Dimethylpyridine was treated with a 2 mole ratio of base in various solvent-base systems, as shown in Table V, usually for a short period of time at room temperature. The anion(s) generated were trapped by addition to a methyl iodide solution with stirring for 30 minutes. Each reaction was poured into water and extracted with ether. Ether extracts were dried over magnesium sulfate and concentrated in vacuo. The resulting mixtures of substituted pyridine compounds were comparatively analyzed by glc (Table V).

**Ethyl 2-(6-Chloropyridyl)acetate (161) and Ethyl 2-(6-Bromopyridyl)-acetate (162).** 2,4,6-Trimethyloxazoline$_{21}$ (2.49 g, 22 mmol) was stirred under nitrogen in 100 ml ether at -70°. A solution of n-butyllithium
TABLE V

REACTIONS OF 2,6-DIMETHYLPYRIDINE ANION(s) WITH METHYL IODIDE

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Base</th>
<th>Time (hrs)(^a)</th>
<th>Ratio of Substituted Pyridines(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>DMF</td>
<td>KOtBu</td>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>THF/Hexane</td>
<td>(\eta)-BuLi(^c)</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>THF/Hexane</td>
<td>(\eta)-BuLi(^c)</td>
<td>(2^d)</td>
<td>1.0</td>
</tr>
<tr>
<td>Et(_2)O</td>
<td>C(_6)H(_5)Li</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>HMPA/Et(_2)O</td>
<td>C(_6)H(_5)Li</td>
<td>0.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

\(^a\) Period of anion generation.

\(^b\) Reactions are complicated by competing quaternization.

\(^c\) Use of \(\eta\)-BuLi also produces products containing \(\eta\)-butyl group(s).

\(^d\) Reaction temperature was -45\(^\circ\); methyl iodide addition at 25\(^\circ\) with stirring for 2 hours.
in hexane (10 ml, 2.37 M, 24 mmol) was introduced via syringe over 5 minutes. The mixture was allowed to slowly warm to -40° over 1.5 hours. 2,6-Dichloropyridine (0.74 g, 5 mmol) in 25 ml ether was added over 45 minutes. The mixture was allowed to stir 1 hour, thus warming to 15°. After refluxing 2 hours, the solvent was evaporated. The residue was suspended in 50 ml absolute ethanol. Concentrated sulfuric acid (5 ml) was carefully added and the mixture refluxed overnight. Ethanol was removed in vacuo, the residue suspended in 10% sodium carbonate solution, and extracted with chloroform. The chloroform was dried over sodium sulfate and carefully concentrated in vacuo. Chromatography (plc, 2 mm in 17% ethyl acetate-cyclohexane) of the residue gave 125 mg (17%) of 2,6-dichloropyridine \( (R_f^* = 0.68; \text{ in } 25\% \text{ EtOAc-C}_6\text{H}_{12}) \) and 237 mg (24%) of 161 \( (R_f^* = 0.51 \text{ in } 25\% \text{ EtOAc-C}_6\text{H}_{12}) \); bp 121-126° (1.5 mm); nmr(CDC\textsubscript{13}) \( \delta 1.27 (-\text{CH}_2\text{CH}_3, \text{ t, } J = 7 \text{ Hz, } 3\text{H}), 3.82 \text{ (pyr-CH}_2^-, \text{ s, } 2\text{H}), 4.18 \text{ (-CH}_2\text{CH}_3, \text{ q, } J = 7 \text{ Hz, } 2\text{H}), 7.05-8.05 \text{ (pyr-H, m, } 3\text{H}); \text{ ir(neat) } 1730 \text{ (C=O, ester), } 1575, 1550, 1425, 1170 \text{ (C-O), } 1155, 1130, \text{ and } 1025 \text{ cm}^{-1}. \) 

**Anal.** Calcd for C\(_9\)H\(_{10}\)N\(_2\)O\(_2\)Cl: C, 54.14; H, 5.05. Found: C, 54.11; H, 5.40.

Similarly, 2,6-dibromopyridine (0.71 g, 3 mmol) and 2,4,4-trimethyloxazoline (1.36 g, 12 mmol) were reacted, solvolyzed, and chromatographed to afford 131 mg (19%) of unreacted 2,6-dibromopyridine, mp 113-115° \( (R_f^* = 0.77 \text{ in } 25\% \text{ EtOAc-C}_6\text{H}_{12}) \), along with 115 mg (16%) of 162 \( R_f^* = 0.53 \text{ in } 25\% \text{ EtOAc-C}_6\text{H}_{12}; \text{ bp } 71-74° \text{ (0.8 mm); nmr (CDCl}_3 \text{) } \delta 1.28 (-\text{CH}_2\text{CH}_3, \text{ t, } J = 7 \text{ Hz, } 3\text{H}), 3.82 \text{ (pyr-CH}_2^-, \text{ s, } 2\text{H}), 4.19 \text{ (CH}_2\text{CH}_3, \text{ q, } J = 7 \text{ Hz, } 2\text{H}), 7.15-7.75 \text{ (pyr-H, m, } 3\text{H}); \text{ ir(neat) } 1735 \text{ (C=O, ester), } 1580, 1550, 1260, 1120 \text{ (C-O), } 1030, \text{ and } 987 \text{ cm}^{-1}. \)
A suitable elemental analysis for 162 could not be obtained, even after repeated chromatography (plc, 2 mm) and molecular distillation.

2-Chloromethyl-6-methylpyridine (163). 2,6-Dimethylpyridine N-oxide (7.4 g, 6.0 mmol) in 60 ml of benzene was stirred with p-toluenesulfonyl chloride (11.5 g, 6.0 mmol) for 3 hours. After removal of the solvent, the residue was heated to 100° for 1 hour, cooled, and washed with ether. The residue was basified with a saturated sodium bicarbonate solution and extracted with chloroform. The chloroform extract was dried over sodium sulfate and concentrated affording a residual oil (7.82 g) which was distilled to give 3.21 g (37.6%) of pure 2-chloromethyl-6-methylpyridine (163): bp 72-75° (7 mm) [lit.43,113 bp 45-50° (0.4 mm)]; nmr (CDCl3) δ 2.55 (pyr-CH3, s, 3H), 4.62 (pyr-CH2–, s, 2H), 6.95-7.80 (pyr-H, m, 3H).

2,6-Di(chloromethyl)pyridine (75). Method A. (via N-Oxide Rearrangement). 2-Chloromethyl-6-methylpyridine (3.21 g, 22.6 mmol), acetic acid (30 ml), and 10 ml of 30% hydrogen peroxide solution were stirred at 80° for 12 hours. Fresh hydrogen peroxide (5 ml, 30% solution) was added and the solution heated for an additional 4 hours. After concentration in vacuo to ca. half volume, water (25 ml) was added and the solution evaporated to dryness. The residue was suspended in 10% sodium carbonate solution, extracted with chloroform, dried over magnesium sulfate, and evaporated. The resultant crude N-oxide (164) was stirred in 40 ml benzene with p-toluenesulfonyl chloride (4.47 g, 23.5 mmol) for 8 hours. The solvent was removed, and the residue was heated at 100° for 1 hour, cooled, and washed with ether. The residue
was treated with 10\% sodium carbonate solution and extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated. Chromatography of the residue on a florisil column in petroleum ether-A using gradient elution with benzene to afford 795 mg (24.8\%) of unreacted 2-chloromethyl-6-methylpyridine and 100 mg (2.5\%) of 2,6-di(chloromethyl)pyridine: \textit{mp} 75-76° (lit. 74-75°).

Method B - (via Thionyl Chloride). 2,6-Di(hydroxymethyl)pyridine (21.0 g, 0.15 mol) was suspended in refluxing chloroform (500 ml) under a nitrogen atmosphere. Thionyl chloride (45 ml, 0.63 mol) in 75 ml of chloroform was added dropwise over 1.5 hours, and then refluxed for 12 hours. Solvent and excess thionyl chloride were removed \textit{in vacuo}. The residue was treated with 10\% sodium carbonate solution and extracted several times with ether. The ether extracts were dried with sodium sulfate, decolorized by rapid filtration through a small column of florisil, and concentrated. The residue was recrystallized from petroleum ether-A to give 23.5 g (89\%) of 2,6-di(chloromethyl)pyridine: \textit{mp} 74.5-76° (lit. 74-75°); nmr (CDCl$_3$) $\delta$ 4.68 (pyr-CH$_2$-Cl, s, 4H), 7.25-7.95 (pyr-H, m, 3H); ir (nujol) 1590, 1250, 1085, 752, 688, and 674 cm$^{-1}$.

2,6-Pyridinediacetonitrile (77). 2,6-Di(chloromethyl)pyridine (17.3 g, 0.098 mol) in 125 ml of dry DMSO was added dropwise over 2 hours to a stirred solution of potassium cyanide (35.3 g, 0.540 mol) in 125 ml of DMSO under nitrogen at 41°. After 21 hours, the mixture was poured into a solution of 10\% aqueous sodium carbonate (1.3 l) containing 15 ml of a 40\% sodium hydroxide solution and extracted sequentially with ether and chloroform. The organic extracts were washed
with water, dried over magnesium sulfate, combined, and concentrated in vacuo. The residue was suspended in chloroform and filtered through a small column of alumina. The filtrate was evaporated and the residue recrystallized from ethanol to afford 14.3 g (92.7%) of 2,6-pyridinediacetonitrile ($\mathcal{J}$): mp 95-96° (lit. 43 mp 97-98°); nmr (CDCl$_3$) δ 3.95 (pyr-CH$_2^-$, s, 4H), 7.15-7.95 (pyr-H, m, 3H); ir(nujol) 2350 (C=NN), 1585, 1570, 1090, 994, 920, 793, and 762 cm$^{-1}$

**Methyl 2,6-Pyridinediacetate ($\mathcal{J}$).** 2,6-Pyridinediacetonitrile (14.9 g, 95 mmol) was stirred in anhydrous methanol (300 ml) and saturated with hydrogen chloride over 2 hours. After cooling to room temperature, water (3.65 ml, 220 mmol) was added dropwise, then stirred for 9 hours. The mixture was refluxed for 1.5 hours and evaporated to dryness. Treatment of the residue with a 10% sodium carbonate solution was followed by extractions with ether then with chloroform. The organic extracts were combined, dried with magnesium sulfate and evaporated. This residue was distilled to give 10.85 g (51.2%) of methyl 2,6-pyridinediacetate: bp 144-151° (1 mm). Recrystallization from hexane produced an analytical sample: mp 62.5-63.5° (lit. 41 mp 62°); nmr (CDCl$_3$) δ 3.67 (-CO$_2$CH$_3$, s, 6H), 3.82 (pyr-CH$_2^-$, s, 4H), 7.1-7.8 (pyr-H, m, 3H); ir(nujol) 1730 (C=O, ester), 1595, 1370, 1200 (C-O), 1155 (C-O), 1000, 887, and 765 cm$^{-1}$.

**Ethyl 2,6-Pyridinediacetate ($\mathcal{J}$)** was prepared in an identical manner from the diacetonitrile $\mathcal{J}$. Chromatography of the crude product on florisil with 25% ethyl acetate in petroleum ether-A afforded (76%) pure ethyl 2,6-pyridinediacetate which was identical to an authentic sample.
2,6-Distyrylpyridine (68). Method A. (via Acetic Anhydride). 2,6-Dimethylpyridine (214 g, 2.0 mol), benzaldehyde (458 g, 4.4 mol), and acetic anhydride (1.5 l, 8.96 mol) were refluxed 48 hours under a nitrogen atmosphere. Concentration to ca. half volume was accomplished in vacuo. The residue was poured into 3 l ice water and allowed to stand overnight. The precipitate was removed and the filtrate extracted with chloroform. The filtered solids were combined with the chloroform extracts and neutralized with a 10% sodium carbonate solution. The chloroform layer was separated, dried, and concentrated in vacuo. Recrystallization of the residue from benzene-ethanol gave 110.5 g (20%) of 2,6-distyrylpyridine (68): mp 165-166.5° (lit. 29 mp 166.5°); nmr (CDCl₃) δ 7.0-7.9 (all H's, m); ir(nujol) 1640, 1570, 1550, 1155, 980, 970, 797, 733, and 690 cm⁻¹; uv (MeOH) 335 (26,150) and 290 nm (41,700).

The mother liquor was concentrated and distilled at reduced pressure. The distillate [bp 160-166° (2-3 mm)] was triturated with petroleum ether-A and filtered to provide 53 g of crude alcohol, mp 106-110°, which upon recrystallization from ethanol-ethyl acetate gave 52 g (20%) of 1-phenyl-2-[2-(6-methylpyridyl)]ethanol (165): mp 116-118° [lit. 38 bp 139° (0.01 mm)]; nmr (CDCl₃) δ 2.96 (pyr-CH₃, s, 3H), 7.15-8.35 (remaining H's, m, 12H); ir(nujol) 3400 (OH), 1630, 1600, 1165, 980, 800, 762, 719, and 693 cm⁻¹.

The petroleum ether filtrate was concentrated and cooled to afford 65.3 g (17%) of 2-methyl-6-styrylpyridine (166): mp 42.5-44° (lit. 29 mp 38°); nmr(CDCl₃) δ 2.52 (pyr-CH₃, s, 3H), 6.75-7.80 (arom-H, and vinyl-H, m, 10H); ir(nujol) 1580, 1560, 988, 979, 785, 734, and 690 cm⁻¹; uv (MeOH) 313 (28,400), 281 (14,570), and 227 nm (12,300).
Method B. (via Imine Condensation).\textsuperscript{123,124} According to procedure in Organic Syntheses,\textsuperscript{122} benzaldehyde (106 g, 1 mol) was stirred rapidly while aniline (93 g, 1 mol) was slowly added. After 15 minutes, this mixture was poured into 165 ml of 95\% ethanol. Further dilution with water and cooling afforded 144 g (86\%) of benzalaniline (167): mp 51.5-52.5° (lit.\textsuperscript{122} mp 52°), nmr (CDCl\textsubscript{3}) δ 6.95-7.60 (arom-H, m, 8H), 7.65-8.05 (o-arom-H, m, 2H), 8.38 (vinyl-H, s, 1H); ir(nujol) 1625 (C=\textit{N}), 1585, 1570, 1190, 762, and 693 cm\textsuperscript{-1}; uv (MeOH) 262 (17,600), and 310 nm (9,170).

2,6-Dimethylpyridine (1.07 g, 10 mmol) and benzalaniline (3.62 g, 20 mmol) in 10 ml DMF were stirred under nitrogen. Potassium t-butoxide (2.24 g, 20 mmol)* was introduced with DMF (10 ml). The mixture was warmed carefully to 90° over at least 30 minutes and then maintained at that temperature for an additional 1 to 2 hours. After cooling slightly, the mixture was poured into 100 ml of water and chilled for several hours. A yellow precipitate was collected, washed with water, and recrystallized from benzene-cyclohexane-ethanol to afford 2.20 g (78\%) of the symmetrical olefin 68: mp 165-166°.

\textit{2,6-Bis(1,2-dibromo-2-phenylethyl)pyridine (168).}\textsuperscript{29} 2,6-distyrylpyridine (70.7 g, 0.25 mol) was refluxed in carbon tetrachloride (2.5 l) while bromine (83 g, 0.52 mol) in 200 ml of carbon tetrachloride was added dropwise over 2 hours. Another 2 l of solvent was added and reflux continued for 2 hours. Unreacted bromine was destroyed by vigorous stirring with aqueous sodium bisulfite. The aqueous layer was decanted.

* By error, only one-half the suggested ratio of base was utilized.
and the organic layer filtered hot. Upon cooling, the tetrabromide recrystallized: 136 g (90%); mp 180-182° (lit.\textsuperscript{125} mp 183°); nmr (DMSO-d\textsubscript{6}) 6 6.23 (arom-CH-, m, 4H), 7.0-8.1 (arom-H, m, 13H); ir(nujol) 1580, 1140, 787, and 800 cm\textsuperscript{-1}.

The mother liquor was concentrated almost to dryness and filtered. The resultant yellow solid was recrystallized from ethanol-chloroform to give an additional 12.6 g (8.2%) of the tetrabromide: mp 183-184°.

2,6-Di(phenylethynyl)pyridine (62).\textsuperscript{41} 2,6-Bis(1,2-dibromo-2-phenylethyl)pyridine (15 g, 0.25 mol) was suspended in 300 ml of benzene. Sodium hydroxide (60 g, 1.5 mol) in 800 ml of 95% ethanol was introduced and the mixture refluxed for 24 hours. Solvents were removed by distillation. The distillation residue was triturated with ether and filtered. The etheral filtrate was concentrated in vacuo and recrystallized from cyclohexane-ethanol (charcoal) to afford 34.1 g (49%) of diacetylene: mp 134-136° (lit.\textsuperscript{51} mp 137-138°); nmr (CDCl\textsubscript{3}) 6 6.8-7.7 (all arom-H); ir(nujol) 2200 (C=), 1550, 1165, 810, 765, 757, and 690 cm\textsuperscript{-1}; uv (MeOH) 318 (29,420), 282 (35,600), and 268 nm (34,950).

2,6-Di(phenacyl)pyridine (70).\textsuperscript{51} 2,6-Di(phenylethynyl)pyridine (32.5 g, 0.116 mol) in 250 ml of 50% sulfuric acid was heated to 135° for ca. 15 minutes and then poured into 250 ml of water. The sulfate salts obtained on cooling were filtered, washed and finally recrystallized from 95% ethanol. The yellow salt (mp 200°) was suspended in methanol, warmed, and basified with concentrated ammonium hydroxide. Dilution with water and cooling produced a yellow solid which was filtered and recrystallized from benzene-hexane affording 28.35 g (64%).

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of the diketone: mp 77-80°. Fractional recrystallization increased
the melting point: mp 85-87° (lit. 91 mp 90°); nmr (CDCl₃) - very com-
plicated since exists as ca. 39% enol; ir(νujol) 1675 (C=O), 1630
(H-bonded C=O), 1590, 1545, 1520, 1495, 804, 784, 758, 737, and 692 cm⁻¹.

2,6-Di(methyltriphenylphosphonium)pyridine Dichloride (162). 2,6-
Di(chloromethyl)pyridine (4.4 g, 25 mmol) and triphenylphosphine (14.2 g,
54 mmol) in 50 ml of DMF were refluxed overnight. The cooled reaction
mixture was diluted with ether, filtered, and stored under vacuum until
a constant weight. The yield was essentially quantitative: mp 274-276°.

Ethyl 2-Pyridylacetate (12). Method A. A suspension of 2-
methylpyridine (27 ml, 0.3 mol), diethylcarbonate (121 ml, 1.05 mol)
and sodium hydride (43 g, 1.0 mol) in 100 ml of dry DME was refluxed
for 12 hours. After cooling and carefully pouring into water, the
aqueous mixture was extracted with ether, dried over anhydrous magnesium
sulfate and concentrated. The residual oil was fractionally distilled
giving 10 g (20%) of ethyl 2-pyridylacetate: bp 110-116° (6 mm) [lit. 4,128
bp 122-125° (12 mm)]; nmr (CDCl₃) δ 1.23 (-CH₂CH₃, t, J = 7 Hz, 3H),
3.83 (CH₂CO, s, 2H), 4.17 (CH₂CH₃-, q, J = 7 Hz, 2H), 7.0-7.8 (arom-H,
m, 3H), and 8.45-8.65 (6-pyr-H, m, 1H); ir( neat) 1738 (C=O, ester), 1587,
1160, and 1036 cm⁻¹.

A higher boiling fraction, bp 110-117° (0.3 mm), was col-
lected. After purification by dry column chromatography, the resultant
yellow oil was distilled affording 850 mg (1.2%) of diethyl 2-pyridyl-
malonate (170): bp 130-132° (1 mm); nmr (CDCl₃) δ 1.21 (-CH₂CH₃, t,
J = 7 Hz, 3H), 4.22 (-CH₂CH₃, q, J = 7 Hz, 2H), 5.04 (pyr-H, m, 3H),
and 8.44-8.65 (6-pyr-H, m, 1H); ir(neat) 1743 (C=O, ester), 1595, 1152,
and 1037 cm⁻¹.

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Method B. Ethyl 2-pyridylacacetate was also prepared in 43% yield by the method of Goldberg, et al.\textsuperscript{16} from 2-picolyllithium and diethyl carbonate at 0°. Workup deviated from the literature procedure to furnish additional compounds, which are the subject of a separate project (see Appendix I).

Ethyl (Z)- and (E)-\(\alpha\)-(2-Pyridyl)cinnamate (171). Ethyl 2-pyridyl-acetate (505 mg, 3.06 mmol), benzaldehyde (358 mg, 3.38 mmol), and piperidine (178 mg, 2.09 mmol) in absolute ethanol (15 ml) were refluxed under nitrogen for 22 hours. Solvent and excess reagents were removed \textit{in vacuo}. The crude reaction mixture was chromatographed (plc, 2 mm) with 2:1 cyclohexane-ethyl acetate affording the (Z)-171: 78 mg, 10% bp 150-160° (0.15 mm), \(R_f = 0.63\), [lit.\textsuperscript{32} methiodide, mp 227-228° (d)], the (E)-171 (=,\textsuperscript{171}): 154 mg, 20%, bp 179-186° (2.5 mm), \(R_f = 0.54\); [lit.\textsuperscript{32} bp 160-161° (1 mm), methiodide, mp 200-201° (d)], and unreacted ethyl 2-pyridylacetate (216 mg, 43%, \(R_f = 0.41\)). Spectral data are in Table VI.

\textbf{Anal. Calcd for C\textsubscript{12}H\textsubscript{15}N\textsubscript{2}: C, 60.76; H, 6.38. Found: C, 61.06; H, 6.40.}

Ethyl (Z)- and (E)-2,3-Di(2-pyridyl)acrylate (172). Method A. Piperidine-Ethanol. A mixture of ethyl 2-pyridylacetate (2.66 g, 15.8 mmol), 2-pyridinecarboxaldehyde (1.72 g, 16.1 mmol), and piperidine (1 ml) in 25 ml of absolute ethanol was refluxed for 12 hours. The solvent and excess volatile reagents were removed \textit{in vacuo} affording
an oil, which was decolorized, and recrystallized from ether-petroleum ether-A affording 980 mg (25%) of (Z)-172: mp 77.5-79°. See Table VI for spectral data.

**Anal.** Calcd for C\textsubscript{15}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2}: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.50; H, 5.30; N, 10.95.

The mother liquor (3.0 g) was chromatographed on silica gel with cyclohexane-ethyl acetate (75:25) and using gradient elution to pure ethyl acetate. Nmr analysis of the weighed combinations indicated: (Z)-172 (820 mg, 20%, R\textsubscript{f} = .45), intermediary alcohols (86 mg, 2%, R\textsubscript{f} = .33), ethyl 2-pyridylacetate (350 mg, 13%, R\textsubscript{f} = .38), and (E)-172 [1.20 g, 30%, R\textsubscript{f} = .14, bp 145-150° (3.5 mm)]. See Table VI for spectral data.

**Anal.** Calcd for C\textsubscript{15}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2}: C, 70.85; H, 5.55. Found: C, 70.73; H, 5.60.

**Method B. Acetic Anhydride-Triethylamine.** The ester (3.3 g, 20.0 mmol) and aldehyde (2.15 g, 20.1 mmol) were stirred in 25 ml of acetic anhydride and 25 ml of triethylamine at 25° for 15 hours under nitrogen and then poured into water. After basifying with sodium carbonate, the solution was extracted with ether. The ether layer was dried over sodium sulfate and evaporated. Nmr of the residue indicated ca. 17.5% of (E)-172 along with (Z)-172 and acetylated compounds. The residue was decolorized by filtration of a methylene chloride solution through silica gel, and recrystallized from cold ether-petroleum ether-A to give 2.32 g (46%) of (Z)-172: mp 77-78°.

**Method C. Triethylamine-Ethanol.** The ester (3.31 g, 20.0 mmol) and aldehyde (2.17 g, 20.3 mmol) were refluxed in 25 ml of absolute
ethanol and 25 ml triethylamine under nitrogen for 16 hours, then the solvents were evaporated. Nmr and tlc showed the presence of some starting materials and alcohol(s) (18%) as well as (E)-172 (17%) and (Z)-172. Recrystallization, as above, gave 1.5 g (30%) of (Z)-172: mp 77.5-79°.

(Z)- and (E)-α-Phenylcinnamic Acids were prepared by standard Perkin127 procedures from benzaldehyde and phenylacetic acid. Utilization of Fieser's method128 for isomer separation afforded the pure Z-acid: 11.0%, mp 138-139° (lit.128 mp 138-139°) and the isomeric E-acid: 59.5%, mp 172-173° (lit.128 mp 174°).

Ethyl (E)-α-Phenylcinnamate was prepared by standard esterification using absolute ethanol and sulfuric acid catalyst: (E)-172, (oil), lit.129 mp 31-32°. Spectral data are in Table VI.

Ethyl (Z)-α-Phenylacinnamate. Lengthy reaction time for preparation of ester (Z)-173 from the acid was obviated by an adaptation of Mills' method.130 The acid (1.26 g, 5.63 mmol), ethyl iodide (0.87 g, 5.60 mmol), and triethylamine (0.55 g, 5.45 mmol) were refluxed for 7 hours under nitrogen. After cooling, the mixture was washed with ether, concentrated, suspended in ethyl acetate and filtered through alumina to give 853 mg (62%) of pure (Z)-173: bp 135-140° (0.1 mm) [lit.128 bp 130° (0.01 mm)]. Spectral data are in Table VI.

Ethyl (Z)- and (E)-2-Phenyl-3-(2-pyridyl)acrylate (174).132 A mixture of sodium hydride (270 mg, 6.43 mmol), diethyl oxalate (1.46 g, 10 mmol), and ethyl phenylacetate (1.64 g, 10 mmol) in 50 ml di(n-butyl)-ether was heated at 65° for 1 hour. The ethanol was removed at aspirator
pressure; then after cooling at 50°, 2-pyridinecarboxaldehyde (1.09 g, 10 mmol) was added and refluxed under nitrogen for 1 hour. The reaction mixture was cooled, poured into water, extracted with ether and chloroform, washed successively with a 10% sodium carbonate solution, water, and saturated sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed (plc, 2 mm) with 2:1 cyclohexane-ethyl acetate giving (Z)-174: 145 mg, 9%, mp 69.5-71.5°, Rf = 0.60 [lit.65 (oil)]; (E)-174: 253 mg, 16%, bp 195-203° (4 mm), Rf = 0.54; unreacted ethyl phenylacetate, and several other minor unidentified products. Spectral data are in Table VI.

Anal. Calcd for C15H13NO2: C, 75.87; H, 5.97; N, 5.53. Found (E-isomer): C, 75.68; H, 5.82; N, 5.46.

Deoxybenzoin (175) was prepared by the method of Kohler and Nygaard:133 mp 54.5-55.5° (lit.234 mp 55°); nmr (CDCl3) δ 4.23 (COCH3, s, 2H), 7.1-7.6 (arom-H, m, 8H); ir(nujol) 1675 (C=O), 1585, 1570, 1320, 1315, 1195, 989, 750, 727, 698, and 685 cm⁻¹.

α-(2-Pyridyl)acetophenone (6).18 A solution of phenyllithium (2.2 M in benzene-ether, 250 ml, 0.6 mol) in 250 ml ether was stirred under nitrogen with addition of 2-methylpyridine (56 g, 0.6 mol) over 10 minutes. The solution was gently refluxed for 30 minutes followed by rapid addition of methyl benzoate (41 g, 0.3 mol) in 50 ml ether. After an additional 30 minutes reflux, the reaction mixture was poured into dilute acid, the ether layer was separated and extracted several times with 5% hydrochloric acid. Acidic extracts were made slightly basic by careful addition of a 40% sodium hydroxide solution. Ether extractions were made until the extract did not give a positive color.
test with alcoholic ferric chloride. The combined extracts were dried over "Drierite", and concentrated. Fractional distillation afforded 41 g (69.5%) of \( \alpha \)-(2-pyridyl)acetophenone [bp 149-155° (2 mm)] which crystallized on standing: mp 52-54°. Recrystallization from cyclohexane raised the melting point: mp 54-57° (lit. \(^{18}\) mp 52.5-54°); picrate mp 179-180.5° (lit. \(^{17}\) picrate mp 179-180°); \text{nmr (CDCl}_3\text{)(keto and enol forms) } \delta 4.43 (\text{pyr-CH}_2\text{, s, } \sim 1 \text{H}), 6.04 (\text{vinyl-H or OH, s, } \sim .5 \text{H}), 6.68-7.70 (\text{arom-H and OH or vinyl-H, m, } \sim 6.5 \text{H}), 7.70-8.27 (\text{o-Bz-H and 6-pyr-H, m, } \sim 2.5 \text{H}), 8.42-8.60 (\text{pyr-H, m, } \sim .5 \text{H}); \text{ir (nujol) } 1630 (\text{H-bonded C=O}), 1595, 1540, 1270, 1145, 1060, 877, 808, 777, 738, \text{ and } 688 \text{ cm}^{-1}.

\( \alpha \)-(4-Nitrophenyl)acetophenone (176) \) was prepared by a published method: \(^{135}\) mp 142-143.5° (lit. \(^{135}\) mp 144°); \text{nmr (CDCl}_3\text{) } \delta 6.40 (\text{COCH}_2\text{, s, 2H}), 7.20-7.75 (\text{arom-H, m, 5H}), 7.90-8.35 (\text{o-Bz-H and o-NO}_2\text{C}_6\text{H}_4\text{, m, 4H}); \text{ir(nujol) } 1689 (\text{C=O}), 1225 \text{ and } 1208 (\text{C=O}).

**General Condensation for 1,2-Diaryl Benzoyl ethylenes.** The appropriate \( \alpha \)-arylacetophenone (25 mmol) and arylaldehyde (29 mmol) were refluxed in 25 ml dry benzene containing 0.1 ml piperidine. After 5-14 hours, the theoretical amount of water had been collected utilizing a Dean-Stark separator. After the solvent and excess volatile reagents were removed in vacuo, the residue was decolorized and recrystallized usually from ethanol-ether. The mother liquors were concentrated and chromatographed (plc, 2mm). Yields were essentially quantitative. The percentage ratios of E/Z isomers and pertinent spectral data are given in Table VII.

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However, when 2-pyridinecarboxaldehyde was used, an equivalent amount of piperidine was necessary to realize the removal of the theoretical amount of water. The dehydrated reaction mixtures were refluxed with 5% HCl resulting in the elimination of piperidine from the intermediary Michael adducts.

Condensation of Desoxybenzoin with 2-Pyridinecarboxaldehyde.

Method A. Piperidine Catalyst. Materials were condensed by the above method and after refluxing for 19 hours, a crude nmr spectrum indicated 20% completion. Addition of 1 ml of piperidine followed by another 2 hours of reflux gave an additional amount of water. Finally, addition of a slight excess of piperidine gave rise to the theoretical amount of water in 6 hours. After the solvent and excess volatile reagents were removed in vacuo, the residue was recrystallized from ether-ethanol affording 2.38 g (27%) of 1-phenyl-2-\(\text{N}-\)piperidino-2-(2-pyridyl)benzoyl-ethane (183): mp 167.5-169°; nmr (CDCl\(_3\)) \(\delta\) 0.85-1.70 (3,4,5-pip-H, m, 6H), 1.95-2.95 (2,6-pip-H, m, 4H), 4.72 (pyr-CH-, d, J = 11.5 Hz, 1H), 5.84 (Ph-CH-, d, J = 11.5 Hz, 1H), 6.80-7.65 (arom-H, m, 11H), 8.00-8.25 (o-Bz-H, m, 2H), 8.13-8.32 (6-pyr-H, m, 1H); ir(nujol) 1673 (C=O), 1592, 1219, 763, and 699 cm\(^{-1}\).

Anal. Calcd for C\(_{25}\)H\(_{26}\)N\(_2\)O: C, 81.04; H, 7.08; N, 7.56.

Found: C, 80.64; H, 6.97; N, 7.47.

The mother liquor was concentrated affording 4.79 g (67%) of (Z)-178: nmr (CDCl\(_3\)) \(\delta\) 6.77-7.68 (arom-H and vinyl-H, m, 12H), 7.83-8.10 (o-Bz-H, m, 2H), 8.13-8.32 (6-pyr-H, m, 1H). Other data are listed in Table VII.
Anal Calcd. for C_{20}H_{15}NO: C, 84.18; H, 5.30; N, 4.91.

Found: C, 84.13; H, 5.18; N, 4.89.

The piperidine adduct \(\text{183}^{\ominus}\) (1.11 g, 30 mmol) in 30 ml of 5% hydrochloric acid was refluxed overnight, poured into ice water, basified with a 10% sodium carbonate solution, extracted with chloroform, dried with anhydrous magnesium sulfate, and evaporated. The residue was recrystallized from 95% ethanol affording 0.78 g (91%) of (z)-178.

Nmr spectral data, and analyses for new compounds, are listed, whereas other data are presented in Table VII.

(E)-177: nmr (CDCl\(_3\)) \(\delta\) 7.05-7.57 (arom-H and vinyl-H, m, 14H), 7.76-7.96 (o-Bz-H, m, 2H).

(z)-174: nmr (CDCl\(_3\)) \(\delta\) 7.00-7.62 (arom-H and vinyl-H, m, 14H), 7.83-8.08 (o-Bz-H, m, 2H).

(z)-180: nmr (CDCl\(_3\)) \(\delta\) 6.95-7.75 (arom-H, m, 11H), 7.85-8.15 (o-Bz-H, m, 2H), 7.92 (vinyl-H, s, 1H), 8.50-8.68 (6-pyr-H, m, 1H).

Anal. Calcd for C_{20}H_{15}NO: C, 84.18; H, 5.30; N, 4.91.

Found: C, 84.51; H, 5.18; N, 4.91.

(z)-182: nmr (CDCl\(_3\)) \(\delta\) 6.82-7.78 (arom-H, m, 9H), 7.85-8.35 (o-Bz-H and 6-pyr-H, m, 3H), 7.92 (vinyl-H, 1H), 8.56-8.75 (6-pyr-H, m, 1H).

Anal. Calcd for C_{18}H_{14}N_{2}O: C, 79.70; H, 4.93; N, 9.79.

Found: C, 79.44; H, 4.75; N, 9.67.

Method B. Dicyclohexylamine Catalyst. Desoxybenzoin (1.96 g, 10.0 mmol) and 2-pyridinecarboxaldehyde (1.07 g, 10.0 mmol) in benzene were refluxed utilizing a Soxlet extractor equipped with a calcium hydride-filled thimble. While refluxing a few hours, dicyclohexylamine
(1.81 g, 10.0 mmol) was added slowly. Evaporation to dryness and trituraton with ether gave 1.76 g (58%) of 3-hydroxy-1,2-diphenyl-3-(2-pyridyl)propanone (184): mp 149-5-150.5°; nmr (CDCl₃) δ 3.50-4.38 (-OH, s, 1H), 5.24 (pyr-CH-, d, J = 5 Hz, 1H), 5.59 (Ph-CH-, d, J = 5 Hz, 1H), 6.90-7.56 (arom-H, m, 11H), 7.73-8.03 (o-Bz-H, m, 2H), 8.38-8.60 (6-pyr-H, m, 1H); ir(nujol) 3400-3000 (broad, OH), 1675 (C=O), 1600, 1294, 1062, and 705 cm⁻¹.

Found: C, 79.25; H, 5.59; N, 4.58.

Chromatography of the mother liquor on silica gel using cyclohexane-ethyl acetate (67:33) gave an additional 390 mg (13%) of 184: (mp 145-148°) and 440 mg (14.5%) of 185: mp ~ 130°; nmr (CDCl₃) δ 3.81-4.48 (-OH, s, 1H), 5.18 (pyr-CH, d, J = 7.5 Hz, 1H), 5.46 (Ph-CH, d, J = 7.5 Hz, 1H), 6.69-7.52 (arom-H, m, 11H), 7.76-8.08 (o-Bz-H, m, 2H), 8.34-8.57 (6-pyr-H, m, 1H). This latter isomer could not be obtained in pure form.

Thermal Equilibration of 183. A benzene solution of 183 showed no change after 15 hours at 85°; therefore, it was sealed in a tube and heated at 160° for 30 minutes. After cooling, the mixture was chromatographed on silica gel eluting with cyclohexane-ethyl acetate (80:20) to give starting material and 116 mg (26%) of crude isomer 186: nmr (CDCl₃) δ 0.87-1.55 (3,4,5-pip-H, m, 6H), 1.73-2.93 (2,6-pip-H, m, 4H), 4.66 (pyr-CH, d, J = 10.5 Hz, 1H), 5.83 (Ph-CH, d, J = 10.5 Hz, 1H), 6.70-7.62 (arom-H, m, 11H), 7.77-8.11 (o-Bz-H, m, 2H), 8.45-8.63 (6-pyr-H, m, 1H).

This isomer was not purified further.
Condensation of α-(4-Nitrophenyl)acetophenone with Benzaldehyde in the Presence of Benzoic Acid via Method A. Crude benzaldehyde (i.e. containing benzoic acid) was condensed with α-(4-nitrophenyl)acetophenone as described above. However, the theoretical amount of water was collected within 1 hour. Reflux was continued for an additional hour then the mixture was cooled and concentrated in vacuo. The residue was recrystallized from benzene-cyclohexane to afford crystals of both isomers. Separation of the low melting Z-isomer was easily achieved by selective solution in warm 95% ethanol.

(E)-181: 62.3%; mp 185-186.5° (lit. mp 188-189°); nmr (CDCl₃) δ 6.85-7.35 (arom-H and vinyl-H, m, 11H), 7.35-8.10 (α-Bz-H, m, 2H), 8.10-8.45 (α-NO₂C₆H₄-H, m, 2H); other data are in Table VII.

(Z)-181: 25.2%; mp 135-136° (lit. mp 135.5-136°); nmr (CDCl₃) δ 7.00-7.78 (arom-H and vinyl-H, m, 11H), 7.86-8.35 (α-Bz-H and α-NO₂C₆H₄-H, m, 4H); other data are in Table VII.

Photoisomerization of Z to E Isomers. A 0.01 M solution of each (Z)-178, (Z)-180, and (Z)-182 in dry benzene were flushed well with argon and allowed to stand in direct sunlight for 4-6 hours. Evaporation of the solvent in vacuo and chromatography (plc, 2 mm) gave 25-35% of the respective E-isomers, with the exception of compound 178, which could not be separated.

(E)-180: nmr (CDCl₃) δ 6.40-7.75 (arom-H and vinyl-H, m, 12H), 7.75-8.11 (α-Bz-H, m, 2H), 8.55-8.84 (6-pyr-H, m, 1H).

Anal. Calcd for C₂₀H₁₅NO: C, 84.18; H, 5.30; N, 4.91. Found: C, 83.81; H, 5.17; N, 4.79.
(E)-172: nmr (CDCl₃) δ 6.79-7.82 (arom-H and vinyl-H, m, 10H), 7.82-8.13 (o-Bz-H, m, 2H), 8.44-8.74 (6-pyr-H, m, 2H).


A 4.5 x 10⁻³ M benzene solution of ethyl (Z)-1,2-di(2-pyridyl)acrylate, (Z)-172, was allowed to stand in sunlight under an inert atmosphere for 4 days. The solvent was removed and the residue chromatographed to afford (88%) ethyl (E)-1,2-di(2-pyridyl)acrylate (E)-172: bp 129-132°C (0.6 mm).

2-Chloromethylpyridine (20). 13, 14 2-Methylpyridine N-oxide (10.9 g, 0.1 mol) and benzenesulfonylchloride (17.7 g, 0.1 mol) in 150 ml of benzene were refluxed for 1.5 hours. After allowing to cool to room temperature, the mixture was extracted with 5% hydrochloric acid. The acidic solution was basified and extracted with ether and chloroform. The combined organic extracts were washed with water, dried over sodium sulfate, and concentrated in vacuo. The residual oil was dissolved in ethyl acetate and rapidly filtered through a small column of silica gel to effect decolorization. The solvent was removed to afford 3.27 g (26%) of 20: nmr (CDCl₃) δ 4.67 (CH₂Cl, s, 2H), 7.0-7.9 (pyr-H, m, 3H), 8.5-8.7 (6-pyr-H, m, 1H).

This compound is known to be unstable; therefore it was reacted immediately without further purification.

2-Pyridylmethyltriphenylphosphonium chloride (187). 2-Chloromethylpyridine (3.27 g, 25.7 mmol) and triphenylphosphate (6.71 g, 25.5 mmol) in 35 ml of DMF were refluxed for 7 hours. After allowing the mixture to stir overnight, dilution with ether afforded 6.75 g (68%) of the phosphonium salt: mp 272-275°C (d).

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trans-1,2-Di[2-(6-methylpyridyl)]ethene \( (120) \). A mixture of 6-methyl-2-pyridinecarboxaldehyde (100 g, 0.826 mol), redistilled 2,6-dimethylpyridine (400 ml, 3.5 mol), and acetic anhydride (150 ml, 1.6 mol) was refluxed for 4 hours. The volatile materials were removed in vacuo and the residue was distilled affording the crude olefin: bp 155-165° (1 mm). Recrystallization from benzene-cyclohexane gave 75 g (43%) of the colorless crystalline olefin: mp 109.5-111.5° (lit. 111-113°); nmr (CDCl$_3$) δ 2.54 (6-pyr-CH$_3$, s, 6H), 6.8-7.8 (pyr-H and vinyl-H at δ 7.67, m, 8H); ir(nujol) 1588, 1569, 1255, 979, and 799 cm$^{-1}$; uv (MeOH) 318 (29,100) and 264 nm (9,750).

The residue from the above vacuum distillation afforded, upon crystallization from benzene, 3.0 g (2%) of trans,trans-2,6-di[2-(6-methylpyridyl)]vinyl]pyridine (89%): mp 132-135°.

Photoisomerization of trans- to cis-1,2-Di[2-(6-methylpyridyl)]-ethene \( (188) \). trans-1,2-Di[2-(6-methylpyridyl)]ethene (0.378 g, 1.8 mmol) was dissolved in 300 ml benzene in a pyrex vessel and flushed well with nitrogen. The stoppered flask was allowed to stand in sunlight for 6 hours or under sunlamp for 11 hours. Solvent was removed in vacuo. The residue was chromatographed (plc, 2mm, 3X, 25% ethyl acetate-cyclohexane) to give 191 mg (51%) of the trans-isomer \( (R_f = .49) \) and 64 mg (17%) of the cis-isomer: bp 98-101° (0.5 mm); \( R_f = .10 \); nmr (CDCl$_3$) δ 2.50 (pyr-CH$_3$, s, 6H), 6.81 (vinyl-H, s, 2H), 6.81-7.65 (pyr-H, m, 6H); ir(neat) 1588, 1570, 1453, 1375, 1157, 1094, 980, 837, and 801 cm$^{-1}$; uv (MeOH) 211 (11,840) and 296 nm (10,200).

**Anal.** Calcd. for C$_{14}$H$_{14}$N$_2$: C, 79.96; H, 6.71. Found: C, 79.76; H, 6.85.
Similarly, a $5 \times 10^{-3}$ M solution in sunlight for 3 days afforded (46%) the cis-isomer.

*Photoisomerization of trans,trans-2,6-Di[2-(2-(6-methylpyridyl))-vinyl]pyridine (82).* In an attempt to obtain other isomers, the trans,trans-isomer (510 mg, 1.63 mmol) was dissolved in 450 ml benzene and flushed well with nitrogen. After irradiation by sunlamp at $40^\circ$ for 25 hours, the solvent was removed in vacuo.* Chromatography (plc, 2 mm, 3X, 25% ethyl acetate-cyclohexane) afforded 146 mg (29%) of trans,trans-isomer: $R_f = .55$, mp 131-133°; a small amount of an unidentified compound ($R_f = .33$) showing an anomalous singlet in nmr spectrum at $\delta$ 5.1 as well as half the methyl resonance shifted upfield, i.e. $\delta$ 2.3; and a crude isomer mixture ($R_f = .27$), impure with previous compound, that definitely contained some cis-olefinic function, i.e. singlet in nmr spectrum at $\delta$ 6.85.

*trans-1,2-Di[2-(6-acetoxyethylpyridyl)]ethene (122).* In a procedure similar to that of Baker, et al.,* trans-1,2-di[2-(6-methylpyridyl)]ethene (64.8 g, 308.5 mmol) in 400 ml glacial acetic acid with 30% aqueous hydrogen peroxide (60 ml, 0.53 mol) was heated at ca. $80^\circ$ for 3 hours. Additional hydrogen peroxide (142 ml, 0.37 mol) was added and the reaction was maintained another 9 hours with stirring at $80^\circ$. The mixture was concentrated in vacuo to half-volume, an equal amount of water added, and again concentrated.

*Caution: This mixture is mildly lachramatory, dermatactic, and ster nutative!*

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The residual solid (ca. 110 g of crude N-oxide) was suspended in a mixture of 150 ml acetic anhydride and 100 ml DME and added drop-wise with stirring to 300 ml acetic anhydride under nitrogen at 108° over 30 minutes. Conditions were maintained for 18 hours before the mixture was concentrated in vacuo. The residue was recrystallized from 95% ethanol (charcoal) to afford 31.1 g (31%) of 122: mp 133-134° (lit. 43 mp 133-134°); nmr (CDCl₃) δ 2.16 (COCH₃, s, 6H), 5.24 (pyr-CH₂, 0, s, 4H), 7.1-8.0 (pyr-H and vinyl-H at δ 7.65, m, 8H); ir(nujol) 1730 (C=O, ester), 1585, 1470, 1245, 1060, 962, and 798 cm⁻¹.

trans-1,2-Di[2-(6-hydroxymethylpyridyl)]ethene (123). Similar to the method of Baker, et al., 43 122 (26.5 g, 81.3 mmol) in 400 ml concentrated hydrochloric acid was refluxed 10 hours. While cooling and vigorously stirring, the solution was slowly made basic by addition of a 40% sodium hydroxide solution. Once basic, the cooled mixture was allowed to stand for 30 minutes. The precipitate was collected, washed with water, and recrystallized from 95% ethanol to afford 11.5 g (58.7%) of 123: mp 139-141° (lit. 43 mp 142-144°); nmr (CDCl₃) δ 3.15 (OH, broad s, 2H), 4.80 (pyr-CH₂O, s, 6H), 7.0-7.9 (pyr-H and vinyl-H at δ 7.72, m, 8H); ir(nujol) 3100 (OH), 1580, 1760, 1325, 1150, 1080, 1020, 789, and 752 cm⁻¹; uv (MeOH) 318 (25,800) and 264 nm (8,490). The mother liquor from the recrystallization and the aqueous filtrate were combined and concentrated to dryness. The organic material was separated from the residual solids by boiling with a large volume of chloroform. Concentration of the filtered chloroform extract and dilution with petroleum ether-A furnished additional quantities [7.6 g, (38.8%)] of 123.
trans-1,2-Di[2-(6-chloromethylpyridyl)]ethene (189). trans-1,2-Di[2-(6-hydroxymethylpyridyl)]ethene (4.84 g, 20 mmol) in 100 ml chloroform was brought to reflux under nitrogen. Thionyl chloride (8 ml, ~112 mmol) in 15 ml chloroform was added slowly. After the addition was complete, reflux was continued for 34 hours. Solvent and excess thionyl chloride were removed in vacuo. The residue was suspended in 10% sodium carbonate solution and extracted with chloroform. The combined chloroform extracts were dried over sodium sulfate and evaporated to dryness. The residue was recrystallized from chloroform-petroleum ether-C to give 4.62 g (83%) of 189: mp 153-154°; nmr (CDCl₃) 6 4.69 (pyr-CH₃, s, 4 H); 7.2-7.9 (pyr-H and vinyl-H at 6 7.66, m, 8H); ir(nujol) 1582, 984, 824, 740, and 721 cm⁻¹; uv (MeOH) 317 (28,600) and 269 nm (12,850).

Anal. Calcd for C₁₄H₁₂N₂Cl₂: C, 60.21; H, 4.33; N, 10.03.
Found: C, 59.97; H, 4.43; N, 9.99.

cis-1,2-Di[2-(6-chloromethylpyridyl)]ethene (190). A benzene solution of trans-1,2-di[2-(6-chloromethylpyridyl)]ethene was isomerized photochemically under an argon atmosphere as follows:

<table>
<thead>
<tr>
<th>Molarity</th>
<th>hv Source</th>
<th>Time</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.8 x 10⁻³</td>
<td>Sunlamp</td>
<td>20.0 hours</td>
<td>21</td>
</tr>
<tr>
<td>3.6 x 10⁻³</td>
<td>Sunlamp</td>
<td>10.5 hours</td>
<td>24</td>
</tr>
<tr>
<td>3.6 x 10⁻³</td>
<td>Sunlight</td>
<td>2 days</td>
<td>54</td>
</tr>
</tbody>
</table>

Separation of isomers was achieved on <300 mg quantities by plc [33% ethyl acetate-cyclohexane: \( R_f^{\text{(trans)}} = 0.50 \), \( R_f^{\text{(cis)}} = 0.30 \), and \( R_f \) (impurity) = 0.24]. Separations of larger scale were effected by column
chromatography on silica gel using benzene to elude all the trans isomer. Then ethyl acetate quickly eluded a mixture of predominantly cis isomer: \[
\text{nmr (CDCl}_3\text{)} \delta 4.56 (\text{pyr-CH}_2, \text{s, 4H}), 6.84 (\text{vinyl-H, s, 2H}), 7.10-7.85 (\text{pyr-H, m, 6H}).
\]

This cis isomer could not be obtained in greater purity than ca. 90%.

**trans-1,2-Di(2-pyridyl)ethene (42).**

2-Methylpyridine (85 g, 0.914 mol), 2-pyridinecarboxaldehyde (40 g, 0.374 mol), and acetic anhydride (40 g, 0.392 mol) were refluxed 14 hours. Excess reagents were removed in vacuo. The residue was suspended in benzene, filtered through silica gel, and finally eluted with ethyl acetate. Evaporation of the solvents provided 25.9 g (38%) of crude material. Recrystallization from ether afforded 14.9 g (22%) of pure olefin: mp 118-122° (lit. \[138\] mp 118-119°); nmr (CDCl\(_3\)) \(\delta 6.95-7.90 (\text{pyr-H, m, 6H}), 7.70 (\text{vinyl-H, s, 2H}), 8.50-8.75 (6-\text{pyr-H, m, 2H}); \text{ir(nujol)} 1575, 1555, 1310, 977, 789, and 744 cm\(^{-1}\); uv (MeOH) 313 (25,900), 263 (12,740), and 216 nm (9,350).

**1,2-Dibromo-1,2-di(2-pyridyl)ethane (192).**

Bromine (10.7 g, 67 mmol) in glacial acetic acid (5 ml) was added dropwise to trans-1,2-di(2-pyridyl)ethene (12.1 g, 67 mmol) in glacial acetic acid (17 ml). After allowing to cool, 10.7 g (47%) of the dibromide was filtered and washed with methanol, mp 159-160° (lit. \[138\] mp 153-154°); nmr (CDCl\(_3\)) \(\delta 5.96 (\text{pyr-CH}, \text{s, 2H}), 7.10-7.95 (\text{pyr-H, m, 6H}), 8.60-8.85 (6-\text{pyr-H, m, 2H}); \text{ir(nujol)} 1585, 1565, 1145, 993, 788, and 749 cm\(^{-1}\).

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**Di(2-pyridyl)acetylene (193).** 1,2-Dibromo-1,2-di(2-pyridyl)ethane (6.91 g, 20.2 mmol) was added in small portions to a refluxing ethanol solution of potassium hydroxide (5.7 g, 102 mmol). After the addition was complete, reflux was continued for an additional 30 minutes. After cooling, the potassium bromide was removed by filtration. The solvent was removed in vacuo, and the residue was suspended in water and extracted with ether. The ether layer was dried over sodium sulfate, evaporated, and the residue recrystallized from petroleum ether-A, affording 3.38 g (93%) of the acetylene 193: mp 69-71° (lit. 139 mp 69-70°); nmr (CDCl₃) δ 7.1-7.5 (pyr-H, m, 2H), 7.50-7.95 (pyr-H, m, 4H), 8.55-8.75 (6-pyr-H, m, 2H); ir(nujol) 1575, 1550, 987, 802, and 774 cm⁻¹; uv (MeOH) 307 (22,200), 298 (25,500), 290 (22,500), and 257 nm (13,200).

**2-(N-Phenylformimidoyl)pyridine (194).** 2-Pyridinecarboxaldehyde (53.5 g, 0.5 mol) was stirred with aniline (46.5 g, 0.5 mol) for 15 minutes and poured into 80 ml of 95% ethanol. Since crystallization could not be induced, the solvent was removed in vacuo. Water was thoroughly removed by azeotropic distillation with benzene for a short period. Fractional distillation afforded 87.7 g (97%) of yellow oil, bp 105-107° (0.2 mm) [lit. 138 bp 165° (13 mm)]. Recrystallization from petroleum ether-A gave 82.2 g (91%) of a pale yellow solid: mp 38.5-39.5° (lit. 140 mp 38.5°); nmr (CDCl₃) δ 6.90-7.75 (arom-H, m, 8H), 8.00-8.25 (6-pyr-H, m, 1H), 8.58 (vinyl-H, s, 1H); ir(nujol) 1620 (C=N), 1580, 1550, 988, 782, 738, and 686 cm⁻¹; uv (MeOH) 280 (9,030) and 277 nm (11,570).

**1,2-Dianilino-1,2-di(2-pyridyl)ethene (196).** 2-(N-Phenylformimidoyl)pyridine (1.82 g, 10 mmol) was stirred in DMF (50 ml) under
a nitrogen atmosphere. Potassium cyanide (0.10 g, 1.54 mmol) was introduced and the mixture stirred at room temperature for 1 hour. The mixture was poured into water (200 ml) and cooled. The bright yellow precipitate \(125\) was removed by filtration and dried under reduced pressure affording (91%) 1.65 g; mp \(\sim 220^\circ\) (d). Recrystallization from chloroform-methanol afforded 1.1 g of pure \(125\); mp 227-235\(^\circ\) (d); ir(nujol) 3190 (sharp, N-H), 1590, 1500, 1305, 1265, 790, 748, 743, and 697 cm\(^{-1}\). This material is too insoluble in all solvents tried to enable a suitable nmr spectrum to be obtained. The compound reacts with acids (even acetic acid) to form a dark red solution, but \(125\) is recovered unchanged upon neutralization.

**Anal.** Calcd for C\(_{24}\)H\(_{20}\)N\(_4\): C, 79.09; H, 5.53; N, 15.38. Found: C, 78.31; H, 5.47; N, 15.23.

\(\alpha\)-Pyrone (196) was prepared from malic acid in two steps, according to published procedures.\(^{141,142}\)

\(1,2\text{-}D\text{I}(2\text{-pyridyl})\text{benzene (197).} \) \(D\text{I}(2\text{-pyridyl})\text{acetylene (250 mg, 1.39 mmol), }\alpha\text{-pyrone (220 mg, 2.29 mmol), and nitrobenzene (5 ml) were heated (sand bath) at 220-250^\circ\) for 9 hours. The mixture was cooled, suspended in ether and extracted with 5% hydrochloric acid. Acidic extracts were basified with sodium carbonate and extracted with chloroform. The chloroform layer was dried over sodium sulfate and concentrated in vacuo. Chromatography (plc, 2 mm) of the residue using 50% ethyl acetate in cyclohexane afforded 53 mg (21%) of unreacted acetylene \(\left(R_f = .15\right)\) and 171 mg (53%) of \(197\) \(\left(R_f = .33\right)\). Recrystallization from petroleum ether-B furnished colorless flakes: mp 123-123.5\(^\circ\); nmr (CDCl\(_3\))
δ 6.8-8.0 (arom-H, m, 10H), 8.5-8.8 (6-pyr-H, m, 2H); IR(nujol) 1580, 1555, 1414, 1145, 799, 757, and 749 cm⁻¹.

Anal. Calcd for C₁₆H₁₂N₂: C, 82.73; H, 5.21; N, 12.06. Found: C, 85.16; H, 5.08; N, 12.05.

Bromination of trans-1,2-Di[2-(6-methylpyridyl)]ethene. To a stirred suspension of trans-1,2-di[2-(6-methylpyridyl)]ethene (11.5 g, 50.5 mmol) in 25 ml glacial acetic acid, a solution of bromine (8.8 g, 55 mmol) in 5 ml acetic acid was added dropwise over 1 hour. During the addition, the crude dibromide slowly crystallized and was stirred overnight: 15.15 g (81%); mp ~ 185° (d). Recrystallization from ethanol increased the melting point to 203° (d), lit. mp 194-196°. Chloroform could also be used as solvent affording a crude product: mp 195° (d).

Di[2-(6-methylpyridyl)]acetylene (199). To a hot solution (70°) of potassium hydroxide (6.0 g, 107 mmol) in absolute ethanol (50 ml), the above solid dibromide (2.0 g, 5.4 mmol) was rapidly added in 50 mg (or less) quantities. Potassium bromide instantaneously precipitated. The suspension was refluxed for an additional 30 minutes, then the solvent was removed in vacuo. The residue was dissolved in ice water and the organic material extracted with ether. The ether layer was washed with a saturated salt solution, dried with sodium sulfate, and concentrated to afford the crude acetylene. Recrystallization from cyclohexane gave 1.10 g (98%) of the white crystalline acetylene: mp 133-135°; NMR (CDCl₃) δ 2.56 (6-pyr-CH₃, s, 6H), 6.96-7.75 (pyr-H, m, 6H); IR(nujol) 1590, 1565, 1155, 1080, 990, and 793 cm⁻¹; UV (MeOH) 313 (21,600), 304 (22,800), 297 (22,300), and 256 nm (11,250).
Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.45; H, 5.78; N, 13.35.

1,2-Di[2-(6-methylpyridyl)]benzene (200). Di[2-(6-methylpyridyl)]-acetylene (4.51 g, 21.7 mmol), $\alpha$-pyrone (4.5 g, 46.9 mmol), and ca. 50 mg of hydroquinone in 40 ml o-dichlorobenzene (bp 178-179°) were refluxed under nitrogen for 45 hours. After cooling, the mixture was diluted with ether and extracted with 5% hydrochloric acid. Acidic extracts were made basic with solid sodium carbonate and extracted with chloroform. The chloroform extract was dried over sodium sulfate, concentrated, and vacuum distilled to afford 3.39 g (60%) of 200; bp 150-170° (1.3 mm). An analytical sample was obtained by chromatography (plc, 2 mm) and then distilled: bp 128-132° (0.5 mm); nmr (CDCl$_3$) $\delta$ 2.49 (6-pyr-$CH_3$, s, 6H), 6.69-7.07 (arom-$H$, broad t, 4H), 7.16-7.79 (pyr-$H$, m, 6H); ir(neat) 1580, 1445, 1300, 1160, 998, 802, and 760 cm$^{-1}$.

Anal. Calcd for $C_{16}H_{16}N_2$: C, 83.04; H, 6.20. Found: C, 82.86; H, 6.37.

1,2-Di[2-(6-carbomethoxypyridyl)]benzene (201). 1,2-Di[2-(6-methylpyridyl)]benzene (4.89 g, 18.8 mmol) and potassium permanganate (3.3 g, 21 mmol) in water (1 l) were vigorously stirred at 80° under nitrogen for 6 hours. Additional potassium permanganate (3.3 g, 21 mmol) was introduced prior to each of three subsequent 6-hour periods. The hot solution was filtered through celite. The cooled, colorless filtrate was extracted with ether to remove unoxidized starting material (ca. 1 g, 21%).
The aqueous layer was evaporated to dryness. Residual solids were suspended in 500 ml methanol, saturated with hydrogen chloride, and refluxed 10 hours. After the solvent had been removed in vacuo, the residue was suspended in a dilute sodium carbonate solution and extracted with chloroform. Chloroform extracts were dried over sodium sulfate and concentrated in vacuo. The residual esters were purified by chromatography (plc, 2 mm, 25% ethyl acetate-cyclohexane) to afford an inseparable mixture of esters: \( R_f = 0.30; 1.73 \text{ g (ca. 30%)} \).

Further elution gave the desired 1,2-di[2-(6-carboxethoxy-pyridyl)]benzene (201): \( R_f = 0.18; 1.34 \text{ g (21%)}; \text{ mp 128-129° (ethyl acetate-petroleum ether-A)} \); nmr (CDCl₃) \( \delta \) 3.91 (CO₂CH₃, s, 6H), 7.0-8.3 (arom-H, m, 10H); ir(nujol) 1700 (C=O, ester), 1580, 1440, 1320, 1280, 1230, 1135, 1115, 988, 834, 783, 770, and 755 cm⁻¹.

Anal. Calcd. for C₂₀H₁₆N₂O₄: C, 68.95; H, 4.63; N, 8.04. Found: C, 68.67; H, 4.62; N, 8.04.

The amount of starting material recovered and the composition of the remaining esters varied with conditions of reaction and purity of starting material. With a large excess of oxidant, further oxidation occurred to give methyl 2-[2-(6-carboxethoxy-pyridyl)]benzoate (204): mp 90-91°; nmr (CDCl₃) \( \delta \) 3.70 (C₆H₄CO₂CH₃, s, 3H), 3.96 (C₆H₅NCO₂CH₃, s, 3H), 7.3-8.2 (arom-H, m, 7H). If chromatographically pure 200 was oxidized, 1-[2-(6-carboxethoxy-pyridyl)]-2-[2-(6-methylpyridyl)]benzene (202) could be isolated: nmr (CDCl₃) \( \delta \) 2.45 (-CH₃, s, 3H), 3.93 (CO₂CH₃, s, 3H), 7.0-8.3 (arom-H, m, 10H). However, oxidation of 200, which had been purified by distillation, afforded in addition to the above products, 155 and methyl 2-(6-methylpyridyl)carboxylate (203): nmr (CDCl₃) \( \delta \) 2.63 (-CH₃, s, 3H), 3.96 (CO₂CH₃, s, 3H), ca. 7.3-8.4 (arom-H, m, 3H).
1,2-Di[2-(6-hydroxymethylpyridyl)]benzene (205). 1,2-Di[2-(6-carbomethoxypyridyl)]benzene (921 mg, 2.64 mmol) in 40 ml methanol was stirred under nitrogen. Sodium borohydride (568 mg, 15.0 mmol) was added in small portions over 30 minutes, then the reaction was stirred for 30 minutes, and finally refluxed overnight. After cooling to room temperature, acetone (5 ml) was added and stirred 3 hours. Volatile reagents were removed in vacuo and the residue treated with 15 ml of 10% sodium carbonate solution for 2 hours at 100°. After concentration to dryness, the residue was powdered and extracted with boiling chloroform (2 x 150 ml). Filtration of the hot extracts through celite and concentration in vacuo afforded 898 mg of the crude diol: mp 179-184°. Recrystallization from 95% ethanol gave 200 mg (26%) of the beige crystalline diol: mp 198-199.5°; nmr (DMSO-d_6) δ 4.44 (pyr-CH_2-, s, 4H), 5.28 (OH, s, 2H), 6.75-7.80 (arom-H, m, 10H); ir (nujol) 3270 (broad, OH), 1575, 1560, 1295, 1160, 1100, 1050, 1030, 813, 807, 772, and 766 cm⁻¹.

A suitable analysis could not be obtained with the small amount of material at hand.

Reaction of α-Phthalaldehyde with Aniline. α-Phthalaldehyde (6.7 g, 0.05 mol) was stirred in 95% ethanol (20 ml). Aniline (9.8 g, 0.105 mol) was added and stirred briskly for 10 min. An additional 25 ml of ethanol was introduced, the mixture heated to boiling, and then allowed to stand at room temperature for 3 hours. The precipitate was collected and recrystallized from benzene-ethanol to afford 2-phenyl-1-phenyliminoisoindolene (213): 9.5 g (67%); mp 146-148° (lit. 151 mp 150-153°); nmr (CDCl₃) δ 4.87 (3'-isoindolene-H, s, 2H), 6.45-7.65
(arom-H, m, 1H), 7.70-8.15 (α-arom-H, m, 2H); IR (nujol) 1660 (C=O), 1585, 1490, 1320, 1300, 1135, 772, 756, and 695 cm\(^{-1}\).

2,6-Bis(2,2-dicarboethoxyethyl)pyridine (219). Small chips of sodium metal (2.3 g, 0.1 mol) were placed in 35 ml absolute ethanol under argon. When all the metal had reacted, the solution was cooled and diluted with 125 ml ether. Diethyl malonate (16 g, 0.1 mol) in 100 ml ether was added dropwise during 30 minutes. An additional 5 ml of ethanol was required to maintain homogeneity. 2,6-Di(chloromethyl)pyridine (8.8 g, 0.05 mol) was added in small portions over 30 minutes. After the addition was complete, the mixture was refluxed 2 hours, cooled, and washed twice with 25 ml water. The pH of the water extracts was adjusted to ~7 and extracted with chloroform. The chloroform and ether extracts were combined, dried over sodium sulfate, and concentrated in vacuo to afford ca. 21 g of crude 219 (nmr showed 82%). This mixture could not be easily analyzed by glc or fractionally distilled due to decomposition at elevated temperatures. However, an analytical sample was obtained by chromatography (plc, 2 mm; 25% ethyl acetate-cyclohexane, R\(_f\) = .50) and molecular distillation: bp 170-173° (0.35 mm); nmr (CDCl\(_3\)) 6 1.22 (-CH\(_2\)CH\(_2\), t, J = 7 Hz, 12H), 3.30 (pyr-CH\(_{2}\)-, d, J = 7.5 Hz, 4H), 4.13 (CH\(_3\)-, t, J = 7.5 Hz, 2H), 4.15 (CH\(_3\)CH\(_2\)-, q, J = 7 Hz, 8H), 6.85-7.65 (pyr-H, m, 3H), methine protons can be resolved by addition of small amount of benzene-d\(_6\); IR(neat) 1730 (C=O, ester), 1445, 1365, 1265, 1220, 1175, 1150, 1030, and 858 cm\(^{-1}\).

Anal. Calcd for C\(_{21}\)H\(_{26}\)N\(_{0}\): C, 59.56; H, 6.90. Found: C, 59.76; H, 7.01.
Reaction of 2,6-Di(hydroxymethyl)pyridine (74) with α,α′-Dibromo-α-xylene (220). Method A. In the Presence of Sodium Hydride and DME.

Sodium hydride suspension (1.32 g, 30 mmol) was washed free of mineral oil with petroleum ether-A and dried under nitrogen stream. 2,6-Di-(hydroxymethyl)pyridine (1.39 g, 10 mmol) in 100 ml DME was introduced. α,α′-Dibromo-α-xylene* (2.94 g, 11.2 mmol) dissolved in 50 ml DME was added dropwise to the stirred suspension over 2 hours at 25°C. The mixture was stirred an additional 6 hours at 25°C, then refluxed 24 hours. The mixture was poured into water and extracted several times with chloroform. The combined chloroform extracts were dried over sodium sulfate and concentrated in vacuo. The residue was separated by chromatography (plc, 2 mm; using 50% ethyl acetate in cyclohexane) to afford 930 mg (40%) of 1,5,9,13-tetraoxa-7,15-di(2,6)pyrda-3,11-di(1,2)-phenacyclohexadecane (221, n = 2):** Rf = .27; mp 142.5-143°C (ethanol-ethyl acetate); nmr (CDCl3) δ 4.53 (arom-CH2-O, s, 8H), 4.59 (pyr-CH2-O, s, 8H), 7.10-7.75 (arom-H, m, 14H); ms (70 eV) m/e (relative intensity) 376 (6), 363 (15), 362 (42), 238 (42), 225 (23), 209 (23), 196 (15), 122 (100), 119 (69), 106 (54), 105 (58), 104 (72), 91 (60), and 79 (26); ms (25 ev-reverse scan) 482 (1.6), 454 (1.5), 377 (21), 363 (100), 333 (13), 256 (28), 240 (80), 226 (40), 210 (42), 197 (32), 122 (100),

* Caution: α,α′-Dibromo-α-xylene is strongly lachrymatory with a somewhat latent effect!
** Named according to Th. Kaufmann's proposed nomenclature, however, IUPAC name for 221 (n = 2) is: 3,12,20,29-tetraoxa-35,36-diaza-pentacyclo[29.3.1.1(14),18.05,10.022,27]hexatriaconta-1(35),5(10),6,8,14-(36),15,17,22(27),23,25,31,33-dodecaene.

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119 (59), 106 (28), 105 (39), and 104 (46); ir(nujol) 1590, 1570, 1330, 1120, 1095, 1060, 797, 757, and 748 cm⁻¹; \( M_W \) \(_{\text{Calcd}} = 482, \ M_W \) \(_{\text{osmotic (benzene): 467, 494}} - \text{Avg.} = 480; \ uv(\text{MeOH}) 265 \text{ nm (9,380).}

Anal. Calcd. for \( \text{C}_{15}\text{H}_{15}\text{N}0_2 \): C, 74.67; H, 6.27; N, 5.81.

Found: C, 74.47; H, 6.16; N, 5.66.

Further elution afforded 210 mg (9%) of 1,5,9,13,17,21-hexaoxa-7,15,23-tri(2,6)pyrida-3,11,19-tri(1,2)phenacyclotetrasane (\( \text{C}_{221 \theta} \), \( n = 3 \)): \( R_f = 0.14 \); mp 129-130° (ethanol-ethylacetate); nmr (CDCl₃) identical to that of cyclic aza-ether (\( n = 2 \)); \( M_W \) \(_{\text{Calcd}} = 723, \ M_W \) \(_{\text{osmotic (benzene): 708, 668}} - \text{Avg.} = 688; \ uv(\text{MeOH}) 265 \text{ nm (13,050).}

Anal. Calcd for \( \text{C}_{15}\text{H}_{15}\text{N}0_2 \): C, 74.67; H, 6.27; N, 5.81.

Found: C, 71.06; H, 6.21; N, 5.45.

Although the analysis, MW, and uv data indicate the compound to still contain a small amount of impurity there is no doubt as to the structure. This compound becomes increasingly more insoluble (even in refluxing methanol) as it is purified, which might have introduced a small amount of error in the uv extinction coefficient.

Method B. via High Dilution Technique. Sodium hydride suspension (2 g, 47 mmol) was washed free of mineral oil with petroleum ether-A, dried under nitrogen stream, and brought to reflux in 1.5 liters of ether. 2,6-Di(hydroxymethyl)pyridine (1.39 g, 10 mmol) in DME (250 ml) and \( \alpha,\alpha' \)-dibromo-o-xylene (2.62 g, 10 mmol) in DME (125 ml) were added

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* IUPAC¹⁴⁷ name for \( \text{C}_{221 \theta} \) \( n = 3 \) is: \( 3,12,20,29,37,46 \)-hexaoxa-52,53,54-triazahapto[46.3.1.14,18,131,35,10,022,27,039,44]tetrapentaconta-1(52),5(10),6,8,14(54),15,17,22(27),23,25,31(53),32,34,39(44),40,42,48,50-octadecaene.
proportionately via dilution technique\textsuperscript{95} over 6 hours, then refluxed an additional 12 hours. Tlc in ethyl acetate indicated that a fair amount of starting material, $\alpha,\alpha'$-dibromo-o-xylene, remained ($R_f = .82$) while the only detectable products were the cyclic aza-ethers $221 (n = 2)$ ($R_f = .53$) and $221 (n = 3)$ ($R_f = .38$). Products that contained the pyridine moiety were extracted with 5% hydrochloric acid and the lachramatory ether layer discarded carefully. Acidic extracts were made slightly basic with sodium carbonate and extracted several times with chloroform. The chloroform extracts were dried over sodium sulfate and concentrated in vacuo to afford 1.36 g (57%) of crude products, $221$.

Method C. via Quaternary Ammonium Base. Benzytrimethylammonium hydroxide (35% solution in methanol, 15.2 g, 32 mmol) was stirred with DME (50 ml) and concentrated in vacuo while maintaining the temperature below 38°. Additional DME (30 ml) was added and again concentrated. The yellow salt suspension was stirred in DME (100 ml) with 2,6-di(hydroxymethyl)pyridine (1.39 g, 10 mmol) for 30 minutes. $\alpha,\alpha'$-Dibromo-o-xylene (2.62 g, 10 mmol) in DME (50 ml) was introduced drop-wise over 2 hours. With each drop, formation of insoluble material (polymer) could be observed. After stirring at room temperature for 8 hours, the mixture was refluxed 10 additional hours. After cooling, the tlc data indicated the absence of starting reagents as well as the previously isolated (via Method A and B) cyclic aza-ethers $221$. However, the mixture was concentrated in vacuo, suspended in water, and shaken with large volumes of chloroform. Filtration removed insoluble polymer. The chloroform layer was separated, dried over sodium sulfate, and evaporated to afford a small amount of unidentified yellow oil.
Sodium thiocyanate complex of 221 (n = 2). According to the method of Pederson\textsuperscript{148,149} for the formation of "crown ether" complex salts, 221 (n = 2) (30 mg, 0.062 mmol) and sodium thiocyanate (20 mg, 0.247 mmol) were refluxed in methanol (15 ml) for 15 min. The solvent was slowly evaporated in vacuo to afford the complex: mp 195\degree (d). The same complex [mp ~ 193\degree (d)] was obtained in a similar experiment using a 1:2 ratio of ligand to salt. That a complex was obtained was indicated by the melting point, which is ca. 50\degree higher than the parent ligand.
RESULTS AND DISCUSSION

Initially, efficient synthetic routes toward \( \mathcal{Z} \) were desired. Baker, et al.,\(^{43} \) have shown that trans,trans-2,6-di[2-(6-methyl-2-pyridyl)vinyl]pyridine (52) was the predominant product from acid-catalyzed condensation of 2,6-dimethylpyridine (50) and 2,6-pyridine-dicarboxaldehyde (55); none of the cis-compound (i.e., \( \mathcal{Z} \)) was detected.

In order to repeat this work as well as explore base-catalyzed condensations, the dialdehyde 55 was needed. Since 55 was no longer commercially available, a convenient laboratory procedure for its preparation was desired.

Two methods for the efficient preparation of 55 have been reported in the literature: selective reduction of carboxylic esters\(^{55} \) and oxidation of 2,6-di(hydroxymethyl)pyridine (74) with activated manganese dioxide.\(^{48} \) Utilization of a reductive method similar to the literature procedure indicated that a complex mixture was obtained, from which the desired dialdehyde 55 was isolated in unsatisfactory

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9k quantities. Therefore, the oxidation of 2,6-di(hydroxymethyl)-pyridine (7h) with diverse oxidizing agents was pursued.

Consecutive N-oxide rearrangements provided 2,6-di(acetoxy-methyl)pyridine (7g), which was hydrolyzed to 7h, but yield data were incomplete.\textsuperscript{11,44} These reported procedures were reinvestigated in order to determine the overall efficiency of the route. The initially violent exothermic N-oxide rearrangement could be controlled by the addition of the appropriate N-oxide to refluxing acetic anhydride.\textsuperscript{112} Dilution of the reagents with a lower boiling co-solvent (DME) lowered the reflux temperature, but did not appreciably increase the reaction yields. Thus, 2,6-di(hydroxymethyl)pyridine (7g) was obtained in four steps (19% overall yield) from commercially available 2,6-dimethyl-pyridine N-oxide with only one purification (distillation) of an intermediate during the process. The diol 7h was isolated with considerable difficulty by means of continuous liquid-liquid extraction of the aqueous hydrolysis mixture over at least 24 hours. However, 2,6-di-(hydroxymethyl)pyridine (7h), was obtained in good to excellent yields by a modification of reported reduction methods of the corresponding diesters.\textsuperscript{45-48} An essentially quantitative yield of methyl 2,6-pyridinedicarboxylate (155) was obtained from the dilute esterification of the commercially available diacid. Reduction of 155 with sodium bis(2-methoxyethoxy)aluminum hydride afforded 7h in a 50-76% yield, whereas reduction with sodium borohydride afforded 7h in a 70-98% yield.

Oxidation of the facilely obtained diol 7h was conducted with both activated manganese dioxide\textsuperscript{48} and lead tetraacetate.\textsuperscript{9} However,
the latter proved to be the better method and resulted in an easily isolated 19% yield of 2,6-pyridinedicarboxaldehyde (R5).

The condensation reported by Baker, et al.,43 of the dialdehyde R5 and 2,6-dimethylpyridine (50) was repeated to afford (37%) trans,trans-2,6-di[2-(6-methyl-2-pyridyl)vinyl]pyridine (R9). The vinylic coupling constant (J = 16.5 Hz) obtained from a 220 MHz nmr spectrum, as well as ir and uv data additionally confirmed the reported all trans configuration.43,72 A mixture of other higher melting point components (probably longer chain trans homologs) was also obtained but was not investigated. In view of the fact that simple pyridine compounds react similarly under acidic conditions to give trans olefins, these results were not too surprising.

The literature review indicated that a simple 2-pyridylacetate ester (12) can be condensed with benzaldehyde to give the cis olefinic product R7,32 whereas the arylacetonitriles and 2-pyridylcarboxaldehydes afforded a trans olefinic product R7 (Table I). These observations also correlate with the well-documented base-catalyzed Perkin and Knoevenagel condensations of phenylacetic acid, phenylacetonitrile, and benzylphenyl ketone with aromatic aldehydes.117-120 Generally, in these non-heterocyclic systems, the nitrile gave the olefinic condensation product with trans aromatic rings, whereas the carbonyl reagents (acid, ester, and ketone) afforded a large predominance of the

*The cis and trans nomenclature will refer to the orientation of the aromatic rings. The (Z) and (E) terminology will refer to the orientation sequence rules as set forth in the IUPAC tentative rules for stereochemical nomenclature.145
corresponding cis olefin. On this basis a multiple condensation of 2,6-disubstituted pyridines was envisioned to have some degree of chance for cyclization to afford substituted analogs of 3. The probability of intramolecular cyclization might also be enhanced by utilization of the high-dilution technique. To attempt such multiple condensations, the 2,6-pyridinediacetates (67 and 70) and 2,6-di(phenacyl)pyridine (72) were needed.

Repetition of the literature method for direct preparation of 67 from 2,6-dimethylpyridine was difficult and afforded only very poor yields. Therefore, other possible direct methods for the synthesis of 67 were attempted. 2,6-Dimethylpyridine (59) was treated with ca. 3 equivalents of tert-butyllithium and the resultant mixture, which should contain some dimetallated derivative, was inversely added to a cold solution of ethyl chloroformate. However, the only other product besides the expected ethyl 2-(6-methylpyridyl)acetate (66) was

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ethyl 2-((1-methylpycolyl)carbonate (156), which cannot be easily rationalized. The origin of 156 should be investigated further. None of the

\[
\begin{align*}
\text{CH}_3 & \text{N} \quad \text{CH}_3 \\
\text{50} & \\
\end{align*}
\]

desired 2,6-diacetic ester 67 was detected. Conversely, when 2,6-dimethylpyridine (50) was allowed to react with sodium hydride and diethyl carbonate, the expected mono-acetic ester 66 was obtained along with diethyl 2-(6-methylpyridyl)malonate (157).

\[
\begin{align*}
\text{CH}_3 & \text{N} \quad \text{CH}_3 \\
\text{50} & \\
\text{NaH} & \text{(EtO)$_2$CO} \\
\text{66} + & \text{157} \\
\end{align*}
\]

Formation of 157 in reasonable yields can be rationalized by further reaction of the intermediary acetate 66 as shown in Scheme XII. The base in the reaction is actually sodium ethoxide which is regenerated from the by-product ethanol by the sodium hydride. The methylene protons
Scheme XII

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of 66, activated by both the pyridyl and the carb.xylate functions, are so much more acidic than the opposing 6-methyl group hydrogens of 66 or the methyl groups of £0 that they are eventually selectively removed by base affording C-acylation to the unsymmetrical diacetic ester 157. Furthermore, the methine hydrogen of 157 is activated by 3 groups and should be even more easily removed by base to give the stable anion 157a-c. The contribution of 157c may also explain why there is apparently no further reaction of 157 to form higher substituted compounds.

In order to determine the extent of dianion formation, methyl iodide was chosen as a suitable trapping agent. The resultant alkylated products would not have an enhanced acidity, not equilibrate efficiently with other anions, and with the utilization of inverse addition would give a good approximation of the efficiency of dianion formation. Thus, 2,6-dimethylpyridine (£0) was treated with various base-solvent systems and the resultant mixture added to a solution of excess methyl iodide. No attempt was made to determine or maximize yields since these are directly affected by a competing quaternization reaction. However, the starting 2,6-dimethylpyridine (£0), which undergoes quaternization more readily than the products, was recovered in each case and therefore used as an internal standard. The ratios of the resulting 2,6-disubstituted pyridines 61 and 62 (Table V, p. 58) indicate that the dilithio intermediate 55 and the mono metallated intermediate were generated in a 1:3 ratio by treatment of £0 with 2 moles of phenyllithium. These simple alkylation experiments thus illustrate that the maximum percentage of dianion formation was not sufficient to warrant any diacylation experiments by this route.
A method of synthesis for symmetrically diacylated 2,6-dimethylpyridines was envisioned by nucleophilic displacement of pyridine-ring halogen(s) by an appropriately metallated acylmethyl reagent. Therefore, 2,6-dichloropyridine (158) or 2,6-dibromopyridine (159) was treated with 4 equivalents of Meyers' reagent, 121 2-lithio- methyl-4,4-dimethylloxazoline (160), and the resulting mixtures solvolyzed to the corresponding esters. However, in both cases only the mono addition product, ethyl 2-(6-chloropyridyl)acetate (161) and ethyl 2-(6-bromopyridyl)acetate (162) was obtained in 24% and 17%, respectively. So this route was also abandoned.

Finally, 2,6-pyridinediacetates (161 and 162) were easily synthesized (51-76%) by solvolysis of the corresponding diacetonitrile (77) which was obtained in almost quantitative yields by treatment of 2,6-di(chloromethyl)pyridine (75) with a cyanide/DMSO reaction. Although 75 could be obtained from 2,6-dimethylpyridine N-oxide via the N-oxide
rearrangement route\textsuperscript{113} (11\% overall), it was more easily prepared from the now readily available 2,6-di(hydroxymethyl)pyridine (74). Thus, the realized overall preparation of the diacetonitrile 77 from the commercially available diacid in 4 steps is 79\%. The solvolysis step was not optimized!

2,6-Di(phenacyl)pyridine (79) was prepared according to the literature procedures as illustrated in Scheme IV.\textsuperscript{3,41} A miserable overall 6\% yield of 79 was obtained for the 4-step sequence, whereas a 16\% yield had been previously reported.\textsuperscript{41} The poor yield was due primarily to the initial condensation of 2,6-dimethylpyridine (70) with benzaldehyde. This acetic anhydride induced condensation afforded the desired diolefin 68 in a meager 20\% yield: \textit{trans}-[2(6-methylpyridyl)-phenylethene (165) and its non-dehydrated precursor 165 were also
isolated, 17% and 20%, respectively. The overall yield of \( T_2 \) was improved to 24-30% by utilization of the "anil synthesis" in the initial step. Since Becker\textsuperscript{123} and Siegrist\textsuperscript{124} reported the condensation of benzalaniline \( (167) \) with arylmethyl compounds to occur in excellent yield, this procedure was attempted for the first time with 2,6-dimethylpyridine \( (50) \), resulting in easy isolation of the diolefin \( 68 \) in 78% yield.

\[
\begin{align*}
\text{CH}_3 & \quad \text{N} & \quad \text{CH}_3 \\
\text{Ph} & \quad \text{N} & \quad \text{Ph}
\end{align*}
\]

The di-Wittig reagent was also prepared from triphenylphosphine and 2,6-di(chloromethyl)pyridine \( (162) \) in essentially quantitative yield. Since preliminary reactions of the diylide \( 162 \), the diketone \( T_0 \), and the diesters \( 67 \) and \( 73 \) with the dicarboxaldehyde \( 85 \) resulted in isolation of no identifiable olefinic compounds, the condensations were undoubtedly more complex than originally envisioned. Therefore, in order to define optimum parameters for the desired cyclocondensations, a decision was made to investigate the analogous but more simple mono-substituted pyridine compounds.
Ethyl 2-pyridylacetate \((12)\) was prepared by two routes. 2-Methylpyridine, diethyl carbonate, and sodium hydride were refluxed 12 hours in DME to afford \((20\%) \ 12\) along with 1\% of the previously unreported diethyl 2-pyrydylmalonate \((170)\). Ester \(12\) was also synthesized \((43-46\%)\) by the method of Goldberg, et al. However, other previously undetected products were also isolated and these are the subject of a separate project reported in Appendix I.

Since Bragg and Wibberley in 1961 reported ethyl 2-pyridylacetate \((12)\) and benzaldehyde condense to give the cinnamate \(17\) containing the desired cis orientation about the double bond, this reaction was repeated in order to substantiate their configurational assignment. The work-up procedure deviated somewhat from their literature method. Rather than distillation of the crude reaction mixture, the volatile materials were removed in vacuo and then the residue subjected to chromatography. Bragg and Wibberley obtained \(17\) in a "46\%" yield. This value was determined by isolation of an unspecified quantity of the picrate derivative of \(17\) from the weighed distillate. However, without this datum the proportion of \(17\) in the distillate and thus the actual percent yield could not be determined. Chromatography of the reaction mixture, however, indicated incomplete reaction since 43\% of the starting ester \(12\) was recovered. Although two products, \((E)-171\) and \((Z)-171\) were obtained in low yield, the predominance of \((E)-171\) \((20\%)\) over \((Z)-171\) \((10\%)\) partially supported the report of Bragg and Wibberley.

Similarly, the more reactive 2-pyridinecarboxaldehyde \((13)\) was condensed with ethyl 2-pyridylacetate \((12)\) to afford ca. 77\% total yield of products \(172\) in half the amount of time required for the Bragg
and Wibberley reaction. However, in this case the trans or (Z)-isomer was obtained in predominance (45%) over the desired cis or (E)-isomer (30%), see Table VI. A small amount of the intermediary alcohols (2%) and some starting ester (13%) was also recovered. Reaction of 12 and 82 under Perkin conditions,127 i.e., triethylamine and acetic anhydride, gave an even higher ratio of (Z)- to (E)-isomers, 46% and 18%, respectively. The predominance of trans or (Z)-isomer was not unexpected in this reaction since this usually is the only product obtained under acidic conditions. The overall yield with this catalytic medium is also diminished, since there are apparently competing reactions of the starting materials and products with the acetic anhydride. In the absence of acetic anhydride, triethylamine effected the condensation but with a poorer conversion to olefinic products as well as a much higher percentage (18%) of intermediary alcohols. The amount of (E)-isomer in the crude mixture was determined by nmr to be only 17%, whereas the predominant (Z)-isomer was detected (≤ 65%) and isolated (30%).

For comparative purposes, the α-phenylcinnamates (172) were prepared by adapting various methods from the literature.127-130 In order to complete the series (See Table VI), the acrylates (E)- and (Z)-174 were synthesized by utilization of Shahak's method132 (Scheme XIII). This route was considered necessary since others had reported only very poor condensation reaction (5%) of ethyl phenylacetate and benzaldehyde by typical basic conditions.150 By an error, the proper amount of base was not utilized; thus, both isomers of 174 were obtained in low yield and the favored (E)-isomer was isolated as the predominant isomer [16% (E) vs. 9% (Z)].

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### TABLE VI

**ETHYL 2,3-DIARYLACRYLATES**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar</th>
<th>Ar'</th>
<th>( % )</th>
<th>IR, ( \text{cm}^{-1} )^{b}</th>
<th>UV, ( \text{nm}(\times 10^{3}) )^{c}</th>
<th>NMR, ( \delta(\text{ppm}) )^{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C=O</td>
<td>C=C</td>
<td>C-0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(E)-172</td>
<td>Ph</td>
<td>Ph</td>
<td>84</td>
<td>1710</td>
<td>1625</td>
<td>1246</td>
</tr>
<tr>
<td>(E)-174</td>
<td>Ph</td>
<td>2-Pyr</td>
<td>64</td>
<td>1713</td>
<td>1644</td>
<td>1245</td>
</tr>
<tr>
<td>(E)-171g</td>
<td>2-Pyr</td>
<td>Ph</td>
<td>67</td>
<td>1712</td>
<td>1630</td>
<td>1253</td>
</tr>
<tr>
<td>(E)-172</td>
<td>2-Pyr</td>
<td>2-Pyr</td>
<td>40</td>
<td>1714</td>
<td>1591</td>
<td>1253</td>
</tr>
<tr>
<td>(Z)-172</td>
<td>Ph</td>
<td>Ph</td>
<td>16(e)</td>
<td>1723</td>
<td>1604</td>
<td>1216</td>
</tr>
<tr>
<td>(Z)-174</td>
<td>Ph</td>
<td>2-Pyr</td>
<td>36</td>
<td>1722</td>
<td>1620</td>
<td>1193</td>
</tr>
<tr>
<td>(Z)-171</td>
<td>2-Pyr</td>
<td>Ph</td>
<td>33</td>
<td>1723</td>
<td>1586</td>
<td>1215</td>
</tr>
<tr>
<td>(Z)-172</td>
<td>2-Pyr</td>
<td>2-Pyr</td>
<td>60</td>
<td>1723</td>
<td>1587</td>
<td>1204</td>
</tr>
</tbody>
</table>

---

*Notes:*
- \( \% \): Percent ratio of the (E)/(Z) isomers.
- **Thin films.** Methanol solvent. Deuterio-chloroform solvent, ca. 10% wt/vol.
- *Value determined on intermediate acid.*
- Litt. \(^{129}\) nmr (CCl\(_4\)) \( \delta 7.49, 4.09, \text{and} 1.25, \text{respectively.}
- (E)-171g is identical to compound 177.

---

*Abbreviations:*
- IR: Infrared
- UV: Ultraviolet
- NMR: Nuclear Magnetic Resonance
- \( \text{cm}^{-1} \): Wavenumber
- \( \text{nm} \): Nanometer
- \( \times 10^{3} \): Multiplication by 1000
Scheme XIII

\[
\begin{align*}
\text{Ph-} & \quad \text{CO}_2\text{Et} \\
+ & \quad \text{EtO}^- \\
\text{EtO}_2\text{CCO}_2\text{Et} & \quad \rightarrow \\
\text{Ph} & \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

2-PyrCHO \quad \rightarrow \quad \text{EtOH}

E-174

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The α-arylacetophenones were condensed with various aryl-aldehydes according to literature procedures and the products are arranged in Table VII.\textsuperscript{18, 133, 135} In general, these α-arylacetophenones were reacted with a slight excess of the appropriate aldehyde and a catalytic amount of piperidine. By utilization of benzene, as solvent, rather than ethanol, azeotropic removal of water was possible; thus, the reaction was forced to completion. The percentage ratios of (E)/(Z) isomers and pertinent spectral data are presented in Table VII. However, when 2-pyridinecarboxaldehyde was used, an equivalent amount of piperidine was necessary to realize removal of the theoretical amount of water and insure completion of the reaction. In this case, piperidine had formed a Michael adduct with the initial condensation product. Therefore, the resultant reaction mixtures were refluxed in dilute acid to effect the elimination of piperidine and afford the olefin.

For example, desoxybenzoin (175) and 173 were reacted by using 3 increments of the equivalent amount of piperidine, each resulting in ca. the respective amount of water removed. Recrystallization of the crude reaction residue afforded the piperidine-Michael adduct 1\textsuperscript{163} in 27% yield. This compound apparently decomposes to the (Z)-isomer on extended heating in protic medium, since (Z)-1\textsuperscript{178} was obtained in 67% yield by simple concentration (boiling) of the alcoholic mother-liquor. Indeed, the adduct 1\textsuperscript{183} smoothly eliminated piperidine on refluxing in 5% hydrochloric acid to give (Z)-1\textsuperscript{178} in 91% yield.

Alternatively, 8\textsuperscript{173} and 175 reacted by tertiary or highly hindered secondary amine catalysis to afford exclusively the intermediary alcohols 1\textsuperscript{184} and 1\textsuperscript{185}, in 72% and 15% yield, respectively. Since
### TABLE VII

**1,2-DIARYL BENZOYLETHENES**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar</th>
<th>Ar'</th>
<th>$\phi^a$</th>
<th>mp, $^\circ$C</th>
<th>$\nu_{IR, cm^{-1}}$</th>
<th>C=O</th>
<th>C=O</th>
<th>UV, nm ($\times 10^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E)-177</td>
<td>Ph</td>
<td>Ph</td>
<td>74(33)$^c$</td>
<td>100.5-101.5</td>
<td>1645</td>
<td>1250</td>
<td>255(16.5)</td>
<td>295(14.4)</td>
</tr>
<tr>
<td>(E)-178</td>
<td>Ph</td>
<td>2-Pyr</td>
<td>0</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>(E)-179$^{13e}$</td>
<td>Ph</td>
<td>4-NO$_2$-Ph</td>
<td>---</td>
<td>155-157</td>
<td>1668$^e$</td>
<td>---</td>
<td>257(16.3)$^f$</td>
<td>318(16.4)$^f$</td>
</tr>
<tr>
<td>(E)-180</td>
<td>2-Pyr</td>
<td>Ph</td>
<td>2</td>
<td>86.5-88.5</td>
<td>1644</td>
<td>1265</td>
<td>268(13.5)</td>
<td>297(15.9)</td>
</tr>
<tr>
<td>(E)-181</td>
<td>4-NO$_2$-Ph</td>
<td>Ph</td>
<td>84(30)$^d$</td>
<td>185.5-186.5</td>
<td>1645</td>
<td>1265</td>
<td>266(18.2)</td>
<td>289(18.2)</td>
</tr>
<tr>
<td>(E)-182</td>
<td>2-Pyr</td>
<td>2-Pyr</td>
<td>&lt; 1</td>
<td>---</td>
<td>1659</td>
<td>1259</td>
<td>259(14.2)</td>
<td>293(12.2)</td>
</tr>
<tr>
<td>(Z)-177</td>
<td>Ph</td>
<td>Ph</td>
<td>26(67)$^c$</td>
<td>86-87.5</td>
<td>1659</td>
<td>1225</td>
<td>254(23.5)</td>
<td>282(21.1)</td>
</tr>
<tr>
<td>(Z)-178</td>
<td>Ph</td>
<td>2-Pyr</td>
<td>100</td>
<td>157.5-158.5</td>
<td>1670</td>
<td>1232</td>
<td>256(21.9)</td>
<td>303(18.9)</td>
</tr>
<tr>
<td>(Z)-179$^{13e}$</td>
<td>Ph</td>
<td>4-NO$_2$-Ph</td>
<td>---</td>
<td>167-168</td>
<td>1672$^e$</td>
<td>---</td>
<td>251(21.6)$^f$</td>
<td>328(20.4)$^f$</td>
</tr>
</tbody>
</table>

---

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Continued
<table>
<thead>
<tr>
<th>Compound</th>
<th>Suffix</th>
<th>R</th>
<th>R'</th>
<th>Method A</th>
<th>Method A</th>
<th>Method A</th>
<th>Method A</th>
</tr>
</thead>
<tbody>
<tr>
<td>(z)-180</td>
<td>2-Pyr</td>
<td>Ph</td>
<td>98</td>
<td>115-116</td>
<td>1682</td>
<td>1240</td>
<td>258(21.5)</td>
</tr>
<tr>
<td>(z)-181</td>
<td>4-NO2-Ph</td>
<td>Ph</td>
<td>16(70)</td>
<td>135-136</td>
<td>1689</td>
<td>1225</td>
<td>251(22.4)</td>
</tr>
<tr>
<td>(z)-182</td>
<td>2-Pyr</td>
<td>2-Pyr</td>
<td>99</td>
<td>154-155.5</td>
<td>1687</td>
<td>1243</td>
<td>254(21.7)</td>
</tr>
</tbody>
</table>

the alcohols can participate in a base-catalyzed enolization with subsequent equilibration, the most stable conformation, \( \text{I}^{184} \), would be the expected major product. In fact, the nmr spectrum of \( \text{I}^{184} \) indicates a methine coupling constant of 5 Hz while the spectrum of \( \text{I}^{185} \) indicates a methine coupling constant of 7.5 Hz. This methine-hydrogen interaction can be easily depicted from the Newman projections of the most stable conformations in which the largest groups (the aromatic rings) occupy the anti-periplanar orientation. Using these projections, it can also be easily seen that the dihedral angle for \( \text{I}^{185} \) (dihedral angle = 0°) would be expected to result in a larger methine vicinal coupling in the nmr spectrum than \( \text{I}^{184} \) (dihedral angle = 60°).

In order to similarly assign the structure(s) of the piperidine adduct \( \text{I}^{183} \), a sample was partially isomerized (26%) at high temperature to the other isomer. Since the methine coupling constants in the nmr spectra of \( \text{I}^{183} \) and its less stable isomer \( \text{I}^{186} \) are 11.5 Hz.
and 10.5 Hz, respectively, the structures could be tentatively assigned as shown in the Newman projections of the most stable conformers (Scheme XIV).

The envisioned reaction pathway is shown in Scheme XIV. The alcohol intermediate loses water with stereoelectronic overlap control\textsuperscript{117} to initially form the (E)-isomer. Since the (E)-isomer is effectively conjugated through the carbonyl, as will be verified in a later discussion of the spectral data, Michael addition of piperidine at the $\beta$-carbon of the $\alpha,\beta$-unsaturated carbonyl system readily occurs. The piperidine adduct(s) then undergoes equilibration to the more stable isomer $18^\alpha$. Piperidine is then eliminated from the favored antiperiplanar orientation, resulting in the (Z)-isomer. Thus, this Michael addition and subsequent elimination equilibrates the (E) and (Z) isomers. However, if such an equilibrium exists under these conditions, it is dramatically shifted toward the (Z)-isomer. The (Z)-olefin, which is not effectively conjugated through the orthogonal carbonyl group (due to steric interactions$^{138}$), resembles a trans-diaryl olefin which, at best, very poorly undergoes nucleophilic addition. However, Friedrich and Cormier$^{137}$ recently have shown that either isomer of 177 can be equilibrated with a 10 mole excess of piperidine to afford a 2/1 (Z)/(E) isomer ratio.

To further illustrate the addition-elimination, $\alpha$-(4-nitrophenyl)acetophenone (176) and benzaldehyde were condensed in a second experiment again utilizing a catalytic amount of piperidine (Method A) but with a small amount of benzoic acid (from crude benzaldehyde) present. The collection of water from this reaction was shown to be at least 5 times as fast as the initial condensation (Method A - Table VII) which did not contain benzoic acid (at least in a significant
amount). But of greater significance is the fact that the (E)/(Z) isomer ratio was reversed in the presence of benzoic acid, e.g. 84/16 and 30/70, respectively. These observations further support the reaction scheme (XIV) since dehydration is more facile under conditions where a proton source is available. The proposed Michael addition would also be enhanced by carbonyl activation as would the subsequent elimination. However, the (Z)-isomer would not be expected to show any enhanced reactivity by the presence of the added acid since this isomer resembles an isolated diaryl olefin.

The (E)-isomers in Table VII could be prepared in more suitable quantity by photoisomerization of the corresponding (Z)-isomer. As reported by Black and Lutz\(^{118}\) previously for 172, a 0.01 M benzene solution of the respective (Z)-isomer under an inert atmosphere in a pyrex flask was allowed to stand in sunlight for ca. 6 hours. In this way, (E)-180 and (E)-182 were isolated by chromatography of the photolysis residues in ca. 30% yields. The photolysis mixture containing (E)- and (Z)-178 could not be separated. From other experiments, it was found that more dilute solutions irradiated for longer periods of time resulted in higher conversions to the (E)-isomer. For example, the ester (E)-172 was obtained in a 88% yield by photolysis of a 0.001 M benzene solution of the (Z)-isomer for 72 hours. The olefinic lability of (E)-isomers with a β-2-pyridyl substituent is partially supported by the fact that neither 178 nor 182 could be obtained in pure form. Indeed, such a phenomenon in the related 3-(2-pyridyl) acrylonitriles (Table I) has been previously observed.\(^{64,67}\) A suitable elemental analysis for (E)-182 could not be obtained since it decomposed...
during an attempted molecular distillation. However, representative spectral data for (E)-162 were obtained on a twice-chromatographed sample.

Structure assignments of the α,β-unsaturated esters and ketones in Tables VI and VII were based on nmr, ir, and uv spectral data and by comparison to the well known diphenyl analogs, 117 and 117. Although each spectral method could enable distinction between an (E)- and (Z)-isomer, the combination of physical properties and several kinds of spectral data provides a formidable proof of structure assignments. Black and Lutz118 have discussed the reactivity and the ultraviolet spectral data for (E)- and (Z)-177. More recently, infrared and ultraviolet data were similarly used to confirm assignments for (E)- and (Z)-177 and 177.138 Likewise, the acid precursors to (E)- and (Z)-177 are well known.117,119 However, the ir and uv data in Tables VI and VII generally correlate well with the assigned structures. In the ir spectra of the esters and ketones, the carbonyl band for the non-conjugated (Z)-isomer appears at higher frequency than the corresponding (E)-isomer, about 10 cm⁻¹ and 25-40 cm⁻¹, respectively. The C-0 stretching frequency of the conjugated (E)-isomers also result at higher frequency. Furthermore, with the esters in Table VI it was also possible to correlate the carbon-carbon double bond bands; the higher frequency band obtaining as expected with the more conjugated (E)-isomer.

With the exception of 177, the ultraviolet data in Tables VI and VII show a higher λmax for each (Z)-isomer. The most distinguishing uv data is the larger molar extinction coefficients for all (Z)-isomers in Tables VI and VII. This effect is more pronounced at the
longer wavelength ($\lambda_{\text{max}}$) absorption band. However, one exception to the extinction-coefficient relationship is noted between isomers of \( \text{I} \) at the shorter wavelength absorption.

The nmr spectrum of the $\alpha,\beta$-unsaturated ketones in Table VII exhibited only a broad aromatic region in which the vinylic hydrogen resonance was superimposed. Nmr spectra of the esters in Table VI enabled distinction between isomers. The methyl group of the ester, being more remote from the side of conjugative effects, exhibits no difference in chemical shifts which can be related to stereochemistry, whereas the methylene exhibits an isomeric relationship. The carbonyl of the (Z)-isomer is less efficiently conjugated (orthogonal to the plane of the double bond) and thus the methylene resonance is shifted downfield to a greater extent (5-18 Hz) than the (E)-isomer. In addition, the vinylic proton resonance can be seen as a very strong singlet.

The cis relationship between the carboxyl function and the vinylic hydrogen of the (E)-isomer as expected results in the appearance of a more deshielded vinylic resonance ($\delta$ 7.8-8.0). The vinylic hydrogens of (Z)-\( \text{I} \) and (Z)-\( \text{II} \) which have a 2-pyridyl moiety cis to the vinylic hydrogen are also more deshielded than the corresponding (Z)-\( \text{II} \) and (Z)-\( \text{III} \) which have a phenyl group cis to the vinylic hydrogen. The pyridine nitrogen lone-pair electrons undoubtedly causes this additional deshielding.

The (Z)-isomers in Tables VI and VII also show a general trend to exhibit the higher melting point and/or boiling point. Although a few exceptions may be noted, this relationship is especially true for the compounds which contain a pyridine moiety.

Although the (Z)-dipyridyl olefin could now be synthesized in nearly quantitative yield and subsequently photoisomerized to the
desired (E)-isomer, further nucleophilic cyclization reactions have not been successful. For similar reasons the 2-pyridyl Wittig reagent was not investigated. However, another pathway was envisioned in which a cis-dipyridyl olefin that did not have an activating carbonyl substituent, might be cyclized. Synthesis of 1,2-di[2-(6-methylpyridyl)]-ethene (120) was accomplished by standard methods (Scheme IX). A low yield of pure olefin was obtained but the previously undetected 82 was also isolated. Olefin 120 was photoisomerized to (17%) the cis-isomer 188 by the usual treatment (6 hours in sunlight) of a 5 x 10^{-3} M benzene solution but on longer exposure time the yield was tripled (46%). Similarly, isomers of 82 were sought but not realized since the photolysis mixture was very difficult to separate. Continuing in this direction, 1,2-di[2-(6-hydroxymethylpyridyl)]ethene (123) was synthesized as shown in Scheme IX. The yields of some steps were less than reported but the hydrolysis of the diacetate 122 was improved from 81% to 98%, resulting in an overall conversion to 123 from 120 equivalent to the reported amount. trans-1,2-Di[2-(6-chloromethylpyridyl)]ethene (182)
was easily obtained (83%) from \( \text{I23} \) by treatment with thionyl chloride. Using various photolysis conditions (see Experimental), \( \text{I23} \) was isomerized to the \textit{cis}-isomer \( \text{I90} \). Although \( \text{I90} \) could be separated from \( \text{I23} \) by thick-layer chromatography, it could not be obtained in pure form due to the co-elution of a small amount (≤ 10%) of a presently unidentified photolysis product. Preliminary coupling reactions with \( \text{I90} \) by such diverse reagents as phenyllithium, \( n \)-butyllithium, magnesium, and sodium were unsuccessful since the only identifiable compound isolated was unreacted starting material. Such metal-halogen exchange reactions are more successful with dibromides but has not been attempted with \( \text{I90} \) (X = Br).

In view of the difficulty in preparing compounds, such as \( \text{I90} \), as well as the apparently enhanced nucleophilic sensitivity of \textit{cis}-oriented di(2-pyridyl)ethenes another route was envisioned which would concomitantly protect and rigidly hold the 2-pyridyl rings in the desired "\textit{cis}" orientation. For example, a Diels-Alder or \( 4 + 2 \) cycloaddition of a suitable diene moiety with a 6-substituted di(2-pyridyl)-acetylene would give a substituted \textit{cis}-1,2-di(2-pyridyl)ethene. To begin investigation of this route preliminary reactions were conducted with the simple di(2-pyridyl)acetylene \( \text{I23} \). Acetylene \( \text{I23} \) was prepared with slight modifications of literature procedures.\(^{138,139}\)

Since the initial condensation in the presence of acetic anhydride was the poor step of the synthetic sequence an attempt was made to improve the yield by utilization of the "anil synthesis".\(^{123,124}\) The 2-pyridinecarboxaldehyde anil \( \text{I44} \) was prepared in excellent yield (91-97%) with an azeotropic modification of similar conventional procedures. However, in contrast to the success obtained in the preparation
of \( \text{194} \), the "anil synthesis" of \( \text{192} \) gave only a poor yield as determined by tlc in preliminary experiments. The major product, (E)-1,2-dianilino-1,2-di(2-pyridyl)ethene (\( \text{195} \)), of the reaction resulted from self condensation of \( \text{194} \). The formation of \( \text{195} \) in the attempted "anil synthesis" can be explained by the t-butoxide liberating the required catalytic cyanide ion from the "hydrogen cyanide impurity"\(^{150} \) in N,N-dimethylformamide. Indeed, the structure of \( \text{195} \) is supported by the fact that a cyanide ion catalyzed benzoin-type condensation of \( \text{194} \) provides a fair yield (61%) of \( \text{195} \).

\[
\text{194} \xrightarrow{-\text{CN}} \text{195}
\]

Di(2-pyridyl)acetylene (\( \text{193} \)) reacted with \( \alpha \)-pyrone (\( \text{196} \)) at high temperatures to afford (53%) 1,2-di(2-pyridyl)benzene (\( \text{197} \) after
concomitant loss of carbon dioxide. Cyclopentadiene and furan failed to react with 197 under these conditions.* Although a retro Diels-Alder reaction of 197 would not be possible, the desired cis-orientation of the 2-pyridyl rings was obtained and at the same time protected with a group inert to subsequent nucleophilic transformations. Therefore, in order to prepare the requisite 1,2-di(2-pyridyl)benzene with suitable substituents for an eventual ring closure reaction, the sequence shown in Scheme XV was initiated. Di[2-(6-methylpyridyl)]acetylene (199), prepared from 120 in two steps, was reacted with α-pyrone (196) to afford 200. Neutral oxidation of 200 with a slight excess of the theoretical amount of potassium permanganate in dilute aqueous medium and subsequent esterification resulted in ca. 21% of the desired diester 201. The amount of starting material recovered and the composition of the remaining products varied with conditions of reaction and purity of starting material. With the equivalent amount of oxidant, about 20% of the starting amount of 200 was recovered, whereas with a large excess of oxidant, further oxidation occurred to give 204, after esterification. If chromatographically pure 200 was oxidized, the monoester 202 could also be isolated. However, oxidation of 200 which had been purified by distillation afforded two additional esters, 205 and 203. These products result from oxidation of acetylene 199, which was detected by tlc in the distillate of 200. Thus, only the desired

*The reactions of diarylacetylenes with arylocyclopentadieneones, which both contain the 2-pyridyl group, are the subject of a separate project (see Appendix II).
Scheme XV

1) Br₂
2) KOH EtOH

Δ

Δ

1) KMnO₄
2) MeOH/H⁺

NaBH₄

SOCl₂

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diester \( \text{201} \) could be separated from the mixture of esters \((\text{201}-\text{204})\)

normally obtained. Preliminary reactions to prepare the diol \( \text{205} \) and

the dichloride \( \text{206} \) have been conducted. Previously discussed methods

were utilized, but the small amounts of \( \text{201} \) available after arduous

chromatography precluded any optimization of these subsequent reactions. However, unless the oxidation step can be improved to give a higher

yield of \( \text{201} \), this route to pyridine macrocycles \( \text{207} \) must also be re-

considered. At the same time these reactions were being pursued, three

additional pathways to various macrocyclic systems were also being

initiated.

A condensation route which could utilize the trans olefinic

linkages was envisioned as shown in Scheme XVI. The phthalaldehyde

moiety contains the necessary "cis" olefinic linkage but protected as

the previously discussed system with the inherent aromatic ring.

Thermal or photochemical electrocyclization of \( \text{202} \) would give \( \text{210} \), which
Scheme XVI

\[ \text{208} \quad \text{CHO} \quad \text{CHO} \quad + \quad \text{CH}_3 \quad \text{N} \quad \text{CH}_3 \quad \text{50} \]

\[ \Delta \]

\[ \text{209} \]

\[ \text{210} \]

\[ [0] \]

\[ \text{211} \]
could be aromatized to \( \text{211} \) by mild oxidation. Before conducting this more complex condensation, an attempt was made to utilize the "anil condensation". Utilization of the phthalaldehyde dianil rather than a pyridine anil should also circumvent the previously encountered problem of self-condensation of the pyridine anil. However, reaction of phthalaldehyde (\( \text{208} \)) with aniline did not give the dianil \( \text{212} \) but 2-phenyl-1-phenyliminoisoindole (\( \text{213} \)) which resulted from further reaction of the initially formed dianil. Therefore, the route was not continued at this time, but should be more thoroughly investigated.

\[
\begin{align*}
\text{CHO} & \quad \text{PhNH}_2 & \rightarrow & \quad \begin{array}{c}
\begin{array}{c}
\text{H}
\end{array}
\end{array} & \quad \text{Ph} \\
\text{CHO} & \quad \text{CHO} & \rightarrow & \quad \begin{array}{c}
\begin{array}{c}
\text{H}
\end{array}
\end{array} & \quad \text{Ph} \\
\text{208} & \rightarrow & \text{212} & \rightarrow & \text{213}
\end{align*}
\]

Vogtle and Zuber\(^{144} \) have shown that 1,3-di(bromomethyl)benzene (\( \text{215} \)) reacts with diethyl sodiomalonate to give \( \text{216} \) and the [3.3.3]-metacyclophane \( \text{217} \) in 90% and 2%, respectively (Scheme XVII). Furthermore, base induced reaction of \( \text{216} \) and additional \( \text{215} \) under high-dilution

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{Py} & \quad \text{CO}_2\text{Et} & \rightarrow & \text{EtO}_2\text{C} \\
\text{EtO}_2\text{C} & \quad \text{Py} & \quad \text{CO}_2\text{Et} & \rightarrow & \text{EtO}_2\text{C}
\end{align*}
\]

\( \text{219} \)
Scheme XVII

\[
\begin{align*}
215 \quad \begin{array}{c}
\text{Br} \\
\text{Br}
\end{array} & \quad + \\
\text{H}_2\text{C(CO}_2\text{Et)}_2 & \quad \xrightarrow{\text{NaOEt, EtOH}} \quad 216 \quad (R=\text{CO}_2\text{Et}) \\
\text{R} & \quad \text{R} \\
217 \quad (R=\text{CO}_2\text{Et})
\end{align*}
\]
conditions provided (7%) the [3,3,3,3]metacyclophe 218. Attempting
the same procedures by substitution of 215 with 2,6-di(chloromethyl)-
pyridine (72) gave (ca. 82%) 219. Unfortunately, no pyridine macrocycle
could be detected in or be induced to crystallize from the reaction
mixture. The crude mixture containing 219 could not be analyzed by
glc or purified by distillation due to decomposition at elevated tem­
peratures, but 219 could be isolated by chromatography and then
distilled without decomposition. The similar high dilution reaction
was conducted but no identifiable product could be isolated.

Finally, pyridine macrocycles have been prepared by utiliza­
tion of the "template effect".111 As illustrated in Scheme XVIII,
reaction of an in situ generated sodium salt(s) of 2,6-di(hydroxymethyl)-
pyridine (74) with α,α'-dibromo-o-xylene (220) afforded the series of
azaether macrocycles 221. However, only the second (22-membered ring)
and third (33-membered ring) members of the sequence 221 have at this
time been isolated in sufficient quantity to determine the structures
with absolute certainty, 40% and 9% yield, respectively. Other products
in the mixture believed to be still larger macrocycles can be detected
by tlc using a more polar solvent system. The structure proof of such
large molecules added still another dimension of difficulty. The nmr
spectra for both compounds exhibited the expected two singlets for the two
different methylene, and the complex aromatic envelope. Normal mass
spectral data for both compounds indicated the benzyl-type ether linkage
to be extremely labile. However, a mass spectrum which exhibited the
parent ion was obtained for 221 (n = 2) using low voltage, a reverse
scan technique, and a superimposed fluorocarbon counting aid. This
combination of techniques increased the relative abundance of high mass peaks and enabled the parent peak (482) to be determined. The molecular weight of both compounds was determined very accurately (0-5% error from calculated values) by osmotic pressure method in benzene. Since Pederson has shown that the molar extinction coefficient of similar "crown ethers" can be correlated with the total number of aromatic rings, this technique was employed to further substantiate the structure of $\underline{221} (n = 3)$. The molar extinction coefficient of $\underline{221} (n = 3)$ was calculated as $3/2$ that of $\underline{221} (n = 2)$, or 14,070, and was found to be 13,050 (8% error). The compounds can be easily named by the proposed methods of Th. Kaufmann (a group-substitution nomenclature) or Vogtle and Neumann (a "phane" nomenclature). Preference is readily given to the proposed nomenclature of Th. Kaufmann in which $\underline{221} (n = 2)$ and $\underline{221} (n = 3)$ would be signified as 1,5,9,13-tetraoxa-7,15-di(2,6)pyrida-3,11-di(1,2)phenacyclohexadecane and 1,5,9,13,17,21-hexaoxa-7,15,23-tri(2,6)pyrida-3,11,19-tri(1,2)-phenacyclotetracosane, respectively. The much more cumbersome IUPAC nomenclature is given in the Experimental Section.

To further substantiate that a template effect was obtaining, two additional reactions were conducted. A high dilution reaction, although in a somewhat different solvent system, showed no appreciable change in the products or in their ratios. The fact that incomplete reaction was observed is probably due only to the lower solvation ability of the mixed solvent system. Another reaction was conducted identical to the preparation of $\underline{221}$, except that Triton B, or benzyltrimethylammonium hydroxide, was substituted for the sodium hydride base. Since
only insoluble polymer(s) resulted, this supported the idea of sodium cation reacting as a template.

As an illustration of the alkali metal complexing ability of similar "crown ethers", Pederson\textsuperscript{148,149} has described the synthesis of various complex salts. In this manner, \(\text{22I}_{\text{n}=2}\) formed a complex with sodium thiocyanate that was unchanged regardless of the number of equivalents of sodium thiocyanate used. That a macrocyclic complex salt was formed was shown by the fact that the melting point of the new complex was higher (ca. 50\(^\circ\text{C}\)) than the melting point of pure \(\text{22I}_{\text{n}=2}\).
SUMMARY AND CONCLUSIONS

As discussed in the Introduction-Part II, there are generally three methods of control that effect ring-closure and form 2,6-pyridino-macrocycles: 1) strong steric interactions between reactants which preclude the formation of unfavorable isomers, 2) utilization of the high dilution technique to increase the probability of intramolecular cyclization, and 3) utilization of a metal ion as a central coordination site, or template. The synthesis of requisite compounds and the subsequent studies of approaches utilizing stereoelectronic overlap control to effect cyclization during condensation were conducted.

Synthetic procedures were found for the efficient preparation of 2,6-pyridinediacetonitrile (77) and the corresponding diacetates 67 and 73. The key intermediate, 2,6-di(hydroxymethyl)pyridine (74), was prepared in 70-98% yield in two steps from the commercially available diacid. An improvement to the reported procedures for preparation of 2,6-di(phenacyl)pyridine (79) utilized the "anil synthesis" in which 2,6-dimethylpyridine (50) was condensed with benzanilidine (167) to afford (78%) 2,6-distyrylpyridine (68). 2,6-Pyridinedicarboxaldehyde (85) was also prepared easily from the intermediate diol 74 by oxidation with lead tetraacetate.

In connection with the above syntheses, a feasibility study was made on methods for the preparation of 2,6-pyridinediacetates directly from 2,6-dimethylpyridine (50). Synthesis of such symmetrically substituted 2,6-dimethylpyridines in situ was shown impossible for any substituent that enhances the acidity of the resultant methylene protons.
For example, further reaction of the initially formed ethyl 2-(6-methylpyridyl)acetate (66) occurred specifically at the methylene (now activated by both the 2-pyridyl and the carboxylate functions) to afford diethyl 2-(6-methylpyridyl)malonate (137). Conversely, 2,6-dimethylpyridine (59) can be symmetrically disubstituted if the substituent group (alkyl) does not enhance the acidity of the resultant pyridyl-methylene hydrogens. Alternatively, a solution of the 2,6-dimethylpyridine symmetrical dianion can be generated and subsequently added to the desired substituting reagent (acyl or alkyl). However, the extent of dianion formation was low (≤ 25%) under the reaction conditions. Therefore, this route to 2,6-pyridinediacetates was abandoned in favor of the previously discussed route from 2,6-di(hydroxy-methyl)pyridine (74).

The envisioned cyclocondensations of these 2,6-disubstituted pyridines resulted in formation of only complex polymeric products. Therefore, in order to define optimum parameters for the desired cyclocondensations as well as to develop a rationalization of the initial failures of this method, an investigation was made of the analogous but more simple mono-substituted pyridine compounds. Perkin and Knoevenagel condensations using the thermally stable ethyl 2-pyridylacetate (12) or α-(2-pyridyl)acetophenone (6) with 2-pyridinecarboxaldehyde (83), led to an unexpected predominance of the (Z)-olefin (trans aromatic rings). This anomaly was found to be a result of nucleophilic addition to the initially formed cis isomer followed by preferred elimination to the trans isomer, which is not subject to further nucleophilic addition. Isolation of the intermediary alcohols or piperidine adducts and subsequent eliminations afforded only the (Z)-olefins. However, the
(E)-isomers of the 2,3-diaryl-1-phenylprop-2-enones and the ethyl 2,3-diarylacrylates were prepared in good to excellent yields by photocchemical isomerization of the corresponding (Z)-isomers. Thus, the requisite (E)-6-substituted-2-pyridyl-olefins (cis oriented aromatic rings) could be obtained from the ca. quantitatively obtained (Z)-isomers but the inherent sensitivity to nucleophiles would preclude success of the examined cyclocondensation procedure.

During the preparation of ethyl 2-pyridylacetate (12) the previously undetected L-carbethoxy-2-hydroxy-3-(2-pyridyl)-4H-quinolin-4-one was isolated and characterized (Appendix I).

trans-6-Substituted-di(2-pyridyl)ethenes were prepared by photocchemical isomerization of the corresponding trans-isomers. Diels-Alder reactions between \( \alpha \)-pyrone and 6-substituted-2-pyridylacetylenes have been utilized to prepare similar cis oriented pyridyl systems. The key cyclization step has not been successful, but should be more facile with the respective bromides rather than chlorides. Although these routes are not very efficient, they would provide unique macrocyclic ligands and therefore should be pursued further.

A study of the Diels-Alder reactions of tetraarylcylopenta
dieneones and diarylacetylenes, which both contain the 2-pyridyl group, has been initiated (Appendix II). Although cyclocondensations using the "anil synthesis" have been envisioned, these routes have been temporarily abandoned for two reasons: 1) 2-pyridinecarboxaldehyde anil (19d) undergoes facile self-condensation under the required reaction conditions, and 2) the dianil of \( \alpha \)-phthalaldehyde cannot be isolated due to intramolecular cyclization to 2-phenyl-1-phenyliminoisoindolene (213).
However, synthesis of 2,6-pyridino-macrocycles by the template control method was shown to easily effect the cyclization step, even with alkali metal cations which are removed during the work-up procedures. In this manner 1,5,9,13-tetraoxa-7,15-di(2,6)pyrida-3,11-di(1,2)phenacyclohexadecane (\(\mathcal{P}_2\), \(n = 2\)) and 1,5,9,13,17,21-hexaoxa-7,15,23-tri(2,6)pyrida-3,11,19-tri(1,2)phenacyclotetracosane (\(\mathcal{P}_3\), \(n = 3\)) were synthesized in 40% and 9% yield, respectively. The scope of this template method has been broadened since it can now be utilized to prepare the parent 2,6-pyridino macrocyclic ligands and subsequently complexed with the desired metal salt.

Future endeavors along these lines should utilize the removable sulfur atom\(^{76, 86, 85}\) rather than oxygen and should incorporate additional \(\alpha\)-pyridyl moieties, or other related \(\alpha\)-heterocycles. For example, 2,6-di(bromomethyl)pyridine (\(\mathcal{O}_6\)) and 2,6-di(methylenethiol)pyridine reacted under template conditions should give 1,5,9,13-tetrathio-3,7,11,15-tetra(2,6)pyridacyclohexadecane (\(\mathcal{S}_5\), \(n = 3\), \(X = S\)) as the major product. Removal of the sulfur atoms, as previously discussed, from \(\mathcal{S}_5\) would afford entrance into the initially desired systems, 1,4,7,10-tetra(2,6)pyridacyclododecane (\(\mathcal{L}_1\), \(n = 3\)) and 1,4,7,10-tetra(2,6)pyridacyclodeca-2,5,8,11-tetraene (\(\mathcal{Z}_3\), \(n = 3\)).
REFERENCES


APPENDIX I

CHEMISTRY OF HETEROCYCLIC COMPOUNDS.

8. A One-Step Synthesis of 2-Hydroxy-4H-quinolizin-4-ones.

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Chemistry of Heterocyclic Compounds

8. A One-Step Synthesis of 2-Hydroxy-4H-quinolizin-4-ones

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In connection with a current project related to construction of heteromacrocycles, we needed large quantities of substituted ethyl 2-pyridylacetates. The simplest preparation of ethyl 2-pyridylacetate is the condensation of 2-picoyllithium with diethyl carbonate under very mild conditions. After prolonged extraction with petroleum ether,


(3) Alternate routes are known; see references in ref. 2, as well as K. Winterfeld and K. Flick, Arch. Pharm., 448 (1956), and K. Winterfeld and K. Nonn, Pharmazie, 22, 337 (1965).

the major side product, 1,3-di(2-pyridyl)acetone, was recovered in trace amounts as indicated by analysis of its dipicrate.2

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Repetition of this procedure is easily accomplished. However, in an initial attempt to isolate increased yields of $\frac{1}{2}$ and $\frac{3}{4}$ during the workup procedure, the strongly alkaline aqueous solution was neutralized to a pH of 7.5 to 8 by addition of dilute hydrochloric acid; extraction with chloroform afforded additional quantities of $\frac{1}{2}$ and $\frac{3}{4}$, as well as the previously undetected 1-carbethoxy-2-hydroxy-3-(2-pyridyl)-4H-quinolizin-2-one($\frac{4}{5}$). Structural assignment of $\frac{4}{5}$ was based upon degradation to 2-hydroxy-3-(2-pyridyl)-4H-quinolizin-2-one($\frac{5}{6}$) and upon nmr

(4) The infrared spectral data of related compounds have been previously assigned.


analysis (see Figure 1). The nmr spectral comparison of $\frac{3}{4}$ and $\frac{5}{6}$ is particularly important in establishing the structure $\frac{4}{5}$. In $\frac{3}{4}$ and $\frac{5}{6}$, the most downfield absorptions at $\delta = 18.3$ and 19.75, respectively, indicate the presence of a hydroxyl group proton that is strongly hydrogen-bonded to the pyridyl ring nitrogen atom. Occurrence of the unusually low field resonance at $\delta 9.34$ and 9.29 for the pyridyl H-3' proton in $\frac{3}{4}$ and $\frac{5}{6}$ is possible only if the pyridyl ring exists in a planar conformation with the quinolinizinone ring; thus proton H-3' is subjected to the close proximity of the C-4 carbonyl function. The signals at $\delta 9.00$ and 9.11 in $\frac{3}{4}$ and $\frac{5}{6}$, respectively, are assigned to H-6. The low field position

is attributed to a combination of a long-range deshielding peri effect due to the C-4 carbonyl function and an α-effect of the amido nitrogen atom. In \( \mathcal{Z} \), the H-9 proton experiences a similar peri effect from the C-1 carboxethoxy group; however, in \( \mathcal{Z} \), the absence of this long-range interaction causes the H-9 resonance to shift upfield by \( \sim 0.5 \) ppm. The remaining chemical shifts and coupling constants are in excellent accord with the assigned structures.

Self condensation of ethyl 2-pyridylacetate (1) has been demonstrated\(^8,9\) to afford \( \mathcal{Z} \) via the pathway \( 1 \rightarrow \mathcal{G} \rightarrow \mathcal{Z} \). Similarly, the preparation of 1-carboxethoxy-3-(2-pyridyl)-4H-quinolin-4-one (8) has been accomplished utilizing ethyl orthoformate as the source of the C-3 ring atom.\(^8\) Unexpected formation of the major isolated quinolinizone \( \mathcal{Z} \),

\[\begin{align*}
(8) & K. \text{ Winterfeld}, G. \text{ Wald}, \text{ and M. Rink}, \text{ Chem. Ann.}, 588, 125 (1955). \\
(9) & (a) G. \text{ R. Clemo}, W. \text{ M. Morgan}, \text{ and R. Raper}, \text{ J. Chem. Soc.}, 1025 (1936); (b) N. \text{ J. Leonard} \text{ and R. E. Beyler}, \text{ J. Amer. Chem. Soc.}, 70, 2298 (1948); (c) \text{ ibid.}, 72, 1316 (1950); (d) S. \text{ I. Goldberg} \text{ and A. H. Lipkin}, \text{ J. Org. Chem.}, 37, 1823 (1972).
\end{align*}\]

which possesses both the 1-carboxethoxy group and functionality in the 2-position, has been envisaged as proceeding through two possible routes (Scheme I). Alterations in reaction conditions permit the distinction between the two routes. More vigorous conditions result in (a) isolation of the intermediate diethyl 2-pyridylmalonate (2) along with \( \mathcal{J} \), and (b) the absence of detectable quantities of ketone \( \mathcal{Z} \), which by further carboxethoxylation and subsequent cyclization would generate \( \mathcal{Z} \). These results suggest the formation of quinolinizone \( \mathcal{J} \) involves carboxethoxylation of \( \mathcal{J} \) then nucleophilic substitution by the carbamion of \( \mathcal{J} \) on \( \mathcal{Z} \).
forming \( \mathcal{J} \), which cyclizes to give \( \mathcal{H} \) (Route a). The alternative of further carbethoxylation of \( \mathcal{F} \) to give \( \mathcal{J} \) was deemed unlikely under the reaction conditions.

Isolation of \( \mathcal{H} \) is uncomplicated, since the major impurities are easily removed by distillation. No attempt has been made to optimize the reaction conditions.

**Experimental Section**

(10) Melting points were recorded in sealed capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 621 spectrophotometer. Nmr spectra were determined on either a Varian Associates Model HA-100 or Perkin-Elmer Model R12-B spectrometers; chemical shifts are given parts per million relative to TMS as an internal standard. Analyses were performed by Mr. R. Seab in these laboratories.

Ethyl 2-Pyridylacetate was prepared by the method of Goldberg, et al., from 2-picolyllithium and diethyl carbonate. Workup procedure deviated slightly from the literature procedure. The reaction mixture was poured into 200 g of ice water and extracted with several 200 ml portions of ether. The combined etheral phases were dried with anhydrous magnesium sulfate, concentrated in vacuo to remove starting 2-picoline, and distilled to afford 13.4 g (41%) of ethyl 2-pyridylacetate: bp 110-116\(^\circ\) (6 mm) [lit\(^2\) bp 110-113\(^\circ\) (6 mm)]; ir (nujol) 1738 (C=O), 1597, 1160 (C-O), 1036 cm\(^{-1}\); nmr (CDCl\(_3\)) \& 1.23 (-CH\(_2\)CH\(_3\), t, J = 7 Hz), 3.83 (-CH\(_2\)CO, s), 4.17 (-CH\(_2\)CH\(_3\), q, J = 7 Hz), 7.0-7.8 (pyr-H, m), and 8.45-8.65 (6-pyr-H, s).
The residue was chromatographed on Silica Gel [cyclohexane-ethyl acetate (1:1)] affording an additional 459 mg of ethyl 2-pyridylacetate and 3.0 g (7.1%) of di-2-picolylketone: bp 170-180° (0.7 mm) [lit11 bp 130-135° (0.05 mm)]; picrate (recrystallized from ethanol) mp 210° (lit11 mp 191-191.5°).


mp 191-191.5°.


The aqueous layer was then adjusted with dilute acid to pH 7.5 to 8.0 and extracted with chloroform. Chromatography of the dried (magnesium sulfate) chloroform extract gave 100 mg of ethyl 2-pyridylacetate, 1.11 g of di-2-picolylketone, and 24 mg of 1-carboethoxy-2-hydroxy-3-(2-pyridyl)-4H-quinolizin-4-one (I): mp 166-167°; nmr (CDCl3) Figure 1; ir (nujol) 1700 (ester), 1652, 1630, 1602, 1557, and 1231 cm⁻¹; mass spectrum: 310 (M⁺), 309, 264 (M⁺-C₈H₆O), 237 (M⁺-C₃H₆O₂), 181, 146, 91, 78 (C₅H₄N).


Reaction of 2-Picolyllithium with Diethyl Carbonate. 1-Carboethoxy-2-hydroxy-3-(2-pyridyl)-4H-quinolizin-4-one (I). To a solution of phenyllithium (alfa Chemical Co., 0.6 mol, 2.2 M in benzene-ether) in 500 ml of ether, 2-picoline (bp 128-129°, 56 g, 0.6 mol) was added over a ten-minute period. The solution was refluxed for 30 minutes, then diethyl carbonate (47 g, 0.4 mol) in 50 ml of ether was added rapidly. Reflux was maintained for an additional 30 minutes. The mixture was cooled, poured into
ice water, adjusted with acid to a pH ~ 8 and extracted with chloroform. After removal of the solvents, as well as unreacted 2-picoline, the residue was fractionally distilled affording 2.0 g of ethyl 2-pyridylacetate: bp 110-113° (6 mm).

The distillation residue (11.7 g) was chromatographed affording 917 mg of ethyl 2-pyridylacetate, 6.0 g (14%) of \( \text{I} \) (mp 166-167°), and 150 mg (1%) of 3-hydroxy-3-(2-pyridyl)-4H-quinolizin-4-one(\( \text{II} \)); mp 175-177° (lit mp 181-182°); nmr (CDCl\(_3\)) Figure 1; ir (nujol) 3500-3100 (broad, OH), 1667, 1641, 1638, and 1589.

2-Hydroxy-3-(2-pyridyl)-4H-quinolizin-4-one (\( \text{II} \)). The ester \( \text{I} \) (1.00 g, 3.22 mmol) suspended in 100 ml of a 5% sodium hydroxide solution was refluxed for 8 hours. After cooling to ambient temperature, the pH was adjusted to 7.5-8. The solution was extracted with chloroform, dried with anhydrous sodium sulfate, and concentrated in vacuo affording 630 mg (82%) of 2-hydroxy-3-(2-pyridyl)-4H-quinolizin-4-one: mp 174.5-176°. Recrystallization from ethanol gave an analytical sample: mp 176.5-178°.

Reaction of 2-Picoline with Diethyl Carbonate and Sodium Hydride. Sodium hydride (50% dispersion, 2.15 g, 0.05 mol) in 1,2-dimethoxyethane (DME, 25 ml) was stirred under nitrogen with addition of a solution of 2-picoline (4.65 g, 0.05 mol), diethyl carbonate (11.8 g, 0.10 mol) and DME (20 ml). After the mixture was refluxed for 8 hours, it was poured into ice water. The pH of the aqueous layer was adjusted with dilute acid to 7.5-8 and extracted with chloroform. The extract was dried with sodium sulfate and concentrated in vacuo removing all solvents and unreacted starting materials. Chromatography of the remaining yellow oil afforded 322 mg (2.7%) of diethyl 2-pyridylmalonate: bp 130-132° (1 mm); nmr (CDCl\(_3\)) \( \delta \) 1.21 (-CH\(_2\)CH\(_3\), t, J = 7 Hz), 4.22 (-CH\(_2\)CH\(_3\), q,
$J = 7 \text{ Hz}$, $5.04$ (CHCO, s), $7.05$ to $7.88$ (pyr-H, m), and $8.44$ to $8.65$ (6-pyr-H, m).

Analyzed. Calculated for $C_{18}H_{13}N_04$: C, 60.76; H, 6.38. Found: C, 61.06; H, 6.40.

Further elution afforded 1.099 g (13.3%) of ethyl 2-pyridylacetate [bp 110-117° (6 mm)], 131 mg (1.7%) of 1-carbethoxy-2-hydroxy-3-(2-pyridyl)-4H-quinolinizin-4-one ($\beta$, mp 166-168°) and only traces of $\beta$. 

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FIGURE 1. Low field region of the 100 MHz pmr spectra of $3 (R=H)$ and $4 (R=CO_2CH_2CH_3)$ in DDCl$_3$. The carbethoxy group in the spectrum of $4$ is not shown [6 1.44 (-CH$_2$CH$_3$, t, $J = 7$ Hz) and 4.47 (-CH$_2$CH$_3$, q, $J = 7$ Hz)].
APPENDIX II

Tetraarylcylopentadieneones and Hexaarylbenzenes
Containing the 2-Pyridyl Moiety
RESULTS AND DISCUSSION

In conjunction with other Diels-Alder cycloadditions in which 2-pyridylacetylenes were reacted with \( \alpha \)-pyrone (1) to afford 1,2-di(2-pyridyl)benzenes 2 and reactions of acetylenes with tetraarylcyclopentadieneones were also investigated. The preparation

\[
\begin{align*}
\text{Ar}^4 \quad \text{Ar}^5 \quad \text{Ar}^6 \\
\text{Ar}^1 \quad \text{Ar}^2 \quad \text{Ar}^3 \\
\text{Ar}^4 \quad \text{Ar}^5 \quad \text{Ar}^6
\end{align*}
\]

of hexaphenylbenzene (8) by this route is well known. However, 2-pyridyl analogues of either 4 or 5 have not been reported (Table I and II).
**TABLE I**

**TETRAARYLCYCLOPENTADIENEONES**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Ar&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Ar&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Ar&lt;sup&gt;4&lt;/sup&gt;</th>
<th>mp °C</th>
<th>vis, λ&lt;sub&gt;max&lt;/sub&gt; nm(s)&lt;sup&gt;a&lt;/sup&gt;</th>
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*a. Methanol solvent.*

*b. Reference. 7.*
TABLE II
HEXAARYLBENZENES

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a. Corrected temperature; by DTA.

b. Reference 7.
To begin studies of these compounds, the 2-pyridyl analogues of 6 were desired (Table I). 2-Pyridyl (55) and dibenzylketone were reacted according to the Organic Syntheses procedure1 for the preparation of tetraphenylcyclopentadieneone (6), but instead of the expected 10 the colorless alcohol 31 was obtained in excellent yield (93%). Dehydration of 31 to the desired dark red 10 did not readily occur under acidic or basic conditions, but was easily accomplished by utilization of hot hexamethylphosphorous triamid (HMPA).2

Thus, other tetraarylcyclopentadieneones can be prepared as shown in Scheme I. For example, 32, prepared from readily available starting materials (28%), reacted with benzil (34) to give 2 (31% overall). Similarly, crude 33 was obtained in 10% overall yields and in preliminary reactions with benzil (34) or 2-pyridil (35) gave only very small amounts of dark crystals, believed to be 11 and 13, respectively.

With these two new cyclones, 2 and 10, and two acetylenes, diphenylacetylene (7) and di(2-pyridyl)acetylene (2), four new hexarylbenzenes were prepared (Table II) using the method of Fieser.7

This project was slowed by the difficulty in preparing pure 33. This preparation is at present only the minor reaction product;
Scheme I

\[
\begin{align*}
\text{Ar}^1 & \quad \text{Ar}^4 \\
+ & \\
\text{Ar}^2 & \quad \text{Ar}^3 \\
\text{OH}^- \quad 2) \text{HMPA} & \quad \Delta \\
\text{ArCH}_2\text{CN} & \quad 32 \quad (\text{Ar} = \text{Ph}) \\
& \quad 33 \quad (\text{Ar} = 2\text{-Pyr})
\end{align*}
\]
the major reaction of picolyllithium with 2-pyridylacetonitrile is apparently hydrogen abstraction. A more efficient route to these propanones is necessary to continue the work.
Reaction of 2-Pyridil with Dibenzylketone. Similar to the published procedure for preparation of tetraphenylcyclohexene,\textsuperscript{1} 2-pyridil (25.3 g, 0.119 mol) and dibenzylketone (25.0 g, 0.119 mol) were dissolved in 150 ml of absolute ethanol. The temperature was raised to 78° and a solution of potassium hydroxide (3.63 g, 0.065 mol) in 30 ml of 95% ethanol was slowly added over 15 minutes. The reaction medium changed to dark red. The mixture was refluxed 15 minutes and upon cooling to 0° afforded 33.2 g (70%) of colorless 2,5-diphenyl-3,4-di(2-pyridyl)-4-hydroxycyclopent-2-ene-1-one (31): mp 178-180°; ir (KBr) 3400 (-OH), 1710 (C=O), 1590, 1460, 1430, 1345, 1145 (C-O), 1000, 753, and 700 cm\(^{-1}\); nmr (CDCl\(_3\)) 6 4.34 (COCH\(-\), s, 1H), 6.55 (-OH, s, 1H), 6.9-7.8 (arom-H, m, 16H), 8.2-8.6 (6-pyr-H, m, 2H).

**Anal.** Calcd for C\(_{27}H\(_{20}\)N\(_2\)O\(_2\): C, 80.18; H, 4.98; N, 6.93.

Found: C, 79.87; H, 4.89; N, 6.72.

The mother liquor was refluxed for several hours before being taken to dryness in vacuo. The residue was dissolved in chloroform and washed with water. The organic layer was evaporated and the residue recrystallized from benzene-ethanol to furnish an additional 10.7 g (93% combined yield) of 31.

**Attempted Dehydration of 31.** Method A. p-Toluenesulfonic Acid Catalysis. The above alcohol (32.2 g, 82.4 mmol) in 200 ml benzene with p-toluenesulfonic acid (0.3 g, 1.58 mmol) was refluxed for 30 minutes. Upon cooling, the starting alcohol was recovered: 20 g (62%); mp 179-180°.
Method B. Acetic Anhydride. The above alcohol (1.03 g, 2.6 mmol) in 20 ml acetic anhydride was refluxed for 30 minutes. Excess solvent was removed in vacuo. The residue was suspended in 400 ml of ether and carefully washed with 10% sodium bicarbonate solution. The organic layer was concentrated and tlc (ethyl acetate-cyclohexane) indicated six components. The reaction products were not determined!

Method C. Strong Base. Alcohol 3 (1.0 g, 2.5 mmol) and potassium t-butoxide (0.3 g, 2.5 mmol) in redistilled t-butyl alcohol (25 ml) were refluxed for 1.5 hours. Upon cooling, a red salt was collected. Treatment of this salt with water afforded unreacted starting material.

Method D. Aqueous Acid. Alcohol 3 (1.0 g, 2.5 mmol) was refluxed in 75 ml of 5% hydrochloric acid for 7.5 hours. After neutralization with sodium carbonate, the mixture was extracted with chloroform. Removal of solvent quantitatively returned starting compound, which recrystallized from ethanol gave 4: 700 mg (70%); mp 179-180°.

2,5-Diphenyl-3,4-di(2-pyridyl)cyclopentadieneone (10). Alcohol 3 (960 mg, 2.4 mmol) in 10 ml HMPA was refluxed 1 to 5 minutes. The solvent was removed by vacuum distillation at 55° (0.15 mm). The residue was recrystallized from benzene-petroleum ether-8 to afford 680 mg (67%) of dark red 10: mp 197.5-198.5°; nmr (CDCl3) δ 6.5-8.8 (arom-H, m); ir (nujol) 1715 (C=O), 1580, 1560, 1115, 1085, 991, 824, 794, 758, 752, 713, and 694 cm⁻¹; uv (MeOH) 250 nm (18,950); vis (MeOH) 493 nm (643).

Anal. Calcd for C27H18N2O: C, 83.92; H, 4.70; N, 7.25. Found: C, 83.59; H, 4.50; N, 7.08.
1,2-Di(2-pyridyl)-3,4,5,6-tetraphenylbenzene (18). 2,5-Diphenyl-3,4-di(2-pyridyl)cyclopentadieneone (510 mg, 1.3 mmol) and diphenylacetylene (500 mg, 2.81 mmol) were mixed thoroughly and heated to ca. 300° using an electrically heated sand bath. The mixture reacted with strong evolution of gas and crystals formed. After cooling, the product was washed with acetone and collected by filtration: 560 mg (83%); mp (DTA) 468°; ir (nujol) 1580, 792, 747, 734, and 697 cm⁻¹.

Anal. Calcd for C₄₀H₂₈N₂: C, 89.52; H, 5.26; N, 5.22.
Found: C, 89.69; H, 5.05; N, 5.17.

1,4-Diphenyl-2,3,5,6-tetra(2-pyridyl)benzene (30). 2,5-Diphenyl-3,4-di(2-pyridyl)cyclopentadieneone (250 mg, 0.65 mmol) and di(2-pyridyl)acetylene (250 mg, 1.39 mmol) were mixed thoroughly and heated to ca. 300° (sand bath) for several minutes. After cooling, the product was washed with acetone and collected: 120 mg (34%); mp (DTA) 479°; ir (nujol) 1575, 1550, 800, 744, and 697 cm⁻¹.

Anal. Calcd for C₃₈H₂₆N₄: C, 84.73; H, 4.87; N, 10.40.
Found: C, 84.44; H, 4.59; N, 10.32.

3-(2-Pyridyl)phenylpropan-2-one (32). To a previously prepared solution of phenyllithium (0.5 mol) in 400 ml ether, 2-picoline (44.7 g, 0.48 mol) was added over 10 minutes and then refluxed 30 minutes. Phenylacetonitrile (21.4 g, 0.183 mol) was introduced as rapidly as reaction permitted. After reflux for 2.5 hours, the reaction mixture was carefully poured into concentrated hydrochloric acid. The organic layer was separated and extracted with additional hydrochloric acid. Acidic extracts were refluxed 2 hours, cooled, and the pH adjusted with a 40% sodium hydroxide solution to ca. 7.5 (hydrion

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Extraction with ether was followed by extraction with chloroform. The organic extracts were combined, dried over sodium sulfate, and concentrated in vacuo. Fractional vacuum distillation of the residual oil afforded 10.94 g (28%) of \(2\), bp 167-173° (3.5 mm) [lit. 3 bp 140-142° (3 mm)], nmr (CDCl\(_3\)) - Exists at 22% enol - 6 3.56 (Ph-CH\(_3\)- of enol), 3.79 (Ph-CH\(_2\)CO), 3.9 (pyr-CH\(_2\)CO), 5.25 (vinyl-H) 6.65-7.75 (arom-H and -OH), 7.97-8.17 (6-pyr-H of enol), 8.42-8.66 (6-pyr-H); ir (neat) 1720 (C=O), 1650 (C=O, enol) 1600, 1470, 1150, 800, 752, 735, and 702 cm\(^{-1}\).

\(2,3,4\)-Triphenyl-5-(2-pyridyl)cyclopentadieneone (2). \(3-(2\)-Pyridyl)phenylpropan-2-one (5.8 g, 27.5 mmol) and benzil (5.2 g, 24.8 mmol) in 30 ml 95% ethanol were heated to reflux. A solution of potassium hydroxide (700 mg, 12.5 mmol) in 10 ml of 95% ethanol was introduced dropwise. After heating an additional 15 minutes, the mixture was diluted with ca. 10 ml water, and after 48 hours afforded 6.72 g (67%) of a crude orange intermediary alcohol, mp 145-190° (d). Since this alcohol could not be purified, it was suspended in 30 ml triethylene glycol and warmed slowly with stirring to 195°. After allowing to stand several hours, the mixture was diluted with an equal volume of methanol. The crystals were filtered and washed with methanol to afford 2.93 g (31% overall) of the dark red crystalline 2; mp 220-221°; nmr (CDCl\(_3\)) \(\delta\) 6.8-7.8 (arom-H, m, 18H), 8.43-8.54 (6-pyr-H, m, 1H); ir (nujol) 1685 (C=O), 1290, 794, 742, 708, and 693 cm\(^{-1}\); uv (MeOH) 290 (13,100) and 241 nm (13,900); vis (MeOH) 443 nm (12,940).

**Anal.** Calcd for C\(_{28}\)H\(_{19}\)NO: C, 87.25; H, 4.97; N, 3.64. Found: C, 86.96; H, 4.88; N, 3.50.
1,2,3-Triphenyl-4,5,6-tri(2-pyridyl)benzene (12). 2,3,4-
Triphenyl-5-(2-pyridyl)cyclopentadieneone (400 mg, 1 mmol) and di(2-
pyridyl)acetylene (400 mg, 2.2 mmol) were heated via bunsen burner
until completely melted. The mixture was recrystallized from diphenyl
ether (bp 259°), and after dilution with benzene afforded 420 mg (75%) of a crude brown solid: mp > 300°. Recrystallization (decolorization
with charcoal) from xylene-chloroform and dilution with petroleum ether-A
gave 350 mg of a fine yellow powder of 12: mp (DTA) 473°; ir (nujol)
1580, 1550, 793, 745, 737, and 698 cm⁻¹.
Anal. Calcd for C₃₃H₂₇N₃: C, 87.12; H, 5.06; N, 7.82.
Found: C, 86.98; H, 4.69; N, 7.77.

1,2,3,4,5-Pentaphenyl-6-(2-pyridyl)benzene (17). 2,3,4-
Triphenyl-5-(2-pyridyl)cyclopentadieneone (350 mg, 0.91 mmol) and di-
phenylacetylene (450 mg, 2.53 mmol) were mixed intimately and slowly
heated to 315° using an electrically heated sand bath. The heat source
was removed and the melt allowed to cool to room temperature. Tritura-
tion with acetone afforded almost colorless crystals of 17: 220 mg
(45%); mp (DTA) 466°; ir (nujol) 1580, 784, 731, and 695 cm⁻¹.
Found: C, 91.82; H, 5.25; N, 2.50.

2-Pyridylacetonitrile (37). 2-Picoline N-oxide (55 g, 0.5
mol) in benzene (400 ml) was brought to reflux under a nitrogen atmos-
phere. Benzenesulfonyl chloride (88 g, 0.5 mol) in benzene (100 ml)
was introduced slowly over 1 hour. After the addition was complete,
reflux was continued for another 1.75 hours. The cooled mixture was
extracted with 5% hydrochloric acid. Acidic extracts were made basic with solid sodium carbonate and extracted with ether and then chloroform. The organic extracts were combined, washed with water, dried over sodium sulfate, and concentrated in vacuo. The residue was dissolved in ethyl acetate and decolorized by rapid filtration through a small column of silica gel. Removal of the solvent afforded 29 g of an oil. An nmr spectrum of this oil indicated that it was predominantly (77%) 2-chloromethylpyridine (36): nmr (CDCl₃), 4.67 (pyr-CH₂-, s, 2H), 7.0-7.9 (pyr-H, m, 3H), 8.5-8.7 (6-pyr-H, m, 1H).

This compound was not purified further, but immediately dissolved in 125 ml DMSO and added over 1 hour to a stirred mixture of potassium cyanide (25 g, 0.382 mol) in 125 ml DMSO. After allowing the mixture to react overnight at 39°, the mixture was poured into water containing a small amount of sodium carbonate. Extractions with ether and then chloroform were washed with water, combined, dried over sodium sulfate, and concentrated in vacuo. The residual oil was fractionally distilled at reduced pressure to afford 15.6 g (26% overall) of 38: bp 94-100° (3 mm) [lit.⁵ bp 118-120° (13 mm)]; nmr (CDCl₃) δ 3.9 (pyr-CH₂-, s, 2H), 6.95-8.10 (pyr-H, m, 3H), 8.4-8.6 (6-pyr-H, m, 1H); ir (neat) 2220 (C=N), 1585, 1490, 1470, 1445, 1235, 759, and 694 cm⁻¹.

1,3-Di(2-pyridyl)propan-2-one (33).⁶ To a previously prepared solution of phenyllithium (0.3 mol) in 200 ml ether, 2-picoline (28 g, 0.3 mol) was added then refluxed 30 minutes. After cooling to room temperature, 2-pyridylacetonitrile (9.98 g, 84.5 mmol) in 50 ml ether was introduced dropwise over 1 hour and refluxed an additional
l.5 hours. After allowing to stir at room temperature overnight, the mixture was carefully poured into cold concentrated hydrochloric acid. The ether phase was separated and washed with additional acid. The acidic extracts were refluxed 1 hour, cooled, and adjusted with a 40% sodium hydroxide solution to pH ~ 8 (hydrion paper). After numerous extractions with chloroform, these were combined, dried over sodium sulfate, and concentrated in vacuo to afford a residual oil, which was distilled to give 6.96 g (39%) of crude [bp 155-195° (0.7 mm) [lit. 6 bp 130-135° (0.05 mm)]; dipicrate mp 210° (d) (lit. 6 dipicrate mp 191-191.5°).

**Anal. for dipicrate:** Calcd. for C₂₅H₁₈N₁₀O₁₅: C, 44.78; H, 2.71; N, 16.72. Found: C, 44.98; H, 2.62; N, 16.77.
REFERENCES FOR APPENDIX II

James Michael Robinson was born October 13, 1945, in Shreveport, Louisiana. He attended public schools in that city and graduated from Fair Park High School in 1961. That same year he entered Louisiana Polytechnic Institute (now Louisiana Tech University), and after an absence of one year (1965) returned to that College for additional study. He was awarded a B.S. in Chemistry in 1967, and an M.S. in Chemistry in 1969. While pursuing the advanced degree at Louisiana Tech he held a Teaching Assistantship, but during the two summers was employed with Dow Chemical Company, Plaquemine, Louisiana, and with Continental Can Company, Hodge, Louisiana. He began additional graduate work at Louisiana State University in Baton Rouge in 1969, and married Mary Ann Williams in August, 1970. From 1969 to 1971 at Louisiana State University, he was employed as a Teaching Assistant. In 1971 he was appointed to Research Assistant under a National Institute of Health grant. Currently, he is a candidate for the Doctor of Philosophy degree with a major in Organic Chemistry and a minor in Analytical Chemistry. He has accepted a Postdoctoral Research Position at Purdue University, Lafayette, Indiana, to begin in the Fall of 1973.
EXAMINATION AND THESIS REPORT

Candidate: J. Michael Robinson

Major Field: Chemistry

Title of Thesis: 2, 6-Pyridinophanes and Related Heteromacrocycles

Approved:

[Signature]
Major Professor and Chairman

[Signature]
Dean of the Graduate School

EXAMINING COMMITTEE:

[Signature]

[Signature]

[Signature]

Date of Examination: September 10, 1973