1979

Organometallic Reactions on Heterocyclic Compounds.

Jerry Monroe Roper

Louisiana State University and Agricultural & Mechanical College

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ORGANOMETALLIC REACTIONS ON HETEROCYCLIC COMPOUNDS

The Louisiana State University and Agricultural and Mechanical Col.

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Organometallic Reactions on Heterocyclic Compounds

A Dissertation

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

in

The Department of Chemistry

by

Jerry Monroe Roper
B.S., University of Georgia, 1974
December 1979
Candidate: Jerry Monroe Roper

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Title of Thesis: Organometallic Reactions on Heterocyclic Compounds

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Dean of the Graduate School

EXAMINING COMMITTEE:

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Date of Examination:

November 28, 1979
Warmly Dedicated to

Lisa, Maris, and Hulert
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Organometallic reagents were employed in the synthesis of desired heterocyclic compounds. Metal acetylides such as acetylenebis(magnesium bromide), sodium acetylide, and lithium acetylide ethylenediamine complex were evaluated for use in the preparation of acetylene-diols that contain an azafluorenone subunit. 9,9'-Ethynylenebis-4,5-diazafluoren-9-ol \((\text{IIa})\) was prepared by treatment of 4,5-diazafluorenone \((\text{Ia})\) with sodium acetylide. The insolvability of 9,9'-ethynylenebis-4,5-diazafluoren-9-ol prohibited conversion to the corresponding cumulene, 1,4-bis(diazabiphenylene)butatriene.

A low valent titanium reagent generated from either titanium trichloride-lithium aluminium hydride \((\text{TiCl}_3-\text{LAH})\) or titanium trichloride-sodium \((\text{TiCl}_3-M)\) was employed to reductively couple a series of heterocyclic ketones to the corresponding olefins. 3-Benzoylpyridine was treated with \text{TiCl}_3-\text{LAH} to afford the \(E\) and \(Z\) isomers of 1,2-diphenyl-1,2-bis(3'-pyridyl)ethene \((\text{IIIa})\). An NMR H\(_\alpha\)-shift study confirmed the identity of each isomer. 4,5-Diazafluorenone was treated with the low valent titanium reagent to afford bis(4,5-diazafluorenylidene) \((\text{IVa})\). \text{TiCl}_3-\text{LAH} produced reductive coupling between an equal molar mixture of 4,5-diazafluorenone and 9-fluorenone to give an unsymmetrical olefin, 4,5-diazafluorenylidenefluorene \((\text{IIIb})\). If the heterocyclic ketone possessed a site of metal complexation, a titanium chelated intermediate forms. This chelated intermediate pursued an alternate reaction pathway and predominately affords the product of simple reduction and other coupled products. Phenyl 2-pyridyl ketone afforded
phenyl(2-pyridyl) methanol and 1,2-diphenyl-1,2-bis(2'-pyridyl)ethane (123a), when treated with the low valent titanium reagent. Likewise, bis(2-pyridyl) ketone afforded bis(2-pyridyl) methanol, under the same conditions.

The preparation of onychine (4-methyl-1-azafluorenone), an alkaloid derived from the trunk wood of Onychopetalum amazonicum (Annonaceae), was attempted starting from 1-azafluorenone. Spiro[9H-indeno[2,1-b]pyridine]-9,2'-[1,3]-dioxolane (136), prepared by ketalization of 1-azafluorenone using standard methods, was treated with lithium dimethylcupper in an attempt to methylate the 4-position of the pyridine ring via a 1,4-addition. The azafluorene moiety is resistant to this type of addition.

Cyclometalation of 2-phenylpyridine was attempted using n-butyllithium as the metalating agent. Treatment of 2-phenylpyridine with n-butyllithium at temperatures ranging from -20°C to -90°C afforded a competition between ortho-metalation of the phenyl ring and α-addition of n-butyllithium to the pyridine ring.

2,6-Dilithiopyridine was prepared by treating 2,6-diido- or 2,6-dibromopyridine with excess n-butyllithium in tetrahydrofuran (THF). The 2,6-dilithiated intermediate was trapped with the following electrophiles: carbon dioxide, dimethyl disulfide, and deuterium oxide. 2,6-Diodopyridine was prepared by treating either 2,6-dibromo- or 2,6-dichloropyridine with excess sodium iodide in refluxing hydroiodic acid.

Heterocyclic acetylenes were prepared by either a dehydrohalogenation reaction or a substitution reaction employing a catalyst, dichlorobis(triphenylphosphine)palladium(II)-copper(I) iodide (153).
bis[2-(6-Methyl)pyridyl]acetylene (166b) was prepared by treating 1,2-di[2'-(6'-methyl)pyridyl]1,2-dibromoethane (164b) with refluxing alcoholic potassium hydroxide. bis[2-(Bromo)pyridyl]acetylene (159) was prepared by treatment of 2,6-dibromopyridine with the catalyst 153 and acetylene in triethylamine. Treatment of 2,6-dibromopyridine with the catalyst 153 and acetylene in diethylamine afforded 1,2-bis[2'-(6'-bromo)pyridyl]ethanol (160). A mechanism involving prior formation of acetylene, addition of solvent, diethylamine, and subsequent hydrolysis is postulated to account for this product.

The preparation of acetylenes 159 and 166b allowed the synthesis of an ortho-cyclophane, which contains the 2,6-pyridino subunit. Treatment of acetylenes 159 and 166b with 2-pyrone afforded 1,2-bis[2'-(6'-bromo)pyridyl]benzene (67a) and 1,2-bis[2'-(6'-methyl)pyridyl]benzene (67b), respectively. Bromination of 67b with N-bromosuccinimide (NBS) afforded 1,2-bis[2'-(6'-bromomethyl)pyridyl]benzene (167), which was cyclized using sodium sulfide nanohydrate in ethanol under high dilution conditions to give 2-thia[3.0.0](2,6)pyridino(1,2)-benzeno(2,6)pyridinophane (168).
Introduction

Organometallic reagents are perhaps some of the most useful synthetic tools available to chemists. These versatile reagents were utilized in this research endeavor to prepare desired heterocyclic compounds or to produce a synthetically useful heterocyclic intermediate. While the structure of organometallic reagents and mechanism of these reactions in solution are of interest, the main thrust of this work was synthetic. The structure and mechanism of organometallic reagents are dealt with in detail in the literature.1 Organometallic reactions were performed on a variety of heterocyclic substrates, and involved diverse types of organometallic reagents. In order to present these reactions and syntheses in a logical fashion the Introduction is divided into the following sections: I. Preparation of Acetylene-Diols, Cumulenes, and Olefins; II. Metallation of Heterocyclic Compounds; and III. Synthesis of Acetylenes and Related Compounds. As well as discussing the synthesis of the title compounds, Section I also introduces the azafluorenones, ketones which played a significant role in the preparation of heterocyclic acetylene-diols and olefins. Section II considers cyclometallation reactions and metallation of haloheterocycles. Section III discusses synthetic routes available to prepare acetylenes and introduces cyclophane chemistry, since the acetylenes are convenient starting material for their preparation.
I. Preparation of Acetylene-Diols, Cumulenes, and Olefins.

Azafluorenone, particularly 4,5-diazafluorenone (1), 1,8-diazafluorenone (2), and 1-azafluorenone (3), were the starting heterocyclic ketones in several synthetic routes involving organometallic reagents.

Prior to 1974 these compounds were only accessible with difficulty by a base-induced benzylic acid rearrangement of the appropriate azaphenanthrenequinone, which is prepared via a tedious sequence involving a Skraup synthesis.\(^2\) Azaphenanthrenequinones are only slightly more accessible as by-products from nitration of the azaphenanthrene.\(^3\) Alkaline work-up of these nitration reactions afforded the desired ring-contracted ketones. Thus, 1,10-phenanthroline (4) gave predominantly 5, when treated with a nitrating mixture.\(^3b\)

Then in 1974, Ekhard and Summers\(^4\) reported the preparation of 1\(^6\) in 20\% yield as a by-product of the permanganate oxidation of 1,10-phenan-
throleine (H), whereas the major product was the dicarboxylic acid (⁶). Preparation of 3 was soon reported from the permanganate oxidation of 5,6-benzoquinoline.⁵ Since the report of Eckard and Summers,⁴ the reaction conditions for the preparation of 1, 2, and 3 have been optimized, and these ketones are presently obtainable in 55 to 80% yield.⁶ Ketone 2 can be prepared by a very convenient method: base-induced benzylic acid rearrangement of 4,7-phenanthroline-5,6-quinone (Phanquone).²

Ketones 1, 2, and 3 could be connected via unsaturated bridges to afford cumulene ⁷, acetylene-diol ⁸, and olefin ⁹.

R in each of these cases represents the heterocyclic moiety, for example ¹⁰ and ¹¹.

Impetus for the preparation of these compounds (⁷, ⁸ and ⁹) and the long range goal of this particular project were to determine the com-
plexing abilities of the cumulenes, acetylene-diols, and olefins. Since these compounds possess nitrogen heteroatoms, which are capable of subsequent complexation and a site of unsaturation, two modes of metal complexation should be possible. Metal complexation could involve the lone pair of electrons on nitrogen and/or the pi electrons of the unsaturated bridge. The type of metal ion complex produced by the ligand was of interest. For example, how would complexation affect the character of the unsaturated bridge, and if two sites of complexation existed, could the heterocyclic ligand accommodate two metal atoms? The fact that compound types such as $\mathcal{A}$, $\mathcal{B}$, and $\mathcal{C}$ are reported only infrequently in the literature provided further impetus to devise improved routes or conditions for their synthesis. There are only a few reports of acetylenic compounds that possess a pyridyl subunit$^7$ and prior to Newkome, Sauer, and Erbland's$^8$ work in 1974, there were no reports of cumulenes that contained the pyridyl moiety.

The majority of synthetic routes to prepare cumulenes $\mathcal{A}$ involve reduction of the corresponding acetylene-diols, which are accessible by reaction of a metal acetylide with a ketone or aldehyde (Scheme I).
Edinger and Day\textsuperscript{9} prepared acetylene-diol \textsuperscript{12} and cumulene \textsuperscript{13} in unspecified yield. They employed acetylenebis(magnesium bromide),\textsuperscript{10} prepared by the Zerevitch method,\textsuperscript{11} which generates the acetylenic reagent by passage of acetylene through a solution of methyl- or ethylmagnesium bromide. Bergmann, Hoffman, and Winter\textsuperscript{10} also reported the use of acetylenebis(magnesium bromide) in the preparation of acetylene-diol.

Alternate organometallic reagents, such as sodium acetylide, can be generated by the "dissolving metal" technique.\textsuperscript{12} In tetrahydrofuran (THF) sodium metal can donate an electron to an acceptor, such as biphenyl or naphthalene, thus producing the brightly colored radical anion and sodium ion. Passage of acetylene through such a solution produces a colorless slurry of sodium acetylide. Nahon and Day\textsuperscript{12} treated benzophenone with sodium acetylide generated by this method to obtain 1,1,4,4-tetraphenylbutyne-1,4-diol.

Another alternate method to produce acetylene-diols was the \textit{in situ} generation of sodium acetylide.\textsuperscript{13} 1,2-Dibromoethane in hexamethylphosphorus triamide (HMPT) was treated with sodium amide. A di-dehydrobromination occurred to produce acetylene, which was subsequently metallated by the sodium amide. This route, however, was not a particularly viable method for the preparation of heterocyclic acetylene-diols because of the marginal yields.
Finally, the production of acetylene-diols was accomplished via lithium acetylde ethylenediamine complex (I\textsubscript{4}).\textsuperscript{14}

\[ \text{LiC} \equiv \text{CH} \cdot \text{H}_2\text{N(C}_2\text{H}_4)_2\text{NH}_2 \]

Monolithium acetylide can be prepared in liquid ammonia (-33°C). Attempts to isolate this metal acetylide resulted in disproportionation to afford dilithium acetylide and acetylene.\textsuperscript{15} Therefore, the liquid ammonia imparts stability to monolithium acetylide. By contrast, ethylenediamine stabilizes monolithium acetylide over a broader range of temperature. Lithium acetylide ethylene-diamine complex, a near colorless crystalline complex, is stable to 45°C.\textsuperscript{14a} An appropriate analogy to this stabilizing effect of ethylenediamine is the ability of tetramethylethylenediamine (TMEDA) to stabilize poly lithiated compounds.\textsuperscript{16}

At first glance reagent I\textsubscript{4} might be expected to afford only terminal acetylenes. However, Beumel and Harris\textsuperscript{14b} noted that in solvents of low dielectric constant the major product of reaction of acetylde I\textsubscript{4} with an aryl ketone was internal acetylene I\textsubscript{6}.

\[
\begin{align*}
\text{R} & \equiv \text{O} \xrightarrow{\text{I}_4} \text{R} - \text{C} \equiv \text{CH} \xrightarrow{\text{R}_2\text{CO}} \text{R} - \text{C} \equiv \text{C} - \text{R} \\
\text{I}_5 & \uparrow \\
\text{I}_6 & \uparrow
\end{align*}
\]

These results were rationalized as ethynylation of a carbonyl unit to afford the initial terminal acetylene I\textsubscript{5}, which was subsequently lithiated by acetylde I\textsubscript{4}. The anion of I\textsubscript{5} reacted with a second carbonyl unit to give acetylene I\textsubscript{6}. In better solvating solvents, ethynylation of a single carbonyl unit occurs to afford the terminal acetylene I\textsubscript{5}. Thus the choice of solvent greatly influences the course of the reaction.
These organometallic reagents, acetylenebis(magnesium bromide), sodium acetylide, and lithium acetylide ethylenediamine complex were investigated in the preparation of the desired heterocyclic acetylene-diols, which are convenient precursors to cumulenes. Cumulenes are generally prepared by reduction of acetylene-diols with stannous chloride-hydrogen chloride. Other alternate reagents more often encountered are sulfuric acid-potassium iodide, hydrochloric acid-iodine in acetic acid, and phosphorus tribromide-pyridine. The reagent utilized in this work was diphosphorus tetraiodide. This reagent was employed because previous workers had successfully prepared cumulenes containing a pyridyl moiety, for example both the and isomers of via application of diphosphorus tetraiodide.

Newkome, Sauer, and Erbland reported the use of diphosphorus tetraiodide in the conversion of butyne-diol to cumulene. Diphosphorus tetraiodide was the reagent of choice because 1,4-butyne-diol undergoes an acid-catalyzed rearrangement to quinolizinone. Utilization of diphosphorus tetraiodide avoided the use of acidic conditions.
Butyne-diol \(8\) was subject to this rearrangement even under such mildly acidic conditions as refluxing ethanol.\(^8\) The acetylene-diols (e.g. \(11\)) containing azafluorenone subunits should be structurally prevented from undergoing this type of acid-catalyzed rearrangement.

Acetylene-diol \(8\) and cumulene \(7\) have two carbon atoms in their unsaturated bridge that connects the heterocyclic subunits. By contrast in olefin \(9\), the heterocyclic moieties are directly connected. In order to prepare compounds of this type, the carbonyl carbons of two azafluorenone molecules would have to be joined and deoxygenated. Thus, a reductive coupling of these carbonyl units would have to occur. McMurry\(^22\) and Mukaiyama\(^23\) have reported the use of a low valent titanium reagent that accomplishes reductive coupling of carbonyls on a variety of substrates in one step.

McMurry has employed low valent titanium generated from primarily titanium trichloride and lithium aluminium hydride (TiCl\(_3\)-LAH), "McMurry's reagent".\(^22\) Another source of low valent titanium, produced by the reduction of titanium tetrachloride by zinc, is sometimes referred to as "Mukaiyama's reagent".\(^23\) The titanium reagent has also been prepared by alkali metal reduction of titanium trichloride or titanium tetrachloride.\(^25\),\(^27\) Therefore, there are numerous available means of reducing titanium(III) or (IV) to the active reagent titanium(0).\(^26\)

The low valent titanium reagent is very versatile and produces reductively coupled products in a remarkable number of substrates. Aryl ketones and aldehydes have been reductively coupled in good yield. For example, 9-fluorenone was coupled to give bis(fluorenylidene)
Benzophenone when treated with low valent titanium afforded tetraphenylenes (23)\(^{22}\) and benzaldehyde was reductively coupled to give trans-stilbene (25)\(^{22}\).

Cyclic as well as linear alkyl carbonyls have also been reductively coupled to yield the corresponding olefins. Cyclohexanone afforded 26 and valeraldehyde gave a mixture of the E and Z isomers of decene 29, when treated with the titanium reagent.\(^{27}\)

Even highly hindered carbonyl compounds are coupled in the presence of low valent titanium. Tetraisopropylethene was produced when isopropyl ketone was treated with TiCl\(_3\)-LAH.\(^{28}\) Other hindered molecules synthesized by this method were adamantylideneadamantane,\(^{22}\) 4,4'-homo-
adamantylidenehomoadamantane, and 2-bornylidenebornane. Low valent titanium has also been utilized to prepare both large and small rings by intramolecular reductive coupling. 1,2-Diphenylcyclobutene \((30)\) was prepared by treatment of \(30\) with McMurry's reagent. Macrocycle \(33\) was obtained by treating diketone \(32\) with titanium trichloride-zinc/copper.

![Chemical structures](image)

These examples demonstrate the range of cyclic compounds prepared by this method. As a final example to point out the versatility of low valent titanium, sensitive substrates have been reductively coupled. \(\beta\)-Carotene was prepared from retinal and Corey prepared a series of compounds related to gibberellic acid by using low valent titanium.

If the appropriate carbonyl substrates are chosen, mixed reductive coupling can occur. McMurry reductively coupled 9-fluorenone and acetophenone to give \(34\).

![Chemical structure](image)

This mixed coupling was produced because 9-fluorenone is a better
electron acceptor than acetophenone.\textsuperscript{35} Therefore, low valent titanium transfers two electrons to 9-fluorenone to produce an anion at the 9-position, which condenses in an aldol fashion with acetophenone.\textsuperscript{34}

Upon examining the differing abilities of 9-fluorenone and 4,5-diazafluorenone to accept electrons, one observes that 4,5-diazafluorenone is a far better electron acceptor. Evans\textsuperscript{36} calculated the equilibrium constant (K) for the disproportionation reaction of a series of fluorenone radicals (Eq. 1).

\begin{equation}
\text{M}^+\text{RI}^- + \text{M}^+\text{RI}^- \xrightleftharpoons{K} 2\text{M}^+ + \text{DI}^- + \text{NC} \tag{Eq. 1}
\end{equation}

Eq. 1, where RI represents a radical anion, DI represents a dianion, and NC is a neutral compound, describes the disproportionation equilibrium between a radical anion and corresponding dianion. If M\textsuperscript{+}, the metal, is lithium, then K for 9-fluorenone is 0.025, but for 4,5-diazafluorenone K is 381;\textsuperscript{36} i.e. 4,5-diazafluorenone has a much greater ability to accept electrons than 9-fluorenone. In a reaction where substrates compete for electrons, the dianionic form of 4,5-diazafluorenone and the neutral form of 9-fluorenone predominate. Therefore, one would predict that these ketones would yield an unsymmetrical olefin when treated with TiCl\textsubscript{3}-IAH.

The above examples should clearly demonstrate the variety of carbonyl substrates reductively coupled by this reagent. However, until this research there were no reported uses of low valent titanium to reductively couple any heterocyclic carbonyl compound.

Organometallic reagents were utilized to transform heterocyclic ketones into the desired cumulenes, acetylene-diols, and olefins.
Heterocyclic ketones treated with metal acetylides afforded heterocyclic acetylene-diols, which are precursors of the corresponding cumulenes. The reduced metal reagent, low valent titanium, conveniently couples appropriate heterocyclic ketones to give the desired olefin.
II. Metallation of Heterocyclic Compounds.

The preparation of cumulenes, acetylene-diols, and olefins employed organometallic reagents or a metal reagent to form new carbon-carbon bonds in heterocyclic substrates. While the formation of new carbon-carbon bonds is an important transformation produced by these reagents, organometallic reagents can also be used to produce a metallated heterocyclic intermediate which is synthetically useful. Metallation of heterocycles was explored using 2-phenylpyridine and 2,6-dihalopyridine. The nitrogen atom played an important directive role in the metallation of 2-phenylpyridine. This heteroatom was utilized to direct the metallating reagent to the ortho-position of an aromatic nucleus. Metallation of dihalopyridines provided a method of introducing substituents onto a pyridyl ring. These metallated compounds are also useful synthetic intermediates.

Directed metallation, cyclometallation, or ortho-metallation refers to a class of reactions where a heteroatom guides a metal, quite often a transition metal, to a specific site on a ligand where a carbon-metal bond forms. Parshall, Bruce, Omae, and Dehand and Pfeffer have reviewed these cyclometallation reactions. Use of the term cyclometallation, first introduced by Trofimenko, arises because the metal, heteroatom, and the site to be metallated form a generally five-membered chelate ring. This cyclic arrangement of atoms is illustrated, where M is the metal, D represents the heteroatom or donor atom, and C is the metallated carbon.
Ortho-metallation is a more specific term and refers to the guiding of a metal to the ortho-position of an aromatic nucleus. These terms are often applied to transition metals, but alkali metals also undergo this type of reaction. One of the early examples of directed metallation was reported by Kleinman and Dubeck. Dicyclopentadienyl nickel was treated with azobenzene to afford complex 36.

\[
\begin{aligned}
 &\text{Ph} \\
 &\text{Ni} \\
 &\text{Ph}
\end{aligned}
\]

The most commonly encountered heteroatom that participates in this type of reaction is nitrogen. Cope and Friedrich outlined the conditions necessary for nitrogen to cyclometallate. These conditions, modified slightly by Dehand and Pfeffer, require the chelate ring to contain five atoms, the nitrogen to be sterically hindered, and if the metal is palladium or platinum, the reaction to proceed by electrophilic attack. Complexes 37, 38, and 39 are examples of compounds formed by directed metallation involving nitrogen.

\[
\begin{aligned}
 &\text{Ph} \\
 &\text{Pd} \\
 &\text{Cl} \\
 &\text{N} \\
 &\text{(CH}_2)_2 \\
 &\text{Ph}
\end{aligned}
\]

\[
\begin{aligned}
 &\text{Ph} \\
 &\text{Pd} \\
 &\text{N} \\
 &\text{Ph}
\end{aligned}
\]

\[
\begin{aligned}
 &\text{Ph} \\
 &\text{N} \\
 &\text{Pd} \\
 &\text{Ph}
\end{aligned}
\]

Phosphines are also capable of producing cyclometallation. Unlike nitrogen where the chelate ring must contain five atoms, phosphorus is
capable of forming four membered rings. Phosphine complexes $\text{H}_3\text{P}$ and $\text{H}_4\text{P}$ demonstrate the ability of phosphorus to form both four and five membered chelate rings, respectively.

Other donor atoms capable of producing directed mettallation are arsenic, sulfur, and oxygen.

The above examples of cyclometallation involve a transition metal. There are, however, examples of alkali metals undergoing similar types of reaction. A difference between cyclometallation involving an alkali metal and transition metal is the reactivity of the carbon-metal bond. The alkali metal-carbon bond is very reactive and this complex cannot generally be isolated but must be trapped by an electrophile in order to prove the existence of a metallated intermediate. For example, 2-ferrocenylpyridine was treated with n-butyllithium, then the intermediate $\text{Li}$ was trapped with benzaldehyde to afford, after hydrolysis, 2-[hydroxy(diphenyl)methylferrocenyl]pyridine, and 2-butyl-6-[hydroxy(diphenyl)methylferrocenyl]pyridine, the product of metallation and $\alpha$-addition of n-butyllithium to pyridine, respectively.

Directed mettallation on an aryl ring using alkali metals is a
regioselective method to introduce substituents onto an aromatic ring. Meyers\textsuperscript{49} reported the ortho-lithiation of aryl oxazolines, in which treatment of oxazoline $\text{43}_b$ with n-butyllithium and subsequent trapping with deuterium oxide afforded $\text{45}_a$. Coordination of the electron pair of nitrogen with n-butyllithium prior to metallation directed the lithiating agent to the ortho-position of the phenyl ring. The directed lithiation of a pyridine analog has also been reported.\textsuperscript{50} When pyridyl oxazoline $\text{43}_b$ was treated with methyl-lithium at $-78^\circ\text{C}$, lithiation of the 3-position occurred to give $\text{44}_b$. Other alternate lithiating agents, such as n-butyllithium, sec-butyllithium, tert-butyllithium, and lithium diisopropyl amide, afforded products arising from a 3-lithiopyridine derivative and $\alpha$-addition to the pyridine ring. Methyllithium, however, did not exhibit the competition between $\alpha$-addition and metallation and afforded almost a quantitative yield of 3-lithiopyridine. The lithiated intermediate $\text{44}_b$ was trapped with deuterium oxide to afford $\text{45}_b$.\textsuperscript{50}

\[
\begin{array}{c}
\text{43} \\
\text{44} \\
\text{45}
\end{array}
\]

\[
\begin{aligned}
a. X &= \text{CH} \\
b. X &= \text{N}
\end{aligned}
\]

Slocum and Jennings\textsuperscript{51} investigated the ortho-lithiation of a series of para-substituted anisoles. They compared the directing ability of various groups to the directing ability of the oxygen of anisole and then ranked them as either more or less effective directors than anisole.
The above examples of cyclometallated compounds demonstrate that metallation of a specific site on a ligand can be accomplished by utilizing a heteroatom functionality. The examples of cyclolithiated compounds show that these metallated intermediates are also synthetically useful. By wisely choosing the appropriate trapping agent, substituents can be introduced to a specific site on a ligand.

Cyclometallated compounds are an interesting class of heterocyclic organometallic compounds, which extend the synthetic utility of heterocyclic substrates. The synthetic usefulness of heterocyclic substrates, such as pyridine, could be expanded by the generation of a dimetallated intermediate, e.g. dilithiated pyridine. This intermediate would increase the synthetic usefulness of the pyridine nucleus by allowing the substituents to be introduced at two ring positions. Before this work, attempts to dimetallate pyridine resulted in the isolation of products arising from either a monometallated intermediate, as was the case with dibromopyridines, or in the recovery of unchanged starting material, as with dichloropyridine.

When Gilman and Spatz \(^{52}\) attempted to generate a pyridine dianion from isomeric dibromopyridines, they isolated only products due to a single metal-halogen exchange. 2,6-Dibromo- or 3,5-dibromopyridine was treated with excess n-butyllithium in diethyl ether at temperatures ranging from -30°C to -10°C and varying lengths of reaction time. In each case, after carboxylation to trap any intermediates, only monocarboxylated products (\(\text{H}_2\text{L}\)) were isolated. \(^{52}\)
Holm, citing Gilman's study that dibromopyridines undergo only monolithiation in diethyl ether, generated 6-lithio-2-bromopyridine (46) from 2,6-dibromopyridine upon treatment with n-butyllithium. Utilization of 46 to prepare numerous bromo-substituted pyridine derivatives confirmed the lithiated intermediate 46. Other workers have also confirmed Gilman's observation that in diethyl ether dibromopyridine undergoes monolithiation.

In the case of 2,6-dichloropyridine no products arising from a metallated intermediate could be isolated. When 2,6-dichloropyridine was treated with n-butyllithium, only unchanged starting material was recovered. However, when 2-bromo-6-chloropyridine was used, lithiation proceeded analogously to dibromopyridine, i.e. only monolithiation occurred. Therefore, these results indicate dibromopyridine in diethyl ether undergoes metallation only once to yield a monometallated intermediate and dichloropyridine is resistant to metallation even under drastic conditions.

While dibromopyridine in diethyl ether cannot be dilithiated, the bis(magnesium) compound, pyridinebis(magnesium bromide), can be prepared. Proost and Wibaut reported the preparation of pyridinebis(magnesium bromide) from 2,6-dibromopyridine by employing Grignard's entrainment procedure. The bis(organomagnesium) intermediate was trapped with either benzaldehyde or allyl bromide. In light of the fact that aromatic dibromides react sluggishly to yield bis(organomagnesium)
compounds, the formation of 2,6-pyridine\textit{bis}(magnesium bromide) by employing entrainment procedures was unexpected.\textsuperscript{56a}

Heterocyclic analogs and derivatives of pyridine have been shown to undergo dimetallation. Abramovitch\textsuperscript{57} reported that pyridine N-oxide, when treated with excess \textit{n}-butyllithium, gave 2,6-dilithiopyridine N-oxide, which was subsequently trapped with a series of aldehydes and ketones. Five-membered, electron-rich heterocycles also have been dilithiated with excess \textit{n}-butyllithium and the \textit{bis}-organometallic intermediate carboxylated to yield the corresponding 2,5-dicarbonyl compound. Furan,\textsuperscript{58,59} thiophene,\textsuperscript{58} and N-methylpyrrole\textsuperscript{58,60} undergo dimetallation to afford the 2,5-dilithio-intermediate. 2,5-Diiodothiophene undergoes metal-halogen exchange with \textit{n}-butyllithium to afford, after carboxylation and esterification, dimethyl 2,5-thiophenedicarboxylate, the product arising from a dimetallated intermediate.\textsuperscript{61}

Since 2,6-dichloropyridine was resistant to metallation and 2,6-dibromopyridine afforded only a product stemming from monometallation, the most likely substrate for attempted dilithiation appeared to be 2,6-diiodopyridine. 2,6-Diiodopyridine was prepared in 1936 by Rodenwald and Plazek\textsuperscript{62} to aid in the structure determination of a pyridine derivative. A literature search of this compound provided no reports of its preparation since the original work of Rodenwald and Plazek. The 2,6-dihalopyridine series from fluorine to iodine is now readily accessible by halogen-halogen exchange. 2,6-Difluoropyridine can be prepared by treatment of the corresponding dichloro-compound with potassium fluoride in refluxing N,N-dimethylformamide.\textsuperscript{63}

The discussion concerning cyclometallation and metallation of
halopyridines clearly demonstrates that organometallic heterocycles, i.e. organometallic pyridines, can be synthetically useful. Region-specific metellation of heterocycles is a means of introducing a substituent onto a specific carbon. Dimetallation of halopyridines enables two substituents to be introduced onto the heterocyclic ring. Therefore, treatment of heterocycles with metalling reagents produces organometallic compounds that can be synthetically exploited.
III. Synthesis of Acetylenes and Related Compounds.

A transition metal complex has been used to synthesize heterocyclic acetylenes. Songashira, Tohda, and Hagihara reported the preparation of numerous acetylenic compounds by employing catalytic amounts of a palladium complex and copper(I) iodide. In order to better appreciate this catalytic method of synthesizing acetylenes, other methods of preparing acetylenes will be briefly reviewed.

There are two main reactions employed in the preparation of most acetylenic compounds: elimination and substitution reactions. Kobrich and Buck and Ziegenben have reviewed these reactions in detail in an excellent, comprehensive survey of acetylenes edited by Viehe. In elimination reactions the functionality is utilized to generate a triple bond, while in substitution reactions an acetylenic reagent is generated by deprotonation of the triple bond, which enables the resultant carbanion to add to an appropriately substituted substrate in a nucleophilic manner.

Preparation of acetylenic compounds by elimination reactions encompasses many different types of reactions such as fragmentation and thermolytic reactions; but by far, the most utilized type of elimination reaction to produce acetylenes is dehydrohalogenation. A reaction sequence involving dehydrohalogenation is illustrated in Scheme II.

SCHEME II

\[
\begin{align*}
&\text{48} \\
\text{R} \quad \text{R} \quad \text{X}_{2} \quad \text{A} \quad \text{R} \quad \text{H} \\
\text{49} \quad \text{H} \quad \text{X} \quad \text{B} \quad \text{R} \quad \text{Ξ} \quad \text{R}
\end{align*}
\]
An ethene can be easily halogenated, usually with bromine, to afford a 1,2-dihalo-compound. With the addition of a base, the dihalide eliminates two equivalents of HX to afford the desired acetylene. Vinyl halides undergo an analogous reaction with elimination of one equivalent of HX to yield the desired acetylene. The reaction sequence depicted in Scheme II is the more classic approach which has been successfully utilized in the preparation of numerous acetylenes and is widely used.

There are many bases available to eliminate hydrohalide from these vicinal dihalides. Oxygen bases (alcoholic potassium hydroxide), organometallic reagents (n-butyllithium and Grignard reagents), and metal amides (sodium amide in liquid ammonia) have been used to prepare acetylenes by elimination reactions. The selection of the base is often important in elimination reactions. The fact that oxygen bases usually allow only trans elimination to proceed smoothly, while metal amides, such as sodium amide in liquid ammonia, often produce both cis and trans eliminations under mild conditions, demonstrates the importance of base selection.

While elimination reactions are convenient and widely utilized to produce acetylenes, they suffer from two disadvantages. One is vinylation, the nucleophilic addition of the base to the newly formed acetylene. For example, vinylation produces vinyl ethers when oxygen bases are utilized. This disadvantage points to the need for careful selection of a base, since the extent of vinylation depends, in part, upon the nucleophilicity of the base. The second major disadvantage in the preparation of heterocyclic acetylenes is the competing
reaction of dehalogenation. Instead of obtaining the desired acetylene by dehydrohalogenation, the olefin is regenerated by dehalogenation. The net result of this competing reaction is a reversal of reaction [A] in Scheme II.

Attempts to prepare acetylenic carboxylic acids containing a heterocyclic subunit via dehydrohalogenation of β-substituted 1,2-dibromopropionic acids 51 and 53 resulted in the formation of olefinic carboxylic acids 52 and 54 respectively. This dehalogenation reaction occurred under conditions as mild as refluxing alcohol or water, without the addition of base. Pfeiffer in 1913 reported the occurrence of this competing reaction. However, it was not until the report of Alberts and Bachman in 1935 that this side reaction of dehalogenation received notable attention. The similar properties of olefins and acetylenes hampered the discovery that dehalogenation is a significant competing reaction.

Newkome and Koppersmith reported that heterocyclic substrates are very sensitive to reaction conditions and depending on conditions, either olefinic or acetylenic products could be obtained. Their procedure utilized rapid addition of small quantities of dihalide to
refluxing alcoholic bases followed by a thirty minute reflux. Treatment of pyridyl dihalide \textsuperscript{55} under these conditions afforded (95%) the desired acetylene \textsuperscript{56}; however, prolonged reaction times resulted in a significantly decreased yield of \textsuperscript{56}.\textsuperscript{70}

\[ \text{CH}_3 \text{NBrH} \quad \text{CH}_3 \text{N} \quad \text{CH}_3 \]

\[ \text{55} \quad \text{56} \]

In addition to dehydrohalogenation reactions, there are other types of elimination reactions used in the preparation of acetylenes. The Fritsch-Buttenberg-Wiechell (FBW) rearrangement,\textsuperscript{71} depicted in Scheme III, has been employed in the preparation of aromatic acetylenes.

\[ \text{PhH} \quad \text{Ph} \quad \text{PhCl} \quad \text{PhC} = \text{C} \quad \text{Ph} \quad \text{Ph} \quad \text{PhC} = \text{C} \quad \text{Cl} \quad \text{PhC} = \text{C} \quad \text{Ph} \quad \text{Ph} \quad \text{PhC} = \text{C} \quad \text{Cl} \quad \text{PhC} = \text{C} \quad \text{Ph} \quad \text{Ph} \quad \text{PhC} = \text{C} \quad \text{Cl} \quad \text{PhC} = \text{C} \quad \text{Ph} \]

\[ \text{SCHEME III} \]

\[ \text{57} \quad \text{58} \quad \text{59} \]

The FBW rearrangement is an \( \alpha \)-elimination which involves aryl migration to the neighboring carbon with loss of the halide. Phenyl substituents which are electron-donating increase the rate of reaction. Therefore, the phenyl ring appears to be cationic during the migration.\textsuperscript{72} Fragmentation reactions\textsuperscript{73} have also been used to generate acetylenes and the reversal of the Diels-Alder reaction, retrodiene cleavage, is another means of preparing acetylenes.\textsuperscript{65}

As the above examples demonstrate, elimination reactions are a versatile means of synthesizing acetylenes. Another often utilized method of preparing acetylenes is substitution reaction.\textsuperscript{66} In this type of reaction an acetylide ion, which is stabilized by a metal or
a group that is capable of interacting or bonding with the electro-
negative carbon, displaces a nucleofuge, usually halide. Viehe\textsuperscript{56} refers to this type of reaction as an alkylation. In contrast he has labeled the reaction of an acetylide ion with a carbonyl unit as an alkynation. Alkynations and the preparation of reactive metal acety-
lides were discussed in relation to the synthesis of acetylene-diols, Section I. Therefore, emphasis can now be placed on the discussion of alkylations as they relate to the preparation of acetylenes.

Metal acetylides, such as sodium acetylide, are capable of under-
going substitution reactions with substrates that possess a good leaving group, e.g. halide. In general, metal acetylides smoothly undergo nucleophilic substitution with primary halides. However with secondary, tertiary, or branched primary halides, elimination is a competing reaction, because of the strong basicity of the acetylide ion.\textsuperscript{66} Aryl halides can also react with metal acetylides. Copper reagents, for example, phenylacetylide \textsuperscript{60}, in the presence of an aryl halide in refluxing pyridine,\textsuperscript{74} \(N,N\)-dimethylformamide,\textsuperscript{75} or acetic acid\textsuperscript{76} couple with the aryl halide to afford a diaryl acetylene \textsuperscript{62}.

\[
\text{PhC} = \text{CCu} + \text{PhI} \rightarrow \text{PhC} = \text{CPh} + \text{CuI}
\]

This reaction was a method frequently used to prepare substituted tolan and heteroaromatic acetylenes.\textsuperscript{66} In this coupling reaction the reactivity of the aryl halide increases in the following order: I > Br > Cl.\textsuperscript{74} Also, if the aryl group is substituted with electron-withdrawing groups, the reactivity of the aryl halide is enhanced.\textsuperscript{81} Therefore, numerous alkyl and aryl substrates undergo substitution reactions to afford acetylenic compounds.
Reactions involving copper acetylide point out potential difficulty of first having to generate a metal acetylide and then react it with an alkyl or aryl halide, sometimes under vigorous conditions. This difficulty can now be circumvented by use of a palladium catalyst. In 1975 three research groups Heck, Cassar, and Songashira reported the use of a palladium complex to synthesize a variety of acetylenic compounds. By employing catalytic amounts of dichlorobis(triphenylphosphine)palladium(II) along with a co-catalyst, copper(I) iodide, in an alkylamine solvent, a surprising number of acetylenic compounds can be prepared from alkyl or aryl halides. Thus, 1-bromocyclopentene, when treated with the catalyst in the presence of propargyl alcohol gave acetylene.

\[
\begin{align*}
\text{Br} & \quad \text{HC} & \equiv & \text{CCH}_2\text{OH} \\
\sim & \quad \rightarrow & \quad \sim \\
63 & \quad & 64
\end{align*}
\]

2-Bromopyridine afforded bis(2-pyridyl)acetylene, when treated with acetylene in the presence of the catalyst, or the mixed acetylene, phenyl 2-pyridylacetylene, when treated with the catalyst and phenylacetylene. Treatment of 1,4-diiodobenzene with the palladium-copper catalyst afforded 4,4'-diiodotolane. Halo-pyrimidines are also coupled to yield bis(pyrimidinyl)acetylenes under
these same conditions.⁸⁰ These are a few examples of the variety of substrates that react with the catalyst to yield acetylenes. The conditions required to enhance the reactivity of an aryl halide are analogous to those of the copper coupling reaction; the most reactive halide is iodine and electron-withdrawing groups increase reactivity.⁷⁷,⁸¹

The palladium-copper catalyst offers a convenient, mild method of preparing a variety of acetylenic compounds. This method adds a new dimension of versatility to substitution reactions used to prepare acetylenes. Moreover, the two general classes of reactions used to prepare acetylenes, substitution and elimination reactions, provide numerous alternate methods to these compounds. By proper choice of method, conditions, and reagents a wide range of acetylenic compounds can be synthesized.

The availability of heterocyclic acetylenes ⁶⁶ and ⁶⁶a affords the possibility of preparing dipyridylbenzenes such as ⁶⁷. Closure of ⁶⁷ to a cyclic compound would afford an ortho-cyclophane.

Phanes are defined as "compounds containing at least one aromatic nucleus and at least one bridge".⁸² Cyclophane chemistry has been reviewed by Vögtle and Neumann,⁸² who surveyed the area of meta-cyclophanes, Cram, who reviewed bond deformations⁸³ and transannular⁸⁴ effects in cyclophanes, and Förster and Vögtle,⁸⁵ who considered the
role of cyclophanes in determining the steric size of substituents.

The main impetus for the preparation of these compounds was synthetic interest. However, before dealing with the synthetic aspects of this work, it is of interest to briefly highlight some of the information that can be gained from the physical studies of cyclophanes. The steric size of substituents, the conformational relationship of aromatic rings in a cyclic compound, and bond angles and bond distances in cyclophanes are some of the areas investigated with the aid of cyclophanes.

Steric interaction or spatial requirements of aryl substituents were measured by varying the chain length of meta-cyclopane. The number of methylene units comprising the bridge was varied until the intra-annular substituent X could just pass through the ring. This is called a topomerization process and yields information concerning the size of substituent X. The energetics of the topomerization process can be studied by variable temperature NMR (VTNMR). From these VTNMR data, the free energy of activation for the process was determined and the relative size of the substituent X was calculated.

Another steric size problem, that was resolved by the study of cyclophanes, is the spatial requirement of the lone pair of electrons on nitrogen. How does the size of this electron pair compare to that of a hydrogen? Spatial requirement of the lone pair of nitrogen vs hydrogen was determined from the conformational flipping threshold.
When X was nitrogen, the flipping threshold was lower than when X was CH.\textsuperscript{87b} Para-cyclophane \textsuperscript{70} also demonstrated a lower flipping threshold when X was nitrogen than when X was CH.\textsuperscript{88} An explanation for the increased conformational flipping when X is nitrogen is that the smaller steric size of the electrons cause them to interact less with the opposing ring than hydrogen.

In para-cyclophane \textsuperscript{70}, when X is nitrogen, the electrons intrude less into the aromatic ring current of the para-bridged benzene ring than the electron cloud of hydrogen.\textsuperscript{88}

Cyclophanes related to \textsuperscript{70} have afforded information concerning the conformational flipping of cyclophanes with saturated vs unsaturated bridges. Cyclophane \textsuperscript{71} has a much faster rate of conformational flipping that the saturated analog \textsuperscript{70}.\textsuperscript{88} Boekelheide\textsuperscript{88} attributed this fact to (a) the differing bond angles which in the saturated bridged cyclophane \textsuperscript{70} allows for more interaction between the substituent X and the pi-electron cloud; (b) conjugative stabilization of unsaturated cyclophane \textsuperscript{71}; and (c) repulsive nonbonded interactions between the methylene hydrogens and X-substituent in \textsuperscript{70}. When X is nitrogen in \textsuperscript{71}, the VTNMR is temperature independent and the ground state is believed to possess a perpendicular arrangement of the two aromatic rings.\textsuperscript{88}
This relationship between cyclophanes with saturated and unsaturated bridges has been extended to naphthalenophanes $\mathcal{N}_2$ and $\mathcal{N}_3$.\(^{89}\)

In this case, like the previous example, the phane $\mathcal{N}_3$ with the unsaturated bridge has the higher rate of conformational flipping.\(^{89}\)

The study of cyclophane chemistry also offers insight into bond deformations of aromatic rings or "bent" aromatic rings.\(^{82,83}\) X-ray structural analysis of [2.2]metacyclophane ($\mathcal{N}_{16}$) revealed that the benzene rings are in a boat conformation, which avoids the nonbonded interaction of carbon atoms C-8 and C-10 and their substituents.\(^{90}\)

When X is methyl, $\mathcal{N}_{16}$, the bond length between the carbons of the bridge increases and the aromatic rings again assume a boat conformation.\(^{91}\) Cram\(^{92}\) reported that [8]paracyclophane also has a bent benzene ring. Recently, Boekelheide\(^{93}\) reported the preparation of the double bridged or stacked compounds, such as $\mathcal{N}_5$, where the benzene rings are stacked in a face to face arrangement. X-ray structural analysis of $\mathcal{N}_5$ showed that the benzene rings are in the boat conformation almost to the same degree as [2.2]paracyclophane.\(^{93,94}\)

Boekelheide performed reactions such as the Birch reduction and cycloaddition reactions on $\mathcal{N}_5$ in order to test the reactivity brought about
by strain energy. The preparation of \([2.2.2.2.2.2]_{1,2,3,4,5,6}\)-cyclophane \((\text{75})\), which has been termed superphane, was recently reported by Boekeleide. Presently, no physical or chemical studies have been conducted on superphane \((\text{76})\).

The above examples convey some of the chemical and physical information that is obtainable from the study of cyclophanes. Synthesis of cyclophanes usually involves two basic steps: (a) cyclization of the reactants to a thiacyclophane; (b) expulsion of the sulfur atom to afford a cyclophane. This reaction sequence is the general method of choice in the preparation of cyclophanes, because of the versatility of the sulfur atom. There are several methods of cyclization that employ a sulfur functionality and several methods of expelling the sulfur atom; hence, the versatility of sulfur.

A method often employed in the synthesis of thiacyclophanes involves the condensation of a thiol-subunit with a halo-subunit. For example, the dianion of \(2,6\)-bis(thiomethyl)pyridine \((\text{77})\) condensed with \(p\)-xylyene dibromide \((\text{78})\) to afford \(2,11\)-dithia\([2.2.2](2,6)\)pyridino-paracyclophane \((\text{79})\). Another frequently encountered cyclization method uses sodium sulfide to effect ring closure. This method of cyclization is demonstrated by the conversion of \((\text{81})\) to the thiacyclophane \((\text{82})\).
Naphthalene derivative 81 afforded 82, when treated with sodium sulfide in aqueous t-butanol/benzene. Utilization of sodium sulfide to produce ring closure necessitated the use of an aqueous or aqueous-alcoholic solvent in order to dissolve the sulfide reagent. This restriction can be avoided by employing thioacetamide and a base in anhydrous benzene/ethanol. Terphenyl 84 was treated with thioacetamide and potassium hydroxide in anhydrous benzene/ethanol to afford thiacyclophane 85. These routes provide synthetic alternatives for the preparation of thiacyclophanes.
Just as there are different routes available for the preparation of thiacyclopahanes, there are alternate methods for the expulsion of the sulfur atom to afford a cyclophane. A route often utilized to expel sulfur employs an oxidizing agent, such as, hydrogen peroxide in glacial acetic acid/benzene, to oxidize a sulfide to the corresponding sulfone. Pyrolysis of sulfones causes extrusion of sulfur dioxide to give the corresponding cyclophane, (e.g. $8^3$). Methylation of a sulfide and subsequent Stevens rearrangement affords sulfides, such as $8^9$. Hoffmann elimination of sulfides (e.g. $7^98$) provides a convenient method of ring contraction and sulfur extrusion.$^8$ As a final method of sulfur explosion, a sulfide treated with benzyne undergoes a rearrangement-ring contraction to afford an aryl sulfide. Oxidation to an aryl sulfide and subsequent pyrolysis eliminates a sulfoxide to afford a cyclophane.$^9$ These three sulfur elimination-ring contraction procedures demonstrate the versatility of sulfur intermediates in the preparation of cyclophanes.

Acetylenes are useful synthetic precursors for the preparation of disubstituted benzenes as demonstrated by dipyrindylbenzene.$^6$ Compounds of this type provide convenient entry into synthetic routes designed to prepare cyclophanes.

Organometallic reagents can be utilized to produce a variety of synthetic transformations in heterocyclic compounds. Heterocyclic
ketones and carbonyl substrates, when reacted with the appropriate metal reagent, afforded acetylene-diols, which are precursors of either cumulenes or olefins. Numerous compounds which contain a heteroatom, including pyridine derivatives, are capable of undergoing cyclometallation, a proven method of introducing a carbon-metal bond at a specific site. Cyclometallated compounds can often be synthetically exploited. Metal-halogen exchange in pyridines is a well documented method of introducing substituents onto the pyridine ring. Metal complexes, such as dichlorobis(triphenylphosphine)palladium(II) along with the cocatalyst copper(I) iodide, are useful for the preparation of numerous disubstituted acetylenes, including heterocyclic acetylenes. Acetylenes are thus convenient starting materials for the preparation of diverse disubstituted benzenes and related compounds.
GENERAL

EXPERIMENTAL

General Comments. The chemicals, excluding solvents, were reagent grade and used without further purification unless otherwise stated in a specific experiment. The extraction solvents were reagent grade and not purified unless stated. Benzene, diethyl ether, petroleum ether (bp 30-60°C), cyclohexane, toluene, and xylene were dried over sodium ribbon. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride (LAH) and dimethoxyethane (DME) was treated initially with calcium hydride, filtered, and distilled from LAH. Both THF and DME were stored over activated molecular sieves (Linde Type 4A) under an argon atmosphere. Hexamethylphosphorus triamide (HMPT) was distilled at reduced pressure from calcium oxide and stored over activated molecular sieves (Linde Type 4A) under an argon atmosphere. Diethylamine and triethylamine were distilled from potassium hydroxide pellets and stored over potassium hydroxide pellets. 1,2-Dichlorobenzene was distilled from phosphorus pentoxide and stored over molecular sieves (Linde Type 4A).

Thin layer chromatography (TLC) was performed on 20 cm glass plates with a 0.25 mm coating of Brinkmann HF-254 + 366 silica gel, eluting with the stipulated solvents. The plates were activated for a minimum of 1 hour at 150°C before use. Thick layer chromatography (ThLC) was performed on 20 cm x 40 cm glass plates with a 2 mm coating of Brinkmann PF-254 + 366 silica gel, eluting with stipulated solvents. The plates were activated for minimum of 4 hours at 150°C prior to use. ThLC plates, that were multiply developed, are listed with the number of elutions. Column chromatography procedures utilized silica
gel (Baker, 60-200 mesh). Initial purification procedures employed silica gel (Baker, 60-200 mesh), alumina (Alcoa F-20, 80-200 mesh), and activated charcoal (Nuchar C-190N). Vapor phase chromatography (vpc) was performed on a Perkin-Elmer 990 with a 1/4" x 6' column packed with the stipulated material or on a Varian Aerograph 90-P with a 3/8" x 10' column packed with 10% OV 101 on 100/120 mesh chromosorb W.

Melting points were measured in capillary tubes with a Thomas-Hoover Unimelt and were uncorrected. Mass spectral (MS) data were obtained on either a Hitachi Perkin-Elmer RMS-4 or a Hewlett Packard Model 5986 gc/ms system. A fluorocarbon was employed as a counting reference. $^1$H Nuclear magnetic resonance (NMR) spectra were recorded on either a Varian Associates A-60A spectrometer, or where noted on a Varian Associates HA-100 or a Bruker WP-200 spectrometer. Tetramethylsilane (TMS) was used as an internal standard and chemical shift values are reported in parts per million ($\delta$) downfield from TMS. Infrared spectra (IR) were recorded on either a Perkin-Elmer IR-137 or a Perkin-Elmer IR-621 grating spectrophotometer. Ultraviolet (UV) and visible (VIS) spectra were recorded on a Cary-14 spectrophotometer, in the stipulated solvents. The spectra were obtained in 1 cm matched quartz cells and were corrected by a solvent blank.

Elemental analyses were performed by Mr. R. L. Seab in these laboratories.

$^4,5$-Diazafluoren-9-one ($5H$-Cyclopenta[2,1-b:3,4-b']dipyridin-5-one) (1). Method A. Oxidation of 1,10-Phenanthroline Monohydrate. A solution of 1,10-phenanthroline monohydrate (20 g, 0.10 mol) and
potassium hydroxide (10 g) in water (1.5 L) was refluxed, then a hot aqueous solution (800 mL) of potassium permanganate (50 g) was added over 15 minutes, refluxed for an additional 10 minutes, then filtered. The orange filtrate was cooled and extracted with chloroform (3 x 500 mL). The combined extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a yellow solid residue, which was recrystallized from acetone to afford 4,5-diazafluorene-9-one, as yellow needles: 4.0 g (20%); mp 211°C (lit.2 mp 211°C); NMR (CDCl₃) 67.28 (dd, 2,7-arom-H, J=8.0, 5.0 Hz, 2H), 7.91 (dd, 1,8-arom-H, J=8.0, 2.0 Hz, 2H), 8.75 (dd, 3,6-arom-H, J=5.0, 2.0 Hz, 2H). IR (KBr) 1725 (C=O), 1575, 1550, 1505, 1390, 1260, 1090 cm⁻¹; MS (70 eV)

**Table I.A.**

**Anal.** Calcd. for C₁₁H₆N₂O: C, 72.53; H, 3.30; N, 15.38. Found: C, 72.22; H, 2.98; N, 15.46.

The aqueous solution was concentrated to ca. 800 mL, then the pH was adjusted to ca. 4 with 5N sulfuric acid. A brown precipitate was collected, dissolved in hot water, and decolorized with activated charcoal. Upon cooling, 2,2'-dipyridyl-3,3'-dicarboxylic acid separated, as colorless crystals: 19 g (78%); mp 263-268°C (dec) [lit.⁴ mp 264-268°C (dec)]; NMR (pyridine-d₅) 67.40 (dd, 5,5'-pyr-H, J=8.0, 5.0 Hz, 2H), 8.50 (dd, 4,4'-pyr-H, J=8.0, 2.0 Hz, 2H), 8.68 (dd, 6,6'-pyr-H, J=5.0, 2.0 Hz, 2H), 10.65 (bs, -CO₂H, 2H). IR (KBr) 3000, 1740 (CO₂H), 1610, 1430, 1230, 1160, 1125, 1060 cm⁻¹.

**Anal.** Calcd. for C₁₂H₈N₂O₄: C, 59.02; H, 3.28; N, 11.48. Found: C, 59.01; H, 3.20; N, 11.35.
Method B. Pyrolysis of Calcium 2,2'-Dipyridyl-3,3'-dicarboxylate.
Calcium chloride (1.8 g, 12.3 mmol) was added to an aqueous solution (40 mL) of potassium hydroxide (2.67 g) and 2,2'-dipyridyl-3,3'-dicarboxylic acid (3 g, 12.3 mmol), then stirred for 9 hours. A beige solid, which slowly separated, was collected and dried in vacuo to afford calcium 2,2'-dipyridyl-3,3'-dicarboxylate, an off-white salt (1.8 g).

A sample of this salt (200 mg) was heated over an open flame and the resulting black mixture was chromatographed (TLC), which indicated that none of the desired ketone, 4,5-diazafluoren-9-one, was formed.

Heating a sample of the salt (800 mg) to 360°C in vacuo afforded similar results, no 4,5-diazafluoren-9-one was formed.

Method C. Directed Metallation of 2,2'-Dipyridyl to form 3,3'-Dilithio-2,2'-Dipyridyl trapping with Ethyl Chloroformate.
An anhydrous THF solution (30 mL) of 2,2'-dipyridyl (3.0 g, 19.2 mmol) was cooled to -50°C (dry ice-acetone bath) under an argon atmosphere, then treated with n-butyllithium (2.4 M in hexane, 16 mL, 38.4 mmol). After stirring for 2 hours, a THF solution of ethyl chloroformate (1.8 mL, 19.2 mmol) was added to the deep red mixture and stirred for 2 hours. This mixture was concentrated in vacuo to afford a black tar (6.7 g). Chromatography (TLC) indicated a complex mixture lacking 4,5-diazafluoren-9-one; no further work-up was conducted.

1-Azafluoren-9-one (9H-Indeno[2,1-b]pyridin-9-one) (3). Method A. Oxidation of 5,6-Benzquinoline. A boiling aqueous solution (1.6 L) of 5,6-benzoquinoline (20 g, 0.11 mol) and sodium hydroxide
(8 g) was treated with a hot aqueous 10% solution (700 mL) of potassium permanganate (70 g). The procedure and work-up, which was previously described, afforded a yellow solid, that was recrystallized from ethanol to give 1-azafluoren-9-one, as yellow crystals: 1.7 g (9%); mp 127-129°C (lit. 99 mp 128-129°C); MNR (CDCl₃) δ 7.05 (dd, 3-arom-H, J=8.0, 5.0 Hz, 1H), 7.45 (m, 6,7-arom-H, 2H), 7.50 (m, 5,8-arom-H, 2H), 7.81 (dd, 4-arom-H, J=8.0, 1.5 Hz), 8.53 (dd, 2-arom-H, J=5.0, 1.5 Hz, 1H); IR (KBr) 1730, 1615, 1585, 1305, 935, 750 cm⁻¹; MS (70 eV) Table I.B.

Anal. Calcd. for C₁₂H₇NO: C, 79.59; H, 3.87; N, 7.73. Found: C, 79.29; H, 3.94; N, 7.44.

The aqueous solution afforded 3-phenylpyridine-2,2'-dicarboxylic acid as an off-white solid: 26.9 g (91%); mp 210-212°C (dec) [lit. 100 mp 204°C (dec)]; NMR (DMSO-d₆) δ 8.48 (m, 5-pyr-H, J=6.0, 5.0 Hz, 1H), 7.60 (m, phe-H, 4H), 8.01 (m, 4-pyr-H, J=6.0, 2.0 Hz, 1H), 8.62 (dd, 6-pyr-H, J=4.0, 2.0 Hz, 1H); IR (KBr) 1740, 1700, 1640, 1400, 1325, 1170, 1100 cm⁻¹.

Anal. Calcd. for C₁₃H₉O₄: C, 64.19; H, 3.70; N, 5.76. Found: C, 63.93; H, 3.56; N, 5.69.

Method B. Pyrolysis of Calcium 3-Phenylpyridine-2,2'-dicarboxylate (92). A mixture of 3-phenylpyridine-2,2'-dicarboxylic acid (4.0 g, 16.6 mmol) and calcium hydroxide (1.2 g, 16.6 mmol) in water (300 mL) was refluxed for 5 days. The mixture was then concentrated in vacuo to afford calcium 3-phenylpyridine-2,2'-dicarboxylate as a colorless salt: 5.2 g, mp >330°C.

Glass beads were coated with a powdered sample of this salt (1.0
g, 3.6 mmol) then placed in a sublimation apparatus and heated to 360°C at 0.05 mm. A yellow solid which slowly collected on the cold finger was recrystallized from acetone to afford 1-azafluoren-9-one as yellow crystals: 140 mg (22%); mp 123-127°C.

Method C. Pyrolysis of 3-Phenylpyridine-2,2'-dicarboxylic Anhydride. A solution of 3-phenylpyridine-2,2'-dicarboxylic acid (2.5 g, 10 mmol), acetic anhydride (10 mL), and pyridine (1 mL) was refluxed for 4.5 hours under a nitrogen atmosphere. The black mixture was concentrated in vacuo to afford a black solid residue, which was column chromatographed eluting with chloroform to afford 3-phenylpyridine-2,2'-dicarboxylic anhydride as a yellow solid: 350 mg (15%); mp 115-118°C; NMR (DMSO-d6) δ 7.51 (dd, 5-pyr-H, J=8.0, 5.0 Hz, 1H), 7.61 (m, 3,6-phe-H, 2H), 7.75 (m, 4,5-phe-H, 2H), 8.20 (dd, 4-pyr-H, J=8.0, 1.5 Hz, 1H), 8.62 (dd, 6-pyr-H, J=5.0, 1.5 Hz, 1H); IR (KBr) 1790, 1640, 1330, 1190, 945 cm⁻¹: MS (70 e/v) see Table I.B.

A sample of the anhydride (100 mg, 0.4 mmol) was heated on an open flame and the resultant black residue extracted with chloroform. Chromatography (TLC) of the extract indicated the formation of 1-azafluoren-9-one along with other components.

1,8-Diazafluoren-9-one (9H-Cyclopenta[1,2-b:4,3-b']dipyridin-9-one) (2).² 4,7-Phenanthroline-5,6-quinone (93)¹⁰¹ (3.0 g, 14 mmol) was added to a refluxing aqueous solution (60 mL) of 1M sodium hydroxide. Oxygen was bubbled through the refluxing mixture over 30 minutes. After cooling, a yellow solid separated and was filtered. The filtrate was neutralized with concentrated hydrochloric acid, extracted with
chloroform (3 x 50 mL). The combined extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a yellow solid. The combined yellow solid was recrystallized from ethanol to give 1,8-diazafuoren-9-one, as yellow crystals: 1.15 g (43%); mp 228°C (lit., mp 205°C); NMR (CDCl₃) δ 7.40 (dd, 3,6-arom-H, J=7.5, 5.0 Hz, 2H), 7.92 (dd, 4,5-arom-H, J=7.5, 1.5 Hz, 2H), 8.62 (dd, 2,7-arom-H, J=5.0, 1.5 Hz, 2H), IR (KBr) 1775, 1571, 1410, 955, 800 cm⁻¹; MS (70 e/ν) Table 1A.


tris(1,10-Phenanthroline)cobalt Perchlorate. An aqueous solution (100 mL) of 1,10-phenanthroline monohydrate (1.0 g, 5 mmol) heated to 80°C was treated with an aqueous solution (10 mL) of cobalt(II) chloride hexahydrate (2.45 mg, 1 mmol) to give a yellow solution. This yellow solution was cooled at 8°C, then chloride gas was introduced through the solution for 10 minutes. The gas flow was continued as the reaction mixture slowly warmed to room temperature, then the flow of chlorine gas was stopped and the mixture was warmed to 60°C. An aqueous saturated solution (40 mL) of sodium perchlorate was added, causing an immediate precipitation of a yellow solid, which was filtered and washed with chloroform to afford tris(1,10-phenanthroline)cobalt perchlorate, as a yellow powder: 1.2 g (92%).

1,10-Phenanthroline-5,6-quinone (88%). tris(1,10-Phenanthroline)cobalt perchlorate (1.0 g, 3.9 mmol) and sodium bromide (500 mg, 4.8 mmol) were dissolved in cold concentrated sulfuric acid (10 mL).
Concentrated nitric acid (5 mL) was added and the red solution was refluxed for 30 minutes. After cooling, the reaction mixture was poured into an aqueous saturated solution (10 mL) of sodium perchlorate. A yellow precipitate was collected by filtration and the filtrate extracted with chloroform (3 x 20 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo to afford tris(1,10-phenanthroline-5,6-quinone)cobalt perchlorate as a yellow solid: 147 mg (11%).

tris(1,10-Phenanthroline-5,6-quinone)cobalt perchlorate (147 mg) in an aqueous solution (25 mL) of tetrasodium ethylenediaminetetraacetate [(EDTA), 1 g] was refluxed for 1 hour. Upon cooling, 1,10-phenanthroline-5,6-quinone precipitated as a yellow solid: 98 mg (82%); mp 247-249°C (lit.2 mp 250°C); NMR (CDCl3) 67.52 (dd, 3.8-arom-H, J=8.0, 4.5 Hz, 2H); 8.40 (dd, 4.7-arom-H, J=8.0, 1.5 Hz, 2H); 9.02 (dd, 2.9-arom-H, J=4.5, 1.5 Hz, 2H); IR (KBr) 1693, 1620, 1125, 1385, 1320, 1022, 810 cm⁻¹; MS (70 e/v) Table I.A.

5-Nitro-1,10-phenanthroline (5).3 A slurry of 1,10-phenanthroline monohydrate (1.0 g, 5 mmol) in concentrated sulfuric acid (5 mL) was cooled in an ice bath, then cautiously treated with cold concentrated nitric acid. By alternate cooling and heating, the reaction temperature was maintained at ca. 130°C for 45 minutes. At the end of this period, the acidic solution was poured onto ice and the pH adjusted to ca. 5 with 10N sodium hydroxide. A solid precipitate was collected to afford 5-nitro-1,10-phenanthroline, as an off-white powder: 855 mg (78%); mp 193-195°C (lit.104 mp 203°C); NMR (CDCl3) 67.60 (m, 3.8-arom-H, 2H), 8.17 (dd, 7-arom-H, J=8.0, 1.5 Hz, 1H),
Table I.A.
Mass Spectra Data for Azaphenanthrene Derivatives

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<th>Mass</th>
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<th>4,5-Diazafluorenone</th>
<th>1,10-Phenanthroline-5,6-quinone</th>
<th>4,7-Phenanthroline-5,6-quinone</th>
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(a) 210 (M<sup>+</sup>, 9.9); (b) 210 (M<sup>+</sup>, 32.1).
Table I.B.

Mass Spectra Data for Azaphenanthrene Derivatives

<table>
<thead>
<tr>
<th>Mass</th>
<th>Ion</th>
<th>Fragment Expelled</th>
<th>1-Azafluorenone</th>
<th>3-Phenylpyridine-2,2'-dicarboxyclic Anhydride</th>
</tr>
</thead>
<tbody>
<tr>
<td>181</td>
<td>C_{12}H_{7}NO</td>
<td>------</td>
<td>100</td>
<td>100^a</td>
</tr>
<tr>
<td>181 to 153</td>
<td>C_{11}H_{7}N</td>
<td>CO</td>
<td>50.8</td>
<td>51.6</td>
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<tr>
<td>153 to 127</td>
<td>C_{9}H_{5}N</td>
<td>C_{2}H_{2}</td>
<td>17.3</td>
<td>16.5</td>
</tr>
<tr>
<td>153 to 126</td>
<td>C_{10}H_{6}</td>
<td>HCN</td>
<td>16.1</td>
<td>16.7</td>
</tr>
<tr>
<td>127 to 100</td>
<td>C_{8}H_{4}</td>
<td>HCN</td>
<td>10.9</td>
<td>8.6</td>
</tr>
<tr>
<td>126 to 98</td>
<td>C_{8}H_{2}</td>
<td>C_{2}H_{2}</td>
<td>6.2</td>
<td>3.4</td>
</tr>
<tr>
<td>100 to 76</td>
<td>C_{8}H_{4}</td>
<td>C_{2}</td>
<td>14.7</td>
<td>8.5</td>
</tr>
<tr>
<td>98 to 74</td>
<td>C_{8}H_{2}</td>
<td>C_{2}</td>
<td>13.8</td>
<td>6.1</td>
</tr>
</tbody>
</table>

(a) 197 (M^+.-28, 60).
8.41 (s, 6-arom-H, 1H), 8.75 (dd, 4-arom-H, J=8.5, 2.0 Hz, 1H), 9.17 (m, 2,9-arom-H, 2H); MS (70 eV) m/e 226 (M⁺, 66%), 179 (M⁺ - 47, 100%), 167 (M⁺ - 59, 20%), 152 (M⁺ - 74, 23%), 135 (12%).

The pH of the filtrate was adjusted to ca. 9 with 10N sodium hydroxide, then the solution was concentrated to about half its volume and extracted with chloroform (3 x 50 mL). The combined organic extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a yellow solid, which was recrystallized from acetone to give 4,5-diazafluoren-9-one, as yellow needles: 47 mg (5%), mp 211°C.

9-Methyl-1-azafluoren-9-ol (9-Methyl-9H-indenol[2,1-b]pyridin-9-ol) (107). To a stirred solution of methylmagnesium bromide (2.8 M in diethyl ether, 0.1 mL, 0.28 mmol) in anhydrous THF (5 mL), a solution of 1-azafluoren-9-one (50 mg, 0.27 mmol) in anhydrous THF (10 mL) was added dropwise at 0°C over 10 minutes, then stirred at room temperature for 1.5 hours. The reaction was quenched with water (15 mL) and the mixture extracted with chloroform (3 x 20 mL). The combined extract was washed with a saturated salt solution (30 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a yellow solid (43 mg), which was chromatographed (ThLC) eluting with ethyl acetate-cyclohexane (3:1) to give 9-methyl-1-azafluoren-9-ol, as a near colorless solid: 32 mg (59%); mp 149-152°C; NMR (CDCl₃) δ 1.78 (s, -CH₃, 3H), 4.50 (s, -OH, 1H), 6.92-7.95 (m, arom-H, 6H), 8.43 (dd, 2-arom-H, J=5.0, 1.5 Hz, 1H); IR (KBr) 3250, 3010, 1610, 1480, 1430, 1290, 945 cm⁻¹.
9-Methyl-4,5-diazafluoren-9-ol (5-Methyl-5H-cyclopenta[2,1-b:3,4-b']dipyridin-5-ol) (105). An anhydrous THF solution (25 mL) of 4,5-diazafluoren-9-one (150 mg, 0.27 mmol) was treated with sodium hydride. The resulting suspension was stirred for 5 minutes under a nitrogen atmosphere, then filtered. The filtrate was added dropwise to an anhydrous THF solution (10 mL) of methylmagnesium bromide (2.8 M in diethyl ether, 0.1 mL, 0.28 mmol). The reaction procedure and work-up, identical to the method previously described, afforded 9-methyl-4,5-diazafluoren-9-ol, as an off-white solid: 21 mg (39%); mp 182-184°C (lit.105 mp 188°C); NMR (CDCl₃) 61.61 (s, -CH₃, 3H), 4.68 (s, -OH, 1H), 7.05 (dd, 2,7-arom-H, J=7.5, 5.0 Hz, 2H), 7.77 (dd, 1,8-arom-H, J=7.5, 1.5 Hz, 2H); IR (KBr) 3400, 2950, 1610, 1420, 1275, 1110, 945 cm⁻¹.

9-Methyl-1,8-diazafluoren-9-ol (9-Methyl-9H-cyclopenta[1,2-b:4,3-b']dipyridin-9-ol) (106). 1,8-Diazafluoren-9-one (30 mg, 0.16 mmol) in an anhydrous THF solution (10 mL) was treated first with sodium hydride, then reacted with methylmagnesium bromide (2.8 M in diethyl ether, 0.1 mL, 0.28 mmol) following the procedure previously described. Standard work-up afforded 9-methyl-1,8-diazafluoren-9-ol, as a yellowish solid: 9 mg (27%); mp 194-197°C; IR (KBr) 3250, 2950, 1690, 1475, 1425, 1260 cm⁻¹.

Attempted and Successful Preparations of Acetylene-Diols. Method A. Acetylenebis(magnesium bromide).⁷⁻¹⁰ To magnesium turnings (270 mg, 11 g-atom) covered with anhydrous THF (3 mL), a solution of ethyl bromide (1.2 g, 11 mmol) in THF (7 mL) was added dropwise under a
nitrogen atmosphere at a rate to sustain a gentle reflux. After the exothermic reaction had subsided, the gray suspension was refluxed an additional 1.5 hours, at which time all the magnesium had reacted. Anhydrous acetylene\textsuperscript{106} was introduced through the reaction mixture at a slow rate for ca. 12 hours. Acetylenebis(magnesium bromide) slowly precipitated as a purple semisolid.

A solution of 9-fluorenone (2 g, 11 mmol) in THF (20 mL) was added and the mixture stirred for 15 hours. At the end of this period, the reaction was quenched with cold 2N hydrochloric acid (25 mL), and then the solution was neutralized with 5N sodium hydroxide. The aqueous suspension was filtered to remove a precipitate, which was recrystallized for methanol-water to give 9,9'-ethynylenebis-9-fluorenol (12), as colorless prisms: 174 mg (6% overall); mp 233-236\degree C (lit.\textsuperscript{9} mp 238\degree C); NMR (CDCl\_3) 6 3.47 (s, -OH, 2H), 6.95-7.45 (m, arom-H, 16H); IR (KBr) 3400, 3365, 1610, 1455, 1205, 1050, 945, 775, 745 cm\(^{-1}\); MS (70 e\(\text{v}\)) m/e 181 (C\(_{13}\)H\(_{9}\)O, 100%), 180 (C\(_{13}\)H\(_{8}\)O, 28.5%), 152 (C\(_{12}\)H\(_{8}\), 52.2%), 126 (C\(_{10}\)H\(_{6}\), 3.4%), 76 (C\(_6\)H\(_6\), 5.7%).

Anal. Calcd. for C\(_{28}\)H\(_{18}\)O\(_2\): C, 87.05; H, 4.66. Found: C, 86.82; H, 4.93.

The filtrate was extracted with chloroform (3 × 30 mL). The combined organic extract was washed with a saturated salt solution (40 mL), dried over anhydrous sodium sulfate, and concentrated \textit{in vacuo} to afford a solid residue, which was chromatographed (ThLC) eluting with ethyl acetate-cyclohexane (1:5) to afford, along with unchanged 9-fluorenone (1.2 g), and 9,9'-ethynylenebis-9-fluorenol (90 mg).
Method B. Sodium Acetylide generated from Sodium-Biphenyl.

Sodium (250 mg, 0.01 g-atom) was added to an anhydrous dimethoxyethane [(DME), (200 mL)] solution of biphenyl (1.7 g, 11 mmol) and stirred under an argon atmosphere for 24 hours, resulting in a blue solution. Anhydrous acetylene was bubbled through the blue solution until all traces of color had dissipated and only a colorless slurry, sodium acetylide, remained.

A DME (40 mL) solution of 4,5-diazafluorenone (1.8 g, 10 mmol), treated with sodium hydride and filtered, was added to the sodium acetylide solution and refluxed for 4 hours. The reaction was cooled and poured into ice cold 2N hydrochloric acid (100 mL), then quickly neutralized with 5N sodium hydroxide. The suspension was filtered to remove a gray precipitate (2.3 g), which was washed with water. This gray precipitate was slurried in hot chloroform and filtered to afford 9,9'-ethynylenebis-4,5-diazafluoren-9-ol (II), as a reddish, insoluble (in most organic solvents) solid: 810 mg (35%); mp 326°C (dec); NMR (F3CO2H) 68.05-8.50 (tm, 2,7-arom-H, 4H), 8.69-9.25 (tm, 1,3,6,8-arom-H, 8H); IR (KBr) 3300 (OH), 1590, 1560, 1500, 1400, 1240, 1100 cm⁻¹.


The chloroform filtrate was dried over anhydrous sodium sulfate and concentrated in vacuo to afford biphenyl, as a yellowish-white solid: 1.3 g, mp 63-65°C.

The initial filtrate was concentrated to half the original volume and extracted with chloroform (3 x 75 mL). The combined extract was dried over anhydrous sodium sulfate and concentrated in vacuo to afford
unchanged 4,5-diazafluorenone: 600 mg, mp 209-210°C.

Method C. Sodium Acetylide generated from Sodium Amide and 1,2-Dibromoethane.\(^\text{13}\) A solution of 4,5-diazafluorenone (3 g, 16 mmol), 1,2-dibromoethane (700 mL, 8.4 mmol), and sodium amide (3.2 g, 82.5 mmol) in hexamethylphosphorus triamide [HMPT, 40 mL] was stirred at 60°C under a nitrogen atmosphere for 17 hours. After cooling, the red mixture was poured onto ice (200 g) and the suspension was neutralized with concentrated hydrochloric acid. The red slurry was filtered and filtrate extracted with chloroform (3 x 200 mL). The combined extract was washed with a saturated salt solution, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a black paste, which was dried in vacuo for 12 hours. The combined solid residue was chromatographed (ThLC) eluting with acetone-methanol to afford, along with unchanged 4,5-diazafluorenone, traces of 9,9'-ethynylenebis-4,5-diazafluoren-9-ol.

Method D. Lithium Acetylide Ethylenediamine.\(^\text{14}\) Acetylene\(^\text{106}\) was bubbled into an anhydrous THF (125 mL) solution of N-lithioethylene-diamine (33 g, 0.5 mol) under an argon atmosphere. After 6 hours, the acetylene flow was stopped and hexane (250 mL) was added to the off-white slurry. The reaction mixture was quickly placed inside a glove-bag which was flushed with argon, and filtered to remove a precipitate, which was then washed with hexane to afford lithium acetylide ethylenediamine, as a tan solid: 32 g (70%).

To a slurry of lithium acetylide ethylenediamine (1.54 g, 16.7 mmol) in anhydrous p-dioxane (15 mL), a solution of 9-fluorenone (3 g,
Table II
Preparation of Acetylene-Diols

<table>
<thead>
<tr>
<th>Substrate (g, mmol)</th>
<th>Method of Generating Metal Acetylde (g, mmol)</th>
<th>Reaction Time, hrs.</th>
<th>Temperature</th>
<th>Solvent</th>
<th>Special Additions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-Fluorenone (2 g, 11 mmol)</td>
<td>A: EtBr (1.2 g, 11 mmol) Mg (270 mg, 0.2 mmol)</td>
<td>30</td>
<td>r.t.</td>
<td>DME</td>
<td>---</td>
<td>9,9'-Ethynylenebig-9-fluoreol (6%)</td>
</tr>
<tr>
<td>4,5-Diastfluorenone (3.7 g, 20 mmol)</td>
<td>A: EtBr (2.2 g, 20 mmol) Mg (590 mg, 0.5 mmol)</td>
<td>23</td>
<td>r.t.</td>
<td>THF</td>
<td>---</td>
<td>N.R.</td>
</tr>
<tr>
<td>4,5-Diastfluorenone (500 mg, 2.7 mmol)</td>
<td>A: EtBr (300 mg, 2.7 mmol) Mg (70 mg, 0.27 mmol)</td>
<td>6</td>
<td>r.t.</td>
<td>THF</td>
<td>ESI^c</td>
<td>N.R.</td>
</tr>
<tr>
<td>4,5-Diastfluorenone (1.3 g, 7 mmol)</td>
<td>A: EtBr (1.2 g, 11 mmol) Mg (260 mg, 1.1 mmol)</td>
<td>12</td>
<td>r.t.</td>
<td>THF</td>
<td>fused substrate</td>
<td>N.R.</td>
</tr>
<tr>
<td>9-Fluorenone (5 g, 27 mmol)</td>
<td>B: Na (600 mg, 27 mmol) biphenyl (4.4 g, 28 mmol)</td>
<td>4</td>
<td>reflux</td>
<td>THF</td>
<td>---</td>
<td>N.R.</td>
</tr>
<tr>
<td>9-Fluorenone (5 g, 27 mmol)</td>
<td>B: Na (600 mg, 27 mmol) biphenyl (4.4 g, 28 mmol)</td>
<td>6.5</td>
<td>reflux</td>
<td>THF</td>
<td>---</td>
<td>9,9'-Ethynylenebig-9-fluoreol (7%)</td>
</tr>
<tr>
<td>9-Fluorenone (5 g, 27 mmol)</td>
<td>B: Na (600 mg, 27 mmol) biphenyl (4.4 g, 28 mmol)</td>
<td>2</td>
<td>reflux</td>
<td>DME</td>
<td>---</td>
<td>9,9'-Ethynylenebig-9-fluoreol (19%)</td>
</tr>
<tr>
<td>4,5-Diastfluorenone (1.8 g, 10 mmol)</td>
<td>B: Na (250 mg, 10 mmol) biphenyl (1.7 g, 11 mmol)</td>
<td>2</td>
<td>reflux</td>
<td>DME</td>
<td>substrate treated CaH2</td>
<td>9,9'-Ethynylenebig-4,5-diastfluoren-9-ol (35%)</td>
</tr>
<tr>
<td>1-Astafluorenone (1.3 g, 7 mmol)</td>
<td>B: Na (250 mg, 11 mmol) biphenyl (2 g, 13 mmol)</td>
<td>4</td>
<td>reflux</td>
<td>DME</td>
<td>---</td>
<td>N.R.</td>
</tr>
</tbody>
</table>
Table II (Continued).

<table>
<thead>
<tr>
<th>Substrate (g, mmol)</th>
<th>Method of Generating Metal Acetylide (g, mmol)</th>
<th>Reaction Time, hrs.</th>
<th>Temperature</th>
<th>Solvent</th>
<th>Special Additions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,5-Diazafluorenone (3 g, 15.5 mmol)</td>
<td>C: NaNH₂ (1.22 g, 52.5 mmol), dibromomethane (0.7 mL, 8.5 mmol)</td>
<td>17</td>
<td>60°C</td>
<td>THF</td>
<td>Excess NaNH₂</td>
<td>9,9-ethylenebis-4,5-diazafluorenone (traces)</td>
</tr>
<tr>
<td>9-Fluorenone (3 g, 1.7 mmol)</td>
<td>D: (1.5 h, g, 1.7 mmol)</td>
<td>2</td>
<td>reflux</td>
<td>p-dioxane</td>
<td>—</td>
<td>N.R.</td>
</tr>
<tr>
<td>9-Fluorenone (5 g, 27 mmol)</td>
<td>D: (2.5 g, 27.3 mmol)</td>
<td>3</td>
<td>r.t.</td>
<td>benzene</td>
<td>—</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

(a) Room Temperature.
(b) No reaction, unchanged starting material isolated.
(c) Hexamethylphosphoramide added to enhance solubility of substrate.

THF = tetrahydrofuran
DME = dimethylethane
16.7 mmol) in p-dioxane (40 mL) was added dropwise under an argon atmosphere. An immediate exothermic reaction occurred and the resultant black mixture was refluxed for 2 hours. Upon cooling, the reaction mixture was poured into a cold mixture of diethyl ether (20 mL)-2N hydrochloric acid (40 mL) with vigorous stirring. The layers were separated and the aqueous layer extracted with ether (3 x 50 mL). The combined organic portion was washed with an aqueous solution of 10% sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford an orange solid residue (2.5 g), which was recrystallized from methanol-water to afford unchanged 9-fluorenone: 2.3 g; mp 68-72°C.

1,4-bisBiphenylenebutatriene (13). Diphosphorus tetraiodide (970 mg, 1.7 mmol) was slowly added in small portions to a vigorously stirred benzene-pyridine [(1:1), 6 mL] solution of 9,9'-ethynylene-bis-9-fluorenol (630 mg, 1.6 mmol) at 8°C. An immediate reaction occurred producing a red solution that was stirred for 18 hours under a nitrogen atmosphere. The reaction mixture was poured into an aqueous solution of 10% sodium thiosulfate (10 mL), then benzene (15 mL) was added. A red precipitate (40 mg) was collected by filtration, washed with water (3 mL) and ethanol (3 mL), then recrystallized from xylene to give 1,4-bisbiphenylenebutatriene, as red needles: 20 mg (h%); mp 309-311°C, (lit.9 mp 316°C); UV (EtOH) λ max 438 nm (ε 1.7 x 10^6).

The mother liquor was concentrated to dryness to afford an unidentified black solid.
Attempted Preparation of 1,4-bis(Diazabiphenylene)butatriene.

9,9'-Ethynylenebis-4,5-diazafluoren-9-ol (103 mg, 0.24 mmol) in benzene-pyridine [(1:1), 10 mL] was treated with diphosphorus tetraiodide (148 mg, 0.26 mmol) in a manner analogous to the procedure previously described.

The filtered material afforded unchanged starting material: 85 mg; mp 313-316°C.

Reactions of Aromatic and Heteroaromatic Ketones with Low Valent Titanium. bis(Fluorenlylidene)[21].22 A solution of titanium trichloride (6.4 g, 41.5 mmol, 2.5 equiv.) in anhydrous THF (60 mL) was treated with lithium aluminium hydride (630 mg, 16.6 mmol, 1 equiv.) under a nitrogen atmosphere. An immediate exothermic reaction occurred to produce a black slurry, which was stirred for 10 minutes. A solution of 9-fluorenone (3.0 g, 16.6 mmol) in anhydrous THF (30 mL) was added, then the mixture was refluxed for 4 hours. After cooling then quenching with water (50 mL), the black mixture was extracted with diethyl ether (3 x 100 mL). The combined organic extract was washed with a saturated salt solution, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford an orange solid (2.3 g), which was recrystallized from petroleum ether-diethyl ether to give bis(fluorenlylidene), as red needles: 2.2 g (81%); mp 184-185°C (lit.108 mp 189-190°C); NMR (CDCl3) δ 6.95-7.45 (m, 8H), 7.55-7.80 (m, 4H), 8.20-8.50 (m, 1,8-arom-H, 4H).

Tetr phenylethene (23).22 To a slurry of titanium trichloride-lithium aluminium hydride (2.5 equiv./1 equiv., 27.3 mmol/10.9 mmol) in anhydrous THF (60 mL), benzophenone (2.0 g, 10.9 mmol) was added,
and then refluxed for 4 hours. The reaction was quenched (\( \text{H}_2\text{O} \)) and worked-up as described above to afford a colorless solid (1.9 g), which was recrystallized from petroleum ether-diethyl ether to give tetraphenylethenene, as colorless crystals: \( 1.5 \text{ g (82%)} \); mp 220-221°C (lit.\(^{109}\) mp 220°C); NMR (\( \text{CDCl}_3 \)) \( \delta 7.05 \) (s).

**E & Z-1,2-Diphenyl-1,2-bis(3'-pyridyl)ethene (115).** To a slurry of titanium trichloride-lithium aluminium hydride (2.5 equiv./1 equiv., 27.5 mmol/11 mmol) in anhydrous THF (30 mL), 3-benzoylpyridine (2.0 g, 11 mmol) was added, then the solution was refluxed for 12 hours. The reaction mixture was cooled, quenched with a saturated solution of aqueous potassium carbonate (50 mL), and filtered through a Celite pad. Both the salts and filtrate were washed and extracted with dichloromethane (3 \( \times \) 50 mL). The combined organic extract was washed with water (50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to afford a yellowish solid (1.78 g), which was chromatographed (ThLC) eluting with ethyl acetate to give unchanged starting material and the following fractions:

**Fraction A** gave E-1,2-diphenyl-1,2-bis(3'-pyridyl)ethene (E-115), as colorless crystals from ether-acetone: 240 mg (13%); mp 202-203°C; NMR, Figure 1; IR (KBr) 1563, 1492, 1414, 1030 cm\(^{-1}\); MS (70 e/v) m/e 334 (\( \text{M}^+ \), 100%), 256 (\( \text{M}^+ - 78 \), 61%), 166 (\( \text{M}^+ - 168 \), 34%), 148 (\( \text{M}^+ - 186 \), 31%), 129 (44%).

**Anal. Calcd.** for \( \text{C}_{24}\text{H}_{18}\text{N}_2 \): C, 86.23; H, 5.38; N, 8.38. **Found:** C, 86.04; H, 5.62; N, 8.01.

**Fraction B** afforded Z-1,2-diphenyl-1,2-bis(3'-pyridyl)ethene (Z-115), as a near colorless solid from diethyl ether-acetone: 340 mg (18%).
mp 199-200°C; NMR Figure 2; IR (KBr) 1563, 1492, 1414, 1030 cm⁻¹; MS (70 eV) m/e 334 (M⁺, 100%), 256 (M⁺ - 78, 86%), 166 (M⁺ - 168, 76%), 148 (M⁺ - 186, 44%), 129 (25%).

Anal. Calcd. for C₂₄H₁₈N₂: C, 86.23; H, 5.38; N, 8.38. Found: C, 86.15; H, 5.53; N, 8.16.

Reaction of Phenyl 2-Pyridyl Ketone with Low Valent Titanium.

Reaction A. To a slurry of titanium trichloride-lithium aluminium hydride (2.5 equiv./1 equiv., 41.0 mmol/16.4 mmol), a THF (30 mL) solution of phenyl 2-pyridyl ketone (3 g, 16.4 mmol) was added. After refluxing for 12 hours, the reaction was cooled, quenched with a saturated solution of aqueous potassium carbonate, and worked-up as described above to afford a yellow oil (3.0 g), which solidified on standing, and was recrystallized from petroleum ether-diethyl ether to give phenyl(2-pyridyl)methanol (122a), as pale yellow crystals: 2.8 g (93%); mp 72-74°C (lit.¹¹⁻mp 78-79°C); NMR (CDCl₃) δ 5.33 (s, -OH (exchanged with D₂O), 1H), 5.73 (s, CHOH, 1H), 6.90-7.65 (m, 8H), 8.12 (ddd, 6-pyr-H, J=5.0, 2.0, 1.0 Hz, 1H).

Reaction B. Phenyl-2-pyridyl ketone (2.0 g, 11 mmol) was added to a THF slurry of titanium trichloride-lithium aluminium hydride (2.5 equiv./1 equiv., 27.5 mmol/11 mmol). After work-up, a yellow solid (1.42 g) was isolated and was chromatographed (ThLC) eluting with ethyl acetate to give as the major product, phenyl(2-pyridyl)-methanol (mp 72-74°C), unchanged starting material, and 1,2-diphenyl-1,2-bis(2'-pyridyl)ethane (123a) as a near colorless solid from ethanol: 110 mg, (6%); mp 237-239°C (lit.¹¹⁺mp 244-245°C); NMR (CDCl₃) δ 5.31 (s, benzyl-H, 2H), 6.75-7.63 (m, pyr and phe-H, 8H), 8.45 (ddd, 6-
pyr-H, \( J = 4.5, 2.0, 1.5 \) Hz, 2H); MS (70 e/\( v \)) m/e 336 (M\(^+\), 28\%), 258 (M\(^+\) - 78, 21\%), 246 (M\(^+\) - 196, 72\%), 168 (M\(^+\)/2, 100\%), 139 (M\(^+\) - 197, 33\%).

Anal. Calcd. for C\(_{24}\)H\(_{20}\)N\(_2\): C, 85.72; H, 5.95; N, 8.32. Found: C, 85.47; H, 5.91; N, 8.66.

Method A. Reaction of bis(2-Pyridyl) Ketone with Low Valent Titanium. To a slurry of titanium trichloride-lithium aluminium hydride (2.5 equiv./1 equiv., 27.3 mmol/10.9 mmol) in anhydrous THF, bis(2-pyridyl) ketone (2.0 g, 10.9 mmol) was added. After refluxing for 12 hours, the black mixture was worked-up as described above to afford a pale yellow oil (1.45 g), which was chromatographed (ThLC) eluting with acetone to give, along with unchanged starting material, the following fractions:

Fraction A gave bis(2-pyridyl)methanol (122b), as a colorless oil: 680 mg (34\%); bp 138-140°C (1.4 mm) [lit.\(^{112}\) bp 110-112°C (1 mm)]; NMR (CDCl\(_3\)) 8 5.95 [s, CH\(_2\)OH (-OH partially exchanged with D\(_2\)O), 2H], 6.80-7.05 (m, 5-pyr-H, 2H), 7.40-7.65 (m, 3,4-pyr-H, 4H), 8.45 (ddd, 6-pyr-H, \( J = 4.5, 1.5, 0.9 \) Hz, 2H); IR (neat) 3250 (br, OH), 1575, 1125 cm\(^{-1}\).

Fraction B afforded a beige solid: 18 mg (<1\%); mp 112-117°C NMR (CDCl\(_3\)) 6 4.35 (s, CH, 2H), 6.95-7.73 (m, pyr-H, 8H), 8.55 (ddd, 6-pyr-H, \( J = 4.0, 2.0, 1.0 \) Hz, 2H); MS (70 e/\( v \)) m/e 370 (M\(^+\), 6\%), 343 (M\(^+\) - 27, 4\%), 335 (M\(^+\) - 35, 4\%), 262 (M\(^+\) - 108, 32\%), 184 (M\(^+\) - 186, 46\%), 170 (C\(_{11}\)H\(_{10}\)N\(_2\), 63\%), 78 (C\(_5\)H\(_4\)N, 100\%).

Method B.\(^{26,27}\) Reaction of Bis(2-Pyridyl) Ketone with Low Valent Titanium. Sodium (2.4 g, 4.8 equiv.) was added to a slurry of
titantium trichloride (3.35 g, 1.5 equiv.) in anhydrous dimethoxyethane (DME, 65 mL) under an argon atmosphere. After refluxing for 20 hours, bis(2-pyridyl) ketone (4.0 g, 22 mmol) in DME was added dropwise. The mixture was stirred and refluxed for 18 hours, and then cooled and quenched with a saturated solution of aqueous potassium carbonate. Following the above work-up procedure, an orange oil (3.20 g) was isolated and chromatographed (ThLC) eluting with acetone to afford unchanged starting material (1.8 g, 45%) and bis(2-pyridyl)-methanol (122b) as a colorless oil: 2.0 g (50%); bp 140-142°C (2 mm).

bis(4,5-Diazafluorenylidene) (10). A solution of 4,5-diazafluorenone (1 g, 5.5 mmol) in anhydrous THF (250 mL) was treated with calcium hydride, then the stirred mixture was heated to 50°C. The yellow solution was filtered then added dropwise to a slurry of titanium trichloride-lithium aluminium hydride (2.5 equiv./l equiv., 13.7 mmol/l mmol). After refluxing for 12 hours, the reaction mixture was worked-up as described above to afford a reddish residue (1.0 g), which was column chromatographed eluting with ethyl acetate to give along with unchanged starting material (710 mg), bis(4,5-diazafluorenylidene) dihydrate, as colorless plates from ethanol: 180 mg (20%); mp 230°C(dec); Rf=0.17 (ethyl acetate); NMR (CDCl3) δ4.80 [s, water of hydration (exchanged with D2O), ca. 4H], 6.95-7.40 (m, 1,2,7,8-arom-H, 8H), 8.55-8.75 (dd, 3,6-arom-H, J=5.0, 2.0 Hz, 4H); IR (KBr) 3490 (bs, H2O), 1620, 1395 cm⁻¹; UV (EtOH) λmax 291 (ε 2.8 x 10⁵); MS (70 e/ν) m/e 336 (M⁺, C₂₂H₁₆N₂, 81%), 184 (M⁺ - 152, 25%), 170 M⁺ - 166, 98%), 169 (C₁₁H₆N₂, 100%), 142 (M⁺ - 194, 35%).

Anal. Calcd. for C₂₂H₁₂N₄. 2H₂O: C, 71.80; H, 4.35; N, 15.22.
Reaction of 1,8-Diazafuorenone with Low Valent Titanium. To a slurry of titanium trichloride-lithium hydride (2.5 equiv./l equiv., 5.75 mmol/2.3 mmol) in anhydrous THF, 1,8-diazafuorenone (420 mg, 2.3 mmol) was added. After stirring 12 hours, the reaction was cooled, quenched with an aqueous saturated solution of potassium carbonate (15 mL). The resultant brown precipitate was removed by filtration. The filtrate and residue were washed extensively with chloroform. The combined washings and extracts were washed with water, dried with anhydrous sodium sulfate, and concentrated in vacuo to afford a gray solid (320 mg), which was chromatographed (ThLC) eluting with ethyl acetate to give two major fractions and an unidentified black solid (ca. 80%).

Fraction A gave unchanged starting material, as a yellow solid: mp 212-215°C.

Fraction B afforded off-white microcrystals of an unidentified compound: 2.2 mg (<1%); mp 143°C(dec); IR (KBr) 3490, 1575, 1415, 1100, 1025, 795 cm⁻¹; MS (70 e/ν) m/e 179 (6%), 178 (67%), 177 (100%), 148 (61%), 121 (53%).

Reaction of 4,5-Diazafuorenone and 9-Fluorenone with Low Valent Titanium. To a slurry of titanium trichloride and lithium aluminium hydride (2.5 equiv./l equiv., 27.5 mmol/11 mmol) in THF, a mixture of 9-fluorenone (1.0 g, 5.55 mmol) and 4,5-diazafuorenone (1.0 g, 5.55 mmol) was added. After work-up as described above, a reddish-brown solid (1.28 g) was isolated and column chromatographed eluting with
ethyl acetate to give the following fractions:

**Fraction A** was a mixture of bis( fluorenylidene) and 9-fluorenone. Rechromatography (ThLC) of this mixture, eluting with ethyl acetate- cyclohexane (1:1), gave bis( fluorenylidene), as red crystals: [250 mg (14%); mp 182-184°C] and 9-fluorenone [500 mg (25%); mp 79°C].

**Fraction B** was subsequently rechromatographed (ThLC) eluting with ethyl acetate to afford \( II^8 \), as a monohydrate: 70 mg (4%); mp 279-282°C(dec); NMR (CDCl₃) δ 4.83 [s, water of hydration (exchanged with D₂O), 2H], 6.95 (m, 10H), 7.55-7.80 (m, 4H), 8.60-8.80 (bd, 3,6- heteroaryl-H J=1.5 Hz, 2H); MS (70 e/v) m/e 332 (M⁺, C₂₄H₁₆N₂, 95%), 180 (M⁺ - 152, 56%), 165 (M⁺ - 167, 100%), 163 (M⁺ - 169, 79%), 168 (M⁺ - 164, 95%), 140 (M⁺ - 192, 47%).

1,8-Diazafluoren-9-ol (9H-Cyclopenta[1,2-b:4,3-b']dipyridin-9-ol) (19). A suspension of 1,8-diazafluoren-9-one (215 mg, 1.2 mmol) in ethanol (5 mL) was treated with sodium borohydride (40 mg, 1.1 mmol) then stirred for 10 minutes and refluxed for 1 minute. The black mixture was diluted with water (7 mL) and again refluxed for 3 minutes, then filtered. The filtrate was extracted with chloroform (3 x 10 mL). The combined extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a yellow solid, which was slurried in hot acetone and filtered to remove a tan powder. This tan powder was recrystallized from 95% ethanol to give 1,8-diazafluoren-9-ol, as silver needles: 63 mg (3%); mp 168°C(dec); IR (KBr) 3250 (br, -OH), 1605, 1538, 1385, 1030, 765 cm⁻¹.

Anal. Calcd. for C₁₁H₉N₂O: C, 71.74; H, 4.35; N, 15.22. 
Found: C, 71.48; H, 4.40; N, 14.98.
4,5-Diazafluoren-9-ol (5H-Cyclopenta[2,1-b:3,4-b']dipyridin-5-
ol).\(^{1,13}\) A suspension of 4,5-diazafluoren-9-one (100 mg, 0.5 mmol) in
ethanol (5 mL) was treated with sodium borohydride (20 mg, 0.5 mmol)
in a manner analogous to the above procedure. Standard work-up
afforded a colorless solid, which was recrystallized from ethanol to
give 4,5-diazafluoren-9-ol, as colorless crystals: 24 mg (25%); mp
217-219°C (dec) (lit.\(^{1,13}\) mp 224°C).

**Anal.** Calcd. for C\(_{11}\)H\(_8\)N\(_2\)O: C, 71.74; H, 4.35; N, 15.22. Found:
C, 71.52; H, 4.39; N, 15.07.

**Spiro[9H-indeno[2,1-b]pyridine]-9,2',-[1,3]-dioxolane (136).** In a
reaction vessel equipped with a Dean-Stark trap, a solution of 1-
azafluoren-9-one (300 mg, 1.6 mmol) and ethylene glycol (6.2 g, 0.10
mol) in anhydrous toluene (150 mL) was treated with concentrated
sulfuric acid (145 mg) and refluxed for 9 hours under a nitrogen atom-
sphere. After cooling, the reaction was quenched with an aqueous 10%
solution (90 mL) of sodium bicarbonate and the layers separated. The
aqueous layer was extracted with ether (3 x 75 mL). The combined
organic extract was dried over anhydrous magnesium sulfate and con-
centrated in vacuo to afford a beige solid, which was recrystallized
from petroleum ether to give spiro[9H-indeno[2,1-b]pyridine]-9,2'-
[1,3]-dioxolane, as colorless crystals: 120 mg (40%); mp 100-101°C;
NMR (CDCl\(_3\)) \(\delta\) 4.46 (m, 3,4-OCH\(_2\)CH\(_2\)O-, 2H), 4.70 (m, 3,4-OCH\(_2\)CH\(_2\)O-, 2H),
7.25 (dd, 3-arom-H, J=8.0, 5.0 Hz, 1H), 7.48 (m, 6,7-arom-H, 2H), 7.60
(m, 5,8-arom-H, 2H), 7.79 (dd, 4-arom-H, J=8.0, 1.5 Hz, 1H), 8.45 (dd,
2-arom-H, J=5.0, 1.5 Hz, 1H); IR (KBr) 1470, 1415, 1285, 1263, 1125,
1078, 1009, 955, 800, 772 cm\(^{-1}\); MS (70 e/v) m/e 225 (M\(^+\), 4.4%), 183
(M^+ - 42, 16.2%), 182 (M^+ - 43, 100%), 166 (M^+ - 59, 6.7%), 153 (M^+ - 72, 4.8%), 140 (M^+ - 85, 7.0%), 127 (M^+ - 98, 8.2%), 126 (M^+ - 99, 5.3%), 100 (M^+ - 125, 3.3%), 77 (C_5H_3N, 2.9%), 76 (C_5H_2N, 4.7%).

Anal. Calcd. for C_{14}H_{11}NO_2: C, 74.67; H, 4.89; N, 6.22. Found: C, 74.74; H, 4.85; N, 5.99.

2-Phenyl-2-(2'-pyridyl)-1,3-dioxolane (137). A solution of phenyl 2-pyridyl ketone (10 g, 54 mmol) and ethylene glycol (33 g, 0.54 mol) in anhydrous toluene (200 mL) was treated with concentrated sulfuric acid (4 g) and refluxed under a nitrogen atmosphere for 24 hours. The work-up, analogous to that described previously, afforded a colorless solid (9.5 g), that was recrystallized from petroleum ether-diethyl ether to give 2-phenyl-2-(2'-pyridyl)-1,3-dioxolane, as colorless crystals: 9.0 g (73%); mp 108-110°C (lit. 114°C); NMR (CDCl_3) δ 6.98-7.79 (m, arom-H, 8H), 8.62 (ddd, 6-pyr-H, J = 5.0, 1.5, 1.0 Hz, 1H).

Reaction of Lithium Dimethylcopper with a Pyridyl Dioxolane and Ketone. General Procedure. A slurry of copper(I) chloride in anhydrous THF (20 mL) was treated with methyllithium (2.18 M) in diethyl ether at 0°C under an argon atmosphere and the resultant black slurry stirred for 20 minutes. An anhydrous THF solution (6 mL) of spiro[9H-indeno[2,1-b]pyridine]-9,2'-[1,3]-dioxolane was added at the temperature indicated in Table III. The mixture was stirred for 3.5 hours, then quenched with cold 2N hydrochloric acid. The aqueous suspension, pH adjusted to ca. 8 with 5N sodium hydroxide, was extracted with chloroform (3 x 25 mL). The combined extract was dried over anhydrous
Table III

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Copper(I) Iodide</th>
<th>Methyllithium</th>
<th>Solvent</th>
<th>Reaction Time (hrs.)</th>
<th>Temperature °C</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dioxolane 136</td>
<td>130 mg, 0.6 mmol</td>
<td>60 mg, 0.6 mmol</td>
<td>0.55 mL, 1.2 mmol THF</td>
<td>3.5</td>
<td>10</td>
<td>N.R.¹</td>
</tr>
<tr>
<td>Dioxolane 136</td>
<td>50 mg, 0.3 mmol</td>
<td>30 mg; 0.3 mmol</td>
<td>0.27 mL, 0.6 mmol THF</td>
<td>4.5</td>
<td>-15</td>
<td>N.R.¹</td>
</tr>
<tr>
<td>Dioxolane 136</td>
<td>85 mg, 0.4 mmol</td>
<td>40 mg, 0.4 mmol</td>
<td>0.37 mL, 0.8 mmol THF</td>
<td>3.5</td>
<td>reflux</td>
<td>N.R.¹</td>
</tr>
<tr>
<td>Phenylpyridyl ketone</td>
<td>3 g, 16 mmol</td>
<td>3.25 g, 32.8 mmol</td>
<td>15 mL, 32.8 mmol DEE</td>
<td>1.5</td>
<td>reflux</td>
<td>1-Phenyl-1-(2'-pyridyl)-1-ethanol (17%)</td>
</tr>
<tr>
<td>Crotonaldehyde</td>
<td>1 g, 14 mmol</td>
<td>1.58 g, 16 mmol</td>
<td>14 mL, 32 mmol DEE</td>
<td>4.5</td>
<td>0</td>
<td>Isovaleraldehyde, 3-pentenal ²</td>
</tr>
</tbody>
</table>

THF = tetrahydrofuran
DEE = diethoxyethane

(a) No reaction, unchanged starting material recovered.
(b) Product mixture identified by NMR.
magnesium sulfate and concentrated in vacuo to afford a colorless solid, which was chromatographed (TLC) eluting with ethyl acetate-cyclohexane (2:1) indicating the presence of only unchanged spiro[9H-indeno[2,1'b]pyridine]-9,2'-[1,3]dioxolane.

Reaction of 2-Phenyl-2-(2'-pyridyl)-1,3-dioxolane with Methylmagnesium Bromide. A solution of 2-phenyl-2-(2'-pyridyl)-1,3-dioxolane (3.0 g, 13 mmol) in anhydrous toluene (40 mL) was added dropwise to a toluene solution of methylmagnesium bromide (2.8 M in diethyl ether, 5.4 mL, 15 mmol) under a nitrogen atmosphere at room temperature. The reaction was refluxed for 19 hours, then poured into cold 2N hydrochloric acid and the layers were separated. The organic layer was extracted with 5N hydrochloric acid (30 mL) and the extract was added to the aqueous layer. The aqueous layer was concentrated to half its volume and the pH adjusted to 10 with 5N sodium hydroxide. An off-white precipitate (1.0 g) was collected by filtration and the filtrate extracted with chloroform (3 x 100 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo to afford a brown semisolid (1 g). The combined precipitate and brown semisolid were recrystallized from diethyl ether-petroleum ether to give unchanged 2-phenyl-2-(2'-pyridyl)-1,3-dioxolane: 2.0 g, mp 109-110°C.

2-Phenylpyridine.115 To lithium metal (3.5 g, 0.5 g-atom) covered with anhydrous diethyl ether (100 mL), a diethyl ether solution (50 mL) of bromobenzene (40 g, 0.25 mol) was added under an argon atmosphere dropwise at a rate to sustain a gentle reflux throughout the addition,
then the reaction mixture was refluxed an additional 2 hours. Pyridine (40 g, 0.5 mol) in anhydrous toluene (100 mL) was added. The diethyl ether was distilled from the reaction mixture and the resultant toluene solution was heated to 110°C for 8 hours. After cooling, water was added to the black mixture. This aqueous slurry was filtered and the layers separated. The organic layer was distilled to afford 2-phenylpyridine, as a colorless oil: 18.1 g, (46%); bp 117-121°C (5 mm) (lit. 116 bp 268-269°C); NMR (CDCl₃) δ 7.10 (dd, 5-pyr-H, J=5.0, 4.5 Hz, 1H), 7.29-7.72 (m, 3,4-pyr-H, 3,4,5-phe-H, 5H), 7.95 (m, 2,6-phe-H, 2H), 8.65 (ddd, 2-pyr-H, J=5.0, 1.5, 1.0 Hz, 1H).

2-(4'-Methylphenyl)pyridine. The procedure employed was identical to the method used to prepare 2-phenylpyridine. The only difference being 1-bromo-4-methylbenzene was used in place of bromobenzene. 2-(4'-Methylphenyl)pyridine was distilled, as a colorless oil: 21.7 g (44%); bp 124°C (5 mm); [lit. 117 bp 93-98°C (1 mm)]; NMR (CDCl₃) δ 2.19 (s, -CH₃, 3H); 6.90 (m, 3-pyr-H, 1H), 7.09 (d, 3,5-phe-H, J=8.5 Hz, 2H), 7.40 (m, 4,5-pyr-H, 2H), 7.88 (d, 2,6-phe-H, J=8.5 Hz, 2H), 8.53 (ddd, 2-pyr-H, J=5.0, 1.5, 1.0 Hz, 1H).

Attempted Directed Lithiation of 2-Phenylpyridine. General Procedure. An anhydrous THF solution (40 mL) of 2-phenylpyridine (4.86 g, 31 mmol) was treated with n-butyllithium (2.4 M in hexane, 12.8 mL, 31 mmol) at -20°C (dry ice-acetone bath) under an argon atmosphere. The red solution was stirred for 30 minutes, then quenched with methanol-d (1.03 g, 32 mmol) in THF (3 mL). Water (50 mL) was added and the layers separated. The aqueous layer was extracted with
Table IV

Reaction of n-Butyllithium with 2-Phenylpyridine.

<table>
<thead>
<tr>
<th>2-Phenylpyridine</th>
<th>n-BuLi</th>
<th>Trapping Agent (g, mmol)</th>
<th>Solvent (mL)</th>
<th>Temperature °C</th>
<th>Reaction Time (hrs.)</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.86 g, 31 mmol</td>
<td>4.86 g</td>
<td>12.8 mL, CH3OD</td>
<td>1.03 g, 32 mmol THF (40)</td>
<td>-60°</td>
<td>0.5</td>
<td>N.R. a</td>
</tr>
<tr>
<td>4.86 g, 31 mmol</td>
<td>4.86 g</td>
<td>12.8 mL, CH3OD</td>
<td>1.03 g, 32 mmol THF (40)</td>
<td>-20°</td>
<td>0.5</td>
<td>6-buty1-2-phenylpyridine (21%)</td>
</tr>
<tr>
<td>4.0 g, 25.8 mmol</td>
<td>4.0 g</td>
<td>11 mL, ethyl chloroformate</td>
<td>2.8 g, 26 mmol THF (40)</td>
<td>-90°</td>
<td>6</td>
<td>N.R. a</td>
</tr>
<tr>
<td>3.0 g, 19.3 mmol</td>
<td>3.0 g</td>
<td>8 mL, ethyl chloroformate</td>
<td>2.1 g, 19.3 mmol THF (30)</td>
<td>-50°</td>
<td>6</td>
<td>6-buty1-2-phenylpyridine (41%) ethyl 2-(2'-6'-buthylpyridyl)benzoate b</td>
</tr>
</tbody>
</table>

(a) No reaction, unchanged starting material recovered.

(b) Determined from vpc/ms data; remainder of material unchanged 2-phenylpyridine.
chloroform (3 × 50 mL). The combined extract and organic layer were dried over anhydrous magnesium sulfate and concentrated in vacuo to afford an orange oil (4.4 g), which was fractionally distilled to give unchanged 2-phenylpyridine [1.2 g; bp 125-128°C (5 mm)] and a fraction which contained two components. This mixture was chromatographed (ThLC) eluting with cyclohexane-ethyl acetate (10:1) to afford, along with unchanged 2-phenylpyridine (1450 mg), 6-butyl-2-phenylpyridine: 1.37 g (21%); bp 178-187°C (5 mm), [lit.118 bp 190°C (1 mm)]; NMR (CDCl₃) δ 0.98 (t, CH₃(CH₂)₃, J=5.5 Hz, 3H), 1.22-2.17 (m, CH₃(CH₂)₂-CH₂-, 4H), 2.86 (t, CH₃(CH₂)₂CH₂-, J=7.0 Hz, 2H), 6.91 (m, 5-pyr-H, 1H), 7.20-7.55 (m, 3,4-pyr-H, 3,4,5-phe-H, 5H), 7.98 (m, 2,6-phe-H, 2H).

2,6-Diiodopyridine (148). Method A. Treatment of 2,6-Dibromopyridine with Potassium Iodide. A stirred mixture of 2,6-dibromopyridine (6.0 g, 25.3 mmol) and potassium iodide (24 g) in N,N-dimethylformamide (100 mL) was refluxed for 4 hours. The cooled mixture was filtered, and the filtrate evaporated in vacuo to near dryness. Water (35 mL) was added and the aqueous slurry extracted with diethyl ether (3 × 50 mL). The combined extract was dried over anhydrous sodium sulfate and concentrated in vacuo to afford an off-white solid (8.80 g), which was recrystallized from petroleum ether to give unchanged 2,6-dibromopyridine, as colorless crystals: 5.65 g; mp 115-117°C.

Method B. Treatment of 2,6-Dibromopyridine with Hydroiodic Acid and Sodium Iodide. A solution of 2,6-dibromopyridine (4.0 g, 16.8 mmol) and sodium iodide (6.0 g) in hydroiodic acid (20 mL, a. 47%) was
refluxed for 5.5 hours. Then the reaction mixture was poured into a solution of 40% sodium hydroxide (20 mL) and ice (20 g), filtered, and the filtrate extracted with diethyl ether (4 x 60 mL). The combined extract was washed sequentially with water (100 mL), a solution of sodium sulfite (100 mL), and water (100 mL), then dried over anhydrous sodium sulfate. The filter cake was washed with water, followed by diethyl ether. To the organic extract, the filter cake and excess diethyl ether-petroleum ether were added. After dissolution the colorless crystals, which had precipitated, were collected affording 2,6-diiodopyridine: 1.0 g (18%); mp 185-186°C (lit. 62 mp 183°C); NMR (CDCl₃) δ 6.98 (t, 4-pyr-H, J=8.5 Hz, 1H), 7.73 (d, 3,5-pyr-H, J=8.5 Hz, 2H); IR (KBr) 3010, 1510, 1408, 1120, 975, 785 cm⁻¹; MS (70 e/ν) m/e 331 (M⁺, 100%), 204 (M⁺ - 127, 46.5%), 127 (I⁺, 18.6%), 77 (C₅H₃N, 20.6%).

Anal. Calcd. for C₅H₃I₂N: C, 18.13; H, 0.90; N, 4.22. Found: C, 18.41; H, 0.87; N, 4.38.

Method C. Treatment of 2,6-Dichloropyridine with Hydroiodic Acid and Sodium Iodide. A stirred mixture of 2,6-dichloropyridine (14.8 g, 0.1 mol) and sodium iodide (20 g) in hydroiodic acid (75 mL, d. 47%) was refluxed for 12 hours. The mixture was cooled, poured into a solution of 40% sodium hydroxide (75 mL) and ice (75 g), then filtered. The filtrate and filter cake were worked-up as described in Method B to give 2,6-diiodopyridine as colorless crystals: 13.85 g (42%); mp 185-186°C.
<table>
<thead>
<tr>
<th>Starting Halide</th>
<th>Reagents</th>
<th>Conditions</th>
<th>Reaction Time (hrs.)</th>
<th>Percent Yield of 2,6-Diiodopyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,6-Dibromo</td>
<td>A</td>
<td>r.t. (^b)</td>
<td>27</td>
<td>24%</td>
</tr>
<tr>
<td>2,6-Dibromo</td>
<td>A</td>
<td>warmed</td>
<td>8</td>
<td>N.R. (^a)</td>
</tr>
<tr>
<td>2,6-Dibromo</td>
<td>B</td>
<td>refluxed</td>
<td>4</td>
<td>N.R. (^a)</td>
</tr>
<tr>
<td>2,6-Dichloro</td>
<td>A</td>
<td>r.t. (^b)</td>
<td>46</td>
<td>N.R. (^a)</td>
</tr>
<tr>
<td>2,6-Dichloro</td>
<td>A</td>
<td>refluxed</td>
<td>18</td>
<td>42%</td>
</tr>
<tr>
<td>2,6-Dibromo</td>
<td>A</td>
<td>refluxed</td>
<td>5.5</td>
<td>18%</td>
</tr>
</tbody>
</table>

A = HI - NaI
B = KI - DMF

(a) No reaction, unchanged starting material recovered.
(b) Room temperature.
Metal-Halogen Exchange of 2,6-Dihalopyridine with n-Butyllithium.

Method A. Preparation of 2,6-Dilithiopyridine from 2,6-Diiodopyridine Trapping with 3-Bromopropene. 2,6-Diiodopyridine (3.31 g, 0.01 mol) in anhydrous THF (125 mL) was cooled to -90°C (liquid nitrogen-petroleum ether bath) under an argon atmosphere. n-Butyllithium (2.2 M in hexane, 17 mL, 0.038 mol) was added, then the solution was stirred at ca. -85°C for 4.5 hours. A solution of 3-bromopropene (6.9 mL, 0.08 mol) in anhydrous THF (70 mL) was added and stirred for 3.5 hours, while the reaction mixture was gradually warmed to room temperature. Methanol (5 mL) was added, and then the reaction mixture concentrated in vacuo to near dryness. The residue was slurried in water (50 mL) and extracted with diethyl ether (3 x 50 mL). The organic extract was washed with 5N sulfuric acid (50 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo to afford an oil (310 mg), which was chromatographed (TLC) eluting with ethyl acetate-cyclohexane (1:1) indicating the mixture to be 2-iodopyridine and several unidentified components.

The pH of the acidic layer was adjusted to 10 with 10N sodium hydroxide, then extracted with ether (3 x 60 mL). The combined ether extract was dried over anhydrous sodium sulfate and concentrated in vacuo to afford a brown oil (810 mg), which was chromatographed (ThLC) eluting with ethyl acetate-cyclohexane (1:2) to give 2-iodopyridine [200 mg (9.8%); $R_f^{1}=0.57$ [ethyl acetate-cyclohexane (1:2)]; NMR (CDCl$_3$) $\delta$7.45 (m, pyr-H, 3H), 8.35 (ddd, 6-pyr-H, $J=5.0, 2.0, 1.0$ Hz, 1H) and 6-(3'-propenyl)-2-iodopyridine [280 mg (11%); NMR (CDCl$_3$) $\delta$3.56 (d, $\alpha$-CH$_2$, $J=6.5$ Hz, 2H), 5.25 (bd, =C=CH$_2$, $J=12.0$ Hz, 2H), 5.88 (m,
Method B. Preparation of 2,6-Dilithiopyridine from 2,6-Diiodopyridine Trapping with Carbon Dioxide. A solution of 2,6-diiodopyridine (3.31 g, 0.01 mol) in anhydrous THF (125 mL) was cooled to -95°C (liquid nitrogen-petroleum ether bath) under an argon atmosphere, then treated with n-butyllithium (2.2 M in hexane, 17 mL, 0.038 mol). The reaction was stirred for 4 hours, strictly maintaining the temperature below -89°C. The golden slurry was rapidly poured with vigorous stirring onto solid carbon dioxide (70 g). After warming to 25°C, the slurry was concentrated in vacuo to afford an oily residue which was dissolved in water and extracted with dichloromethane (3 x 50 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo to afford an unidentified oil: 550 mg; NMR (CDCl₃) δ 0.60-1.80 (m). The aqueous portion was concentrated in vacuo to give a solid, which was suspended in anhydrous methanol and saturated with dry hydrogen chloride gas and refluxed for 24 hours under nitrogen. After concentration in vacuo, the residual oil was dissolved in water (25 mL), adjusted to pH 7 with solid potassium carbonate, and extracted with dichloromethane (3 x 25 mL). The combined organic extract was dried over anhydrous sodium sulfate and column chromatographed eluting with acetone to give a colorless solid, which was recrystallized from acetone to afford methyl 2,6-pyridine-dicarboxylate (150a), as colorless crystals: 115 mg (6%); mp 118-121°C (lit.,¹¹⁹ mp 124-125°C); NMR (CDCl₃) δ 3.91 (s, -CO₂CH₃, 6H), 8.20 (m, pyr-H, 3H); MS (70 e/v) m/e 195 (M⁺, 2.1%), 164 (M⁺-31, 7.2%), 139 (M⁺-58, 100%), 105 (C₆H₃NO, 41.7%).
The aqueous portion was adjusted to pH 5 with 5N hydrochloric acid, then extracted with dichloromethane (2 × 30 mL). The organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo to give 2-carbomethoxy-6-pyridinecarboxylic acid, as a pink solid: 50 mg (3%); mp 144-146°C (lit.120 mp 151°C); NMR (CDCl₃) 64.07 (s, -CO₂CH₃, 3H), 8.00-8.53 (m, pyr-H, 3H), 9.39 [s, -CO₂H (exchanged with D₂O), 1H].

Method C. Preparation of 2,6-Dilithiopyridine from 2,6-Dibromo-pyridine Trapping with Anhydrous Gaseous Carbon Dioxide. An anhydrous THF (125 mL) solution of 2,6-dibromopyridine (2.37 g, 0.01 mol) was cooled to -95°C (liquid nitrogen-petroleum ether bath) under an argon atmosphere, then treated with n-butyllithium (2.2 M in hexane, 17 mL, 0.038 mol). The slurry was stirred at -95°C for 4 hours, then gaseous carbon dioxide₁²¹ was introduced over a 13 hour period. Care must be taken to avoid clogging of the gas inlet tube. The slurry was then poured onto solid carbon dioxide with stirring. The solvent was evaporated to afford a solid, which was suspended in water (30 mL), adjusted to pH 8 with solid potassium carbonate, and extracted with dichloromethane (3 × 25 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo to afford an unidentified oil (260 mg). The aqueous layer was concentrated in vacuo to give a solid, which was slurried in anhydrous methanol, saturated with gaseous hydrogen chloride and refluxed for 12 hours. After concentration in vacuo, the oily residue was dissolved in water (35 mL), neutralized with solid potassium carbonate, and extracted with dichloromethane (3 × 25 mL). The combined extract was dried over
anhydrous sodium sulfate and column chromatographed eluting with acetone to give an oil (1.64 g), which solidified upon standing.

Recrystallization from acetone gave methyl 2,6-pyridinedicarboxylate, as colorless crystals: 370 mg; mp 116-119°C. The mother liquor was concentrated to afford an oil, which was chromatographed (ThLC) eluting with ethyl acetate-cyclohexane (2:1) affording methyl 2,6-pyridinedicarboxylate: 20 mg (20% overall).

Method D. Preparation of 2,6-Dilithiopyridine from 2,6-Dibromopyridine Trapping with Carbon Dioxide. This procedure was conducted in a manner analogous to that of Method B, except 2,6-dibromopyridine was used instead of 2,6-diiodopyridine. Fractional recrystallization of the reaction residue from diethyl ether-petroleum ether afforded methyl 2,6-pyridinedicarboxylate, as colorless crystals: 115 mg (8%); mp 117-120°C.

A second fraction was recrystallized from hexane to give methyl 6-chloro-2-pyridinedicarboxylate, as colorless crystals: 520 mg (30%); mp 78-81°C; NMR (CDCl₃) δ 4.02 (s, CO₂CH₃, 3H), 7.63 (dd, 3-pyr-H, J=8.0, 2.0 Hz, 1H), 7.92 (dd, 4-pyr-H, J=8.0 Hz, 1H), 8.11 (dd, 5-pyr-H, J=8.0, 2.0 Hz, 1H); MS (70 eV) m/e 171 (M⁺, 12.2%), 141 (M⁺ - 30, 32.3%), 113 (M⁺ - 58, 100%), 76 (C₅H₂N, 52.6%).

Anal. Calcd. for C₇H₆ClNO₂: C, 49.16; H, 3.50; N, 8.16. Found: C, 49.45; H, 3.64; N, 7.93.

Method E. Preparation of 2,6-Dilithiopyridine from 2,6-Dibromopyridine Trapping with Methanol. 2,6-Dibromopyridine (4.7 g, 20 mmol) in THF (20 mL) was treated with n-butyllithium (2.4 M in hexane, 31
mL, 0.076 mol) under the conditions described in Method B. After stirring for 4.5 hours, the reaction mixture was rapidly quenched with a chilled THF (20 mL) solution of anhydrous methanol (6.4 g, 0.2 mol). The temperature rose briefly to -78°C but was quickly returned to -90°C. The quenched reaction mixture was stirred for 6 hours, while slowly warming to room temperature. Then, the mixture was concentrated by fractional distillation collecting only the material that boiled below 60°C. The residue was slurried in hot petroleum.ether-diethyl ether, then filtered. The ethereal filtrate was concentrated and the liquid residue was analyzed by vapor phase chromatography, which indicated the presence of pyridine and 2-bromopyridine. This mixture was distilled, collecting between 60°-90°C to afford, along with low boiling solvents, pyridine (52-58%) as determined by vpc.

The residue of the distillation was column chromatographed eluting with ethyl acetate to afford 2-bromopyridine (7-12%), as indicated by vpc.

Method F. Preparation of 2,6-Dilithiopyridine from 2,6-Dibromo-pyridine Trapping with Dimethyl Disulfide. The reaction was repeated except using dimethyl disulfide (9.4 g, 10 mmol) in THF (40 mL) to quench the reaction. The quenched reaction was distilled to afford, along with low boiling solvents, a mixture [2.55 g, bp 98-112°C (3 mm)] of 2,6-dithiomethoxypyridine: 36-40%; MS (70 e/v) m/e 173 (M⁺ +2, 8.0%), 172 (M⁺ +1, 12.2%), 171 (M⁺, 80.5%), 156 (M⁺ -15, 8.5%), 138 (M⁺ -33, 22.7%), 125 (M⁺ -46, 17.3%), 109 (M⁺ -74, 27.9%), 45 (HCS, 100%); and 2-bromo-6-thiomethoxypyridine: 26-28%; MS (70 e/v) m/e 206 (M⁺ +3, 10.9%); 205 (M⁺ +2, 96.2%); 203.9 (M⁺, 100%), 203 (M⁺ -1,
76.6%), 202 (M⁺ -2, 78.2%), 157 (M⁺ -47, 35.6%), 109 (M⁺ -95, 34.7%),
78 (C₅H₄N, 13.1%); which was determined by vpc/ms analysis. Attempts
to separate the mixture by distillation proved unsuccessful.

2,6-Pyridinebis(magnesium bromide). To magnesium turnings (4.86
g, 0.20 g-atom) an anhydrous diethyl ether (10 mL) solution of ethyl
bromide (700 mg, 6 mmol) was added under a nitrogen atmosphere to
initiate the reaction. An ethereal (90 mL) solution of ethyl bromide
(22.5 g, 0.21 mol) and 2,6-dibromopyridine (9.6 g, 0.04 mol) was then
added over a 1.5 hour period at a rate to sustain a constant reflux.
A tan solid separated during the course of the addition. The ethereal
slurry was refluxed for 30 minutes, then the solvent was removed to
give a viscous brown oil, which was suspended in anhydrous diethyl
ether (100 mL) and refluxed for 2 hours. The slurry was rapidly poured
with stirring onto carbon dioxide (100 g). The solvent was evaporated
to give an off-white solid, which was suspended in water (100 mL) and
the pH adjusted to ca. 6 with 5N hydrochloric acid. A tan solid was
filtered and sublimed to give unchanged 2,6-dibromopyridine: 2.60 g;
mp 114-115°C.

The filtrate was extracted with dichloromethane (3 × 100 mL).
The organic extract was dried over anhydrous magnesium sulfate and
concentrated in vacuo to afford an oil (2.62 g), which was shown by
NMR to be a mixture of 2-ethylpyridine (400 mg), 2,6-dibromopyridine
(500 mg), and propionic acid.

The pH of the filtrate was adjusted to ca. 1 with concentrated
hydrochloric acid and then concentrated in vacuo to give a solid residue,
which was dried in vacuo at 130°C for 24 hours, slurried in anhydrous
methanol and saturated with dry hydrogen bromide gas. The solution was refluxed under a nitrogen atmosphere for 12 hours, then filtered to remove a colorless inorganic salt (8.9 g). The filtrate, pH adjusted to ca. 8 with solid potassium carbonate, was extracted with dichloromethane (3 × 100 mL). The combined organic extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a brown solid (1.0 g), which was recrystallized from hexane-ether to give methyl 2,6-pyridinedicarboxylate (152): 90 mg (1.2%), mp 113-118°C; \( R_f = 0.50 \) [ethyl acetate-cyclohexane (2:1)].

**Copper(I) Iodide.** A solution of potassium iodide (3.32 g, 20 mmol) in saturated sulfuric acid was added rapidly with stirring to a solution of copper(II) sulfate pentahydrate (5.0 g, 20 mmol) in water (20 mL) to afford a colorless precipitate. This precipitate was collected, washed sequentially with 5 mL portions of water, ethanol, and ether, then dried in vacuo over phosphorus pentoxide at 100°C for 12 hours to give copper(I) iodide: 3.2 g (84%).

**Attempted and Successful Preparations of Heterocyclic Acetylenes.**

**General Procedure.** A mixture of bis(triphenylphosphine)dichloropalladium(II) (0.1 mmol) and a haloheterocycle (10 mmol) in anhydrous diethyl- or triethylamine (60 mL) was treated with copper(I) iodide (0.3 mmol) under a nitrogen atmosphere. The mixture was stirred at 25°C and dry acetylene gas was introduced through the mixture at a slow rate for 8 hours. At the end of this period, the solvent was evaporated in vacuo to afford a residue, which was slurried in water (30 mL). Then toluene (60 mL) was added and the suspension filtered.
Table VI

Reactions of Dichlorobis(triphenylphosphine)palladium(II)-copper(I)-iodide with a Heterocycle and Acetylene.

<table>
<thead>
<tr>
<th>Substrate (mmol)</th>
<th>Dichlorobis(triphenylphosphine)palladium (mmol)</th>
<th>Copper(I) Iodide (mmol)</th>
<th>Solvent (ml)</th>
<th>Reaction Time/Conditions</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Bromopyridine (13)</td>
<td>0.065</td>
<td>0.13</td>
<td>A (60)</td>
<td>10 hrs./r.t. †</td>
<td>bis(2-pyridyl)acetylene (25%)</td>
</tr>
<tr>
<td></td>
<td>2-Bromopyridine (13)</td>
<td>0.13</td>
<td>A (60)</td>
<td>4.5 hrs./r.t. †; 5.5 hrs./reflux</td>
<td>bis(2-pyridyl)acetylene (18%)</td>
</tr>
<tr>
<td>2-Iodopyridine (10)</td>
<td>0.10</td>
<td>0.30</td>
<td>A (50)</td>
<td>6 hrs./r.t. †</td>
<td>bis(2-pyridyl)acetylene (44%)</td>
</tr>
<tr>
<td>2-Chloroquinoline (12.2)</td>
<td>0.06</td>
<td>0.12</td>
<td>A (60)</td>
<td>6 hrs./r.t. †</td>
<td>N.R. b</td>
</tr>
<tr>
<td>2-Chloroquinoline (12)</td>
<td>0.12</td>
<td>0.36</td>
<td>A (60)</td>
<td>1 hrs./r.t. †; 9 hrs./reflux</td>
<td>N.R. b</td>
</tr>
<tr>
<td>3-Chloropyridine (17,6)</td>
<td>0.176</td>
<td>0.53</td>
<td>A (60)</td>
<td>2.5 hrs./r.t. †; 4 hrs./reflux</td>
<td>N.R. b</td>
</tr>
<tr>
<td>1-Bromo-4-(k'-pyridyl)-benzene (132) (1.1)</td>
<td>0.009</td>
<td>0.018</td>
<td>A (10)</td>
<td>12 hrs./r.t. †</td>
<td>N.R. b</td>
</tr>
<tr>
<td>1-Bromo-4-(k'-pyridyl)-benzene (132) (1.1)</td>
<td>0.011</td>
<td>0.033</td>
<td>A (10)</td>
<td>1 hrs./r.t. †; 8.5 hrs./reflux</td>
<td>N.R. b</td>
</tr>
<tr>
<td>2,6-Dibromopyridine (20)</td>
<td>0.20</td>
<td>0.50</td>
<td>A (100)</td>
<td>9 hrs./r.t. †</td>
<td>bis[2-(6-bromo)pyridyl]acetylene (1.5%)</td>
</tr>
<tr>
<td>2,6-Dibromopyridine (100)</td>
<td>1</td>
<td>3</td>
<td>A (100)</td>
<td>11.5 hrs./r.t. †</td>
<td>1,2-bis[2-(6-bromo)pyridyl]-ethanol (7.5%)</td>
</tr>
<tr>
<td>2,6-Dibromopyridine (20)</td>
<td>0.4</td>
<td>0.6</td>
<td>B (100)</td>
<td>12 hrs./r.t. †</td>
<td>bis[2-(6-bromo)pyridyl]acetylene (14%)</td>
</tr>
</tbody>
</table>
Table VI (Continued).

<table>
<thead>
<tr>
<th>Substrate (mmol)</th>
<th>Dichlorobis(triphenylphosphine)palladium (mmol)</th>
<th>Copper(I) Iodide (mmol)</th>
<th>Solvent (mL)</th>
<th>Reaction Time/Conditions</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,6-Dibromopyridine (100)</td>
<td>1</td>
<td>3</td>
<td>B (400)</td>
<td>9.5 hrs./r.t.</td>
<td>bis[2-(6-bromo)pyridylacetylene (13%)]</td>
</tr>
<tr>
<td>2,6-Dibromopyridine (100)</td>
<td>1</td>
<td>3</td>
<td>B (400)</td>
<td>0.75 hrs./r.t.; 5 hrs./-reflux</td>
<td>bis[2-(6-bromo)pyridylacetylene (5%)]</td>
</tr>
<tr>
<td>2,6-Dibromopyridine (100)</td>
<td>1</td>
<td>3</td>
<td>B (400)</td>
<td>3 hrs./40°C</td>
<td>bis[2-(6-bromo)pyridylacetylene (21%)]</td>
</tr>
</tbody>
</table>

A = Diethylmine
B = Triethylamine
(a) Room temperature.
(b) No reaction, unchanged starting material recovered.
The layers were separated and the aqueous layer extracted with toluene (3 x 60mL). The combined organic extract was column chromatographed on alumina eluting with toluene then ethyl acetate to afford a crude residue, which was treated in the manner described in the following sections to afford unchanged starting material and the corresponding bis(heterocyclic)acetylene.

bis(2-Pyridyl)acetylene (66a). The crude residue was column chromatographed eluting with ethyl acetate to give an oil, which was distilled [bp 100-105°C (46 mm)] to afford unchanged starting material and bis(2-pyridyl)acetylene, as off-white crystals from diethyl ether-petroleum ether: mp 67-69°C (lit.70 mp 69-71°C); $R_f=0.50$ (ethyl acetate).

E-1,2-bis[2'-(6'-bromo)pyridyl]ethenol (160). The residue was recrystallized from ethyl acetate-cyclohexane to give 1,2-bis[2'-(6'-bromo)pyridyl]ethenol, as pale yellow crystals: mp 203-205°C; IR (KBr) 1630, 1590, 1550, 1450, 1430, 1375 cm⁻¹; MS (70 eV) m/e 356 (M⁺, 100%), 327 (M⁺ -29, 91.7%), 200 (M⁺ -156, 72.1%), 156 (M⁺ -200, 74.4%).

Anal. Calcd. for C₁₂H₈Br₂N₂O: C, 40.67; H, 2.24; N, 7.86.
Found: C, 40.35; H, 2.30; N, 7.75.

A solution of 1,2-bis[2'-(6'-bromo)pyridyl]ethenol (50 mg, 0.14 mmol), acetic anhydride (3 mL) and pyridine (1 mL) was stirred and refluxed for 12 hours under a nitrogen atmosphere. After standard work-up procedures, the yellow solid (38 mg) was recrystallized from cyclohexane to give 1,2-bis[2'-(6'-bromo)pyridyl]ethenyl acetate (161) as off-white crystals: 30 mg (53%); mp 133-137°C; NMR (CDCl₃) δ2.49
(s, -CH₃, 3H) 7.48 (m, pyr-H, 6H), 7.55 (s, HC=C, 1H); MS (70 eV) m/e 398 (M⁺, 1.5%), 356 (M⁺ -42, 100%), 327 (M⁺ -71, 37.3%), 200 (M⁺ -198, 44.8%), 158 (C₅H₄BrN, 19.7%).

**Anal.** Calcd. for C₁₄H₁₀Br₂N₂O: C, 42.21; H, 2.51; N, 7.03. Found: C, 42.32; H, 2.51; N, 7.26.

**bis[2-(6-Bromo)pyridyl]acetylene (159).** The residue was suspended in hot petroleum ether and filtered. The filter cake was recrystallized from ethyl acetate-cyclohexane to give **bis[2-(6-bromo)pyridyl]acetylene**, as colorless microcrystals: mp 206-209°C(dec); NMR (CDCl₃) δ7.55 (m); IR (KBr) 2355 (vw, -C≡C-), 1578, 1550, 1448, 1130, 795 cm⁻¹; MS (70 eV) m/e 338 (M⁺, 100%), 257 (M⁺ -81, 27.3%), 177 (M⁺ -162, 12.0%), 89 (C₆H₃N, 23.7%).

**Anal.** Calcd. for C₁₂H₆Br₂N₂: C, 42.60; H, 1.77; N, 8.28. Found: C, 42.41; H, 1.73; N, 8.26.

The filtrate was concentrated in vacuo to afford unchanged 2,6-dibromopyridine: mp 115-117°C.

**1,2-Di[2'-(6'-hydroxymethyl)pyridyl]-1,2-dibromoethane (165a).** A chloroform (50 mL) solution of bromine (2.3 g, 14.5 mmol) was added dropwise over 1.5 hours to a stirred suspension of 1,2-bis[2'-(6'-hydroxymethyl)pyridyl]ethene (3.5 g, 14.5 mmol) in chloroform (350 mL). The resultant yellow-orange slurry was filtered to afford 1,2-di[2'-(6'-hydroxymethyl)pyridyl]-1,2-dibromoethane as a yellow-orange solid: 4.45 g (77%); mp 185-190°C(dec).

**Attempted Preparation of bis[2'-(6-Hydroxymethyl)pyridyl]-acetylene.** General Procedure. To a vigorously stirred, refluxing
Table VII

 Attempted Dehydrobromination of Dibromoethane $165^a$.

<table>
<thead>
<tr>
<th>KOH (g, mol)</th>
<th>Solvent (mL)</th>
<th>Molarity</th>
<th>1,2-bis[2′-(6′-hydroxymethyl)pyridyl]ethane</th>
<th>Percent Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 g, 0.054 mol</td>
<td>MeOH (20)</td>
<td>2.7</td>
<td></td>
<td>59%</td>
</tr>
<tr>
<td>630 mg, 0.011 mol</td>
<td>EtOH (20)</td>
<td>0.56</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>630 mg, 0.011 mol</td>
<td>H2O (20)</td>
<td>0.56</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>1 g, 0.017 mol</td>
<td>MeOH (20)</td>
<td>0.85</td>
<td></td>
<td>72%</td>
</tr>
<tr>
<td>1 g, 0.017 mol</td>
<td>t-BuOH (20)</td>
<td>0.85</td>
<td></td>
<td>17%</td>
</tr>
</tbody>
</table>
solution of potassium hydroxide in methanol, 1,2-di[2'-(6'-hydroxy-methyl)pyridyl]-1,2-dibromoethane was added in ca. 50 mg quantities, then refluxed for 30 minutes. The reaction mixture was concentrated in vacuo to give an off-white solid residue, that was slurried in ice water. A near colorless solid was removed by filtration and recrystallized from ethyl acetate to afford E-1,2-bis[2'-(6'-hydroxymethyl)-pyridyl]ethene (164a), as colorless crystals: mp 137-140°C (lit.124 mp 142-144°C); NMR (CDCl3) δ 4.84 (s, -CH2OH, 4H), 7.19 (dd, 5-pyr-H, J=6.0, 1.0 Hz, 2H), 7.30 (s, HC=CH, 2H), 7.35 (dd, 3-pyr-H, J=7.0, 1.0 Hz, 2H), 7.78 (dd, 4-pyr-H, J=7.0, 6.0 Hz, 2H).

The filtrate was extracted with dichloromethane. The combined organic extract was washed with a saturated salt solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford a small quantity of an unidentified oil.

1,2-Di[2'-(6'-methyl)pyridyl]-1,2-dibromoethane (165b).70 A chloroform (25 mL) suspension of 1,2-bis[2'-(6'-methyl)pyridyl]ethene (2.5 g, 12 mmol) was treated with bromine (1.9 g, 12 mmol) in chloroform (25 mL) as described in the above procedure. The crude dibromide was recrystallized from ethanol to give 1,2-di[2'-(6'-methyl)pyridyl]-1,2-dibromoethane, as a yellow solid: 4.2 g (95%); mp 211-215°C(dec), [lit.70 mp 208-209°C(dec)].

bis[2-(6-Methyl)pyridyl]acetylene (166b).70 1,2-Di[2'-(6'-methyl)pyridyl]-1,2-dibromoethane (1.0 g, 2.7 mmol) was added to a methanol (20 mL) solution of potassium hydroxide (3 g, 54 mmol) as previously described to afford an off-white solid. This solid was
recrystallized from cyclohexane to give bis[2-(6-methyl)pyridyl]acetylene, as colorless crystals: 280 mg (50%); mp 133-136°C, (lit.70 mp 138-139°C); NMR (CDCl3) δ 2.56 (s, pyr-Me, 6H), 7.10-7.90 (m, pyr-H, 6H).

Attempted Preparation of 1,2-bis[2'-(6'-methyl)pyridyl]ethene. To a slurry of titanium trichloride-lithium aluminium hydride (3 equiv./1 equiv., 73.2 mmol/24.4 mmol) in anhydrous dimethoxyethane (300 mL), 2-hydroxymethyl-6-methylpyridine (3.0 g, 24.4 mmol) was added. After refluxing for 16 hours, the reaction was worked-up as described above; an orange oil (3.61 g) was isolated and distilled to give unchanged starting material, as a yellow oil: [602 mg; bp 106-110°C (7.5 mm) lit.123 bp 105-110°C (14 mm)]; and 2,6-dimethylpyridine, as a colorless oil: [1.9 g (73%); bp 48-52°C (7.5 mm) lit.125 bp 143.8°C]; NMR (CDCl3) δ 2.51 (s, CH3, 6H), 6.95 (ά, 3,5-pyr-H, J=7.0 Hz, 2H), 7.42 (t, 4-pyr-H, J=7.0 Hz, 1H).

1,2-bis[2'-(6'-Bromo)pyridyl]benzene (67a). A solution of 1,2-bis[2-(6-bromo)pyridyl]acetylene (5.0 g, 14.8 mmol), hydroquinone (50 mg) and 2-pyron (2.88 g, 30 mmol) in dichlorobenzene (50 mL) was refluxed for 24 hours under nitrogen. A second portion of 2-pyron (2.0 g, 21 mmol) was added and the solution refluxed for an additional 24 hours. The solution was concentrated in vacuo to afford a black residue (6.41 g), which was column chromatographed on silica gel eluting with dichloromethane, then ethyl acetate to afford a red residue. This residue was dissolved in hot 95% ethanol and decolorized with activated charcoal. After dissolution, pale orange crystals,
which precipitated, were collected, then recrystallized in cyclohexane to give 1,2-bis[2'-(6'-bromo)pyridyl]benzene, as colorless needles: 1.4 g.

The 95% ethanol solution was concentrated in vacuo to afford a red semisolid, which was column chromatographed on silica gel eluting with ethyl acetate to afford an orange residue. This residue was dissolved in hot 95% ethanol, then treated as described above to afford 1,2-bis[2'-(6'-bromo)pyridyl]benzene: 400 mg (28% overall); mp 173-174°C; NMR (CDCl₃) δ 7.18 (dd, 5-pyr-H, J = 6.0, 3.0 Hz, 2H), 7.23-7.62 (m, arom-H, 6H), 7.66 (m, phe-H, 4H); IR (KBr) 1565, 1580, 1420, 1385, 1260, 790, 750 cm⁻¹; MS (70 eV) m/e 390 (M⁺, 43.9%), 309 (M⁺ - 80, 42.8%), 229 (M⁺ - 161, 26.8%), 203 (M⁺ - 187, 17.0%).

Anal. Calcd. for C₁₆H₁₀N₂Br₂: C, 49.23; H, 2.56; N, 7.18. Found: C, 48.94; H, 2.49; N, 6.94.

1,2-bis[2'-(6'-Methyl)pyridyl]benzene (67b). A mixture of bis[2-(6-methyl)pyridyl]acetylene (4.0 g, 19.2 mmol), 2-pyrone (3.8 g, 40 mmol), and hydroquinone (50 mg) in 1,2-dichlorobenzene (45 mL) was refluxed under a nitrogen atmosphere for 48 hours. The mixture was concentrated in vacuo to afford a viscous black oil, which was distilled to give an orange, highly viscous oil: 4.2 g, bp 155-165°C (0.35 mm). This oil was redistilled to afford 1,2-bis[2'-(6'-methyl)-pyridyl]benzene, as a viscous yellow oil: 3.2 g (64%); bp 148-155°C (0.3 mm) [lit. bp 110-114°C (0.2 mm)]; NMR (200MHz, CD₂Cl₂) δ 2.49 (s, CH₃, 6H), 6.82 (d, 5-pyr-H, J = 8.5 Hz, 2H), 6.98 (d, 3-pyr-H, J = 8.5 Hz, 2H), 7.35 (t, 4-pyr-H, J = 8.5 Hz, 2H), 7.52 (m, 4,5-phe-H, 2H), 7.65 (m, 3,6-phe-H, 2H); IR (neat) 1578, 1455, 1310, 1163,
1003, 805, 765 cm\(^{-1}\).

1,2-bis[2'-(6'-Bromomethyl)pyridyl]benzene (16\%\(\text{a}\)).\(^{126}\) A benzene (100 mL) solution of 1,2-bis[2'-(6'-methyl)pyridyl]benzene (2.8 g, 10.7 mmol) and azoisobutyronitrile [(AIBN), 50 mg] was treated with N-bromosuccinimide (4.6 g, 26 mmol) and illuminated with a 150 watt lamp. After stirring and refluxing under nitrogen for 12 hours, the red suspension was extracted with a 10% aqueous solution of sodium carbonate (100 mL), water (100 mL), and then concentrated \textit{in vacuo} to afford a red oily residue (5.21 g). This red residue was column chromatographed eluting with ethyl acetate to afford a mixture (3.81 g), which was again column chromatographed eluting with ethyl acetate-cyclohexane (1:4) to afford a mixture (1.04 g) containing three major components. This mixture was rechromatographed (ThLC) eluting with ethyl acetate-cyclohexane (1:5) to afford the following fractions:

\textbf{Fraction A} gave 1-[2'-(6'-bromomethyl)pyridyl]-2-[2'-(6'-dibromomethyl)pyridyl]benzene (170), as a semisolid: 243 mg (5\%); R\(_f\)=0.35 [ethyl acetate-cyclohexane (1:5)]; NMR (CDCl\(_3\)) \(\delta\) 4.39 (s, -CH\(_2\)Br, 2H), 6.48 (s, CHBr\(_2\), 1H), 7.05-7.80 (m, arom-H, 10H); MS (70 e/\(\text{v}\)) m/e 497 (M\(^+\), 4.4\%\), 417 (M\(^+\) -80, 70.6\%), 337 (M\(^+\) -160, 9.9\%), 257 (M\(^+\) -240, 30.2\%), 217 (M\(^+\) -280, 100\%), 191 (26.0\%).

\textbf{Fraction B} afforded 1,2-bis[2'-(6'-bromomethyl)pyridyl]benzene (16\%\(\text{a}\)), as a semisolid: 297 mg (7\%); R\(_f\)=0.24 [ethyl acetate-cyclohexane (1:5)]; NMR (CDCl\(_3\)) \(\delta\) 4.39 (s, CH\(_2\)Br, 4H), 6.95-7.80 (m, arom-H, 10H); MS (70 e/\(\text{v}\)) m/e 418 (M\(^+\), 11.7\%), 339 (M\(^+\) -79, 98\%), 337 (M\(^+\) -81, 88.9\%), 257 (M\(^+\) -161, 67.2\%), 218 (M\(^+\) -200, 100\%), 191 (22.6\%).
Preparation of Ortho-pyridinophane (168). An ethanol (25 mL) solution of 1,2-bis[2'-(6'-bromomethyl)pyridyl]benzene (300 mg, 0.72 mmol) in a constant addition dropping funnel and an ethanol (25 mL) solution of sodium sulfide nanohydrate (173 mg, 0.72 mmol) in a second constant addition dropping funnel were added dropwise at a simultaneous rate to refluxing ethanol (40 mL) over 1.5 hours. After refluxing for 22 hours, the solution was concentrated in vacuo to afford a red solid residue, which was slurried in dichloromethane (20 mL) and filtered. The filtrate was concentrated in vacuo to afford a solid residue (233 mg), which was chromatographed (ThLC) eluting with ethyl acetate-cyclohexane [(1:4), 3x] to give the following fractions:

Fraction A afforded ortho-pyridinophane 168, a near colorless solid: 17 mg (8%); mp 162-166°C(dec); NMR (200 MHz, CD2Cl2) δ3.83 (s, (-H2C)2-S, 4H), 7.03 (d, 5-pyr-H, J=7.0 Hz, 2H), 7.45-7.75 (m, arom-H, 10H); MS (70 eV) m/e 292 (M+ + 2, 1.9%), 291 (M+ + 1, 6.4%), 290 (M+, 23.4%), 258 (M+ - 32, 32.7%), 257 (M+ - 33, 100%), 243 (M+ - 47, 9.3%), 242 (M+ - 48, 11.7%), 228 (M+ - 62, 14.4%), 217 (M+ - 73, 13.2%), 204 (M+ - 88, 23.6%), 182 (M+ - 108, 17.3%), 149 (9.5%), 128 (10.9%).

Fraction B gave 1,2-bis[2'- (6'-thiomethyl)pyridyl]benzene (171), as brown solid: 18 mg (8%); mp 178-181°C(dec); NMR (CDCl3) δ2.25 [bs, -SH (exchanged D2O), 2H], 3.61 [bs, -CH2SH, 4H], 7.05 (d, 5-pyr-H, J=2.0 Hz, 2H), 7.17 (d, 3-pyr-H, J=2.0 Hz, 2H), 7.40-7.85 (m, arom-H, 6H); MS (70 eV) m/e 324 (M+, 5.3%), 322 (M+ - 2, 37.9%), 321 (M+ - 1, 10.8%), 258 (M+ - 66, 57.6%), 257 (M+ - 67, 100%), 243 (M+ - 81, 11.7%), 229 (M+ - 95, 18.7%), 219 (M+ - 105, 16.5%), 204 (M+ - 120, 25.3%), 191 (10.0%), 128 (15.1%), 108 (10.2%), 102 (5.5%), 45 (4.1%).
Results and Discussion

Organometallic reagents have long been recognized as powerful synthetic tools that have often played prominent roles in synthetic strategies. Organometallic reagents were employed in this research to transform simple heterocyclic substrates into synthetically useful compounds. Mechanistic aspects of these reagents, while of interest, were not the thrust of these research endeavors. Because the compounds synthesized and utilized in subsequent reactions are diverse, the Results and Discussion is divided into three main sections: I. Organometallic Reactions with Heterocyclic Ketones; II. Organometallic Heterocycles, Pyridine Directed Metallations and Polymetallated Pyridine; and III. Synthesis of Heterocyclic Acetylenes and Related Derivatives. These sections are presented in the order listed. Within each of these main sections, there are further subdivisions in order to described in detail this research endeavor.
I. Organometallic Reactions with Heterocyclic Ketones.

4,5-Diazafluorenone (1), 1,8-diazafluorenone (2), and 1-azafluorenone (3) were synthons in a variety of reactions. Organometallic reagents were employed to transform each of these compounds into the desired products. The types of reactions and reagents involved varied. Therefore, in order to thoroughly and logically treat each particular reaction, as well as derived products, this section is subdivided into:

(a) Synthesis of Heterocyclic Ketones; (b) Synthesis of Acetylene-Diols; (c) Synthesis of Cumulenes; (d) Reactions of Heterocyclic Ketones with Low Valent Titanium; and (e) Onychine, an Azafluorenone Alkaloid.

Scheme IV better illustrates the unique relationships between these subdivisions and further indicates that the heterocyclic ketones are pivotal to each of the synthetic sequences.

\[ \text{Scheme IV} \]

\[ \text{Ketone Precursors} \]
\[ \rightarrow \text{Reaction w/ low valent Titanium} \]

Synthesis of Heterocyclic Ketones. 4,5-Diazafluorenone (1) and 1-azafluorenone (3) were obtained in moderate yield (ca. 20%) by the potassium permanganate oxidation of 1,10-phenanthroline monohydrate.
The oxidations proceed through the quinone intermediate \( \text{88} \), which undergoes a facile benzylic acid rearrangement in the basic media. This sequence is totally analogous to the rearrangement of non-heterocyclic model \( \text{87} \).\(^1\)\(^2\) In non-heterocyclic systems, e.g. phenanthrenequinone (\( \text{87} \)), the hydroxy-acid \( \text{90} \) must be heated in air in order to affect decarboxylation and subsequent oxidation.\(^1\)\(^2\) However, in the corresponding heterocyclic analogs, decarboxylation and oxidation proceeded rapidly in solution without the isolation of the intermediate hydroxy-acid \( \text{90} \).\(^2\)\(^3\)

Gillard and Hill\(^2\)\(^3\) attributed the spontaneous decarboxylation and oxidation of these heterocyclic compounds to the stability of the final product, the azafluorenone. A more plausible explanation is the enhanced ability of the heterocyclic compounds to delocalize the negative charge generated at the 9-position during the course of decarboxylation. The activation energy of the decarboxylation-oxidation steps would be lowered and thereby induced to proceed under
milder conditions.

One major drawback to this permanganate oxidation procedure, when applied to heterocyclic systems, is the low (10-20%) overall conversion. Ketones $\text{IIa,b}$ were readily isolated as by-products from the oxidation procedure; whereas, the main products were the corresponding dicarboxylic acids $\text{IIc,d}$. A recent report$^6$ indicated that the yields of these desired ketones could be increased, while the yields of the dicarboxylic acids minimized. By the use of a more dilute permanganate oxidizing medium and longer reaction time, the yield of $\text{IIa}$ could be increased to 55%. The yield of $\text{IIb}$ could be increased to 80% by using diiodide pentoxide in acetic acid as the oxidant, instead of permanganate.

Since dicarboxylic acids $\text{IIa}$ and $\text{IIb}$ were significant (ca. 80%) products in the permanganate oxidation of $\text{Ia}$ and $\text{Ib}$, respectively, alternate methods of converting these acids to the desired ketones were explored. The most fruitful and logical route to $\text{IIb}$ from $\text{IIb}$ was pyrolysis ($360^\circ$C) of calcium 3-phenylpyridine-2,2'-dicarboxylate ($\text{III}$); $\text{IIb}$ was isolated in 22% yield.

$$\text{IIb} \xrightarrow{\text{Ca(OH)}_2} \text{III} \xrightarrow{\Delta} \text{IIb}$$

The corresponding anhydride of $\text{IIb}$ was similarly transformed into $\text{IIb}$ when heated strongly. These alternate methods of preparing $\text{IIb}$ were particularly valuable, in that an unwanted product could be conveniently converted into the desired ketonic products.
4,5-Diazafluorenone (91) was prepared by treatment of 1,10-phenanthroline monohydrate (37) with a nitrating mixture, nitric acid-sulfuric acid.3,104 The major nitrination product was 5-nitro-1,10-phenanthroline; however 1,10-phenanthroline-5,6-quinone (88) was also isolated (5%) as a minor side product, which during basic work-up underwent a facile benzilic acid rearrangement to give 91. Gillard, et al.103 found that the reaction profile of phenanthroline nitrilation could be altered to afford additional quinone by first forming a metal complex, tris(1,10-phenanthroline)cobalt(II) perchlorate, followed by nitrilation of the complex. Nitrilation of 1,10-phenanthroline represents one of the few reactions that compare the reactivity of a metal ion complex vs the free ligand.128,129 A related example of a complex reacting differently from the free ligand is the coupling of tris(1,10-phenanthroline)iron(II) with azobenzene. This reaction does not occur with the free ligand.130

1,8-Diazafluorenone (21) was obtained (43%) by application of the procedure described by Druey and Schmidt2, which again involved a benzilic acid rearrangement of 4,7-phenanthroline-5,6-quinone [Phenquione (20)].

The mass spectra of 1, 2, and 3 as well as their phenanthroline precursors share a common mass spectral fragmentation pattern, which is analogous to the corresponding carboxylic compounds, phenanthrenequinone and 9-fluorenone. The mass spectrum of 9-fluorenone (20) shows the initial loss of CO to produce a biphenylene ion 21, which undergoes further fragmentation.131
Scheme IV depicts the general fragmentation pattern for 1,10-phenanthroline-5,6-quinone (97,128), 4,7-phenanthroline-5,6-quinone (93), 4,5-diazafluorenone (1),128,132 and 1,8-diazafluorenone (2), all of which proceed through an analogous diazabiphenylene ion (95). This ion then fragments by two routes, loss of C2H2 (path A) or loss of HCN (path B). The peak intensity indicates that 1,8-diazafluorenone (2) prefers path A, while 4,5-diazafluorenone (1) shows only a slight preference for path B; see Table I.A. Keats and Summers132 reported that 1 has a strong tendency to fragment by path A. Gillard and Hill,128 who investigated the mass spectra of several 1,10-phenanthroline and bipyridyl derivatives, noted that 4,5-diazafluorenone and the subsequent diazabiphenylene are very stable ions (relative intensity 100% and 49.5%, respectively) and that most of the phenanthroline derivatives fragment via these ions. The fragmentation pattern of 4,7-phenanthroline-5,6-quinones (93) and 1,8-diazafluorenone (2) correlate well with this study.

1-Azafluorenone (2) and related compounds fragment by a route identical to that of the phenanthroline derivatives (Scheme VII).
Anhydride $n^8$, which does not exhibit a parent ion peak (m/e 225), fragments by loss of CO$_2$ either stepwise as illustrated in path B or directly as shown in path A to give 1-azafluorenone (3). Ketone $n^8$ easily loses CO to afford 1,2-pyridylphenylene $i^{100}$, which further fragments via either loss of C$_2$H$_2$ or of HCN.

The NMR spectra of the isomeric diazafluorenones $[\ ^1\ ]$ and $[\ ^2\ ]$, exhibited a doublet of doublet (dd) pattern characteristic of these symmetrical ketones. The protons $\alpha$ to nitrogen in ketones $[\ ^1\ ]$ (3,6-hydrogens) and $[\ ^2\ ]$ (2,7-hydrogens) absorbed at $\delta^{8.75}$ with coupling constants of 5.0 and 2.0Hz and at $\delta^{8.62}$ with coupling constants of 5.0 and 1.5Hz, respectively. The protons $\gamma$ to nitrogen in $[\ ^1\ ]$ (1,8-hydrogens) and $[\ ^2\ ]$ (4,5-hydrogens) absorbed at $\delta^{7.91}$ ($J=8.0$, 2.0Hz) and at $\delta^{7.29}$ ($J=7.5$, 1.5Hz), respectively. Unsymmetrical azafluorenone $[\ ^3\ ]$ exhibited a more complex NMR spectrum. A doublet of doublet pattern for the protons $\alpha$ and $\gamma$ to nitrogen appeared at $\delta^{8.52}$ ($J=5.0$, 1.5Hz) and at $\delta^{7.81}$ ($J=8.0$, 1.5Hz), respectively.

The infrared spectra of these ketones $[\ ^1\ ]$, $[\ ^2\ ]$, and $[\ ^3\ ]$ exhibited strong carbonyl absorbance at 1725, 1730, and 1775 cm$^{-1}$, respectively.

**Synthesis of Acetylene-Diols.** The general procedure used to prepare acetylene-diols is shown in Scheme VIII.

![Scheme VIII](image-url)
The metal acetylide \(^{103}\) adds sequentially to one carbonyl unit to give an acetylenic alcohol, which condenses with a second carbonyl unit to afford the \(^{104}\) 1,4-acetylene-diol. Organometallic reagents used (Scheme VIII) were acetylene-bis(magnesium bromide), sodium acetylide, and lithium acetylide ethylenediamine complex. Each of these reagents has advantages as well as disadvantages in their reactivity and preparation. However, before these factors are considered a brief general description about organometallic reagents is warranted.

Organometallic reagents often form dimers, trimers, and/or higher aggregates in solution.\(^{1d}\) The structure and number of aggregates depend on the solvent, nature of the organic moiety, and temperature. Boiling point elevation studies on simple alkyllithium compounds in ether indicate that aggregates can range from dimers to pentamers.\(^{133}\) Grignard reagents, which are governed by the Schlenck equilibrium,\(^{134}\) appear to be monomers in tetrahydrofuran and diethyl ether at low concentration.\(^{135}\) Just as the structures of organometallic reagents in solution differ, the reactivities of organometallics sometimes vary. Alkyllithium compounds add smoothly to ketimines, while Grignard reagents simply reduce ketimines.\(^{136}\) Organosodium reagents cause acetophenone to enolize, but Grignard reagents and organolithiums undergo 1,2-addition.\(^{137}\) The consistency of organometallic reagents in solution also varies; sodium acetylide in tetrahydrofuran is a colorless slurry; whereas acetylene-bis(magnesium bromide) is a reddish semisolid. Therefore, of the three organometallic reagents used; acetylene-bis(magnesium bromide), sodium acetylide, and lithium acetylide ethylenediamine complex each particular reagent varies in
both structure and reactivity.

4,5-Diazafluorenone (4), 1-azafluorenone (3), and 9-fluorenone (20) were the specific ketones used in the synthesis of acetylene-diols. The methyl derivatives 105-107 of 4,5-diazafluorenone, 1,8-diazafluorenone, and 1-azafluorenone, respectively, were prepared (ca. 35%) by addition of the ketone to a stirred tetrahydrofuran solution of methylmagnesium bromide. These reactions served to gain experience in handling organometallic reagents and further to probe the reactivity of the carbonyl unit prior to attempting the generation and addition of metal acetylides.

A classical metal acetylide employed in this type of reaction is acetylenebis(magnesium bromide), generated by passage of acetylene through a solution containing ethylmagnesium bromide.7-10 Edinger and Day,9 used acetylenebis(magnesium bromide) to prepare 9,9'-ethylenebis-9-fluorenol (12) in unspecified yield. Following their procedure, 12 was prepared (6%). The preparation of 12 served as a model for the reaction of 4,5-diazafluorenone with the Grignard acetylide.
Reaction of diazafluorenone with acetylenebis(magnesium bromide) afforded unchanged starting material. This reaction indicated the following drawbacks: (1) the acetylene gas inlet frequently got plugged, and thus requires constant maintenance; and (2) the lack of a method to readily determine when all acetylenebis(magnesium bromide) is generated, i.e. there is no end point for the acetylene addition. The following method of generating metal acetylide in part circumvented these problems.

A more viable route to the acetylene-diols was via sodium acetylide. The method used to generate sodium acetylide incorporated a convenient color change which permitted an end point determination. Sodium metal was added to a stirred tetrahydrofuran solution of either biphenyl or naphthalene. An electron-transfer from the metal to aromatic nucleus occurred producing a blue solution; passage of acetylene through the solution generated a colorless slurry of sodium acetylide. When all traces of color had disappeared from the reaction mixture, the sodium acetylide was completely formed. Therefore, an end point was utilized (Scheme IX).

\[
\text{Na} + \overset{\text{108}}{\text{Biphenyl or Naphthalene}} \rightarrow \text{Na}^+ \left[ \overset{\text{108}}{\text{Biphenyl or Naphthalene}} \right]^- \\
\downarrow \text{HC}≡\text{CH} \\
\overset{\text{108}}{\text{NaC}≡\text{CNa}}
\]

\[
\begin{array}{c}
\text{diazfluorenone} \\
\text{108}
\end{array}
\rightarrow
\begin{array}{c}
\text{product with hydroxyl groups}
\end{array}
\]
9-Fluorenone was treated with sodium acetylide and then hydrolyzed with dilute mineral acid to give \( \text{I} \) in 19% yield. \( \text{I},\text{5-Diazafluorenone} \), treated with sodium hydride prior to reaction to remove traces of water of hydration,\textsuperscript{138} was reacted with sodium acetylide to obtain the expected acetylene-diol \( \text{II} \). Scheme IX outlines the reaction sequence for \( \text{I} \). Acetylene-diol \( \text{II} \) is a high melting solid, which is extremely insoluble in most organic solvents. This was a major factor which impeded the purification and complete identification of this acetylene-diol. In view of the minimal solubility in common organic solvents, the NMR spectrum of \( \text{II} \) was obtained in trifluoroacetic acid. The spectrum shows a broad multiplet at \( 88.2 \) for the 2,7-hydrogens and a multiplet \( 88.8 \) for the remaining aromatic hydrogens.

When 1-azafluorenone was treated with reagent \( \text{III} \), unchanged starting material was isolated.

A convenient procedure to generate in situ sodium acetylide has been described.\textsuperscript{13} 1,2-Dibromoethane was treated with sodium amide in hexamethylphosphorus triamide (HMPT) to afford sodium acetylide via a didehydrobromination. When \( \text{I},\text{5-Diazafluorenone} \) was treated under these conditions, \( \text{II} \) was isolated in trace quantities.

Lithium acetylide ethylenediamine complex,\textsuperscript{14} a stable crystalline metal acetylide, was easily prepared in good yield by the passage of acetylene through a solution of \( \text{N-lithioethylenediamine} \). The stability of this metal acetylide was attributed to the ability of ethylenediamine to complex lithium.\textsuperscript{14a} Monolithium acetylide in liquid ammonia (-33°C) is a stable compound, but attempts to isolate the reagent result in disproportionation and formation of dilithium acetylide;\textsuperscript{15}
therefore, liquid ammonia stabilizes the organometallic reagent. In comparison, ethylenediamine is able to stabilize monolithium acetylide as a crystalline compound at higher temperatures (150°C);\textsuperscript{14a} thus giving rise to a more useful acetylide reagent.

Lithium acetylide ethylenediamine complex (\textsuperscript{14}) normally reacts with a ketone to produce an ethynylcarbinol (\textsuperscript{109}).

\[
\text{R} \overset{\text{O}}{\text{C}} + \text{LiC≡CH} \cdot \text{H}_2\text{N(CH}_2\text{)}_2\text{NH}_2 \rightarrow \text{OLi} \quad \text{R} \quad \text{C≡CH} + \text{H}_2\text{N(CH}_2\text{)}_2\text{NH}_2
\]

\[
\text{\textsuperscript{109}} + \text{\textsuperscript{14}} \rightarrow \text{OLi} \quad \text{R} \quad \text{C≡CLi} \rightarrow \text{OLi} \quad \text{R} \quad \text{C≡C} \rightarrow \text{OLi} \quad \text{R}
\]

A competing reaction, especially in solvents of low dielectric constant, is metallation of (\textsuperscript{109}) and further reaction with a second ketone to yield a 1,4-butyne-diol (\textsuperscript{111})\textsuperscript{14b}.

As a model, 9-fluorenone was treated with (\textsuperscript{14}) in benzene or p-dioxane (solvents of low dielectric constant) in an attempt to generate the desired 1,4-butyne-diol. However, this procedure afforded only unchanged 9-fluorenone.

Of the methods for the synthesis of 1,4-acetylene-diols, the best results were obtained by the use of sodium acetylide generated from a dissolving metal procedure. For example, acetylene-diol (\textsuperscript{11}) was successfully prepared by this method. The overall progress of this
sequence was however impeded by solubility problems, 4,5-diaza-fluorenone has only limited solubility in ethereal solvents (12mg/mL in THF and 1.3mg/mL in diethyl ether) and further by difficulty in obtaining sufficient quantities of starting material, 4,5-diaza-fluorenone and 1-azafluorenone.

**Synthesis of Cumulenes.** 1,4-Acetylene-diols are converted to the corresponding butatriene by reduction of the diol. Many reagents, such as sulfuric acid-potassium iodide,9,16 hydroiodic acid-iodine,19 stannous chloride-hydrogen chloride12,17 and phosphorus tribromide-pyridine,20 have successfully brought about this transformation with a variety of alkyl and aryl substrates. Fischer139 has provided an excellent discussion of these reagents in his review of cumulenes. A reagent, that is not commonly encountered in these types of reactions, is diphosphorus tetraiodide,21 which has been utilized in these laboratories to convert pyridyl butyne-diols to the corresponding butatrienes in reasonable yield.7,8 Diphosphorus tetraiodide is particularly useful, when the butyne-diol is sensitive to acid-catalyzed rearrangements, e.g. 17,15

\[
\begin{array}{c}
\text{Ph} \quad \equiv \quad \text{Ph} \\
\text{Py} \quad \equiv \quad \text{Py}
\end{array} \xrightarrow{\text{H}^+} \quad \begin{array}{c}
\text{Ph} \quad \equiv \\
\text{Py}
\end{array}
\]

Although rearrangements should present no problems in the fluorenylethyne-1,4-diols, diphosphorus tetraiodide was used to convert 9,9'-ethylenebis-9-fluorenol (12) to the red crystalline bisbiphenylene-butatriene (13).
The UV/VIS spectrum of cumulene $\text{13}$ exhibits a strong absorption at 483 nm, a characteristic absorption for cumulenes. When 9,9'-ethynylenebis-[4,5-diazfluoren-9-ol (11) was treated with diphosphorus tetraiodide, only unchanged starting material was recovered. This unreactivity may be accounted for by the very limited solubility of 11. Further studies in an attempt to circumvent these problems were not undertaken in light of the numerous unforeseen difficulties: synthetic unavailability of starting ketones, low ketone to diol conversion, and the insolubility of the heterocyclic diols.

Reactions of Heterocyclic Ketones with Low Valent Titanium. A variety of aliphatic and aromatic aldehydes and ketones has been reductively coupled using low valent titanium reagents.$^{22,23}$ The overall reaction is depicted in Scheme X.

![Scheme X](image)

**Scheme X**

\[
\begin{align*}
\text{R} = &\text{R} \quad \xrightarrow{\text{a or b}} \quad \text{R} = \text{R} \\
\text{a. TiCl}_3 - \text{LiAlH}_4 \\
\text{b. TiCl}_3 - \text{M} \\
\text{M = Li, Na, or K}
\end{align*}
\]

The active titanium reagent is prepared by reduction of either titanium trichloride or titanium tetrachloride with lithium aluminium...
hydride or a metal such as sodium lithium, potassium or zinc.\textsuperscript{22,23,25}

McMurry and Mukaiyama have each utilized low valent titanium to accomplish intra- and intermolecular reductive coupling on numerous substrates.\textsuperscript{22,23} There were, however, no examples of the use of low valent titanium to reductively couple heterocyclic ketones. A series of heterocyclic ketones has now been treated with low valent titanium.

Before discussing the reaction of low valent titanium with heterocyclic compounds, a brief overview of the mechanism is needed. The postulated mechanism\textsuperscript{26,33} is depicted in Scheme XI.

\begin{center}
\textbf{SCHEME XI}
\end{center}

\begin{center}
\begin{align*}
\text{R} \to \text{O} & \quad \text{Ti}^0 \quad \text{R}_2 \text{C} \text{O} \text{Ti} \quad \rightarrow \quad \text{R} \quad \text{TiO} \text{OTi} \quad \text{R} \\
\text{(I12)} & \quad \text{R} \quad \text{R} \\
\text{(I13)} & \quad \text{R} \quad \text{R} \\
\end{align*}
\end{center}

The first step of the mechanism involves transfer of an electron from Ti\textsuperscript{0} to the carbonyl compound. A pinacol coupling reaction occurs, followed by deoxygenation of I12 or I13 by Ti(III) or Ti(IV). McMurry\textsuperscript{26,27} stated that intermediate I13 is the "most likely" species and probably collapses in a nonconcerted manner to give the respective olefin.

In order to gain knowledge in handling the titanium reagent two carbocyclic ketones, 9-fluorenone and benzophenone, were treated with low valent titanium generated from titanium trichloride-lithium aluminium hydride (method a) to give (ca. 85\%) bis(fluorenylidene) (21) and tetraphenylethene (23), respectively.
The NMR spectrum of the red crystalline \( 2_1 \) showed a multiplet at \( \delta 8.2 \) for the 1,8-hydrogen, whose position is due to the close proximity of the aromatic rings. Since these compounds were prepared in yields consistent with published values, the quality of the titanium reagent and reaction conditions were similar to those described in the literature.

3-Benzoylpyridine (115) was treated with low valent titanium generated by method a to give the isomeric E- and Z-1,2-diphenyl-1,2-bis(3'-pyridyl)ethene (115).

The isomers were easily separated by chromatography (ThLC) and identified by Eu-shift [Eu(FOD)\(_3\)] NMR studies; see Figures 1 and 2. The first and most obvious characteristic of these spectra is the 5 ppm downfield shift of the 2,6-pyridyl hydrogens at 21% mole ratio of Eu(FOD)\(_3\). This shift confirmed that the Eu-shift reagent was coordinated with the nitrogen atoms. The comparative shift value of the ortho-phenyl hydrogens, decoupling experiments, and the comparison of the aromatic region (ca. \( \delta 7 \)) permitted the identification of the geometrical isomers. Decoupling experiments conducted on the Z-isomer of 115 at 21% mole ratio of Eu(FOD)\(_3\) allowed assignment of signals.
Figure 1. $^1$H NMR (100 MHz) spectra of (E)-1,3 at 30°C in CDCl$_3$ solution containing the substrate (0.16 M) at various mole ratios of Eu(fod)$_3$: (a) 0%; (b) 1%; (c) 5%; (d) 11%; (e) 21%.
Figure 2. $^1$H NMR (100 MHz) spectra of (Z)-$^\text{FCC}$ at 30°C in CDCl$_3$ solution containing the substrate (0.16 M) at various mole ratios of Eu(fod)$_3$: (a) 0%; (b) 1%; (c) 5%; (d) 11%; (e) 21%.
appearing farthest downfield (Figure 2). Irradiation of the broad singlet at δ12.8 (Z-isomer) collapsed the signal (dd) at δ8.5 to a doublet, thereby confirming the singlet at δ12.8 as the 6-pyridyl hydrogen and the collapsed signal at δ8.5 as the 5-pyridyl hydrogen. These spectra also showed that the signal for the 2,6-pyridyl hydrogens of the E-isomer appears farther downfield than the corresponding hydrogens of the Z-isomer. The orientation in the E-isomer allows close contact of the Eu-shift reagent to the nitrogen atom. Since these nitrogens are directed away from one another, the Eu-shift reagent undergoes facile coordination with the nitrogen atoms. However, the orientation in the Z-isomer, where the nitrogens are in close proximity causes some crowding of the Eu-shift reagent as its coordinates, which results in less contact between the Eu and the nitrogen atom. Therefore, the degree of change of chemical shift of $^{115}$Eu in the Z-isomer was diminished.

Mass spectral data of the two isomers exhibited a strong parent ion at m/e 334 (100%) and nearly identical fragmentation patterns differing only slightly in relative intensities.

When 4,5-diazafluorenone was treated with low valent titanium under the conditions of method a, $\text{bis}(4,5$-diazafluorenylidene) (10) was obtained as a dihydrate. The structure of dihydrate 10 was confirmed by mass spectral data and by the NMR spectrum, which exhibited a broad singlet at δ4.80 that exchanged with D$_2$O. Attempts to thermally dehydrate 10 resulted in structural decomposition.

![Diagram of molecular structure]
The above examples have dealt with reductive coupling of carbonyl units to afford symmetrical olefins. Unsymmetrical olefins can also be prepared by using this same method. McMurry\textsuperscript{34} first reported this type of unsymmetrical coupling between acetophenone (1\textsubscript{16}) and 9-fluorenone (2\textsubscript{0}), in which the unsymmetrical olefin 3\textsubscript{4} would be formed. \[ \begin{array}{c} 20 \\ \rightarrow \\ 34 \end{array} \]

Reductive coupling to yield unsymmetrical olefins occurred in larger than statistical amounts, since the two ketones have differing abilities to accept and stabilize electrons. The energy requirement to 9-fluorenone to accept two electrons from titanium is lower than that of acetophenone to accept one electron. Therefore, the anion of 9-fluorenone was generated in preference of the radical of acetophenone. The anion of 9-fluorenone then condensed in an "aldol fashion" with acetophenone to afford the unsymmetrical olefin 3\textsubscript{4}.\textsuperscript{34,35}

A mixed reductive coupling between 4,5-diazafluorenone (1) and 9-fluorenone (20) afforded olefin 118. When an equal molar mixture of 1 and 20 was treated with low valent titanium (method a), a mixed coupling occurred to give the unsymmetrical olefin 118 along with bis-(fluorenylidene).
The ability of 4,5-diazafluorenone to accept and stabilize electrons is about $10^5$ times greater than the ability of 9-fluorenone.\textsuperscript{36} Therefore, in the presence of electron donors such as low valent titanium, 4,5-diazafluorenone exists almost completely as anion $\text{I7}$ and not the corresponding radical. In the reductive coupling reaction, anion $\text{I7}$ would condense in aldol fashion with 9-fluorenone with then subsequent deoxygenation to give $\text{I8}$. The symmetrically coupled product of $\text{20}$, $\text{21}$ was formed in greater yield, but this can be accounted for by the solubility differences between ketones $\text{1}$ and $\text{20}$.

1,8-Diazafluorenone ($\text{2}$) was treated with the titanium reagent generated by method $\text{a}$ to give predominantly an insoluble black solid, instead of bis(1,8-diazafluorenylidene) ($\text{120}$), and traces (1%) of a reduced compound (mp $143^\circ$C). Sodium borohydride reaction of 1,8-diazafluorenone afforded the corresponding alcohol $\text{119}$. Comparison of spectral data confirmed that the compound melting at $143^\circ$C was not 1,8-diazafluorenol ($\text{119}$). However, due to the limited quantity of the unknown compound, further structural analysis was not undertaken.

bis(1,8-Diazafluorenylidene) ($\text{120}$) has been prepared by the UV induced
condensation of 1,8-diazafluorene and ketone 2. Dehydration of an intermediate alcohol afforded 120,140

Phenyl 2-pyridyl ketone (121a) was treated with low valent titanium (method a) to give not 1,2-diphenyl-1,2-bis(2'-pyridyl)-ethene, but rather the product of simple reduction, phenyl(2-pyridyl)-methanol (122a) and 1,2-diphenyl-1,2-bis(2'-pyridyl)ethane (123a) (6%).

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The mass spectrum of ethane 123a exhibited a very intense peak (100%) at m/e 168 due to the facile fragmentation of the central bis(benzyllic) bond. Also, bis(2-pyridyl) ketone (121b), when treated under the conditions of method a or method b, titanium trichloride-metallic sodium, afforded predominantly bis(2-pyridyl)methanol (122b), which undergoes air oxidation to give the starting ketone plus several minor uncharacterized products.

Clearly, a different reaction pathway was favored with phenyl
2-pyridyl ketone and bis(2-pyridyl) ketone, in which both a simple reduction product and an ethane were obtained. In order to account for these products, the following mechanisms are postulated (Scheme XII). First, electron transfer from titanium to the carbonyl moiety produces a radical anion which complexes titanium, $\text{II}_4$. This complex abstracts a proton from the solvent to give $\text{III}_4$, which has three viable pathways. Hydrolysis of $\text{II}_4$ affords the predominant product, alcohol $\text{IV}_4$. Deoxygenation of $\text{III}_4$ to give the ethane is envisioned as occurring by either of the two routes depicted in Scheme XII.

Deoxygenation can afford a stable radical, which dimerizes to afford the ethane or formation of complex $\text{V}_4$, which deoxygenates to afford the ethane. These mechanisms are the major reaction pathways in these heterocyclic ketones, which possess a site of metal ion complexation.

Onychine, an Azafluorenone Alkaloid. The synthesis of onychine, 4-methyl-1-azafluorenone ($127$), which is an alkaloid isolated from the trunk wood of *Onychopetalum amazonicum* (Annonocene),$^{141}$ was attempted starting from 1-azafluorenone.

\[
\begin{align*}
\text{II}_4 & \quad \text{III}_4 \\
\text{IV}_4 & \quad \text{V}_4
\end{align*}
\]

In order to prepare onychine from 1-azafluorenone, a 1,4-addition to the heterocyclic ring would be required, and 1,2-addition of the carbonyl moiety would have to be minimized.

Very few examples of 1,4-addition to the pyridine nucleus are known. Frank and Weatherbee$^{142}$ have reported the occurrence of 1,4-addition in pyridyl compounds, in which nicotinonitrile ($128$) reacted
with propylmagnesium bromide to afford, after dehydrogenation, propyl 3-(4-propylpyridyl) ketone (129).

\[
\text{CN} \quad \text{prMgBr} \quad \text{ConH} \quad \text{OPr}
\]

\[
\text{pr} = \text{CH}_2\text{CH}_2\text{CH}_3
\]

Fuson and Miller\textsuperscript{143} also accomplished 1,4-addition to 3-benzoylpyridine (114) and 3-benzoylquinoline (132) in good yield.

\[
\text{PhOH} \quad \text{PhMgBr} \quad \text{PhCON} \quad \text{PhOH}
\]

\[
\text{Ph} \quad \text{PhMgBr} \quad \text{PhCON} \quad \text{Ph}
\]

In each of these examples, no \( \alpha \)-substitution on the pyridine nucleus occurred.

Most examples of this type of addition were limited to pyridyl compounds that have strong electron-withdrawing groups, such as cyano, at the 3- and/or 5-position. Recent reports,\textsuperscript{144} involving work with acridine derivatives, have shown that 1,4-addition can be accomplished without the presence of strong electron-withdrawing substituents, using lithium dimethylcopper, which is known for its ability to undergo conjugate addition.\textsuperscript{145} The reaction of acridine derivative 132 with lithium dimethylcopper illustrates this mode of conjugate addition.
In order to avoid the competing reactions of 1,2- vs 1,4-addition in 1-azafluorenone, the carbonyl unit was blocked by ketalization to give spiro[9H-indeno[2,1-b]pyridine]-9,2'-[1,3]-dioxolane (136). The NMR spectrum of ketal 136 showed that the hydrogens of the ethylene bridge absorb at $\delta_{4.46}$ and $\delta_{4.70}$, indicative of the diastereotopic nature of the geminal hydrogens.

The organometallic reagent would now add to the 4-position of the pyridyl ring as indicated by the arrow in structure 136. However, when dioxolane 136 was treated with lithium dimethylcopper under a wide range of temperature, no reaction occurred and only unchanged starting material was isolated.

Phenyl 2-pyridyl ketone, which served as a model for 1-azafluorenone, was also treated with lithium dimethylcopper. Product analysis indicated only the presence of 1-phenyl-1-(2'-pyridyl)-1-ethanol, the product of 1,2-addition. As a control to assure the quality of the lithium dimethylcopper reagent, crotonaldehyde was treated with this copper reagent to afford both the 1,4-addition product, isovaleraldehyde, and the 1,2-addition product, 3-penten-2-ol. Therefore, the organometallic reagent was of sufficient quality, but did not give the
desired 1,4-addition of either dioxolane 136 or phenyl 2-pyridyl ketone.

\[
\text{dioxolane } 136 \\
\text{phenyl 2-pyridyl ketone}
\]

2-Phenyl-2-(2'-pyridyl)-1,3-dioxolane (137) was treated with methylmagnesium bromide to attempt 1,4-addition; however, only unchanged dioxolane was recovered.

These results were not entirely unexpected in light of attempted 1,4-addition to the indenoquinoline nucleus 138.144

\[
\text{indenoquinoline } 138 \\
\text{1,4-addition}
\]

Product analysis from the reaction of 138 with lithium dimethylcopper indicated that only 1,2-addition had occurred to give alcohol 139, exclusively. Cromwell and Mitsck146 also treated 138 with a series of Grignard reagents and in every case obtained only the 1,2-addition product. They stated that 138 showed no tendencies toward 1,4-addition and postulated that the reason for lack of 1,4-addition may lie in the inability of the 5-membered ring to accommodate a double bond. Comparing indenoquinolinone 138 with dioxolane 136, it was observed that indenoquinolinone 138 should be more receptive to 1,4-addition than dioxolane 136, since in 138 the carbonyl unit and the nitrogen would both enhance the reactivity of the 4-position and thereby afford a facile addition of the copper reagent at that position. In dioxolane 136, the relationship of the protected carbonyl unit to the position
where addition is desired is not 1,4 (see 136). Therefore, the carbonyl does not aid in activation of that position towards addition.

Reactions in related systems also indicate that heteroaromatic compounds containing fused rings are often resistant to 1,4-addition. When acridine derivative 140 was treated with lithium dimethylcopper, the reagent was consumed, but only unchanged starting material was isolated.144a

\[ \text{CH}_3\text{SOCH}_2\text{Na} \]

Also, when benzo[f]quinoline 141, the aza-analog to phenanthrene, was treated with methylsulfinyl carbanion, no 1,4-addition to the pyridyl moiety occurred. Only addition to the 9- and 10-positions occurred to afford 142 and 143, respectively.147

In ketones containing the pyridyl moiety, in order to produce 1,4-addition in the pyridine ring, it is essential that a carbonyl unit be situated so as to activate the 4-position. As 140 and dioxolanes 136 and 137 clearly demonstrate, that without an appropriately situated carbonyl unit no 1,4-addition occurs. Also, the ability of nitrogen to activate a position towards 1,4-addition may be overshadowed by other electronic considerations, such as reactivity:
associated with aromatic character, as seen in compound \(^{1}11\). More specifically, azafluorenones and related compounds appear to be resistant to 1,4-addition to the pyridyl ring,\(^ {146}\) as indicated by the example of indenoquinolinone \(^{138}\). The results obtained from the reaction of dioxolane \(^{136}\) with lithium dimethylcopper are consistent with these conclusions.
II. Organometallic Heterocycles, Pyridine Directed Metallation and Polymetallated Pyridine.

Organometallic heterocycles encompass a broad and growing area of synthetic chemistry. In this section two specific topics are considered: (a) Pyridine Directed Metallations and (b) Polymetallated Pyridine. The subsection on pyridine directed metallations considers the use of the nitrogen heteroatom to guide an organometallic reagent to a specific site prior to metallation. The dilithiation of halopyridines is discussed in the subsection on polymetallated pyridine.

Pyridine Directed Metallations. There are numerous examples of heteroatoms, such as: nitrogen, phosphorus, sulfur, and oxygen, that have been utilized to direct a metal to a specific site on a ligand.\(^{37-40}\) If a metallation reaction occurs at that site, a new metal-carbon bond is formed. This class of reactions is often called "cyclometallation" or "ortho-metallation", if the metal is directed to the ortho-position of an aromatic ring.\(^{38}\) A significant percentage of the examples of directed metallations involve transition metals. Alkali metals, such as lithium, are also known to metallate at a specific site, when directed by nitrogen or other heteroatoms.\(^{48-51}\) For example, deuterium trapping experiments have shown that phenyl oxazoline undergoes ortholithiation upon treatment with n-butyllithium.\(^{49}\) Slocum and Jennings\(^{51}\) reported that ortho-lithiation occurs in a variety of substituted anisoles. Their detailed report provides insight into regiospecific metallation of benzene and ranks the directing ability of various phenyl substituents.
Attempts were made to lithiate 2-phenylpyridine at the ortho-position of the phenyl ring (Scheme XIII).

SCHEME XIII

The trapping agents, represented by E (electrophile), were deuterion (from methanol-OD) and ethyl chloroformate. 2-Phenylpyridine was treated with one equivalent of n-butyllithium at temperature ranging from -20°C to -90°C and with reaction times that varied from 0.5 to 6 hours. At low reaction temperatures (-90°C) or with short reaction times coupled with temperatures of ca. -60°C, only unchanged 2-phenylpyridine was recovered. When higher temperature (-20°C) was employed α-addition of n-butyllithium became a major competing reaction affording 6-butyl-2-phenylpyridine. 6-Butyl-2-phenylpyridine was identified by NMR spectral data, which no longer showed a signal due to the 6-pyridyl hydrogen but exhibited signals characteristic of an n-butyl group; and by comparison of the physical data (boiling point) to literature values. Using reaction times of 6 hours, temperatures of -50°C and trapping with ethyl chloroformate, a mixture of products was obtained. Unchanged 2-phenylpyridine was isolated by fractional distillation leaving a crude high boiling residue, which was separated via preparative vpc to show that 6-butyl-2-phenylpyridine was again the
major component. Analysis of the other products by NMR indicated traces of ethyl 2-(6'-butylpyridyl)benzoate, the product of metallation and substitution had formed. The NMR spectrum of exhibited signals due to both the n-butyl group and the carboethoxy group.

These results indicated that at temperatures below ca. -65°C no reaction occurred, while at -20°C only substitution of n-butyllithium on the pyridine ring occurred, which is not an unexpected reaction. When the reaction temperature was ca. -50°C, the product analysis indicated that a competition between substitution and metallation had taken place. In related systems other workers have found that similar competition reactions between substitution and metallation occurred.

When ferrocene derivative was treated with n-butyllithium at ambient temperatures and trapped with benzophenone, the major product arose from metallation at the 2-position of the cyclopentyl ring. However, a major component of this reaction was also the product of both metallation and substitution. Booth and Rockett reported that as reaction times increased the amount of α-addition to the pyridine ring also increased. Directed metallation of both 2-phenylpyridine and ferrocenyl pyridine involves ortho-lithiation of an aromatic nucleus by means of the pyridyl nitrogen atom. Therefore, it was not unexpected to find that both systems exhibited competing reactions, substitution and metallation.

The examples of the ferrocene derivative still do not afford the reasons for the general resistance of the pyridyl nucleus to
direct lithiation to the phenyl nucleus. One reason is reaction
temperature. There is possibly a narrow temperature range (ca. -50°C)
where metallation occurs to a significant extent, but yet substitution
is suppressed. Also a factor to consider in the directed lithiation
of the phenyl ring is the electronic nature of the ortho-position
prior to metallation and the electronic requirements necessary for
n-butyllithium to metallate, i.e. the mechanism by which lithiation
proceeds. When a substrate, 2-phenylpyridine, is treated with n-
butyllithium, it is generally recognized that the nitrogen heteroatom
is able to stabilize the electropositive lithium reagent and also
stabilize the ortho-lithiated intermediate. It is, however, uncertain
whether the actual lithiation is of a nucleophilic or electrophilic
nature. Gilman\textsuperscript{11} observed that nucleophilic and electrophilic
lithiation represent the limiting mechanisms of lithiation and that
depending upon the individual reaction, lithiation may lie closer to
one of these limiting mechanisms. It is uncertain which of these
limiting mechanisms is favored in the lithiation of 2-phenylpyridine.
In the case of 2-phenylpyridine, the electronic nature of the ortho-
position also influences the reaction course. Pyridine, an electron-
withdrawing substituent, might deactivate the ortho-position towards
metallation.

In comparison to directed metallation involving an alkali metal,
directed metallation involving a transition metal is fairly well
understood.\textsuperscript{37,38,40} For example, 2-phenylpyridine reacts readily with
dilithium tetrachloropalladate(II) to give \textsuperscript{44} as a dimer.\textsuperscript{149}
All evidence indicates that this reaction proceeds by an electrophilic aromatic substitution pathway, because in similar systems, the reactivity increases as the phenyl ring becomes more electron rich. But, as Parshall has noted, a comparison between lithiation and palladation is probably not valid especially in light of the fact that lithiation of arenes is not an electrophilic reaction. Therefore, the reaction temperature, electronic environment of the site to be metallated, and the metallating reagent influence the reaction profile of directed metallation reactions and also aids in determining whether metallation or substitution will occur.

Polymetallated Pyridine. 2,6-Dichloropyridine does not undergo metal-halogen exchange, when treated with an organometallic reagent, such as n-butyllithium. Gilman and Spatz reported that 3,5-dibromo-or 2,6-dibromopyrididine when treated with n-butyllithium under a wide range of temperature (-10°C to -30°C) and varying lengths of reaction time, affords products derived from a monometallated intermediate \( \text{LiPy}^+ \). Park, Wagner, and Holm citing Gilman's study that 2,6-dibromopyridine in diethyl ether produced only a monolithiated intermediate, generated 2-lithio-6-bromopyrididine for use as a synthetic intermediate. Other workers have also reported that dibromopyridine undergoes only monolithiation. Therefore, in order to achieve dimetallation of
pyridine at the 2- and 6-positions, 2,6-diiodopyridine was prepared.

Either 2,6-dibromopyridine, or better 2,6-dichloropyridine, was treated with an excess of sodium iodide in refluxing hydroiodic acid. A facile halogen-halogen exchange occurred to afford (42%) 2,6-diiodopyridine (110), as colorless needles. Mass spectral data showed a very intense parent ion at m/e 331 (100%) and a loss of I⁺ to give m/e 204 (C₅H₃NI) and m/e 77 (C₅H₃N). The NMR spectrum of 2,6-diiodopyridine exhibited a triplet at δ 6.98 for the 4-pyridyl hydrogen and a doublet at δ 7.73 for the 3,5-pyridyl hydrogens. When 2,6-diiodopyridine was treated with 3.8 equivalents of n-butyllithium at -90°C, metal-halogen exchange occurred. The metallated intermediate was trapped with carbon dioxide, and subsequent esterification afforded methyl 2,6-pyridinedicarboxylate (150a). Also isolated was 2-carbomethoxypyridine-6-carboxylic acid (150b). Therefore, dimetallation occurred and produced the 2,6-dilithiopyridine (110). No products arising from monometallated intermediates were isolated in this reaction.

Since it was now known that 2,6-dilithiopyridine can be generated, the reaction of n-butyllithium with 2,6-dibromopyridine was reinvestigated. As stated previously, 2,6-dibromopyridine undergoes only monometallation when treated with an excess of n-butyllithium at low temperature in diethyl ether. The literature reports only the use of diethyl ether as the solvent in these reactions. Therefore, THF was used as the solvent in this reaction in order to determine if the solvent effects the reaction course.

2,6-Dibromopyridine was treated with n-butyllithium in a manner
identical to that described for 2,6-diodopyridine, using THF as the solvent. Following esterification, methyl 2,6-pyridinedicarboxylate (150a) was isolated, indicating dimetallation had occurred. A second product, methyl 2-chloro-6-pyridinecarboxylate, was also isolated. The chloro-ester arose from halogen-halogen exchange that occurred during the hydrochloric acid catalyzed esterification procedure. This type of halogen-halogen exchange has been shown to occur in similar systems under these mild conditions. Therefore in THF, dimetallation was achieved, while in diethyl ether only monometallation occurred. There are other examples of the enhanced solubilizing ability of THF over diethyl ether effecting the reaction of organoalkali compounds. The exact property that enables THF to solubilize organolithium reagents better than diethyl ether is not well understood but such factors as solvent dielectric constant, basicity of the ethereal oxygen, and the number of aggregates certainly are involved.

The product yields, which arise from the dimetallated intermediate, were low, on the order of ca. 10%. Further experiments were conducted
with different trapping agents in order to more accurately determine
the exact quantity of 2,6-dilithiopyridine (\(1_{l}^{g}\)) generated. Inter-
mediate \(1_{l}^{g}\), generated from 2,6-dibromopyridine, was trapped with
dimethyl disulfide to afford 2,6-dithiomethoxypyridine in 36-40% and
2-bromo-6-thiomethoxypyridine in 26-28%. In a second experiment, 2,6-
dilithiopyridine was trapped with methanol to give pyridine in 52-58%
and 2-bromopyridine in 7-12%. Therefore, the low yields obtained from
trapping with carbon dioxide reflect mechanical loss during carboxy-
lation followed by esterification and not the actual amount of 2,6-
dilithiopyridine formed.

![Chemical Reaction](image)

Proost and Wibaut\(^{56}\) prepared the bis-Grignard reagent of 2,6-
dibromopyridine, \(1_{51}\), using the vigorous conditions of Grignard's
entrainment procedure.\(^{151}\) Their work was repeated but instead of
trapping with benzaldehyde or allyl bromide, carbon dioxide was employed
to provide an instantaneous quench. After esterification, diester \(1_{52}\)
was isolated along with 2-ethylpyridine and unchanged dibromopyridine,
in low yields comparable to the above lithiation procedure. Therefore
2,6-pyridinebis(magnesium bromide) can be generated. The fact that
this reagent is table in refluxing diethyl ether, contrasts sharply
with 2,6-dilithiopyridine being unstable above ca. -80°C.

There are no known examples of systems that are isoelectronic
with 2,6-dilithiopyridine. 2-Bromopyridine does not metallate in the
presence of n-butyllithium even at -110°C.\textsuperscript{152} Unsubstituted 1,2,3-triazine is an unknown compound, although theoretical calculations predict it should be stable and exhibit a slight degree of electron delocalization.\textsuperscript{153} The preparation of substituted 1,2,3-triazines has recently been reported.\textsuperscript{154} 4,5,6-Trihalo-1,2,3-triazine was prepared by treating tetrahalocyclopropene with trimethylsilyl azide and (dialkylamino)cyclopropenylium perchlorate afforded 5-dialkylamino-1,2,3-triazine when treated with potassium azide.
III. Synthesis of Heterocyclic Acetylenes and Related Derivatives.

There are numerous methods available for preparing acetylenic compounds, for example dehydrohalogenation,\textsuperscript{65,70} nucleophilic substitution employing a metal acetylide,\textsuperscript{66} and Stephans-Castro coupling, which employs copper to couple iodoarenes or iodoalkenes.\textsuperscript{155} These methods are somewhat limited in scope and often employ vigorous reaction conditions. There is, however, a mild, convenient, catalytic method of preparing a variety of acetylenic compounds, that has recently been discovered. In order to present the advantages of this catalytic procedure for preparing acetylenes and to discuss related topics, this section is subdivided into two sections. The first section, Synthesis of Heterocyclic Acetylenes, deals with two methods of synthesizing acetylenic compounds: the catalytic procedure and the conventional route, dehydrohalogenation. The second section, Synthesis of Ortho-pyridinophane, considers the heterocyclic acetylenes as starting materials in the preparation of an ortho-cyclophane.

Synthesis of Heterocyclic Acetylenes. A mixture of dichlorobis-(triphenylphosphine)palladium(II) and copper(I) iodide in catalytic amounts in an alkylamine solvent was successfully used to prepare a number of acetylenic compounds.\textsuperscript{64} The active catalyst, dichlorobis-(triphenylphosphine)palladium(II)-copper(I) iodide (\textsuperscript{153}), in the presence of alkyl or aryl halides and a source of an acetylene, either acetylene itself or an alkyl or aryl acetylene, couples these reactants to afford corresponding alkyl or arylacetylene. Before presenting the heterocyclic acetylenes that were prepared by this catalytic method a brief description of the mechanism will facilitate the understanding of
(\(\mathcal{P}_3\mathcal{P}\))\(_2\)PdCl\(_2\) \(\sim\) CuI

SCHEME XIV

(\(\mathcal{P}_3\mathcal{P}\))\(_2\)PdCl\(_2\)

\[
\begin{array}{c}
HC=CR \\
\text{CuI/Et}_2\text{NH} \\
\rightarrow \\
\text{H}_2\text{NEt}_2\text{Cl}^-
\end{array}
\]

(\(\mathcal{P}_3\mathcal{P}\))\(_2\)Pd \(\sim\) (C=CR)\(_2\)

R = H
R' = aryl, pyridyl

K. Sonogashira, Tetrahedron Letters, 1975, 4467
these reactions.

The proposed mechanism\textsuperscript{64,78} for the coupling process is outlined in Scheme XIV. Palladium(II) is alkylated by substitution of the chlorines to give \textsuperscript{154}. Hydrochloric acid is generated in this step and removed by the solvent. Derivative \textsuperscript{154} undergoes a reductive elimination reaction to produce \textit{bis}(triphenylphosphine)palladium(0) \textsuperscript{155} the catalytic species and a butadiyne. Oxidative addition to \textsuperscript{155} by alkyl or aryl halide followed by alkylation affords \textsuperscript{157}, with palladium in the +2 oxidation state. A reductive elimination occurs to give the desired acetylene and to regenerate \textsuperscript{155}, which completes the catalytic cycle.

In order to test the reaction conditions, 2-bromopyridine and 2-iodopyridine were treated with the catalyst \textsuperscript{153} and acetylene in diethylamine to give the known compound, \textit{bis}(2-pyridyl)acetylene in 25\% and 44\% yield, respectively. 3-Chloropyridine was reacted under the same conditions, but instead of obtaining the desired \textit{bis}(3-pyridyl) acetylene, only unchanged 3-chloropyridine was isolated. When 8-chloroquinoline was treated with the catalyst \textsuperscript{153} and acetylene using diethylamine as the solvent, no reaction occurred, only unchanged starting material was obtained. Therefore, heterocyclic acetylenes were successfully prepared from bromo- or iodo-substrates, whereas chloro-substrates proved to be unreactive, e.g. 8-chloroquinoline and 3-chloropyridine. These results indicated the order of reactivity to be I, Br > Cl. Also, utilizing the yield data for \textit{bis}(2-pyridyl)acetylene as a reactivity gauge, the iodopyridine was more reactive than bromopyridine. Therefore, the order of reactivity was I > Br > Cl. This reactivity order is expressed in the oxidation addition of the halocompound
to palladium(0) to give Fitton and Rick related this observed order of reactivity to the leaving ability of the halide series. When palladium undergoes an oxidative addition with a halo compound, the rate determining step appears to be the loss of halide, rather than the addition of the metal to the alkyl or aryl haloide. It should also be noted that electron-withdrawing substituents enhance the reactivity of aryl halo compounds.

![Diagram](image)

Bearing the above facts in mind, should be an ideal substrate to react with catalyst because it possesses an electron-withdrawing group, pyridine, para to the site of reaction and has a bromine substituent, which was proven to be of sufficient reactivity. However, when was treated with the palladium-copper catalyst and acetylene in diethylamine only unchanged starting material was recovered. This unreactivity may be explained by a complexation of the pyridyl nitrogen with the palladium, thereby removing the reactive bromine from the proximity of the metal.

2,6-Dibromopyridine was treated with the catalyst in the presence of acetylene using triethylamine as the solvent to give the expected acetylenic product, bis[2-(6-bromo)pyridyl]acetylene. The overall yield (21%) was optimized using a reaction time of three hours at 40°C. The mass spectral data for showed an intense parent ion peak at m/e 338 (100%) and sequential loss of bromine to give signals at m/e 257 and 177. The NMR spectrum exhibited a multiplet at δ7.55, 4,4'-Diodotolan, a compound functionally related
to 159, has been prepared by this same procedure starting from 1,4-
diiodobenzene.\(^7\) When 2,6-dibromopyridine was treated with the
catalyst and acetylene using diethylamine, instead of triethylamine,
as the solvent, the reaction product was not the expected acetylene
159, but rather E-1,2-bis[2'- (6'-bromo)pyridyl]ethanol (160). The
E-isomer was the only isomer obtained from the reaction. Other workers
have reported a similar predominance of the \text{trans}-isomer.\(^{157}\) Enol
160 was of limited solubility in most common organic solvents.

\[
\begin{align*}
\text{N} \quad \text{[C}_2\text{H}_5\text{]}_3 \quad \text{HC} &= \text{CH} \\
\text{HC} &= \text{CH} \\
\text{X} = \text{Br}
\end{align*}
\]

Therefore, to enhance solubility and to aid in structure determination,
the acetyl derivative 161 was prepared by reacting 160 with acetic
anhydride and pyridine.

\[
\begin{align*}
\text{O} \quad \text{[CH}_3\text{O]}_2 \quad \text{O} \quad \text{CH}_2\text{CH}_2\text{O} \\
\text{O} \quad \text{[O]} \quad \text{CH}_3\text{CO} \\
\text{Br} \\
\text{160} \\
\text{161}
\end{align*}
\]

The NMR spectrum of 161 exhibited singlets at 62.49 for the methyl
group and at 67.55 for the \text{trans} olefinic hydrogen.

The formation of enol 160 using the secondary amine, diethylamine,
as the solvent is explained by the nucleophilic addition of the solvent to the acetylene to an intermediate Schiff's base (Scheme XV).

**Scheme XV**

First, the expected acetylene 159 is produced, then under the prolonged reaction conditions, the secondary amine adds to the triple bond which results in the formation of a Schiff's base 162. During aqueous work-up, intermediate 162 is hydrolyzed to the corresponding ketone 163, which tautomerizes to 160. The fact that acetylene 159 was isolated using triethylamine as the solvent supports the postulated mechanism depicted in Scheme XV. Any additions of the tertiary amine, triethylamine, to the triple bond would be reversible.

A more conventional route used in the preparation of acetylenes is dehydrohalogenation. 65 1,2-Di[2'-{(6'-hydroxymethyl)pyridyl}]1,2-dibromoethane (165a) was prepared in good yield by treating 1,2-bis-[2'-{(6'-hydroxymethyl)pyridyl}ethene (164a) with bromine in chloroform. The dibromoethane 165a was isolated as a yellow-orange powder that decomposed at 185°C. It was known that dehydrobromination of compounds similar to 165a were very sensitive to reaction conditions and that debromination of 165a to give 164a was possible. 70 Following the procedure of Newkome and Koppersmith, 70 which employs the rapid
addition of small amounts of the dibromoethane to refluxing methanolic potassium hydroxide, resulted in debromination to regenerate (ca. 65%) ethene. Different solvents such as ethanol, t-butanol, and water; and various base concentrations were employed in hopes of circumventing the debromination problem. But in each case the only identifiable acetylenic products resulted from debromination.

\[
\begin{align*}
\text{N} & \equiv \text{N} \\
\text{R} & \equiv \text{Br} \\
\text{H} & \equiv \text{H} \\
\text{Br} & \equiv \text{Br} \\
\end{align*}
\]

\(\text{R} = -\text{CH}_2\text{OH}\)

\(\text{R} = -\text{CH}_3\)

1,2-Di[2′-(6′-methyl)pyridyl]-1,2-dibromoethane (167b) was prepared by treating the ethene with bromine in chloroform. Dibromoethane (165b) was dehydrobrominated following the previously described procedure to afford acetylene (166b) in 50% yield. The fact that (165b) can be dehydrobrominated, while (165a) undergoes only debromination indicates that not only is dehydrobromination very sensitive to reaction conditions but also to substituent effects.

**Synthesis of an Ortho-pyridinophane.** The investigation of cyclophane chemistry has provided much insight into nonbonded interactions and bond deformations. When the synthesis of (169) was undertaken two synthetic routes were considered. These routes are shown in Scheme XVI. Both routes A and B begin with the heterocyclic acetylenes discussed in the previous section and each route converges to the thiacyclopahne (168) which can be converted to the ortho-pyridino-
bis[2-(6-Bromo)pyridyl]acetylene (159) was treated with 2-pyrone to give (28%) 1,2-bis[2'-(6'-bromo)pyridyl]benzene (67a), as colorless needles, via a [4 + 2] cycloaddition followed by elimination of carbon dioxide. The mass spectrum of 67a exhibited sequential loss of bromine to give peaks at m/e 309 and 229. The NMR spectrum showed a multiplet at 67.66 for the phenyl hydrogens. Considering the yield (28%) of the cycloaddition reaction and the yield (21%) of the reaction to prepare acetylene 159, the overall yield of the first two steps was 6%. At this point it was decided route B might be a more viable synthetic sequence.

Following the procedure of previous workers124 bis[2-(6-methyl)pyridyl]acetylene (166a) was treated with 2-pyrone to obtain 1,2-bis-[2'-(6'-methyl)pyridyl]benzene (67b) in 64% yield, a marked improvement over the analogous reaction in route A. Dipyridylbenzene 67b
was isolated as a highly viscous oil. The NMR spectrum (200MHz) of 67b exhibited a singlet at δ2.49 due to the pyridyl methyl group, a triplet at δ7.35 for the 4-pyridyl hydrogen, and doublets at δ6.82 and 6.98 for the 5- and 3-pyridyl hydrogens, respectively. The assignment of the 3,5-pyridyl hydrogens was based upon an analogy to 2-phenylpyridine. The 5-pyridyl hydrogen of 2-phenylpyridine absorbs farthest upfield at δ6.99. Similarly, the 5-pyridyl hydrogen of 67b would also be expected to absorb farthest upfield at δ6.82. The methyl groups of pyridylbenzene 67b underwent free radical bromination when treated with N-bromosuccinimide (NBS) in benzene with irradiation for 12 hours. Wügtele reported that this type of reaction involving pyridyl compounds is very sensitive to reaction conditions and that in order to achieve side chain bromination rather than ring bromination, benzene is the solvent of choice. The reaction yielded a red oil which was shown to be a complex mixture. Intensive efforts to separate the mixture by chromatographic means afforded the desired product 167 in 7% yield and a tribrominated product 170.

\[
\begin{align*}
\text{NMR spectral data for 167 revealed a singlet at } & \delta_4.39 \text{ due to the bromo-substituted methylenes and multiplet at } \delta 6.95 \text{ to } \delta 7.80 \text{ from the } \\
& \text{aromatic hydrogens. The mass spectrum of 167 showed the expected } \\
& \text{sequential loss of bromine with signals at m/e 339 and 257. The NMR } \\
& \text{spectrum of 170 exhibited a singlet at } \delta 4.39 \text{ for the methylene}
\end{align*}
\]
hydrogens and also a singlet at $\delta 6.48$ for the hydrogen of the dibrominated carbon. A weak parent ion peak at m/e 497 (4.4%) and peaks at m/e 417, 337, and 257 due to the sequential loss of bromine characterized the mass spectrum of 170.

The cyclization reaction to convert 167 to the cyclophane 168 employed sodium sulfide-nanohydrate in ethanol under high dilution conditions. Cyclophane 168 was obtained as a near colorless crystalline compound. The NMR spectrum (200MHz) of the cyclized compound exhibited an upfield shift of the methylene hydrogens to $\delta 3.83$, a doublet at $\delta 7.03$ due to the 5-pyridyl hydrogen, and a complex aromatic region centered at $\delta 7.60$. The mass spectral data showed an intense signal at m/e 259 due to $M^+ -33$ (100%) and a weak parent ion signal at m/e 292. Also isolated from the cyclization reaction was dithiol 171.

\[ \text{Cyclic compound} \]

In the mass spectrum a parent ion signal at m/e 324 and in the NMR spectrum a signal at $\delta 2.55$ that exchanged with deuterium oxide confirmed the structure of 171.

The final step of this sequence can be carried out by treating 168 with triethylphosphite under illumination for ca. 12 hours to afford cyclophane 169. However, due to the limited amount of thiacyclophane 168 available this final step was not attempted.
Summary and Conclusions

Of the methods available for preparing active metal acetylides, four were evaluated for use in the subsequent synthesis of acetylene-diols that contain an azafluorene subunit. The four methods/reagents evaluated were: acetylenebis(magnesium bromide), generated by passage of acetylene through a solution of methylmagnesium bromide; sodium acetylide, generated by passage of acetylene through a solution containing an aromatic base and sodium as a counterion; sodium acetylide, generated in situ by treating 1,2-dibromoethane with sodium amide in hexamethylyphosphorus triamide (HMPT); and lithium acetylide ethylenediamine complex, a reactive monolithiated acetylide. The most fruitful of these methods for the generation of an active metal acetylide proved to be sodium acetylide prepared from the passage of acetylene through a solution containing an aromatic base and sodium counterion. This method was utilized to prepare 9,9'-ethynylenebis-1,5-diazafluoren-9-ol. The extreme insolubility of this acetylene-diol prohibited conversion to the corresponding cumulene.

A low valent titanium reagent generated from either titanium trichloride-lithium aluminium hydride (method a) or titanium trichloride-sodium (method b) was used to prepare a series of heterocyclic olefins. This low valent titanium reagent reductively couples carbonyl substrates to the corresponding olefin. 3-Benzoylpyridine was treated under the conditions of method a to afford both the E and Z isomers of 1,2-diphenyl-1,2-bis(3'-pyridyl)ethene. A NMR Eu-shift study confirmed the identity of each of the isomers. 4,5-Diazafluorenone was treated with the low valent titanium reagent (method a) to obtain
Treatment of an equal molar mixture of 4,5-diazafluorenone and 9-fluorenone with low valent titanium (method a) afforded 4,5-diazafluorenylidenefluorene (118). If the heterocyclic carbonyl substrates possess a site of metal complexation, it is postulated that a titanium chelated intermediate forms. This chelated intermediate pursues an alternate reaction pathway and affords predominantly the product of simple reduction and a coupled product. Phenyl 2-pyridyl ketone afforded phenyl(2-pyridyl)methanol and 1,2-diphenyl-1,2-bis(2'-'pyridyl)ethane (123a), when treated with the low valent titanium reagent. Similarly, bis(2-pyridyl) ketone afforded bis-(2-pyridyl)methanol, when treated under the conditions of method a or b.

The preparation of onychine (4-methyl-1-azafluorenone), an alkaloid isolated from the trunk wood of Onychopetalum amazonicum (Annonaceae), was attempted starting from 1-azafluorenone. In order to synthesize 4-methyl-1-azafluorenone a 1,4-addition to the pyridine ring was necessary. To avoid 1,2-addition, the carbonyl unit of 1-azafluorenone was blocked by ketalization to afford spiro[9H-indeno-[2,1-b]pyridine]-9,2'-[1,3]-dioxolane (136). The dioxolane 136 proved to be resistant to 1,4-addition. When treated with lithium dimethylcopper, unchanged starting material was isolated. Similar systems have also proven to be resistant to this type of addition.

Cyclometallation is a regiospecific method of introducing a substituent onto a desired position on a ligand. 2-Phenylpyridine, when treated with n-butyllithium at temperatures ranging from -20°C to -90°C undergoes a competition between ortho-metallation of the phenyl ring and α-addition of n-butyllithium to the pyridine ring. Ethyl 2-
(6'-butylpyridyl)benzoate (144), 6-butyl-2-phenylpyridine, and unchanged starting material were the products of this reaction. Similar systems undergo this competition between directed metallation and α-addition to the pyridine ring.

2,6-Dilithiopyridine was generated by treatment of either 2,6-diiodo- or 2,6-dibromopyridine with excess n-butyllithium in tetrahydrofuran (THF) at -90°C. The dilithiated intermediate was trapped with various electrophiles such as carbon dioxide, dimethyl disulfide, and deuterium oxide. Previous attempts to prepare 2,6-dilithiopyridine by treating 2,6-dibromopyridine in diethyl ether with excess n-butyllithium resulted in a monometallated intermediate, e.g. 6-bromo-2,6-lithiopyridine. Therefore, in the case of 2,6-dibromopyridine changing the solvent from diethyl ether to THF affects the course of the reaction. 2,6-Diiodopyridine was prepared by treating either 2,6-dibromo- or 2,6-dichloropyridine with excess sodium iodide in refluxing hydroiodic acid.

Heterocyclic acetylenes were prepared by two methods: a dehydrohalogenation reaction and a substitution reaction, which employed dichlorobis(triphenylphosphine)palladium(II)-copper(I) iodide as a catalyst. bis[2-(6-Methyl)pyridyl]acetylene (166b) was prepared by treating 1,2-di[2'-(6'-methyl)pyridyl]-1,2-dibromoethane (166b) with alcoholic potassium hydroxide. bis[2-(6-Bromo)pyridyl]acetylene (152) was prepared by treating 2,6-dibromopyridine with the catalyst, dichlorobis(triphenylphosphine)palladium(II)-copper(I) iodide and acetylene, employing triethylamine as the solvent. When 2,6-dibromopyridine was treated with the catalyst and acetylene in diethylamine,
1,2-bis[2'-(6'-bromo)pyridyl]ethanol (160) was isolated instead of the expected acetylene 159. The postulated mechanism to account for the formation of ethenol 160 involves prior formation of the expected acetylene 159, then subsequent addition of the solvent, diethylamine, to the acetylene. Hydrolysis of an intermediate imine produces a ketone which tautomerizes to the ethenol 160.

The preparation of bis[2-(6'-bromo)pyridyl]acetylene (159) and bis[2-(6'-methyl)pyridyl]acetylene (166) allowed the convenient synthesis of an ortho-cyclophane, which contains 2,6-pyridino subunits. Treatment of the above acetylenes with 2-pyrone afforded 1,2-bis[2'-(6'-bromo)pyridyl]benzene (67a) and 1,2-bis[2'-(6'-methyl)pyridyl]benzene (67b), respectively. Bromination of pyridyl-benzene 67 with N-bromosuccinimide (NBS) afforded 1,2-bis[2'-(6'-bromomethyl)pyridyl]benzene (167). Cyclization of 167 with sodium sulfide-nanohydrate in ethanol under high dilution conditions afforded the desired thiacyclophane, 2-thia[3.0.0](2,6)pyridino(1,2)benzene(2,6)pyridinophane (168).
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121. Passed through: (1) concentrated sulfuric acid, (2) calcium
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Vita

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