1976

The Synthesis of Heteromacrocycles Containing the 2,6-Pyridine Moiety.

Joe Dean Sauer
Louisiana State University and Agricultural & Mechanical College

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A Dissertation

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Doctor of Philosophy

in

The Department of Chemistry

by

Joe Dean Sauer
B.S., Oklahoma Southwestern State College, 1970

May, 1976
to Carolyn
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ABSTRACT

This research effort dealt primarily with the synthesis of heteromacrocycles incorporating the 2,6-pyridino subheteromacrocyclic moiety.

Initial synthesis of small pyridyl units involved the preparation of 6-bromo-2-picolinic acid, 6-bromo-2-picolinoyl bromide, 6-bromo-2-picolinamide and 6-bromo-2-picolinonitrile. It was noted that halogen exchange occurred when the pyridine moiety was quaternized in the presence of chloride ion.

Addition of a lithiopyridine to a nitrile afforded intermediate substituted ketimines which, upon acid hydrolysis, produced the expected series of symmetrical and unsymmetrical pyridyl ketones. A shorter route to symmetrical ketones involved treatment of substituted 2-lithiopyridine at low temperatures (<-40°C) with ethyl chloroformate. This procedure allowed preparation of bis(2-pyridyl)ketone and bis(6-bromo-2-pyridyl)ketone in \( \approx 50\% \) yield. Utilization of either cyanogen bromide or pyrocatechol dichloromethylene ether instead of ethyl chloroformate afforded, after hydrolysis, lower yields of the desired ketone.

Bis(6-bromo-2-pyridyl)mercury was carbonylated in the presence of \( \text{K}_2[\text{Ni(CO)}_2(\text{CN})_2] \) to afford bis(6-bromo-2-pyridyl)ketone.

2-Bromo-6-lithiopyridine was reacted with either 2,6-dicyano-pyridine, 2,6-dipicolinoyl chloride, or methyl 2,6-pyridinedicarboxylate at \(<-40°C\) to produce the dibromodiketone(50%) in good yields.
Standard procedures for forming a 1,3-dioxolane from these ketones failed. A new method involving treatment of bis(2-pyridyl)ketone with gently refluxing 2-chloroethanol (or 2-bromoethanol) in the presence of lithium carbonate afforded (50%) the desired ketal. Compounds prepared via this method were 2,2-bis(2'-pyridyl)-1,3-dioxolane(99), 2-pyridyl-2-(6'-bromo-2'-pyridyl)-1,3-dioxolane(100), 2,2-bis-2'-(6'-bromopyridyl)-1,3-dioxolane(46), and 2,6-bis[2-(6'-bromo-2'-pyridyl)]-1,3-dioxolane-2-yl]pyridine(51).

Various 2-pyridones were prepared in 65-90% yields by refluxing a mixture of 2-halopyridine, potassium tert-butoxide, and tert-butanol for twelve hours.

Ketone (46) was treated with n-butyllithium at various temperatures. Deuterium incorporation indicated specific metallation occurred at the 3-position of one pyridine ring at temperatures above -40°C. These conditions give rise to ring fragmentation and recyclication to afford pyridone products. Normal metal-halogen exchange was observed in DME or THF solvent at temperatures below -60°C.

The macrocycles 19,20,21-triazatetracyclo[13.3.1.1.3.7.9.13]-heneicosa-1(19),3,5,7(21),9,11,13(20),15,17-nonane-2,8,14-trione(40); 14,17-dioxa-22,23,24-triazatetracyclo[16.3.1.1.3.7.9.13]tetracosa-1(22),3,5,7(24),9,11,13(23),18,20-nonane-8',2''-[1,3]dioxolane(114); 14,17-dioxa-22,23,24-triazatetracyclo[16.3.1.1.3.7.9.13]tetracosa-1(22),3,5,7(24),9,11,13(23),18,20-nonane-2,8-dione(115); and 23,24,25,26-tetraazapentacyclo[17.3.1.1.2.6.1.8.12.13.17]hexacosa-1(23),2,4,6(26),8,10,12(25),13,15,17(24),19,21-dodecane-7,18-dione (54; n=2, also n=3,4,5) were synthesized along with linear ketones.
Several of the pyridyl ketones were treated with a Wittig reagent generated from methyltriphenylphosphonium bromide. This resulted in the formation of 1-phenyl-1-(2'-pyridyl)ethene, bis-1,1-(2'-pyridyl)ethene, and bis-1,1-(6'-bromo-2'-pyridyl)ethene, respectively, in medium yields (15-20%).

Pyridylcarboxaldehydes were prepared by treating a halopyridine with methyl methylsulfinylmethyl sulfide anion in DME to generate an S-oxide intermediate which is thermally decomposed to generate the aldehyde directly.

Reaction of phenyl(2-pyridyl)ketone or bis(2-pyridyl)ketone with acetylene bismagnesium bromide afforded 1,4-diphenyl-1,4-bis(2'-pyridyl)-2-butyne-1,4-diol and 1,1,4,4-tetra(2'-pyridyl)-2-butyne-1,4-diol, respectively.

Phosphorous trichloride, potassium iodide, and diethyl ether react smoothly to produce diphasphorous tetraiodide. The pyridyl substituted butyne-diols were reacted with this reagent to yield (E) and (Z)-1,4-diphenyl-1,4-bis(2'-pyridyl)buta-1,2,3-triene and 1,1,4,4-tetra(2'-pyridyl)buta-1,2,3-triene respectively. The geometrical isomers were isolated.
INTRODUCTION

Since the beginnings of recorded human endeavor, mankind has attempted to improve the nature of his environment. Two recurring themes have been, first, to increase the value of one's personal property, and second, to safeguard one's personal health and livelihood. No implied order has been intended in the statement of these goals—this would obviously depend entirely upon the unique values of the individual. Early legends often revolve about the acquisition of immense wealth, (e.g. King Midas and his ill-fated touch) and in fact, tremendous energies were expended on the "scientific" field, as exemplified by ancient alchemists' quests for the "philosopher stone" with its mystical capability to transmute objects into gold. As we all know, although the forefathers of modern chemistry failed in this quest, modern nuclear physicists have, in fact, attained the goal of elemental transmutation. Even so, no practical, financial gains have been made by increasing the world's supply of gold at the expense of the supply of lead! If the premise is accepted that relative abundances of the world's rare elements must, for all practical purposes, remain constant, then we are forced to orient our thoughts and endeavors toward increased efficiency in handling the existing stock-piles of these valuable elements. Today's mining methods and survey techniques have progressed to the point that many of the once "worked-out" or exhausted sources of elements such as gold, silver, uranium, etc. have been re-examined and, in fact, often times re-worked to yield more of the materials our modern industrial
civilization and economy must have in order to prosper, and indeed survive. The ocean is one potential source that has been untapped so far in the quest for the useful and valuable metallic elements. [Some estimates on concentrations of a few examples of these metals are: gold, $7 \times 10^7$ tons; copper, $7 \times 10^9$ tons; uranium, $5 \times 10^8$ tons.] Research in this area has already been started, and in fact Bayer, et al. reported some success in synthesis of polymeric systems $I$ and $II$ that allowed a thousand-fold concentration of gold and uranium from sea-water.

![Chemical structures](image)

It was shown that inclusion of larger hetero-atoms (such as sulfur in place of oxygen) altered the specificity of the chelating core of these polymers in favor of larger metals (uranium). Also vital to this series of chelating polymers, is the presence of nitrogen atoms in the donor ring of these molecules.

Although work has begun, severe difficulties arise from the fact that the absolute concentrations of the desirable metals are extremely minute (e.g. gold ca. 1μl/l in sea water). A more damning problem, however, may stem from the fact that the metals are not only very dilute, but some species probably exist as an encapsulated, solvated, naturally chelated ion in these solutions. If any success is to be met in this ambitious undertaking, then, specific complexing
agents must be designed with the aim of being extremely selective for a particular metal specie(s).

This desired specificity has not been obtained via synthetic chelating agents, but successful complexation of classes of metals is currently possible up to and including the alkali metal ions (via crown-ether macrocycles). Although human efforts in the laboratory environment have met with limited results in the field of specific metal complexation, our biological systems have been more successful as evinced by the very stable complex of iron via the porphyrin ring in hemoglobin. In fact, natural systems very commonly exhibit extreme ion-specificity in complex formation. Some examples are (Figure I): (1) Myoglobin: specific iron complex with porphyrin ring structure at chelation site; (2) Phthalocyanine: has been studied with several different metal ions present (e.g. Fe, Cu, Co, Ni); (3) Actiomyces: specific alkali metal complex; K⁺ > Rb⁺ > Cs⁺ = Na⁺ >> Li⁺.

It is readily apparent that this selectivity exhibited by the biological systems is enhanced by the size and complexity of the chelating species. Hemocyanin, for example, has a molecular weight of approximately 3 x 10⁶; hemovanadine, although a very good Vanadium complex, irreversibly loses this specificity upon removal of the central metal ion. This property of immense size and/or irreversible changes in the organic ligand character upon removal of the complexed metal immeasurably limits practical (from the biased point of view of this dissertation) applications for this type of chelate.
Although the complexity of the natural systems is currently beyond the scope of normal synthetic methods, they might tend to direct the design of potential new **in vitro** ligands along similar lines. Some of these points are: (a) incorporation of selected hetero-atoms into the chelation sphere; (b) structuring a cyclic or macrocyclic ligand system; and (c) allowing for inner cavity flexibility both in number of donor atoms and general physical dimensions of the chelation sphere.

In order to not appear too financially oriented, attention should be focused at this point on one's personal health and live-
likelihood. An extremely important facet of this general topic would obviously be physiologically active materials. It would seem appropriate to list first among physiologically active substances those materials which either fight pathological manifestations of human ailments or seem to be necessary for simple maintenance of a healthy specimen. A house-hold word for the first of these categories is obviously "anti-biotics", while the second category elicits a response of "vitamins" (vital-amines).

The total scope of this area is undeniably vast and far-reaching; nevertheless, a general history and brief survey of some practical examples are in order. Antibiotic action has been observed for centuries\(^2\) and in fact, Pasteur noticed that certain "microbes" seemed to inhibit growth of other species of microbes. In 1889, P. Vuillemin first spoke of "antibote" substances isolated from these cultures and as early as 1897, F. Duchesne inoculated infected mice with a medium of *Penicillium glaucum* and noted a remission of the bacterial infection. Better known is the identification and partial purification of penicillin in 1927 by Alexander Fleming and subsequent use by Florey and Chain in 1938 against Staphylococcus infections.

![Penicillin G](image-url)
Subsequent workers have isolated and identified six naturally occurring penicillins. (Shown on the preceding page is Penicillin G). Commercially prepared penicillin is still a product of fermentation, although recently numerous total syntheses have been accomplished.

Classification of naturally occurring antibiotics is relatively involved since one can approach the problem by: (a) listing the organism that produces the particular antibiotic; (b) listing the antibiotic according to activity against particular organisms; or (c) classifying them via chemical structure. Since methods (a) and (b) result in confusion due to overlap and/or non-specific classification, method (c) is perhaps a better technique. One arbitrary approach to chemical classification is: (1) amino acids and peptides; (2) sugars; (3) macrocycles; (4) fused rings; and (5) composites. Illustrative examples of useful antibiotics for all five groups are shown in Figure II. (The word useful is stressed, since the material should not only retard the action of bacterial infection, etc., but it should also be relatively harmless to the host organism—a stipulation which is commonly difficult to meet.)

Figure II—Chemical Classification of Antibiotics

(1) Amino acids and peptides:

<table>
<thead>
<tr>
<th>Orn—Leu—Phe</th>
<th>Tyr—Phe</th>
<th>Gly—Asn—d—Phe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val—Pro</td>
<td>Phe</td>
<td></td>
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</tbody>
</table>

Tyrocidine A: useful for topical applications (as in burns, abrasions) to retard infections. (Orn, ornithine; Leu, leucine; Phe, phenylalanine; Pro, proline; Asn, asparagine; Gln, glutamine; Tyr, tyrosine; Val, valine. All amino acids are in L-form unless otherwise indicated.)
(2) Sugars:

Streptomycin: a broad-spectrum antibiotic—useful against tuberculosis.

(3) Macrocycles:

Pimaricin: useful as fungicide; not as anti-bacterial agent.

Nonactin from Actinomyces.

(4) Fused rings:

Oxytetracycline: [(or Terramycin) one of the first isolated tetracyclines].
Puromycin: (from S. alboniger) effective against sleeping sickness and has potential antitumor activity.

Vitamin $\text{B}_12^\text{a}$: growth enhancer and antipernicious anemia factor. Although not commonly classed "antibiotic" it is a good example of the "composite" class of antibiotics and, in fact, is very necessary to promote healthy human organisms.
Although it would be very difficult to identify a structure that a priori would engender useful physiological properties, at this stage however, one might be able to see general structural properties and/or chromophores that are recurrent in these valuable substances. One striking similarity is the fact that all of these species have at least one "hetero" atom present (in fact, most have several). Although one might suspect this list of examples would tend to be biased to show trends of this nature however, the fact that common aspirin (acetylsalicylic acid) has no fewer than four hetero-atoms present in its structure further emphasizes the necessity of heteroatoms in biologically important compounds.\(^{6}\)

Another similarity common to these "drugs" is the specificity evinced in placement of the hetero-atoms within the structure. It is common to find that altering the "donor" atom'(s) relative location(s) in the carbon backbone will severely change both the physiological effects and properties of these materials.

Common denominators, then, in both the analysis of specific metal chelates and physiological activity of diverse substances would be the introduction of hetero-atoms as well as some specific (possibly symmetric) placement of appropriate donor atoms.

In an attempt (admittedly very long-range) to be able to make some progress toward understanding metal-ion specificity and physiological properties of heterocyclic compounds, a synthesis of relatively complicated chelatropic reagents has been in vogue over the past decade. The herein described research has been limited to the production of polycyclic, large-ring chelates (hetero-
macrocycles) that might exhibit some of the previously mentioned desirable properties. It was also decided, at least initially, that nitrogen donor atoms would be the primary hetero atom of interest. Furthermore, since little work had been done by way of a systematic approach to heteromacrocyclic pyridine-containing compounds, the decision was made to further limit synthetic attempts toward incorporation of the 2,6-pyridino moiety into the final products.

Before outlining the systems attempted in this work, a literature survey on macrocyclic systems containing a subheterocyclic ring, e.g. the pyridino moiety; is in order. It was noted at the outset of this project that no review articles were available that would approach the problem of heteromacrocycles from this standpoint. Several lengthy reviews were available on the general subject of multidentate macrocyclic ligands and these are listed in Table (22). It should be noted that only review articles which include general macrocyclic ligands have been listed; other very good articles have intentionally been omitted due to the fact that they do not reference any work on ligands incorporating the pyridine moiety (early reviews on crown-ethers and cyclophanes, for example). Also, only synthetically available macrocycles are effectively reviewed in this compilation, as no serious attempt was made to screen the naturally-occurring systems (curare alkaloids, etc.) for pyridine incorporation in macrocyclic arrays.

It should be pointed out that the Tables and illustrations pertaining to this review stress the design and nature of the ligand sometimes at the expense of the complex itself. Although a compilation

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of metals incorporated in each macrocyclic ligand has been made, and, when identified in the original work, the nature of the complex is reported, the majority of the geometries shown are not necessarily indicative of the true geometry of any of the known complexes. It is also noteworthy that in some of the cases (especially in systems where the ligand is "templated" about a metal ion during the cyclization step), the ligand has not been isolated free of a central metal ion and, in fact, some of these ligands apparently exist only as the corresponding metal complex.

Nomenclature of the heteromacrocycles included often times becomes extremely complicated when I.U.P.A.C. general rules of numbering and identification are followed. Other (Figure III)

Figure III

"I.U.P.A.C. Name: 19,20,21-triazatetracyclo[13.3.1.1\(^{3,7}\).\(^{19,13}\)]heneicosa-1(19),3,5,7(21),9,11,13(20),15,17-nonane-2,8,14-trione."

"'Phane' Name: 1,3,5-Tri[2.4.6]pyridacyclohexaphane-2,4,6-trione."

forms of nomenclature have been proposed to simplify this problem and several lengthy articles have been presented dealing with the necessary rules for successful labeling of these compounds. These references are compiled in Table (23) of the review. The "Phane"
system of nomenclature proposed by Vogtle and Neumann has been utilized when a formal identification of a macrocycles was necessary in this dissertation. Other than this brief introduction and the example cited above, these systems of nomenclature were not considered to be within the scope of this dissertation.

Although length requirements of this introduction preclude a detailed discussion of the synthesis of all known (2,6)pyridino-phanes, a brief synopsis of the synthetic pathways to some of the more striking examples is in order. For the sake of clarity, these examples will be covered as a unit and placed immediately before the Tables of macrocycles included in the literature review. For illustrative purposes, the Schemes depicting the reaction pathways are placed adjacent to the individual discussions and the numbering of these compounds will follow a linear order throughout the discussion. These numbers will not correspond to any numbers in the literature review. For ease in handling, the literature review tables will be considered a completely autonomous unit in this dissertation. All references cited in these Tables are to be found immediately following the last Table of the collection. The normal bibliographical reference list for the dissertation is included at its usual location at the end of the work.

Both chronologically and taxonomically (with respect to the divisions in this review) speaking, the first (2,6)pyridinophane studied was that of 9-methyl-[10](2,6)pyridinophane (trivial name "muscobpyidine"). This substance was first isolated in 1946 by Büchi, et al. from the perfume gland of the musk deer and was
subsequently synthesized in 1957 via a multistep synthesis.  The over-all pathway is illustrated in Scheme (I), but highlights of the procedure include: (a) the Stobbe condensation of cyclododecanone (1) with diethyl succinate to afford the unsaturated ester (2); (b) cyclization to the bicyclic vinylogous 3-ketoester (3) via polyphosphoric acid followed by acid catalyzed decarboxylation to the bicyclic ketone (4); (c) Wolff-Kishner reduction and treatment with hydrazoic acid to yield the olefin mixture (5a,b) which (d) on dehydrogenation gave the parent [10](2,6)pyridinophane (6). The final steps involve simply (e) a rearrangement of the pyridine

Scheme (I)
N-oxide followed by hydrolysis and (f) a Sarett oxidation to the macrocyclic ketone(7) which upon direct α-methylation and reduction produced racemic muscopyridine(8). A resolution via di-p-toluoyl-D-tartaric acid was achieved and the final product was in fact the desired (+)muscopyridine.

Although the first pyridinophane incorporating more than one pyridine moiety was synthesized in 1958 by Baker et al., a synthesis utilized by Boekelheide and Lawson in 1970 is presented here (Scheme II) for this class of compounds, since Boekelheide's synthesis bridges two classes of macrocycles reviewed in Tables (1) and (6). The reaction of 2,6-bis-(bromomethyl)pyridine(9) with sodium sulphide afforded the macrocycle 2,11-dithio[3.3]pyridinophane (10) in 25% yield. Methylation of this sulphide with trimethyl-oxonium fluoroborate afforded 11 which, upon treatment with potassium

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$\text{t-} \text{butoxide in tetrahydrofuran, underwent a Stevens rearrangement to yield as a major product the mixture of isomers (12). This mixture was treated with trimethyloxonium fluoroborate to give 13 in essentially a quantitative yield. This product was treated with 2,6-bis(t-butyl)phenoxide ion to eliminate dimethyl sulfide and produce [2.2](2,6)pyridinophane-1,9-diene (14). It should be noted that in order to have an efficient production of 10, it was necessary to use high-dilution techniques.}^{10}$

In a very brief note, Undheim and co-workers$^{11}$ mention the synthesis of macrocycle (15) via an intermolecular condensation of 6-chloropyridine-2-thione (16). This reaction affords the only known example of a sulfur-bridged (2,6)pyridinophane. The reference cited also notes the fact that an X-ray analysis showed this macrocycle to be essentially non-planar.

The family of compounds found in Table 4 could be further subdivided into the systems (A) and (B) shown in Scheme (III).

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In class (A), the pyridine ring is directly attached to an oxygen atom while class (B) has at least one or more methylene group "insulating" the pyridine moiety from the heteroatom in the macrocycle. A typical example of class (A) originated from the reaction of 2,6-dibromopyridine(17) with the dianion of diethylene glycol (this dianion was generated by the action of sodium hydride on the necessary glycol in diethylene glycol diethyl ether [DEE]). The corresponding heteromacrocyclic ether (18) was generated in 18% yield.

A "Class B" carbon-oxygen (2,6)pyridino macrocycle synthesis is admirably illustrated by the synthesis of the macrocyclic azaether(23).
Methyl 2,6-pyridinedicarboxylate(19) was reduced with sodium borohydride to the corresponding diol (20). Treatment of 20 with sodium hydride in dimethoxyethane (DME) resulted in the formation of the dialkoxide(21) which, when reacted with \( \alpha,\alpha' \)-dibromo-o-xylene, afforded the macrocyclic azaethers(23).

The C,S-macrocycles (Table 6) have been introduced briefly as one intermediate in a synthesis of [2.2](2,6)pyridinophane. Although the sulfide intermediate(10) mentioned in this light is an important member of this family, another example is cited in the work by Vogtle and Risler.\(^1^4\) 2,6-Bis(bromomethyl)pyridine N-oxide(24) was treated with the dianion of 1,2-ethanedithiol in ethanol. The reaction was carried out via "infinite dilution" techniques\(^1^0\) and 2,5-dithia[6]-(2,6)pyridinophane N-oxide(25) was obtained in 8% yield.

\[
\begin{align*}
\text{CH}_2 & \quad \text{O} \quad \text{CH}_2 \\
\text{Br} & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
&\xrightarrow{\text{S}^- \xrightarrow{\text{EtOH}} \text{S}^-} \\
&\xrightarrow{(\text{CH}_2)_n} \\
&\xrightarrow{n=2,3,\ldots,10}
\end{align*}
\]

The C,S macrocycles have very similar synthetic origins to the C,O,S macrocycles listed in Table 8. One very interesting item of information about some of these macrocycles has come to light, however. It has been known for the last few years that crown ethers are relatively good complexing agents for all of the alkali metals as well as many other main-group cations (\( \text{Ca}^{++}, \text{Sr}^{++}, \text{Hg}^+, \text{Hg}^{++}, \text{etc.} \)). In the example of 5,8,11-trioxa-2,14-dithia[15](2,6)pyridinophane(26), sodium permanganate was completely solubilized by the ligand in
chloroform or benzene, whereas the corresponding potassium salt was completely undissolved. The researchers\textsuperscript{15} also note that lithium, rubidium, cesium, ammonium, and silver salts are not solubilized in organic solvents by the cited pyridinophane. This serves then as an example of not only family specificity in chelation but specificity for an individual cationic species, which is indeed remarkable!

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

The synthetic routes commonly used to prepare members of the macrocyclic ligand families listed in Tables 5, 7, and 9 are all very similar and will be treated with a single synthetic example shown in Scheme (IV). These macrocycles closely mimic naturally occurring systems such as the porphyrins and phthalocyanines and much of their chemistry has been examined with exactly that similarity in mind. These model systems have given theoretical chemists opportunities to analyze bio-systems via readily available, closely related (both structurally and electronically) artificial materials, and several groups of researchers have diligently applied themselves to the task (as can be seen by glancing at the series of complexes known for these families.)

A typical synthesis is exemplified by the preparation of 2,16-dimethyl-3,6,9,12,15,21-hexaazabicyclo[15.3.1]heneicosa-11(21),2,15,-17,19-pentaene\textsuperscript{(29)}\textsuperscript{16}, by essentially a one-step reaction of

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iron(II) chloride tetrahydrate with 2,6-diacetylpyridine to prepare the iron(II) complex (28), which subsequently was gently warmed with tetraethylenepentamine. After twenty-four hours, potassium iodide was added and, on concentration, the iron(III) complex diiodide (29) was isolated in 11% yield.

Scheme (IV)

Although it is possible in some cases (see Table 5) to remove the central metal ion from the cyclized ligand, this step is often very difficult to achieve without damaging the desired ligand. Some measure of success has been met when the complex is destroyed by addition of the template metal. Even with this method, however, good analysis of the resulting free ligand is very difficult to achieve in practice. 17

The remaining (2,6)pyridino macrocycles are listed in Table 10. These molecular creations not only have the distinction of incorporating hetero-atoms phosphorous and/or boron, but one class was
made even more illustrious in the eyes of a synthetic chemist by the fact that it is bicyclic in nature as opposed to being a single "cycle" ligand. Scheme (V) shows a detailed synthesis of the "clathro-chelate" (34) from 2,6-dibromopyridine.18

This synthetic procedure is similar to that shown for preparation of the phthalocyanine/porphyrin mimics in that templation about a central metal provides the driving force for the cyclic (in this example, bicyclic) ligand formation. This synthesis is a relatively involved, elegant piece of work and merits looking closely at some details.18 First, lithiation of 2,6-dibromopyridine will give only the monolithio product(30) which on treatment with dimethylformamide followed by acid hydrolysis gives the unsymmetrical aldehyde (31). It should also be noted that low temperatures (-60 to -100°) were
used in this procedure whenever lithiation reactions are undertaken. The aldehyde was protected as a 1,3-dioxolane (32) by standard reagents (ethylene glycol, p-toluenesulfonic acid, benzene) for the next lithiation and subsequent reaction with phosphorous trichloride to afford tris[2-(1',3'-dioxolan-2'-yl)-6-pyridyl]phosphine (40). Anaerobic acid hydrolysis of 40 followed by treatment with hydroxylamine gave an intermediate aldoximinopyridyl phosphine which was reacted with first Fe(BF$_4$)$_2$ to give a metal-complex which was treated finally with boron-trifluoride etherate to complete the metal encapsulation and afford the bicyclic ligand-iron complex (34) shown. The clathro-chelate complexes showed trigonal-prismatic geometry to be the probable stereochemistry by the preliminary NMR, X-ray, and absorption spectral data reported.19

Tables (11) through (16) deal with macrocycles incorporating pyridine substituted at the (2,5) or (3,5) positions. In most of the cases, reaction pathways are similar in nature to sequences illustrating the first nine Tables of ligands, and therefore will not merit a second examination. In the case of (3,5) substitution (Table 14), however, an interesting approach was utilized and will stand closer attention. A. T. Balaban19 constructed 11,13-dimethyl-[9](3,5)pyridinophane (38) via the route shown in Scheme (VI). Treatment of cyclododecene with 70% perchloric acid followed by addition of acetic anhydride afforded the diacylation product of cyclododecene, 11,13-dimethyl[9](2,6)pyrilophanium perchlorate (36) which, upon treatment with ammonia, yields the macrocyclic pyridinium salt and, finally the product pyridinophane (38) shown. Although

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the simplicity of this approach is certainly an attractive feature, there are certain physical draw-backs to handling perchlorate intermediates, and, in fact, the author notes that some of these materials detonate on strong heating!

The following pages will include the Tables of known macrocycles containing the pyridino subunits.
<table>
<thead>
<tr>
<th>Compound</th>
<th>n</th>
<th>Substituents</th>
<th>Physical Data</th>
<th>Spectral Data Available</th>
<th>Metal Complex(es)/General Comments</th>
<th>References</th>
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<tbody>
<tr>
<td>6</td>
<td>H</td>
<td>-</td>
<td>[70-75°(5)]</td>
<td>A</td>
<td>-</td>
<td>93b</td>
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<tr>
<td>7</td>
<td>H</td>
<td>[105°(7)]</td>
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<tr>
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<td>-</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>O</td>
<td>33.5-14.0°</td>
<td>A</td>
<td>-</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>dt (One)</td>
<td>[80°(0.06)]</td>
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<td>-</td>
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<td></td>
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<td>α, 2-2-dt (Me)</td>
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</tr>
<tr>
<td>8</td>
<td>H</td>
<td>-</td>
<td>--</td>
<td>--</td>
<td>93b</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>93b</td>
<td></td>
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<tr>
<td>10</td>
<td>H</td>
<td>15.6-16.6° [152-153°(3.7)]</td>
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<td>--</td>
<td>n-oxide (75-80.5°); Picrolonate (185-189°)</td>
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<td>OH</td>
<td>201-202°</td>
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<td>Subl: 125-130°(0.1)</td>
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<tr>
<td>11</td>
<td>OMe</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>17</td>
<td></td>
</tr>
<tr>
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<td>66-89°</td>
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</tr>
<tr>
<td>11</td>
<td>OMe</td>
<td>--</td>
<td>--</td>
<td>--</td>
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<tr>
<td>(+)-2-Me</td>
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<td>[135-145°(2.2)]</td>
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<td>103-105°</td>
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<td>2,2-di(2-Me)</td>
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<tr>
<td>12</td>
<td></td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>28-ONH₂</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>93b</td>
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<td>26</td>
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<td>94</td>
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<tr>
<td>26</td>
<td>R = H</td>
<td>181-183°</td>
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<td>26</td>
<td>R = NH₂</td>
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<td>B</td>
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<td>m = 11</td>
<td>R = H</td>
<td>177-178°</td>
<td>B</td>
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<tr>
<td>--</td>
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<tr>
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<td>H</td>
<td>80.5-81.5°</td>
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<tr>
<td></td>
<td>H</td>
<td>83-84°</td>
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<td>7</td>
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<tr>
<td>1(2),5(6)-di-3Me</td>
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<td>A,D</td>
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<td>9</td>
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<tr>
<td>1(2),5(6)-[3Me&lt;sub&gt;2&lt;/sub&gt;N]</td>
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<tr>
<td>12-NH(3Me)</td>
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<td>9</td>
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</tr>
<tr>
<td>12 NH-o</td>
<td>165-166°</td>
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<td>1,2,5,6-de tetra (II)</td>
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<td>1,2,5,6-de tetra (II)</td>
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<tr>
<td></td>
<td>H</td>
<td>256-258°</td>
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<tr>
<td>trans- 1,6-di-sMe</td>
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<tr>
<td>1,6(1)-di-sMe</td>
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<tr>
<td>1,2,6,7-de</td>
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<tr>
<td>2 H</td>
<td>191-192°</td>
<td>A</td>
<td>--</td>
<td></td>
<td>13,19</td>
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</tr>
<tr>
<td>3 H</td>
<td>--</td>
<td>A</td>
<td>Subl: 190-160°(0.31)</td>
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<tr>
<td></td>
<td>205-206°</td>
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<td>4</td>
<td>H</td>
<td>158-159(^\circ)</td>
<td>A</td>
<td>Subl: 200-210(^\circ)(0.01)</td>
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<tr>
<td>5</td>
<td>H</td>
<td>160-161(^\circ)</td>
<td>A</td>
<td>--</td>
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</tr>
<tr>
<td>6</td>
<td>H</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>13</td>
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</tr>
<tr>
<td>7</td>
<td>H</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>16</td>
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</tr>
<tr>
<td>10</td>
<td>12,25-41 (^\circ)</td>
<td>103-105(^\circ)</td>
<td>B</td>
<td>--</td>
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</tr>
<tr>
<td>2</td>
<td>H</td>
<td>134.5-135(^\circ)</td>
<td>A,S</td>
<td>--</td>
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<tr>
<td>1</td>
<td>H</td>
<td>176-179(^\circ)</td>
<td>A,S</td>
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<td>2</td>
<td>H</td>
<td>185-187(^\circ)</td>
<td>A,S</td>
<td>--</td>
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<tr>
<td>3</td>
<td>H</td>
<td>196-199(^\circ)</td>
<td>A</td>
<td>--</td>
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<td>H</td>
<td>218-221(^\circ)</td>
<td>A</td>
<td>--</td>
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<td>R = OMe</td>
<td>154.5-156.5(^\circ)</td>
<td>A,S</td>
<td>Lythraceae Alkaloids</td>
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</table>

Notes:

\(^a\) A = NR; B = ON; C, H, N; D, ms. \(^b\) Samples were isolated by preparative gas-liquid chromatography and characterized by NMR, IR, MS, and elemental analysis.}\(^{102}\)
### Table II. N-Macrocycles Containing a 2,6-Pyridino Moiety

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<th>Substituents</th>
<th>Physical Data</th>
<th>Spectral Data Available</th>
<th>Metal Complex(es)/General Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R=(<em>-CH-CH-</em>)&lt;sup&gt;−&lt;/sup&gt;</td>
<td>&gt;150&lt;sup&gt;°&lt;/sup&gt;[Subl: 400&lt;sup&gt;°&lt;/sup&gt;(13*−4)]</td>
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<td>Co,Cu,Mn</td>
<td>90,91,103</td>
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### Table III. 5-Macrocycles Containing a 2,6-Pyridino Moiety

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<th>Physical Data</th>
<th>Spectral Data Available</th>
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<th>References</th>
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<tr>
<td></td>
<td></td>
<td>H</td>
<td>--</td>
<td>--</td>
<td>X-Ray</td>
<td>22</td>
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### Table IV. C6,O-MACROCYCLES CONTAINING A 2,6-PYRIDINO NTIETY

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<th>Substituents</th>
<th>Physical Data</th>
<th>Spectral Data Available</th>
<th>Metal Complex(es)/ General Comments</th>
<th>References</th>
</tr>
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<tr>
<td><img src="image1" alt="Compound 1" /></td>
<td>n=3, m=0</td>
<td>H</td>
<td>40-41°C</td>
<td>A</td>
<td>pKₘ 4.8(40.2)</td>
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<td>n=3, m=0</td>
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<td>--</td>
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<td><img src="image3" alt="Compound 3" /></td>
<td>n=0, m=2</td>
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<td>85-86°C</td>
<td>A</td>
<td>--</td>
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<tr>
<td><img src="image4" alt="Compound 4" /></td>
<td>n=0, m=3</td>
<td>H</td>
<td>76-78°C</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td><img src="image5" alt="Compound 5" /></td>
<td>n=0, m=0, p=0</td>
<td>H</td>
<td>215-216°C</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td><img src="image6" alt="Compound 6" /></td>
<td>n=1, m=0, p=1</td>
<td>H</td>
<td>94.5-95.5°C</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td><img src="image7" alt="Compound 7" /></td>
<td>n=1, m=1, p=1</td>
<td>H</td>
<td>111-112°C</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td><img src="image8" alt="Compound 8" /></td>
<td>n=1, m=0, p=2</td>
<td>H</td>
<td>117-120°C</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td><img src="image9" alt="Compound 9" /></td>
<td>n=0, m=1, p=1</td>
<td>H</td>
<td>120.5-121.5°C</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td><img src="image10" alt="Compound 10" /></td>
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<td>R = CO_{2}H</td>
<td>172-181°C</td>
<td>A, D</td>
<td>--</td>
</tr>
<tr>
<td><img src="image11" alt="Compound 11" /></td>
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<td>R = CO_{2}Me</td>
<td>171</td>
<td>A, D</td>
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TABLE IV. C$_2$O-MACROCICLES CONTAINING A 2,6-PYRIDINO NOITY (cont'd.)

<table>
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<tr>
<th>Compound</th>
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<th>Metal Complex(es)/General Comments</th>
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<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>172-175$^0$</td>
<td>A</td>
<td></td>
<td>pka 7.9 (&lt; 3)</td>
<td>23, 24</td>
</tr>
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<td>2</td>
<td>H</td>
<td>125-128$^0$</td>
<td>A</td>
<td></td>
<td>pka 5.3 (3.7)</td>
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</tr>
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<td>3</td>
<td>H</td>
<td>175-176$^0$</td>
<td>A</td>
<td></td>
<td>pka 4.8 (&gt; 3)</td>
<td>23, 24</td>
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<tr>
<td>4</td>
<td>H</td>
<td>117-148$^0$</td>
<td>--</td>
<td></td>
<td>pka 5.3 (3.6)</td>
<td>23, 24</td>
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<td>5</td>
<td>3, 4, 12, 13-dibenzo</td>
<td>184-186$^0$</td>
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<td>23</td>
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<tr>
<td>6</td>
<td>3(8) ,4(8),12(8),13(8)-tetra-00898</td>
<td>224$^0$</td>
<td>--</td>
<td></td>
<td>[a]$_D^{24}$ + 107$^0$</td>
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<tr>
<td></td>
<td>H</td>
<td>--</td>
<td>--</td>
<td></td>
<td>(impure sample)</td>
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<td>A,C</td>
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<td>NaN$_2$ (195-196$^0$)</td>
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<tr>
<td>2</td>
<td>4,5, 15,16-dibenzo</td>
<td>192-193$^0$</td>
<td>C</td>
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<td>4,5, 15,16-dibenzo</td>
<td>108-109$^0$</td>
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<td>104-105$^0$</td>
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<td>A</td>
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<td><img src="image1" alt="Image" /></td>
<td>H</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>( \alpha^0_{578} \approx 23^0 )</td>
<td>92</td>
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<td><img src="image2" alt="Image" /></td>
<td>R</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>( \alpha^0_{578} \approx 24^0 )</td>
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<td><img src="image3" alt="Image" /></td>
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<td>--</td>
<td>--</td>
<td>( \alpha^0_{578} \approx 25^0 )</td>
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<td>A, B</td>
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<td><img src="image5" alt="Image" /></td>
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<td>122-124</td>
<td>A, B</td>
<td>--</td>
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<td>General Comments</td>
<td>Reference(s)</td>
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<td>1</td>
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<td>55, 56, 57, 58, 59</td>
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<td>Mg</td>
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<td>Na, Zn [X-Ray: Na(CIO₄)₂]</td>
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<td>56</td>
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<td>Fe</td>
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<td>Ni</td>
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<td>40, 43, 45, 46, 47, 48, 49, 52</td>
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<td>Zn</td>
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<td>40, 44</td>
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<td>dimer (151-154°C)</td>
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<td>meso-dimer (83-85°C)</td>
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<td>from meso: Co</td>
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<td>44, 50, 51</td>
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<td>from meso: Ni</td>
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<td>Ni</td>
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<td>47, 48</td>
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<td></td>
<td>Cu</td>
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### TABLE V. C,H-MACROCYCLES CONTAINING A 2,6-PYRIDINO MOIETY (cont'd.)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Substituents</th>
<th>Physical Data</th>
<th>Spectral Data Available</th>
<th>Metal Complex(es)/ General Comments</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Diagram" /></td>
<td>6-Me; 2,10-di(Tos)</td>
<td>164-166°</td>
<td>--</td>
<td>Cu [mp 196-198(dec)]</td>
<td>29</td>
</tr>
<tr>
<td><img src="image2.png" alt="Diagram" /></td>
<td>H</td>
<td>226-228°</td>
<td>--</td>
<td>--</td>
<td>29</td>
</tr>
<tr>
<td><img src="image3.png" alt="Diagram" /></td>
<td>2,13-di(Tos)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>29</td>
</tr>
<tr>
<td><img src="image4.png" alt="Diagram" /></td>
<td>1,13-di(Ph)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>97</td>
</tr>
<tr>
<td><img src="image5.png" alt="Diagram" /></td>
<td>3,4; 15,16-dibenzo (Abr: HADA)</td>
<td>--</td>
<td>--</td>
<td>Theoretical Calculations</td>
<td>61</td>
</tr>
<tr>
<td><img src="image6.png" alt="Diagram" /></td>
<td>1,6,10,15-tetram(Me); 3,4; 12,13-dibenzo (Abr: trmd)</td>
<td>300°/1mm (Subl)</td>
<td>--</td>
<td>Cu</td>
<td>60</td>
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<tr>
<td><img src="image7.png" alt="Diagram" /></td>
<td>X=Y=CH</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>65</td>
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<tr>
<td><img src="image8.png" alt="Diagram" /></td>
<td>X=Y=CH</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>63,64</td>
</tr>
<tr>
<td><img src="image9.png" alt="Diagram" /></td>
<td>X=Y=O</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>63,64</td>
</tr>
<tr>
<td><img src="image10.png" alt="Diagram" /></td>
<td>X=Y=S</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>63,64</td>
</tr>
<tr>
<td><img src="image11.png" alt="Diagram" /></td>
<td>X=Y=S (Abr: OAP1)</td>
<td>--</td>
<td>--</td>
<td>Theoretical Calculations</td>
<td>61</td>
</tr>
<tr>
<td>Compound</td>
<td>Substituents</td>
<td>Physical Data</td>
<td>Spectral Data Available</td>
<td>Metal Complex(es)/General Comments</td>
<td>References</td>
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<tr>
<td></td>
<td>H</td>
<td>3850°</td>
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<td></td>
<td>2,5,11,14-tetra(fos)</td>
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<tr>
<td>E= (\text{N=N=C-Cl} )</td>
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<td>C</td>
<td>Cu</td>
<td>62</td>
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</tr>
<tr>
<td>E= (\text{N=N=C} )</td>
<td>--</td>
<td>C</td>
<td>Cu</td>
<td>62</td>
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</tr>
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<td>E= (\text{N=N=\text{NO}_2} )</td>
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<td>C</td>
<td>Cu</td>
<td>62</td>
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<td>E= (\text{N=N=C} )</td>
<td>--</td>
<td>C</td>
<td>Cu</td>
<td>62</td>
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<tr>
<td>E= (\text{N=N=C} )</td>
<td>--</td>
<td>C</td>
<td>Cu</td>
<td>62</td>
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<tr>
<td>1,4,8,11-tetra(he)</td>
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<td>+</td>
<td>Fe</td>
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<td><img src="image1.png" alt="Image" /></td>
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<td>N → O</td>
<td>152-154°</td>
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<tr>
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<td>78-79°</td>
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<td>4</td>
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<td>107-109°</td>
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<td>N → O</td>
<td>98-99°</td>
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<tr>
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<td>6</td>
<td>N → O</td>
<td>147-148°</td>
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<tr>
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<td>7</td>
<td>N → O</td>
<td>138-140°</td>
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<td>8</td>
<td>N → O</td>
<td>85°</td>
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<tr>
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<td>9</td>
<td>N → O</td>
<td>73-75°</td>
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<td>10</td>
<td>N → O</td>
<td>117-120°</td>
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<td><img src="image2.png" alt="Image" /></td>
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<td>H</td>
<td>162-163°</td>
<td>A</td>
<td>Ag(gap 217-215°; A)</td>
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<td>H</td>
<td>131-133°</td>
<td>A</td>
<td>Ag(gap 138-200°; A)</td>
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<td>172-173°</td>
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<td>195-196°</td>
<td>A</td>
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</tr>
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<td>11-Me</td>
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<td>11-Ome</td>
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<td>206-208°</td>
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<td>11-F</td>
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<td>142-144°</td>
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<td>(Attempted)</td>
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<td>228-229°</td>
<td>A</td>
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<td>H</td>
<td></td>
<td>173-175°</td>
<td>A</td>
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<tr>
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<td>13-Me</td>
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<td>135-136°</td>
<td>A</td>
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<td>13-F</td>
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<td>174-175°</td>
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<td>13-NO₂</td>
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<td>159-160°</td>
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<td>H</td>
<td></td>
<td>177-178°</td>
<td>A, C, D</td>
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<tr>
<td></td>
<td>2,7-di[Ru₂ (BF₄)₂]</td>
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<tr>
<td>N = O₁; 2,7-bis (mulfona)</td>
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<td>310°</td>
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### TABLE VI. C,S-MACROCYCLES CONTAINING A 2,6-PYRIDINO MOIETY (cont'd.)

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<th>Substituents</th>
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<td></td>
<td></td>
<td></td>
<td>--</td>
<td>--</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>--</td>
<td>--</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A,D</td>
<td>--</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>185-186°</td>
<td>A,D</td>
<td>--</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td></td>
<td>A,D</td>
<td>--</td>
<td>98</td>
</tr>
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<td></td>
<td>H</td>
<td>150-152°</td>
<td>A,D</td>
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<td>98</td>
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TABLE VII. C,N,O-MACROCYCLES CONTAINING A 2,6-PYRIDINO MOIETY

<table>
<thead>
<tr>
<th>Compound</th>
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<th>Spectral Data Available</th>
<th>Metal Complex(es)/General Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Substituents</td>
<td>M(\text{P}_{50}(\text{mp}))</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>3,4,9,10-dibenz</td>
<td>--</td>
<td>--</td>
<td>Na, Zn</td>
</tr>
<tr>
<td>0</td>
<td>X: H; X: O</td>
<td>228-230(^\circ)</td>
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<tr>
<td></td>
<td>2,11-di(tos); X: H</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>X: H; X: O</td>
<td>200-201(^\circ)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,11-di(tos); X: H</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td>2</td>
<td>X: H; X: O</td>
<td>125-129(^\circ)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,14-di(tos); X: H</td>
<td>163-165(^\circ)</td>
<td>A</td>
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<td>Compound</td>
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<td>Spectral Data Available</td>
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<td>---------------</td>
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</tr>
<tr>
<td><img src="https://example.com/image1.png" alt="Image" /></td>
<td>0</td>
<td>H</td>
<td>135-135°</td>
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<tr>
<td><img src="https://example.com/image2.png" alt="Image" /></td>
<td>1</td>
<td>H</td>
<td>90-91°</td>
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<tr>
<td><img src="https://example.com/image3.png" alt="Image" /></td>
<td>2</td>
<td>H</td>
<td>98-99°</td>
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</tr>
<tr>
<td><img src="https://example.com/image4.png" alt="Image" /></td>
<td></td>
<td>N→O</td>
<td>oil</td>
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</tr>
<tr>
<td><img src="https://example.com/image5.png" alt="Image" /></td>
<td>3</td>
<td>H</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><img src="https://example.com/image6.png" alt="Image" /></td>
<td>1</td>
<td>H</td>
<td>92-94°</td>
<td>--</td>
</tr>
<tr>
<td><img src="https://example.com/image7.png" alt="Image" /></td>
<td>2</td>
<td>H</td>
<td>75-77°</td>
<td>--</td>
</tr>
<tr>
<td><img src="https://example.com/image8.png" alt="Image" /></td>
<td>3</td>
<td>H</td>
<td>74-76°</td>
<td>--</td>
</tr>
<tr>
<td>Compound</td>
<td>n</td>
<td>Substituents</td>
<td>Physical Data</td>
<td>Spectral Data Available</td>
</tr>
<tr>
<td>----------</td>
<td>---</td>
<td>--------------------</td>
<td>---------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td><img src="image1.jpg" alt="Compound 1" /></td>
<td>1</td>
<td>3,4; 9,10-dibenzo</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><img src="image2.jpg" alt="Compound 2" /></td>
<td></td>
<td></td>
<td>--</td>
<td>--</td>
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<tr>
<td>Compound</td>
<td>Substituents</td>
<td>Physical Data</td>
<td>Spectral Data Available</td>
<td>Metal Complex(es)/General Comments</td>
</tr>
<tr>
<td>----------</td>
<td>--------------</td>
<td>---------------</td>
<td>-------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>-</td>
<td>1,11-di(Me)</td>
<td>--</td>
<td>--</td>
<td>Fe, Zn, Ni, Co</td>
</tr>
<tr>
<td>-</td>
<td>1,11-di(Me); 1,2,10,11-tetra-(hydro) (Abr: pMeH4) &quot;Neso&quot;</td>
<td>--</td>
<td>--</td>
<td>Fe</td>
</tr>
<tr>
<td>1,11-di(Me); 1,2,10,11-tetra-(hydro); 6-S</td>
<td>--</td>
<td>--</td>
<td>Fe</td>
<td>70</td>
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</tbody>
</table>

**TABLE X. C,N,P,-MACROCYCLES CONTAINING A 2,6-PYRIDINO NOIkTY**
<table>
<thead>
<tr>
<th>Compound</th>
<th>Substituents</th>
<th>Physical Data</th>
<th>Spectral Data Available</th>
<th>Metal Complex(es)/General Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>H</td>
<td>[70-75°C(0.01)]</td>
<td>A,B,C</td>
<td>--</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>1-OC</td>
<td>43-48°C [105-110°C(0.02)]</td>
<td>A,B,C</td>
<td>--</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>1-OH</td>
<td>[125-135°C(0.02)]</td>
<td>A,B</td>
<td>Isomeric Mixture</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>1-OAc</td>
<td>[110-115°C(0.01)]</td>
<td>A</td>
<td>Isomeric Mixture</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>(+) - H</td>
<td>[50-81°C(0.04)]</td>
<td>A,B,C</td>
<td>--</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>(+) - H</td>
<td>[50°C(0.01)]</td>
<td>--</td>
<td>[Ca]²⁺ + 152°C, [Ca]²⁺ + 157°C</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>1-OH</td>
<td>[145-149°C(0.05)]</td>
<td>A,B</td>
<td>Mixture</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o11</td>
<td>--</td>
<td>Isomer B</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96-99°C</td>
<td>--</td>
<td>Isomer A</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>1-OAc</td>
<td>17-39°C [135-140°C(0.01)]</td>
<td>A</td>
<td>Mixture</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-75°C</td>
<td>--</td>
<td>Isomer A</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66-68°C</td>
<td>A</td>
<td>Isomer B</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>1-OC</td>
<td>[125-115°C(0.03)]</td>
<td>A,B,C</td>
<td>--</td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>[75-78°C(0.01)]</td>
<td>A,B,C</td>
<td>--</td>
<td>84</td>
</tr>
<tr>
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<td>1-OH</td>
<td>[135-160°C(0.02)]</td>
<td>A,B</td>
<td>Mixture</td>
<td>84</td>
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<tr>
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<td>1-OAc</td>
<td>[120-130°C(0.01)]</td>
<td>A</td>
<td>Mixture</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>1-OC</td>
<td>79-86°C [140-150°C(0.01)]</td>
<td>A,B,C</td>
<td>--</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
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<td>[50-95°C(0.03)]</td>
<td>A,B,C</td>
<td>--</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>1-OH</td>
<td>[140-149°C(0.03)]</td>
<td>A,B</td>
<td>Mixture</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>1-OAc</td>
<td>[110-115°C(0.02)]</td>
<td>A</td>
<td>Mixture</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-75°C</td>
<td>--</td>
<td>Isomer A</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66-68°C</td>
<td>Isomer B</td>
<td>--</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>1-OC</td>
<td>35-37°C [120-130°C(0.03)]</td>
<td>A,B,C</td>
<td>--</td>
<td>84</td>
</tr>
<tr>
<td>Compound</td>
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<td>Substituents</td>
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<td>Spectral Data Available</td>
<td>Metal Complex(es)/General Comments</td>
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<tr>
<td>----------</td>
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<td>---------------</td>
<td>-------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>12</td>
<td>H</td>
<td>[100±0.01°C]</td>
<td>A,B,C</td>
<td>--</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>1-0H</td>
<td></td>
<td>[140-150°C (0.05)]</td>
<td>A,B</td>
<td>--</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>1-OAc</td>
<td></td>
<td>[100-110°C (0.02)]</td>
<td>A,B</td>
<td>--</td>
</tr>
<tr>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>1-o</td>
<td>15-18°C</td>
<td>256-258°C</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure" /></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>4-Isomers (separable)</td>
</tr>
<tr>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>3</td>
<td>1,1'-H</td>
<td>107-108°C</td>
<td>A,B,C</td>
<td>--</td>
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<tr>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>9</td>
<td>1,1'-H</td>
<td>147-148°C</td>
<td>A,B,C</td>
<td>--</td>
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<tr>
<td><img src="image8" alt="Chemical Structure" /></td>
<td></td>
<td>H</td>
<td>94.5-95.5</td>
<td>A,B,C</td>
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</table>
### TABLE XII. C,6-MACROCYCLES CONTAINING A 2,5-PYRIDINO MOIETY

<table>
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<th>Spectral Data Available</th>
<th>Metal Complex(es)/General Comments</th>
<th>References</th>
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<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>H</td>
<td>101-104^o</td>
<td>A, B</td>
<td>--</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>H</td>
<td>72-73^o</td>
<td>A, B</td>
<td>--</td>
<td>84</td>
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</table>

### TABLE XIII. C,5-MACROCYCLES CONTAINING A 2,5-PYRIDINO MOIETY

<table>
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<th>Compound</th>
<th>n</th>
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<tbody>
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<td>1</td>
<td>H</td>
<td>204-205^o</td>
<td>A</td>
<td></td>
<td>--</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>2,7-di(sulfo)</td>
<td>350^o(4)</td>
<td>--</td>
<td>--</td>
<td>Two Isomers</td>
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<td>Compound</td>
<td>n Substituents</td>
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<td>Spectral Data Available</td>
<td>Metal Complex(es)/General Comments</td>
<td>References</td>
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<td>-----------------------------------</td>
<td>------------</td>
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<tr>
<td></td>
<td></td>
<td>H_2O/2H_2O(mmol)</td>
<td>A, D</td>
<td></td>
<td>71</td>
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<tr>
<td>14,16-d4(He)</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
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<td>75, 76, 77</td>
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<tr>
<td>14-He; 16-H</td>
<td>mp(d)</td>
<td>A, B</td>
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<td></td>
<td>75</td>
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<td>14-COCH_3; 16-CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>75</td>
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<tr>
<td>14-COCH_3; 16-H</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>14-COCH_3; 16-CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
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<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
<td></td>
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<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>14-CH_2CH_3; 16-CH_2CH_3</td>
<td>mp(d)</td>
<td>A</td>
<td></td>
<td></td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- H: 240–290°C
- A: α
- B: β
- K (anion formation)
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### TABLE XIV. C-MACROCYCLES CONTAINING A 3,5-PYRIDINO MOIETY

<table>
<thead>
<tr>
<th>Compound</th>
<th>n</th>
<th>Substituents</th>
<th>Physical Data</th>
<th>Spectral Data Available</th>
<th>Metal Complex(es)/General Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Np/Sp (cm⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>1</td>
<td>20-H; 18-CO₂CH₃</td>
<td>236-237°C</td>
<td>A, D</td>
<td></td>
<td>81,101,82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>259-260°C</td>
<td>A, D</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3,4,8,10,11,12-hexa (Me)</td>
<td>244-246°C</td>
<td>A</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>H</td>
<td>277-278°C</td>
<td>A, D</td>
<td></td>
<td>13,82</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>H</td>
<td>--</td>
<td>--</td>
<td></td>
<td>13</td>
</tr>
</tbody>
</table>

8,10,11,12-tetra (Me) 89.1-99.6°C  
A, C                        
--                           
HCl                         
73                           
89.1-99.6°C [subl: 60-65°C (0.3)]  
A                           
74
### TABLE XV. C₅N-MACROCYCLES CONTAINING A 3,5-PYRIDINO MOIETY

<table>
<thead>
<tr>
<th>Compound</th>
<th>n</th>
<th>Substituents</th>
<th>Physical Data</th>
<th>Spectral Data Available</th>
<th>Metal Complex(es)/General Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mº(Tp(m))</td>
<td></td>
<td></td>
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<td>261-262°C</td>
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<td>6-OH; 13-CH₃C₆H₅(2c,6)</td>
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<td>6,12-di(0B); 13-CH₃C₆H₅</td>
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### TABLE XVI. C₅N-MACROCYCLES CONTAINING A 3,5-PYRIDINO MOIETY

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<td>syn-isomer</td>
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<td>1-Cl, 1-Br (syn)</td>
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<td>149.5-151$^\circ$</td>
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<td>N → O (186-188$^\circ$)</td>
<td>109, 114, 159</td>
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<td>Picroate (185.5-186$^\circ$)</td>
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<td>13-Cl; 1-OAc (syn)</td>
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<td>13-Cl; 1-OAc (anti)</td>
<td>149-150$^\circ$</td>
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<td>144-145$^\circ$</td>
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<td>189.5-191$^\circ$</td>
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<td>101-102$^\circ$</td>
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<td>A</td>
<td>--</td>
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<tr>
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<td>13-Cl; 1-O2tos (anti)</td>
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<td>N → O (anti)</td>
<td>166-167$^\circ$</td>
<td>A</td>
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<td>Picroate (189-191.5$^\circ$)</td>
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<td>oil</td>
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<td>--</td>
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<td>--</td>
<td>116</td>
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<td>A</td>
<td>--</td>
<td>--</td>
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<td>H</td>
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<td>147-148$^\circ$</td>
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<td>--</td>
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<td>N → O (syn)</td>
<td>oil</td>
<td>A</td>
<td>HCl (140-150$^\circ$)</td>
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<td>13-Cl; 1-OCOC$_2$H$_5$ (anti)</td>
<td>116-118$^\circ$</td>
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### TABLE XVII. C-MACROCycles Containing a 2,1-PYRIDINO MOIETY (cont'd)

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<th>Metal Complex(es)/General Comments</th>
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<td>H 13-Cl; 1-OPO(OCH$_2$CH$_2$)$_2$(syn)</td>
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<td>B=COCH$_2$Br</td>
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<td>237-238$^o$</td>
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<td>B=CO(NH)$_2$(CH$_2$)$_2$ 13-Cl</td>
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<td>R=C$_2$-pyrCO-</td>
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<td>13-Br, 11-CO₂H</td>
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<td>13,14-di(Me); 11-CO₂H</td>
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<td>11-CO₂H</td>
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<td>Picrate (165°C)</td>
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<td></td>
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<td>H</td>
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<td>15-CO₂H</td>
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<td>260°C</td>
<td>--</td>
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<td>14</td>
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<td>H</td>
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<td>16-CO₂H</td>
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<td>250°C (d)</td>
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<td>8,9-dide(II)</td>
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<td>Picrate (161°C)</td>
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<td></td>
<td>8,9-dide(II), 16-CO₂H</td>
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<td>256°C</td>
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<td></td>
<td>8,9-dide(II), 16-CO₂H, 18-Br</td>
<td></td>
<td>270°C</td>
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## Table XX. C,N-Macrocycles Containing a 2,5-Pyridino Moiety

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<th>Number</th>
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<th>Spectral Data Available</th>
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<th>References</th>
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<td>Co, Cu</td>
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## Table XXI. C-Macrocycles Containing a 2,5-Pyridino Moiety

<table>
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<th>Physical Data</th>
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<td>281.5-282°</td>
<td>B, C</td>
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TABLE XXII. COLLECTION OF LITERATURE REVIEWS ON THE SYNTHESIS OF HETERO-MACROCYCLES.


TABLE XXIII. LITERATURE REFERENCES PERTAINING TO NOMENCLATURE SYSTEMS FOR HETERO MACROCYCLES.


REFERENCES

34. M. Newcomb, unpublished results.

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102. J. D. Sauer, unpublished data.


107. A. Marchesini, S. Bradamante, R. Fusco, and G. Pagani, 


   37, 3248 (1972).

   5767 (1971).


   16, 1335 (1933).

Proposed Research

The area of research so-far outlined in this introduction is obviously too broad in its present scope. The general skeletal Systems focused on in this work are shown below. The major emphasis however, was directed specifically toward Systems III and IV, with also preliminary synthetic work being directed toward the remaining System V.


In dealing with compounds with the III skeleton, the specific structures of initial interest are those in which the pyridine rings are separated by carbonyl functionality. The simplest compound of this type structure would obviously be 39. Compound (39), however, possesses a 8-membered (medium-ring) core and would be expected to have a correspondingly high strain energy. The simplest practical
member of this class then is triketone (40), the next higher homolog. The only close relative of 40 is the trisulfide (15). This ligand was found to have a nonplanar conformation.\textsuperscript{11} Whereas the expected structure of 40 should be flat. Ligand (41), tribenzo-[b,f,j][1,5,9]-triazacyclododecane, was synthesized by Busch, \textit{et al.}\textsuperscript{20} via a condensation of 2-aminobenzaldehyde in the presence of cobalt ions. Although drawing VI indicates the close structural relationship of 41 and 40, detailed studies indicate that ligand (41) is a non-planar, highly flexible species.

One approach to the skeletal make-up of III might consist of a formal union such as the one illustrated by Figure IV.

Since it has been demonstrated that 2,6-dibromopyridine undergoes monolithiation, it was envisioned that this mode of reaction
might be applicable to the desired fragment \( \text{ii} \). The total synthesis of fragment \( \text{ii} \) is outlined in Scheme (VII). This synthesis was the route proposed at the initiation of this project. (Like most things, this proposal was altered by the force of reality as the work continued!) Compound (46) then, in Scheme (VII), would be equivalent to fragment \( \text{ii} \) in the overall synthesis of ligand (40). The reagents necessary to affect these transformations would be: (a) n-butyl-lithium at \(-20^\circ\text{C}\) in diethyl ether; (b) \( \text{CO}_2 \) and, (c) the series \( \text{SOCl}_2, \text{NH}_4\text{OH}, \text{SOCl}_2 \) [a textbook approach to convert an acid to a nitrile (43)]; (d) 2-lithio-6-bromopyridine at \(-20^\circ\text{C}\); (e) acid hydrolysis of ketamine to ketone (45); and finally; (f) protection of the carbonyl group via ethylene glycol, \( \text{p-toluenesulfonic acid} \) ketalization to afford the bis(6-bromo-2-pyridyl)ketone ketal (46).

Fragment \( \text{i} \) was visualized as either 2,6-dicyanopyridine or dimethyl 2,6-pyridinedicarboxylate and the coupling, or ring-formation step was projected to be the one outlined in Scheme (VIII).
An alternate route to ligand (40) was also envisioned as potentially proceeding through fragment (iii). This course was only lightly considered due to the fact that no exact precedent was available for a one-step cyclization of this fragment that would yield directly the desired ligand skeleton for III. One possible track utilizing this fragment is put forth in Scheme (IX). Step (d) was postulated to be the reaction with a reagent such as phosgene or cyanogen bromide to afford a ligand (40) precursor in a single reaction step.
Both Scheme (VIII) and (IX) obviously contain the inherent capability to generate higher homologs of ligand (40). The most likely are illustrated as ligands (52) and (53). It seems obvious, nevertheless, that the molecular size of especially ligand (53) (m.wt.=945) but probably 52 (m.wt.=630), as well, would severely limit solubility and other physical parameters that would allow one
to work with these substances. The larger macrocycles, then, were not expected to be obtainable by these sequences.

Since it is possible to generate polypyridyl functionality having halogens substituted in the (6,6') positions, a path to ligand \((54)\) is an obvious off-shoot of Scheme (IX), provided a method is obtainable to make practical step (d) of that scheme.

As with the ligand skeleton III, back-bone IV could be constructed by three possible approaches. These diverse tracks are illustrated by the dissection of System IV into fragments iv, v, and vi. Since fragments iv and vi would undergo the exactly analogous reaction shown in Scheme (IX) step (d), no further explanation of this sequence is necessary for an understanding of the synthetic tools required. Fragment v, however, will necessitate the use of a synthon for the bipyridyl moiety. Several techniques were available for this transformation but one of the most versatile involves the
organo-copper intermediate shown in Scheme (X). The copper intermediate (55) will undergo an oxidative carbon-carbon bond formation readily when, during the work-up, air is forced through the reaction medium.

Scheme (X)

As in the case of ligands related to skeleton III, the macrocycles related to IV can also yield a series of ever-increasing molecular weight homologs. Hence, the reactions described for this family would probably afford 59a, b, etc. [besides ligand (54)].

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Part 2. Cyclic Pyridyl Acetylenes and Cumulenes. System V.

Before directly attacking the problem of forming macrocycles related to rings V, a few facts must be mentioned about linear acetylene and cumulene molecules incorporating the (2,6)pyridine moiety. The operative word in the preceding sentence is few! A literature survey has uncovered only 40 examples of 2-pyridyl-acetylenes, 22 examples of allenes, 23 and no examples of pyridyl-cumulenes.

In light of this information, it seemed appropriate to limit initial studies to simple, linear systems to develop an understanding of the problem at hand. The systems studied are outlined in Scheme (XI).

A very good review of cumulenes by Fischer 24 illustrates adequately that the most common route to the butatriene systems is via reduction of butyne-1,4-diols with stannous chloride-HCl-ether, PBr₃/pyridine, or KI/H₂SO₄.

Scheme (XI)

The compounds (60) and (61) where (R = R₁ = Ph) 25 and (R = Ph; R' = 2-Pyr) 26 were known in the literature, so these could be utilized.
as model systems to develop an effective method for conversion of the acetylene diols into the corresponding butatrienes. It had been reported by Sisenwine and Day\textsuperscript{26} that, with the acetylene (61), one obtained not the desired cumulene but in fact the rearrangement product (63).

Other workers subsequently reported\textsuperscript{27} the rearrangement product (63) to be incorrectly assigned and that the correct rearrangement pathway was depicted by Scheme (XII). With the product being reassigned to 3-hydroxy-4,9a-diphenyl-4,9a\- (2'-pyridyl)-4H-quinolinizin-1(9aH)one (66). Although the acetylene diol 61 had been demonstrated

\textbf{Scheme (XII)}
to be isolable in excellent yield, this compound had also been shown to undergo the rearrangement to \( \text{66} \) under conditions as gently as refluxing ethanol. This information would seem to preclude the use of the previously noted "normal" reagents to effect the didehydroxylating step, since all of these include relatively acidic conditions. Recent work by Hanafusa, et al.\(^\text{28} \) indicated that a homo-1,4-elimination of 1,2-di-(α-hydroxybenzyl)cyclopropane (\( \text{67} \)) could be accomplished via treatment with diphosphorous tetraiodide/pyridine to

![Chemical Structure](image)

yield the corresponding diene \( \text{68} \). Even though this system was not an exact precedent for the didehydroxylation desired in this work, it was envisioned that a reagent as mild as \( \text{P}_2\text{I}_4/\text{Pyr} \) might not initiate the unwanted rearrangement while still allowing for the formation of the cumulenes \( \text{69a,b} \). It was expected that \( \text{62} \) would

![Chemical Structure](image)

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exist as E and Z geometrical isomers, although previous examples of actual separation of related systems are rare.\textsuperscript{29,30}

This preliminary information indicated some of the potential difficulties associated with cumulenic systems incorporating the subheteromacrocyclic pyridine unit. On the positive side, most aryl-substituted cumulenes already known are stable compounds, so it seemed reasonable to expect that the pyridyl analogues would be isolable if a satisfactory synthetic method was realized.

Long-range work would involve the synthesis of \textsuperscript{70} from (2,6)-dibenzoylpyridine \textsuperscript{69} and acetylene bis-magnesium bromide. This macrocycle could possibly survive a traditional metal-acid type reduction to afford \textsuperscript{71}, since \textsuperscript{70} has severe structural constraints that should hamper the facile rearrangement observed in the linear systems.
This class of macrocycles would be particularly interesting due to the fact that several modes of metal complexation are feasible. For example, 72 illustrates the "typical" electron donation by the hetero atoms present while 73 typifies the mode of electron donation via the π-orbital of the butatriene system itself.
EXPERIMENTAL

Unless indicated otherwise in a specific experiment, all of the chemicals utilized in this work were reagent grade and no purification steps were taken. An exception to this statement would be the SOLVENT preparation. Benzene, cyclohexane, diethyl ether, petroleum ether (A, bp 30-60°; B, bp 60-90°; C, bp 90-120°), toluene, xylene, and mesitylene were dried over sodium ribbon. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were passed through an alumina column activity I, distilled from lithium aluminum hydride (LAH), and stored over activated molecular sieves (Linde Type 4A) under an argon atmosphere. Dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), and hexamethylphosphoroustriamide (HMPA) were distilled from calcium hydride at reduced pressure and stored over activated molecular sieves (Linde Type, 4A) under an argon atmosphere.

Thin layer chromatography (tlc) procedures utilized 20 cm glass plates with a 0.25 mm coating of Brinkmann HF-254 + 366 silica gel. The plates were activated at 150° C for a minimum of one hour before use. Frontal retention values (Rf) are reported along with the solvent system used. Preparation thick layer chromatography (plc) utilized silica gel thicknesses of either 2 mm (Brinkmann PF-254 + 366) or 5 mm (Brinkmann PF-254 = 13% CaSO₄ binder). The plates were activated at 150° for a minimum of 4 hours before use. Multiply developed plates are listed with the number of elutions per solvent system. Column chromatographic procedures involved either silica gel (Baker, 60-200 mesh) or florisil (60-100 mesh), activity I grade. Dry column chromatography was performed with various diameter nylon
tubing and Waters Associates Dry Column Grade, Activity III, silica
gel or alumina. Preliminary purification procedures utilized silica
gel (Baker, 60-200 mesh), Florisil (60-100 mesh), alumina (Alcoa F-20,
80-200 mesh), and charcoal (Nuchar C-190N). Gas phase chromatography
(glpc) was performed on a Varian Aerograph 90-P with a 3/8" x 10'
column packed with 20% SE30 on 60/80 mesh chromosorb W.

Melting points below 250° were measured in sealed capillary
tubes with a Thomas-Hoover Unimelt and are uncorrected. Thermal data
above 250° were obtained on a Dupont-900 Differential Thermal Analyzer
or Thermal Gravimetric Analyzer and are reported as a corrected value
via a thermocouple conversion chart. Boiling points were recorded
uncorrected with reduced pressure specified in millimeters (mm Hg)
of mercury.

Nmr (60 MHz) spectra were recorded on either a Varian Associates
A-60A or a Perkin-Elmer R12-B spectrophotometer. Where specified,
100 MHz, 220 MHz, and 300 MHz nmr spectra were determined on Varian
Associates HA-100, HA-220, and HA-300 spectrometers, respectively,
by Professor N. S. Bhacca. Chemical shifts are reported in parts
per million (δ) downfield from tetramethylsilane (TMS) as the internal
standard.

Infrared (ir) spectra were obtained with either a Perkin-Elmer
IR-137 or a Perkin-Elmer IR-621 grating spectrophotometer.

Ultraviolet (uv) and visible (vis) spectra were determined in
the specified solvent on a Cary-14 recording spectrophotometer in
1 cm matched quartz cells and were corrected by a solvent blank.
Absorbance values were reported in wavelength (nm) followed by molar
extinction coefficients (ε).
Mass spectrograms were obtained on either a Hitachi-Perkin-Elmer RMS-4 mass spectrometer by Ms. Paula Moses or on a Finnigan F 1015-D Electron-impact Mass Spectrometer. Conditions were usually 70 eV and 80 µA. A fluorocarbon was used as a counting reference.

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

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

Methyllithium\textsuperscript{32,33} (74). Lithium wire (2.7 g, 0.4 mol) in anhydrous diethyl ether (150 ml) was stirred under a nitrogen atmosphere. A solution of methyl iodide (28.4 g, 0.2 mol) in anhydrous diethyl ether (50 ml) was added at such a rate that a gentle reflux was maintained throughout the addition. At the end of this addition, since small unreacted scraps of metal remained, a few additional drops of methyl iodide were added. The resultant solution was then cooled to the desired reaction temperature by immersion in the appropriate cooling bath.

2-Bromo-6-pyridyllithium\textsuperscript{32,33} (30). 2,6-Dibromopyridine (30.0 g, 0.126 mol) was dissolved in anhydrous ether (1:1) under an argon atmosphere. This solution was added dropwise to the above standard ethereal methyllithium solution (0.2 mol) cooled to -40°. The temperature was maintained at -30° ± 5° by varying the depth of immersion in a dry-ice/acetone slurry for one hour. After the addition was
complete, the mixture was allowed to warm to -20° and maintained at -20° ± 5° for an additional hour. This preparation of 2-bromo-6-pyridyllithium typically yielded approximately 50% of the theoretical amount of product when isolated by any of the standard trapping methods (carboxylation, ...).

6-Bromo-2-picoline Acid (75). An ethereal solution of 2-bromo-6-pyridyllithium [prepared from 2,6-dibromopyridine (30.0 g, 0.126 mol) via Method A] was poured rapidly into an excess of crushed dry-ice with rapid stirring. Upon sublimation of the dry-ice, water (200 ml) was added and the mixture extracted several times with diethyl ether. The aqueous layer was neutralized with ice-cold HCl and was again extracted with several portions of ether. The latter combined ether extracts were dried over anhydrous magnesium sulfate and concentrated to afford 15.2 g (59.6%) of the crude acid, which was recrystallized from benzene to give 12.3 g (48.4%) of 6-bromo-2-picoline acid: mp 194-196° (lit. mp 192-194°); nmr (CD$_3$COCD$_3$) 7.1-7.3 (CO$_2$H, b s, 1 H), 7.8-8.2 (Pyr-H, m, 3 H).

6-Bromo-2-picolinoyl Chloride (76). Method A. Treatment of 6-bromo-2-picolinic Acid with Thionyl Chloride. A slurry of 6-bromo-2-picolinic acid (6.00 g, 0.03 mol) and thionyl chloride (50 g, 0.42 mol) was maintained at gentle reflux conditions for 18 hours followed by removing the excess thionyl chloride at reduced pressure to afford a tacky solid. This material was rinsed with dry petroleum ether and dissolved in 200 ml of dichloromethane. A solution of 2-amino-2-methyl-1-propanol (4.95 g, 0.03 mol) in 50 ml of dichloro-
methane was added dropwise and the mixture was stirred at ambient conditions for 12 hours. The suspension was filtered and the resulting solid was recrystallized from water/ethanol to afford 4.88 g (59%) of the expected amide: mp 97.5-99°. A satisfactory elemental analysis was not obtained for this material, however, mass spectral analysis indicated this sample to be a mixture of chloro- and bromo-substituted picolinamides. No attempt was made to separate and purify these components.

6-Chloro-2-Picolinic Acid (77). via Halogen Exchange on 6-Bromo-2-picolinic Acid. 6-Bromo-2-picolinic acid (0.10 g, 0.495 mmol) and potassium chloride (1.0 g, 18.4 mmol) were suspended in anhydrous dimethylformamide (25 ml). This mixture was refluxed with stirring for 24 hours, followed by standing at ambient temperature for an additional 12 hours. The mixture was suspended in an equal volume of water, the pH was adjusted to ca. 4 with 5N hydrochloric acid, and the solution was extracted several times with chloroform. The organic phase was dried over sodium sulfate and concentrated to afford >95% unchanged 6-bromo-2-picolinic acid: mp 194-196°; ms (70 eV) m/e 204 (33), 202 (100), 200 (33).

Transhalogenation of 2,6-Dichloropyridine. A mixture of 2,6-dichloropyridine (7.4 g, 50 mmol), sodium bromide (20 g, 0.20 mol), and 5N sulfuric acid (50 ml) was refluxed for 24 hours. After cooling to room temperature, the solution was neutralized with 10% sodium carbonate and extracted with dichloromethane (5 x 50 ml). The organic phase was dried over anhydrous sodium sulfate and con-
centrated to afford 7.7 g of a white amorphous powder: mass spectral analysis indicated this sample to be a mixture of chloro- and bromo-substituted pyridines. No attempt was made to separate and purify these components.

**2-Picolinoyl Bromide (78). Method A. Treatment of 2-Pyridine-carboxylic Acid with Thionyl Bromide.** A suspension of 2-pyridine-carboxylic acid (1.0 g, 8.1 mmol) in anhydrous benzene (15.0 ml) and thionyl bromide (10.0 g, 47.3 mmol) was refluxed for three hours. The solution was cooled and mixed with anhydrous dimethoxyethane (50.0 ml). The yield of 2-picolinoyl bromide was estimated to be 20% of theoretical as based on the yield of 2-picolinamide upon reaction of the acylbromide with ammonium hydroxide. 2-Picolinoyl bromide was not purified.

**2-Picolinoyl Bromide (78). Method B. Treatment of 2-Picolinic Acid with Phosphorous Tribromide.** A suspension of 2-picolinic acid (1.0 g, 8.1 mmol) in anhydrous benzene (50.0 ml) was refluxed with an efficient mechanical stirrer. Phosphorous tribromide (2.8 g, 10.0 mmol) was added drop-wise and the resulting mixture was refluxed for an additional three hours. The yield of 2-picolinoyl bromide was estimated to be 78% of theoretical, as based on the formation of 2-picolinamide.

**2-Picolinamide (79).** A solution of 2-picolinoyl bromide (6.4 mmol) in anhydrous benzene (50.0 ml) was poured quickly into cold, concentrated ammonium hydroxide (100.0 ml) was stirred vigorously for 5 minutes. The mixture was diluted with an equal portion of
water and extracted with chloroform (10 x 100 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford (98%) 2-picolinamide: 770 mg, mp 105-7° (lit.\(^{34}\) mp 107°); ir (CHCl\(_3\)) 3520, 3390, 2980, 1690 (CONH\(_2\)), 1590, 1560, 1465, 1440, 1375, 1258, 1085, 1007, 770, 587 cm\(^{-1}\).

2-Cyanopyridine (\(\text{80}\)). 2-Picolinamide (1.0 g, 8.1 mmol) was mixed with phosphoric anhydride (2.0 g, 14.0 mmol) under an argon atmosphere. The mixture was heated to 150° C at 0.5 mm for three hours to afford a low melting solid which solidified in the probe of the sublimation apparatus (cooled to -10° C). Distillation of this solid afforded 390 mg (49%) of pure 2-cyanopyridine: mp 27-28°; bp 85-87° (12 mm) [lit.\(^{35}\) mp 26-28°; bp 212-215 (760 mm)].

6-Bromo-2-piclinoyl Bromide (\(\text{81}\)). Method B. Treatment of 6-Bromo-2-picolinic Acid with Thionyl Bromide. A suspension of 6-bromopicolinic acid (1.0 g, .0049 mol) in anhydrous benzene (15 ml) and thionyl bromide (10.8 g, 0.051 mol) was refluxed for three hours under a nitrogen atmosphere. The mixture was cooled and dissolved in anhydrous dimethoxyethane (50 ml). 6-Bromo-2-picolinoyl bromide was isolated in 22.6% (estimated value based on 6-bromo-2-picolinamide when quenched with ammonium hydroxide.) 6-Bromo-2-picolinoyl bromide was not isolated, but used directly!

6-Bromo-2-picolinoyl Bromide (\(\text{81}\)). Method C. Treatment of 6-Bromopicolinic Acid with Phosphorous Tribromide. A suspension of 6-bromopicolinic acid (1.0 g, .0049 mol) in anhydrous benzene

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(80.0 ml) was refluxed with an efficient mechanical stirrer under a nitrogen atmosphere. Phosphorous tribromide (2.8 g, 0.01 mol) was added drop-wise maintaining the reflux conditions for 6 hours. The yield of 6-bromo-2-picolinoyl bromide was estimated to be essentially quantitative (98%+) as based on 6-bromo-2-picolinamide when quenched with ammonium hydroxide. The 6-bromo-2-picolinoyl bromide was not purified.

6-Bromo-2-picolinamide (42). A solution of 6-bromo-2-picolinoyl bromide (0.0049 mol) in anhydrous benzene (80.0) was poured carefully into ice-cold, concentrated ammonium hydroxide (200 ml) and stirred for 5 minutes. The mixture was diluted with an equal volume of distilled water and extracted several times with chloroform, dried over magnesium sulfate, and concentrated to afford 1.0 g (100%) of the 6-bromo-2-picolinamide: mp 135-138°. Recrystallization from benzene gave 0.75 g (75%) of pure 6-bromo-2-picolinamide: mp 137-138°; nmr (CDCl$_3$) $\delta$ 6.2 (-NH$_2$, bs. 2H), 7.65-8.25 (Py-H, m, 3H); ir (CHCl$_3$) 3520, 3395, 2962, 1694 (CONH$_2$), 1560, 1440, 1400, 1370, 1260, 1090, 1010, 800 (broad) cm$^{-1}$.

Anal. Calcd. for C$_6$H$_5$N$_2$OBr: C, 35.8; H 2.5; N 13.9. Found: C, 35.7; H 2.6; N, 13.7.

2-Bromo-6-cyanopyridine (43). 6-Bromo-2-picolinamide (1.0 g, 0.005 mol) was mixed with phosphoric anhydride (2.0 g, 0.014 mol) under an argon blanket. This solid was sublimed at 150° (0.5 mm) over four hours affording 0.62 g (60%) of 2-bromo-6-cyanopyridine: mp 98-99°; nmr (CDCl$_3$) $\delta$ 7.73 (Py-H, s); ir (CHCl$_3$) 3155, 3020, 2958,
2400, 2250 (C≡N), 1820, 1572, 1560, 1467, 1425, 1380, 1246, 1215, 1158, 1121, 1093, 980, 900, 750, 630 cm⁻¹.

**Anal. Calcd. for C₆H₃N₂Br:** C, 39.9; H, 1.6; N, 15.3. *Found:* C, 40.1; H, 1.6; N, 15.5.

**Bis(2-pyridyl)ketone (82). Method A.** Reaction of 2-Lithiopyridine and 2-Picolinonitrile. An ethereal solution of 2-lithiopyridine [from 2-bromopyridine (10.0 g, 0.063 mol), n-butyllithium (2.42 M in hexane, 29 ml, 0.070 mol), and diethyl ether (100 ml)] was cooled to -40° C and 2-picolinonitrile (6.55 g, 0.063 mol) in ether (50 ml) was added *slowly* with rapid stirring. The resulting red suspension was maintained at -20 to -15° C for thirty minutes and subsequently hydrolyzed with 50 ml 5N HCl. The mixture was gently heated on a steam-bath for two hours and the aqueous suspension extracted with chloroform. The combined extracts were dried over sodium sulfate and concentrated to produce 4.1 g of an oily semi-solid, which was triturated with boiling diethyl ether. The solid residue was recrystallized from benzene-cyclohexane affording 2.35 g (40%) of the beige, crystalline bis(2-pyridyl)ketone: mp 55-56° (lit. mp 54-56°); nmr (CDCl₃) δ 7.44 (H₅, ddd, J = 7.6, 7.4, 1.8Hz), 7.85 (H₄, ddd, J = 7.6, 7.4, 1.8Hz), 8.15 (H₃, ddd, J = 7.4, 1.5, 1.OHz), 8.72 (H₆, ddd, J = 5.0, 1.8, 1.OHz); ir (KBr pellet) 3020, 1680, (C=O), 1580, 1570, 1470, 1425, 1400, 1330, 1320, 1280, 1255, 1235, 1225, 1180, 1155, 1090, 1045, 992, 975, 950, 942, 900, 828, 786, 755, 744, 702, 694 cm⁻¹.

**Bis(2-pyridyl)ketone (82). Method B.** via Coupling with Ethyl Chloroformate. An ethereal solution of 2-lithiopyridine [from
bromo-pyridine (5.0 g, 32 mmol), n-butyllithium (2.26 M in hexane, 15.5 ml, 35 mmol), and diethyl ether (100 ml)] was cooled to -78° C, then a solution of ethyl chloroformate (1.73 g, 16 mmol) in 10 ml diethyl ether was added as quickly as possible maintaining the temperature below -60° C. The solution was stirred 30 minutes at -60°, an additional 15 minutes at -40°, then sequentially methanol (30 ml), 12 M HCl (10 ml), and water (50 ml) were added. The organic solvent was removed at reduced pressures and the aqueous slurry extracted with chloroform (10 x 50 ml). The combined organic phases were dried over anhydrous sodium sulfate and concentrated to afford an oily solid, which was recrystallized from benzene/petroleum ether (B) to afford 2.1 g (35.7%) of the crystalline bis(2-pyridyl)-ketone: mp 55-56°.

Catechol Carbonate (83). Method A. Treatment of Catechol with Diethyl Carbonate. Catechol (5 g, 0.046 mol), diethyl carbonate (50 g, 0.58 mol), and concentrated sulfuric acid (2 drops) were refluxed with a Dean-Stark water separator for two days while the reaction was monitored via chromatographic analysis [tlc, 0.25 mm silica gel, cyclohexane-ethyl acetate (1:1)], which evinced only starting catechol (Rf = 0.60) and diethyl carbonate (Rf = 0.72) with complete absence of the desired product, upon subsequent removal of solvent, only unreacted catechol was isolated: [mp 102-105°; lit.37 mp 105°)].

Catechol Carbonate (83). Method B. Treatment of Catechol with Phosgene. Catechol (22.0 g, 0.2 mol) was dissolved in degassed water

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(250 ml) that contained sodium hydroxide (17.5 g, 0.44 mol). To this solution toluene (150 ml) was added and the mixture was cooled to 0° C. Phosgene was slowly bubbled through the mixture for one hour while maintaining the temperature between 0-5° C. Following the introduction of the phosgene, a nitrogen stream was passed through the mixture for another hour to flush out unreacted phosgene. The mixture was then stirred at ambient temperature for an additional hour. The mixture was filtered and the two liquid phases were separated. Any solids from the filtration step were returned to the organic phase and then heated to effect dissolution. After cooling to room temperature, the crude catechol carbonate crystallized. Recrystallization from toluene gave 6.3 g (23%) of beige prisms of pure catechol carbonate: mp 119-119.5° (lit.37 mp 119-120°); nmr (CDCl3) δ 7.21 (Ph-H,5); ir (KBr pellet) 3350, 3000, 2250, (w), 2050 (w), 1870, 1820, 1800, 1780, 1760, 1630, 1600 (w), 1460, 1440, 1320, 1280, 1230, 1225, 1105, 1040, 1020, 950, 940, 760, 754, 700 cm⁻¹; [tlc, 0.25 mm silica gel, cyclohexane-ethyl acetate (4:1), Rf 0.74).

Catechol Dichloromethylene Ether (84). Five pyrex tubes were made up with the following contents (per tube): catechol carbonate (1.0 g, 7.35 mmol) and phosphorous pentachloride (2.0 g, 9.6 mmol). The tubes were cooled, evacuated, sealed, and all five were heated to 200° for 24 hours. After cooling the tubes were opened (one burst in heating bath) and the combined liquids distilled to give 2.3 g (42%) of catechol dichloromethylene ether: bp 82-84° (10 mm) [lit.38 bp 85-85.5° (12 mm)].
Phenyl(2-pyridyl)ketone (R5). 2-Lithiopyridine [generated from 2-bromopyridine (10.0 g, 0.63 mol) and methyllithium (2.63 M in diethyl ether; 25.0 ml, 0.66 mol)] was cooled to -30° C and redistilled benzonitrile (6.5 g, 0.63 mol) dissolved in diethyl ether (50 ml) was added slowly with efficient stirring. After stirring for one hour, the reaction mixture and 5N HCl (60 ml) were heated on the steam bath for five hours. Sodium bicarbonate was added to adjust the pH to ca. 7.0, then the aqueous solution was extracted with chloroform. The combined extract was dried and concentrated to afford 5.5 g of the crude phenyl(2-pyridyl)ketone. Recrystallization from cyclohexane-ethyl acetate afforded 3.2 g (27.8%) of pure phenyl(2-pyridyl)ketone: mp 43-44° (lit. 39 mp 42-44°); nmr (CDCl$_3$) δ 7.33-8.15 (Ph-and Py-H, m, 8H), 8.65-8.70 (6-Py-H, dd, J = 4.5, H$_2$, 1H); ir (CHCl$_3$ solution) 3050, 1670 (C=O), 1600, 1590, 1460, 1450, 1440, 1320, 1300, 1280, 1240, 1160, 1150, 1100, 1080, 1050, 1025, 990, 940, 930, 820, 780, 750, 730, 705 cm$^{-1}$.

6-Bromo-2-acetylpyridine (R6). To a solution of 2-bromo-6-lithiopyridine [prepared from 11.85 g (0.05 mol) of 2,6-dibromo-pyridine and 23 ml (2.2N; 0.05 mol) of n-butyllithium] in diethyl ether (150 ml) cooled to -90° acetonitrile (2.05 g, 0.05 mol) was added. The mixture was maintained at -40° C for one hour then hydrolyzed with 5N hydrochloric acid. The aqueous layer was extracted with chloroform (10 x 50 ml). The combined organic extract was dried over anhydrous sodium sulfate, then the solvent was removed at reduced pressure to afford a beige residue, which was recrystallized from diethyl ether-cyclohexane affording 4.1 g (41%)

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of white crystalline 6-bromo-2-acetylpyridine: mp 54-55°; nmr
(CDC1\textsubscript{3}-1\% TMS) \delta 2.60 (s, 3H, -CH\textsubscript{3}), 7.6-8.0 (m, 3H, pyr-H); ir
(KBr) 3050, 1700 (C=O), 1590, 1460, 1320, 1280, 1260, 1150, 1100,
990, 730 cm\textsuperscript{-1}.

**Anal.** Calcd. for C\textsubscript{7}H\textsubscript{6}NOBr: C, 42.0; H, 3.0; N, 7.0. Found: C,
42.2; H, 3.1; N, 6.9.

**Phenyl-2-(6-bromopyridyl)ketone (87).** A solution of 2,6-
dibromopyridine (11.0 g, 0.046 mol) in diethyl ether (300 ml) was
cooled to -70° C and n-butyllithium [2.4 M in hexane; 23.0 ml,
0.055 mol] was added slowly with vigorous stirring never allowing
the temperature to rise above -60° C. The solution was maintained
at -60° C for one additional hour after the addition, then a solution
of benzonitrile (4.75 g, 0.046 mol) in diethyl ether (20 ml) was
added. The reaction vessel was allowed to warm to -30° for an
additional hour. The reaction was terminated by adding sequentially
methanol (50.0 ml), 12 M HCl (30.0 ml), and water (50.0 ml). The
organic solvents were removed at reduced pressures, the aqueous
phase was diluted with an equal volume of methanol, and the solution
was refluxed for 12 hours to effect complete hydrolysis of the
intermediate ketimine. The methanol was removed at reduced pressures
and the residue extracted with chloroform (5 x 50 ml). The combined
extracts were dried and concentrated to give a mixture of desired
ketone and unreacted dibromopyridine. This mixture was trituated
with diethyl ether removing most of the starting dihalide and sub-
sequent column chromatography (silica gel G; chloroform eluent)
afforded 5.4 g (44.8\%) of the colorless needles (recrystallized from
\( \text{CH}_2\text{Cl}_2/\text{CHCl}_3 \) of phenyl-2-(6-bromopyridyl)ketone: mp 64.5-65.5°;
nmr (CDCl\textsubscript{3}) \( \delta \) 7.27-8.20 (Ph-H and Py-H, m); ir (KBr pellet) 3150,
1690, (C=O), 1640, 1610, 1580, 1560, 1450, 1425, 1400, 1320, 1310,
1245, 1175, 1155, 1120, 1115, 1075, 985, 955, 926, 824, 800, 770,
740, 705, 695, 670 cm\textsuperscript{-1}.

Anal. Calcd. for \( \text{C}_{12}\text{H}_7\text{NOBr} \): C, 55.40; H, 3.01; N 5.34. Found: C, 55.69; H, 2.96; N, 5.31.

2-Pyridyl-2-(6-bromopyridyl)ketone (88). An ethereal solution
of 2-bromo-6-lithiopyridine [generated from 2,6-dibromopyridine
(2.37 g, 0.01 mol) and methyllithium (0.02 mol)] was cooled to -30° C
(dry-ice/acetone bath). 2-Cyanopyridine (1.14 g, 0.01 mol) in
anhydrous diethyl ether (25 ml) was added slowly with stirring,
while allowing the temperature to rise to 25° C in one hour. The
mixture was hydrolyzed with 5N HCl on a steam bath for one hour,
followed by extraction with chloroform. The chloroform extracts
were dried over magnesium sulfate and concentrated to afford 3.185 g
of a semi-solid residue, which was shown (tlc) to be a mixture of
2,6-dibromopyridine, picolinic acid (from hydrolysis of 2-cyanopyridine),
and desired 2-pyridyl-2-(6-bromopyridyl) ketone.

A sample (680 mg) of this mixture was chromatographed [plc,
2 mm, 1x, ethyl acetate-cyclohexane (1:1)] to give 233 mg (42%) of
the pure crystalline ketone: \( R_f = 0.40 \); mp 85-86° (lit.\textsuperscript{21} mp 84.5-
86.5°); nmr (CDCl\textsubscript{3}) \( \delta \) 7.27-8.20 (Py-H, m, 6H), 8.73 (6-Py-H, m, 1H);
ir (CHCl\textsubscript{3}) 3000, 1687 (C=O), 1572, 1555, 1428, 1400, 1320, 1284,
1155, 1123, 995, 953, 822 cm\textsuperscript{-1}.

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Bis-2-(6-bromopyridyl)ketone (45). Method A. Treatment of 2-Bromo-6-cyanopyridine with 2-Bromo-6-lithiopyridine. A solution of 2-bromo-6-lithiopyridine [prepared from 2,6-dibromopyridine (1.42 g, 0.006 mol) and methyllithium (0.010 mol)] in anhydrous diethyl ether (70 ml) was cooled to -65° C by use of a dry-ice/acetone cooling bath. 2-Bromo-6-cyanopyridine (1.0 g, 0.005 mol) dissolved in anhydrous diethyl ether (50 ml) was added slowly and then the mixture was allowed to spontaneously warm to ambient temperature. After stirring for one hour, the mixture was hydrolyzed with 2.5 N HCl for one hour at 100°, followed by neutralization with sodium carbonate and extraction with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford (81%) 1.68 g of a beige residue which was chromatographed [plc, 2 mm; ethyl alcohol-chloroform (1:99)] affording 242 mg (14.1%) of the pure bis-2-(6-bromopyridyl)ketone: mp 155-156° (lit.21 mp 155-156.5°); nmr (CDCl₃) δ 7.69-8.05 (Py-H, m).

Potassium Hexacyanodinickelate(I)₄ (89). Potassium tetra-cyanonickelate(II) (7.64 g, 31.7 mmol) was placed in a flame-dried, 300 ml round-bottom flask equipped with a dry-ice/acetone condensor under an anhydrous nitrogen atmosphere. Approximately 200 ml liquid ammonia was collected by passing ammonia gas (dried through KOH) into the reaction vessel. The system was intermittently opened and small quantities of potassium metal (0.87 g, 22.0 mmol) were added. The system was allowed to slowly warm to ambient temperature over 24 hours and remaining traces of ammonia were removed at reduced pressure. The bright red powder remaining in the flask

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was washed with anhydrous methanol (5 x 50 ml) to remove potassium cyanide, and finally was dried in vacuo to afford 5.8 g (86.5%, based on potassium metal) of potassium hexacyanodinickelate(II):  
ir (nujol mull) 2128, 2079, 2055 cm⁻¹; since this material is readily oxidized to \( \text{K}_2[\text{Ni(CN)}_4] \) no other physical constants are readily obtainable. This compound was stored in vacuo or under an inert atmosphere until ready for use.

Bis-2-(6-bromopyridyl)ketone (45). Method B. Treatment of 2,6-Dibromopyridine with Carbon Monoxide in the Presence of \( \text{K}_2\text{Ni}_2(\text{CN})_6 \). \( \text{K}_2\text{Ni}_2(\text{CN})_6 \) (2.5 g, 7.1 mmol) was dissolved in a mixture of water (100 ml) and acetone (90 ml). Carbon monoxide was slowly bubbled into the solution for about ten minutes (the color of the solution changes from brick-red to yellow-green), then 2,6-dibromopyridine (3.4 g, 14.2 mmol) dissolved in acetone (30 ml) was added. Carbon monoxide was bubbled into the mixture for 40 hours, then the solution was filtered and the acetone was removed at reduced pressure. Extraction of the aqueous slurry with chloroform (5 x 50 ml), followed by drying over anhydrous magnesium sulfate and concentration at reduced pressure afforded only unreacted 2,6-dibromopyridine [mp 117-118°; nmr (CDCl₃) \( \delta \) 7.45 (Py-H, s)] and none of the desired bis-2-(6-bromopyridyl)ketone.

The reaction sequence was modified by using both N,N-dimethylformamide and a mixture of dimethoxyethane/dimethylsulfoxide as solvent systems in lieu of water/acetone. These modifications still failed to permit any of the desired reaction to occur.
**Bis(2-pyridyl)mercury (90).** A solution of n-butyllithium (2.37 M in hexane; 26.0 ml, 56 mmol) in diethyl ether (50 ml) was cooled to -30° C. 2-Bromopyridine (5.0 g, 31 mmol) dissolved in diethyl ether (50 ml) was added while maintaining the temperature below -20°. Solid mercuric chloride (8.43 g, 31 mmol) was added and the reaction was allowed to warm to ambient temperatures for 30 minutes. The solution was hydrolyzed with aqueous 7 N ammonium chloride (200 ml), extracted with chloroform (10 x 50 ml), dried over sodium sulfate, and slowly concentrated at reduced pressure to ca one quarter the original volume. At this point a precipitate began to form, so the solution was cooled and the solid collected affording 2.3 g (41%) of bis(2-pyridyl)mercury as crystalline needles: [tlc, 0.25 mm silica gel, cyclohexane-ethyl acetate (1:1), Rf 0.49]; mp 197-199° (lit. mp 198-200°).

**Bis(6-bromo-2-pyridyl)mercury (91).** A solution of 6-bromo-2-pyridyllithium, [prepared from 2,6-dibromopyridine (11.85 g, 0.05 mol) and methyllithium (0.06 mol)] in diethyl ether (160 ml), was cooled to -30° C and mercuric chloride (13.6 g, 0.05 mol) was added with vigorous stirring. A white-grey precipitate was formed immediately and the reaction was allowed to warm to ambient temperature for one hour. The reaction was hydrolyzed with aqueous ammonium chloride (7 N, 200 ml), extracted with first diethyl ether (100 ml), then chloroform (5 x 50 ml). The combined organic extract was dried over anhydrous sodium sulfate and the volume reduced in vacuo to ca. one-third the original volume. At this point the solution was chilled and 3.1 g (2.4%) of bis(6-bromo-2-
pyridyl)mercury were collected as white needles: mp 121-123° (dec.
sealed tube); nmr (CDCl₃) δ 7.05-7.75 (Py-H, m); ir (KBr Pellet)
3100, 2340, 1550, 1540, 1530, 1510, 1410, 1400, 1170, 1160, 1120,
1090, 790, 780, 730 cm⁻¹.

Anal. Calcd. for C₁₀H₆N₂Br₂Hg: C, 23.3; H, 1.2. Found: C,
23.5; H, 1.5.

**Bis-2-(6-bromopyridyl)ketone. Method C.** Reaction of Bis(6-
bromo-2-pyridyl)mercury with K₂Ni₂(CN)₆ in the Presence of CO.

Protic, Aqueous Solvents. Potassium hexacyanodinickelate (1.4 g,
4 mmol) was dissolved in 50% acetone/water (50 ml) and the solution
was thoroughly saturated with carbon monoxide. Bis(6-bromo-2-
pyridyl)mercury (1.0 g, 1.95 mmol) dissolved in acetone (10 ml)
was added slowly with stirring while CO was slowly bubbled through
a celite pad and the acetone was removed at reduced pressure. The
aqueous solution was extracted with chloroform, then the combined
extract was dried over anhydrous sodium sulfate, and the solvent
was removed in vacuo. Chromatographic techniques (p.l.c., 2.0 mm
silica gel, 80% cyclohexane-ethyl acetate) afforded (24%) 160 mg
of bis-2-(6-bromopyridyl)ketone (mp 155-156°), which is identical
to the sample from Method A.

**Bis-2-(6-bromopyridyl)ketone (45). Method D.** Coupling Reaction
via Ethyl Chloroformate. A solution of 2,6-dibromopyridine (10.0 g,
0.042 mol) in diethyl ether (250 ml) was cooled to -78° C and a
solution of ethyllithium (1.2 M in hexane; 35.0 ml, 0.042 mol) was
slowly added, while the temperature is rigorously maintained below
-60° C. The resultant solution was stirred at -60° C for one hour, followed by the fairly rapid addition of ethyl chloroformate (2.75 g, 0.026 mol) dissolved in diethyl ether (100 ml). The reaction mixture was stirred one hour at -60° C, followed by thirty minutes at -40° C. The reaction was quenched by adding methanol (30 ml) and 5N HCl (30 ml). The organic solvent was removed at reduced pressures and the aqueous suspension extracted with chloroform. The combined phase was dried and concentrated affording 7.3 g of a beige solid, which was further purified via chromatographic techniques [column chromatography, silica gel G, chloroform] affording 3.26 g (48.5%) of bis-2-(6-bromopyridyl)ketone: mp 155-156° (lit. mp 155-156.5°).

**Bis-2-(6-bromopyridyl)ketone (45). Method E. Coupling Reaction**

Cyanogen Bromide. The reaction described in Method D was run in an identical manner except for the substitution of ethyl chloroformate by cyanogen bromide. The reaction was quenched by adding methanol (30 ml) and 5N hydrochloric acid (30 ml). The organic solvent was removed at reduced pressures and the resulting acidic aqueous suspension was maintained at gentle reflux conditions for twelve hours. This solution was extracted with chloroform and the resulting organic phase was dried and concentrated to yield a beige solid which was separated and purified via chromatographic techniques [column chromatography, silica gel G, chloroform] to afford 0.8 g (18.9%) of 6-bromo-2-picolinic acid: mp 192-193° (lit. mp 192-194°) and 0.4 g (7.2%) of bis-2-(6-bromopyridyl)ketone: mp 153-155° (lit. mp 155-156.5°).
Bis-2-(6-bromopyridyl)ketone (45). Method F. Coupling Reaction via Catechol Dichloromethylene Ether (84). The reaction described in Method D was run (on a 4 mmol scale) in an identical manner except for the substitution of ethyl chloroformate by catechol dichloromethylene ether (84). After a work-up procedure as described in Method F, only traces of the desired bis-2-(6-bromopyridyl)ketone were observed [via tlc, silica gel 0.25 mm, ethyl acetate-cyclohexane (1:1)]. The majority of material isolated appeared to be a mixture of 2-bromopyridine (Rf 0.9) and 2,6-dibromopyridine (Rf 0.8).

Diketone (50b). Method A. Treatment of Methyl 2,6-Pyridinedicarboxylate with 2-Bromo-6-lithiopyridine (30). A solution of 2-bromo-6-lithiopyridine [prepared from 2,6-dibromopyrididine (24.0 g, 0.1 mol) and n-butyllithium (0.1 mol, N) in anhydrous diethyl ether (500 ml) was cooled to -90°. Solid methyl 2,6-pyridinedicarboxylate (10.0 g, 0.05 mol) was added with vigorous stirring and the reaction
was maintained first for one hour at -90°, followed by thirty minutes at -40°. The mixture was hydrolyzed with methanol (50 ml), 12N hydrochloric acid (10 ml), and water (50 ml), respectively, then the ethereal solvent was removed at reduced pressure. The acidic aqueous suspension was refluxed for six hours, cooled, then neutralized with 10% aqueous sodium carbonate and extracted with dichloromethane (10 x 50 ml). The combined extract was dried over anhydrous sodium sulfate and concentrated in vacuo to afford a brown, pasty mass, which was triturated with several 20 ml portions of boiling diethyl ether and the residue was recrystallized from benzene to afford 11.0 g (48%) of the diketone (506): mp 142-143° tlc Rf 0.39 [petroleum ether-ethyl acetate (4:1)]; nmr (CDCl₃-1% TMS) δ 7.33-8.38 (m, pyr-H); ir (KBr) 3040, 3000, 2890, 1685, (C=O), 1575, 1550, 1427, 1425, 1395, 1320, 1295, 1260, 1240, 1170, 1130, 1125, 1090, 1025, 1000, 990, 964, 852, 830, 820, 775, 762, 750, 735, 709, 694 cm⁻¹.

Anal. Calcd. for C₁₇H₉N₃O₂Br₂: C, 45.6; H, 2.0; N, 9.4; Found: C, 45.4; H, 2.1; N, 9.4.

Ketone (50b). Method B. Treatment of 2,6-Dicyanopyridine with 2-Bromo-6-lithiopyridine (30). The reaction was conducted in an analogous manner to Method A, with the exception that 2,6-dicyanopyridine was used in place of the dimethyl ester. The work-up was the same and the diketone (after hydrolysis of the di-imine) was identical in all respects to the sample from Method A: mp 142-144°. The yield of this reaction was 41%.
Ketone (50b). Method C. Treatment of 2,6-Dipicolinoyl Chloride with 2-Bromo-6-lithiopyridine (30). See Method A for reaction conditions and work-up procedure. When 2,6-dipicolyl chloride is substituted for methyl 2,6-pyridinedicarboxylate one must be careful to cool efficiently the reaction vessel during and immediately after the addition of the solid acid chloride. Overall yield of diketone (mp 142°) via this method was 35%.

Methyl(2-pyridyl)ketone Ketal (92). A mixture of 2-acetylpyridine (5.0 g, 0.04 mol), ethylene glycol (5.0 ml, 0.08 mol), p-toluenesulfonic acid monohydrate (2.3 g), 2,2-dimethoxypropane (3.5 g, 0.05 mol), and benzene (150 ml) was slowly distilled through a Vigreaux column for 3 hours or until the distillation temperature exceeded 60°. After cooling, the mixture was added to 10% aqueous sodium carbonate solution (150 ml) and the mixture was extracted several times with benzene (50 ml ca). The organic extract was dried over anhydrous magnesium sulfate and concentrated to afford (33%) 2.1 g of methyl(2-pyridyl)ketone ketal: bp 103-104 (6 mm) [lit.42 bp 106° (6.2 mm)]; nmr (100 MHz, CDCl₃-1% TMS δ 1.74 (-CH₃, s, 3H), 3.75-4.10 (-O-CH₂-CH₂-O-, m, 4H), 7.18 (H₃-pyr, ddd, J = 6.8, 4.8, 2.0Hz, 1H), 7.50-7.75 (H₃-pyr, ddd, J = 6.8, 2.0, 1.0Hz; H₄-pyr, ddd, J = 6.8, 6.8, 2.0), 8.58 (H₆-pyr, ddd, J = 4.8, 2.0, 1.0Hz).
Attempted and Successful Preparations of Protected Pyridyl Ketones.

2,2-Bis(2′-pyridyl)-1,3-dioxolane (93). Method A. Bis(2-pyridyl)ketone (119 mg, 0.64 mmol) was dissolved in anhydrous benzene (70 ml) along with p-toluenesulfonic acid (365 mg, 1.92 mmol) and ethylene glycol (238 mg, 3.84 mmol). To this solution was added Linde 4A molecular sieve (2 g) and the mixture was gently refluxed under an argon atmosphere for 36 hours. The reaction mixture was cooled and poured into ice-cold 10% sodium bicarbonate (150 ml). This suspension was filtered and extracted with chloroform. The organic extract was dried over anhydrous magnesium sulfate and concentrated at reduced pressure giving a residue which was chromatographed [tlc, 0.25 mm; ethyl acetate-cyclohexane (1:1)] and identified as an authentic sample of unreacted bis(2-pyridyl)ketone: \( R_f \) 0.25. The residue also gave an immediate, positive test with 2,4-dinitrophenylhydrazine, as does bis(2-pyridyl)ketone. Authentic 2,2-bis(2′-pyridyl)-1,3-dioxolane, prepared by Method F, gives no test with this reagent.

Method B. Bis(2-pyridyl)ketone (119 mg, 0.64 mmol) was dissolved in anhydrous benzene (100 ml) along with p-toluenesulfonic acid (365 mg, 1.92 mmol) and ethylene glycol (240 mg, 3.9 mmol). The mixture was refluxed with vigorous magnetic stirring for 24 hours. Any water formed was continually removed via a Soxhlet extractor containing calcium hydride. The reaction mixture was allowed to cool and poured into ice-cold 10% aqueous sodium bicarbonate.
(150 ml). The suspension was extracted with chloroform, which, upon drying with anhydrous magnesium sulfate and concentration, gave only unreacted bis(2-pyridyl)ketone and traces of a yellow oil subsequently identified as 2-hydroxyethyl p-toluenesulfonate\(^4\): tlc: R\(_f\) 0.40 [cyclohexane-ethyl acetate (1:1)]; ir (CHCl\(_3\)) 3700, 2900, 1600, 1400, 1350, 1180, 1100, 920, 818 cm\(^{-1}\); nmr (CDCl\(_3\)-1% TMS) \(^{6}\) 2.37 Ar-CH\(_3\), s, 3H), 3.62 (O-H, broad s, 1H), 3.73 (–CH\(_2\)_OSO\(_2\)-, t, J = 5 Hz, 2H), 4.10 (–CH\(_2\)_OSO\(_2\)-, t, J = 5 Hz, 2H), 7.33 (3,5-Ar–H, d, J = 8.5, 2H), 7.81 (2,6-Ar–H, d, J = 8.5, 2H).

Method C\(^4\). Bis(2-pyridyl)ketone (0.128 g, 0.70 mmol) was dissolved in anhydrous toluene (70 ml) along with p-toluenesulfonic acid (1.14 g, 6.0 mmol) and ethylene glycol (6.2 g, 0.1 mol). The reaction mixture was refluxed for 10 hours and water formed during the reaction was continually removed via a modified Dean-Stark water separator. Standard work-up afforded only unreacted bis(2-pyridyl)ketone and small amounts of previously elucidated 2-hydroxyethyl-p-toluenesulfonate. This reaction sequence was also attempted with phenyl(6-bromo-2-pyridyl)ketone; no ketal was detected in this case.

Method D\(^4\). A mixture of bis(2-pyridyl)ketone (119 mg, 0.64 mmol), p-toluenesulfonic acid (1.14 g, 6.0 mmol), ethylene glycol (9.3 g, 150 mmol), and toluene (50 ml) was slowly distilled. The solvent (toluene) was replaced in 10 ml increments until a total volume of 250 ml had been added and distilled. Since the distillation was intentionally performed at a very slow rate, the total reaction
time was 30 hours, after which the distillation residue was cooled, poured into 25 ml cold aqueous 10% sodium bicarbonate, and extracted several times with chloroform. The combined organic extract was dried over anhydrous magnesium sulfate and concentrated via reduced pressure to yield only unreacted bis(2-pyridyl)ketone and 2-hydroxy-ethyl-$\alpha$-toluenesulfonate. This reaction sequence was also attempted on bis 2-(6-bromo-pyridyl)ketone with no success; only starting material was isolable.

**Method E**. A mixture of bis(2-pyridyl)ketone (128 mg, 0.70 mmol), ethylene glycol (744 mg, 12.0 mmol), and benzene (70 ml) was treated with gaseous HCl for one hour. The mixture was refluxed for 10 hours. After subsequent neutralization with cold, aqueous sodium bicarbonate and extraction with chloroform, analysis via thin-layer chromatography showed only unreacted bis(2-pyridyl)ketone.

**Method F**. Bis(2-pyridyl)ketone (128 mg, 0.70 mmol), sulfuric acid (98 mg, 10.0 mmol), ethylene glycol (6.2 g, 100 mmol), and p-xylene (70 ml) were refluxed for 10 hours. Any water formed was continually removed via a Dean-Stark water separator. At the conclusion of reflux, the mixture was quenched with cold, aqueous 10% sodium bicarbonate (50 ml) and extracted with chloroform. The combined organic extract was dried over anhydrous magnesium sulfate and concentrated to give a beige semi-solid, which was chromatographed [cyclohexane-ethyl acetate (4:1)] giving 31 mg (20%) of a white crystalline ketal: mp 164-166° (needles from petroleum ether); tlc $R_f$ 0.14 [cyclohexane-ethyl acetate (1:1)]; ir (KBr) 1575, 1460,
1435, 1225, 1120, 1090, 990, 945, 805 cm\(^{-1}\); nmr (CDCl\(_3\)-1\% TMS) 
\[ \delta 6.10 (-\text{OCH}_2, s, 4H), 7.0-8.0 (\text{Py-H}, m, 6H), \text{and } 8.5 \text{ (6-Py-H, ddd, } J = 5.0, 1.8, 1.0 Hz, 2H). \]

**Anal.** Calcd. for C\(_{11}\)H\(_8\)N\(_2\)O: C, 71.7; H, 4.3; N, 15.2; Found: C, 71.7; H, 4.2; N, 15.1.

The remainder of bis(2-pyridyl)ketone was recovered unchanged during the course of the reaction. This reaction sequence was attempted on both phenyl-2-(6-bromopyridyl)ketone and bis 2-(6-bromo- pyridyl)ketone; standard work-up procedures afforded only unreacted ketone in both of these cases.

**Bis(2-pyridyl)ketone Dimethyl Ketal**\(^{48}\). Bis(2-pyridyl)ketone (110 mg, 0.60 mmol), p-toluenesulfonic acid (760 mg, 4.0 mmol), 2,2-dimethoxypropane (4.16 g, 40.0 mmol), and toluene (50 ml) were refluxed under an argon atmosphere for 12 hours. The reaction mixture appeared charred although the solvent had not escaped. Standard work-up as in previous methods gave starting bis(2-pyridyl)ketone as the only isolable material.

**Bis(2-pyridyl)ketone Diethyl Ketal**\(^{48}\)\(^{95}\). Bis(2-pyridyl)ketone (110 mg, 0.60 mmol), concentrated sulfuric acid (980 mg, 10.0 mmol), triethyl orthoformate (5 g, 30.0 mmol), absolute ethanol (920 mg, 20.0 mmol), and 50 ml toluene were refluxed under a nitrogen atmosphere for 8 hours. Standard work-up, as previously described, followed by tlc analysis showed only unreacted bis(2-pyridyl)ketone.

**2,2-Bis(2-pyridyl)propane**\(^{49}\)\(^{96}\). Bis(2-pyridyl)ketone (368 mg, 4.0 mmol), CoCl\(_2\)·6H\(_2\)O (1.19 g, 5.0 mmol), and 50 ml acetone were

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refluxed with stirring under nitrogen for 24 hours. The reaction was cooled and the solvent removed at reduced pressure to give a semi-solid residue. Analysis of this residue indicated no traces of the desired substituted propane but instead only unchanged bis-(2-pyridyl)ketone was isolated.

\[ \text{2,2-Bis-2'(6-bromopyridyl)-1,3-dithiane} \] . A mixture of bis 2-(6-bromopyridyl)ketone (169 mg, 0.05 mmol), absolute methanol (1 ml), anhydrous toluene (5 ml), and propane-1,3-dithiol (1 g, 9.2 mmol) was saturated with anhydrous HCl at ambient temperature. The mixture was stirred for 24 hours and then poured into 25 ml 10% aqueous sodium carbonate. The aqueous slurry was extracted with diethyl ether and the organic layer dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and analysis (tlc) revealed only unreacted bis-2-(6-bromopyridyl)ketone.

\[ \text{Bis(2-pyridyl)phenylcarbinol (98)} \] . Bis(2-pyridyl)ketone (200 mg, 1.09 mmol) in diethyl ether (50 ml) was cooled to -30° C. An ethereal solution of phenyllithium (3 mmol) was slowly added and the resultant mixture was stirred for two hours. The temperature was allowed to gradually rise to 0° C, at which point the reaction was stopped by adding a cold, saturated aqueous sodium chloride solution. Extraction with chloroform and subsequent concentration of the organic layer gave 175 mg of a beige crystalline product, which was recrystallized from petroleum ether affording 120 mg (42%) of bis(2-pyridyl)phenylcarbinol as white needles: mp 96-97° (lit. 32 mp 96.5-97.5°); nmr (CDCl\textsubscript{3}) \( \delta \) 4.1 (OH, broad s, 1H), 6.95-8.0 (Py-H, m, 11H), 8.55 (6-Py H, m, 2H).
Tris(2-pyridyl)carbinol (99). 2-Bromopyridine (160 mg, 1.0 mmol) dissolved in anhydrous diethyl ether (50 ml) was cooled to -50° C. A solution of n-butyllithium [2.0M in hexane, 0.75 ml, 1.5 mmol] in ether (5 ml) was added slowly maintaining the temperature at -45 to -40° C for 45 minutes. A solution of bis(2-pyridyl)ketone (200 mg, 1.0 mmol) in diethyl ether (10 ml) was added drop-wise allowing the reaction mixture to warm to -20° C, at which point the reaction was quenched with saturated aqueous sodium chloride. Extraction with chloroform and concentration of the organic layer afforded a brown semi-solid, which was recrystallized from petroleum ether to give tris(2-pyridyl)carbinol: 80 mg (36.0%); mp 126-127° (lit. 32 mp 127-128°): picrate: mp 113.5-114° (ethanol) (lit. 32 mp 114-115° C).

2,2-Bis(2'-pyridyl)-1,3-dioxolane (93). Method A 50. Ketalization via 2-Chloroethanol under Basic Conditions. A mixture of di(2-pyridyl)ketone (1.06 g, 0.57 mmol), redistilled 2-chloroethanol (40 ml), and anhydrous lithium carbonate (12 g) was refluxed for 20 hours, after which most excess solvent was removed by reduced pressure (water aspirator) distillation. A chloroform suspension of the residue was filtered and the filtrate was evaporated affording a crude product, which was chromatographed [silica gel P, cyclohexane-ethyl acetate (4:1)] affording 550 mg (45%) of the white crystalline ketal: mp 164-166° (needles from petroleum ether); tlc: Rf 0.14 [cyclohexane-ethyl acetate (1:1)]; ir (KBr) 1575, 1460, 1435, 1225, 1120, 1090, 1010, 990, 945, 805 cm⁻¹; nmr (CDCl₃-1% TMS) δ 4.10 (s,
4H, –OCH₂), 7.0–8.0 (m, 6H, pyr-H), and 8.5 (m, 2H, J = 5.0 Hz, 6-pyr-H).

Anal. Calc. for C₁₃H₁₂N₂O₂: C, 68.4; H, 5.3; 12.3. Found: C, 68.4; H, 5.2; N, 12.2.

**Method B** ⁵⁰. **Ketalization via 2-Bromoethanol under Basic Conditions.** The above reaction was run in an identical manner except for the substitution of 2-chloroethanol by 2-bromoethanol. The reaction time is reduced to 3–5 hours since the corresponding reflux temperature is higher. The product obtained is identical in all respects; yields are typically ca. 50–55% with this reagent.

**2-Pyridyl-2-(6'-bromo-2'-pyridyl)-1,3-dioxolane**⁵⁰ (100).

**Ketalization via 2-Bromoethanol under Basic Conditions.** 2-Pyridyl-2-(6-bromopyridyl)ketone (1.03 g, 3.5 mmol) was suspended along with lithium carbonate (15.0 g, 200 mmol) in excess 2-bromoethanol (25 ml). The slurry was refluxed gently with stirring for four hours then cooled and poured into 150 ml of 10% aqueous sodium bicarbonate. The undissolved solids were removed by filtration and the solution extracted with chloroform (10 x 50 ml). The combined organic extract was dried over anhydrous potassium carbonate and concentrated to afford a pale amber liquid (ca. 20 ml). The attendant 2-bromoethanol was removed via vacuum distillation and the residue was chromatographed [p.l.c., 2.0mm silica gel, cyclohexane-ethyl acetate (1:1)] to afford 140 mg (13.1%) of 2-pyridyl-2-(6'-bromo-2'-pyridyl)-1,3-dioxolane as colorless rhombohedron: (recrystallized from ethyl acetate-
cyclohexane, ca. 1:1) mp 117-117.5°; nmr (CDCl$_3$) $\delta$ 4.12 (-o-CH$_2$-, s, 4H), 7.0-7.85 (Py-H, m, 6H), 8.47-8.52 (6-Py-H, dd, $J = 5.0$, 1.8, 1.0Hz, 1H); ir (CHCl$_3$) 3000, 1650, 1620, 1575, 1550, 1435, 1430, 1390, 1345, 1280, 1230, 1160, 1100 (broad), 995, 953, 948, 888 cm$^{-1}$.

Anal. Calcd. for C$_{13}$H$_{11}$N$_2$O$_2$Br: C, 50.86; H, 3.61, N, 9.13; Found: C, 50.62; H, 3.83; N, 9.23.

2,2-Bis-2''-(6''-bromopyridyl)-1,3-dioxolane (46). Ketalization via 2-Bromoethanol under Basic Conditions. A mixture of bis-2''-(6-bromopyridyl)ketone (1.0 g, 2.9 mmol) and anhydrous lithium carbonate (15.0 g, 200 mmol) was suspended in excess 2-bromoethanol (25 ml). This slurry was refluxed gently with stirring for four hours then cooled and poured into 150 ml of 10% aqueous sodium bicarbonate. After filtering the undissolved solids, the solution was extracted with dichloromethane (10 x 50 ml). The extracts were dried over anhydrous potassium carbonate and distilled at reduced pressure to afford a brownish semi-solid. Chromatographic separation [silica gel P, 2.0 mm, cyclohexane-ethyl acetate (4:1)] afforded 630 mg (56%) of crystalline 2,2-bis-2''-(6''-bromopyridyl)-1,3-dioxolane: mp 146-148°; tlc: $R_f$ 0.41 [cyclohexane-ethyl acetate (1:1)]; nmr (CDCl$_3$, 1% TMS) $\delta$ 4.14 (s, 4H, -OCH$_2$), 7.35 (dd, $J = 2.0$, 7.0 Hz, 5-pyr-H), 7.58 (dd, $J = 7.0$, 7.7 Hz, 4-pyr-H), 7.82 (dd, $J = 2.0$, 7.7 Hz, 3-pyr-H); ir (KBr) 1460, 1272, 1107, 1042, 1006, 807, 788, 754, 740, 710 cm$^{-1}$.

Anal. Calcd. for C$_{13}$H$_{10}$N$_2$O$_2$Br$_2$: C, 40.4; H, 2.6; N, 7.1 Found: C, 40.4; H, 2.5; N, 7.0.
Hydrolysis of 2,2-Bis-2'-((6'-bromopyridyl)-1,3-dioxolane.

Method A. 2,2-Bis-2'-((6'-bromopyridyl)-1,3-dioxolane (38 mg, 0.1 mmol) was refluxed in 5% HCl (5 ml) for 12 hours. The suspension was neutralized with 10% sodium bicarbonate and extracted with chloroform (5 x 15 ml). The organic extract was dried over anhydrous sulfate and concentrated at reduced pressure to afford 38 mg of unchanged 2,2-bis-2'-((6'-bromopyridyl)-1,3-dioxolane.

Method B. 2,2-Bis-2'-((6'-bromopyridyl)-1,3-dioxolane (38 mg, 0.1 mmol) was dissolved in methanol (15 ml), and 12N HCl (1 ml). This solution was refluxed 24 hours and worked up as described above to afford 31 mg (91%) of pure bis-2-(6-bromopyridyl)ketone [mp 153-156°; tlc Rf 0.6; ir (CHCl₃) 1690 (C=O) cm⁻¹; nmr (CDCl₃) δ 7.65-8.0 (pyr-H, m)], which is identical to an authentic sample.

2-Pyridone⁵¹ (101). A mixture of 2-bromopyridine (1.0 g, 6.34 mmol), potassium t-butoxide (7.17 g, 6.4 mmol), and t-butyl alcohol (25.0 ml) was refluxed for 24 hours. The solvent was removed in vacuo, ice-water was carefully added, and the aqueous layer was extracted with chloroform to remove unreacted 2-bromopyridine. The aqueous layer was acidified with 3N hydrochloric acid, extracted with chloroform, dried over anhydrous magnesium sulfate, and concentrated to afford 385 mg (64%) of 2-pyridone: mp 104-106° (lit.⁵² mp 106-107°); nmr (CDCl₃) δ 6.12-7.65 (pyr-H, m); ir (CHCl₃) 3350, 2900, 1670 (amide), 1640, 1600, 1470, 1200 (broad), 1150, 1090 cm⁻¹.

6-Bromo-2-pyridone⁵¹ (103). A mixture of 2,6-dibromopyridine (1.0 g, 4.2 mmol), potassium t-butoxide (5.0 g, 4.47 mmol), and t-butyl
alcohol (25.0 ml) was refluxed for 24 hours, cooled, and then concentrated at reduced pressure. The residue was suspended in ice-water and extracted with chloroform to remove the unreacted 2,6-dibromopyridine (92 mg). The aqueous layer was acidified with 3N hydrochloric acid and re-extracted with chloroform. Upon drying with anhydrous magnesium sulfate and concentration, 6-bromo-2-pyridone was isolated as a pure crystalline solid: 670 mg (89%); mp 119-120° (lit. mp 123-124°); nmr (CDCl₃) δ 6.56-7.58 (pyr-H, m); ir (CHCl₃) 3370, 2970, 1660 (amide), 1610, 1580, 1470, 1440, 1225 (broad), 1165, 1080, 990 cm⁻¹.

Anal. Calcd. for C₅H₄BrNO: C, 34.5; H, 2.3; N, 8.0. Found: C, 34.5; H, 2.3; N, 8.1.

Attempted Preparation of 3-Pyridone (104). A mixture of 3-bromopyridine (1.0 g, 6.34 mmol), potassium t-butoxide (7.17 g, 6.4 mmol), and t-butyl alcohol (25.0 ml) was refluxed for 24 hours. Chromatographic analysis (tlc, 0.25 mm silica gel, 50% cyclohexane-ethyl acetate) indicated the presence of only starting 3-bromopyridine (Rf 0.94) and no evidence for formation of the desired pyridone. Reaction was discontinued and extraction with chloroform effected a 90% recovery of 3-bromopyridine: bp 172° (lit. bp 173°).

Attempted Preparation of 4-Pyridone (105). A mixture of 4-chloropyridine hydrochloride (1.0 g, 6.7 mmol), potassium t-butoxide (15.7 g, 14.0 mmol), and t-butyl alcohol (25.0 ml) was refluxed for 24 hours. Chromatographic analysis (tlc, 0.25 mm silica gel, 50% cyclohexane-ethyl acetate) indicated only starting 4-chloropyridine (Rf 0.89) and no evidence for pyridone formation. The reaction was quenched in
3N HCl and extraction with chloroform yielded (on concentration) a 95% recovery of 4-chloropyridine hydrochloride: mp 208° (sealed tube); (lit.\textsuperscript{55} mp 210°).

**Dioxolane (106).** A mixture of 2-pyridyl-2'-(6'-bromopyridyl)-1,3-dioxolane (130 mg, 0.425 mmol), anhydrous t-butyl alcohol (8 ml), and potassium t-butoxide (4 g) was refluxed for 12 hours. After cooling, the solvent was removed in vacuo, ice water was slowly added, and the solution was extracted with chloroform. After drying over anhydrous sodium sulfate, the combined extract was concentrated and the residue, after chromatographic purification (plc, 2.0 mm silica gel, 3X, 50% cyclohexane-ethyl acetate), afforded 72.7 mg (75%) of 106: \( R_f \) 0.04; mp 185-187°; nmr (CDCl\textsubscript{3}, 100 MHz) \( \delta \) 4.16 (OCH\textsubscript{2}CH\textsubscript{2}O, s, 4H), 6.38 (H\textsubscript{5}, dd, J = 6.5, 1.0 Hz), 6.49 (H\textsubscript{3}, dd, J = 8.0, 1.0 Hz), 7.35 (H\textsubscript{4}, dd, J = 8.0, 6.5 Hz), 7.2-7.4 (H\textsubscript{5}', m, J = 7.2, 4.7, 1.6 Hz) 7.65-7.8 (m; H\textsubscript{3}', J = 8.0, 1.6, 0.9 Hz; H\textsubscript{4}', J = 8.0, 7.2, 1.5 Hz), 8.65 (H\textsubscript{6}', bd, J = 4.7, 1.5, 0.9 Hz), and 10.45 [-NH, bs (exchanged with D\textsubscript{2}O)]; ir (CHCl\textsubscript{3} solution) 3350, 3000, 2900, 1670 (amide), 1630, 1600, 1470, 1440, 1200 (broad), 1150, 1120, 1090, 1040, 1000, 950 cm\textsuperscript{-1}.

**Anal. Calcd. for C\textsubscript{13}H\textsubscript{12}N\textsubscript{2}O\textsubscript{3}:** C, 63.93; H, 4.96; N, 11.47. Found: C, 64.11; H, 5.03; N, 11.38.

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Reaction of Bis(2-pyridyl)ketone Ketal with Methyl Iodide.

A sample of bis(2-pyridyl)ketone ketal (91 mg, 0.4 mmol) was dissolved in deuterated chloroform (0.3 ml, spectral grade, Aldrich Chemical):

\[
\text{nmr (CDCl}_3\text{-1% TMS)} \delta 4.10 (s, 4H, -OCH}_2\text{-), 7.0-8.0 (m, 6H, pyr-H), and 8.5 (m, 2H, 6-pyr-H).}
\]

Freshly distilled methyl iodide (70 mg, 0.5 mmol) was added and the sample was held at +42°C for one hour. Spectral data were unaltered at the end of this time span. Removal of solvent at reduced pressure afforded total recovery of unchanged bis(2-pyridyl)ketone ketal: mp 164-165°.

Treatment of 2,2-Bis-2'-(6-bromopyridyl)-1,3-dioxolane (46) with n-Butyllithium. Reaction A. A solution of 2,2-bis-2'-(6-bromopyridyl)-1,3-dioxolane (0.1 g, 0.26 mmol) in diethyl ether (100 ml) was cooled to -40°C and n-butyllithium (0.2 ml, 2M in hexane; 0.4 mmol) was slowly added. (Note: The reaction was conducted under an argon atmosphere with complete exclusion of oxygen.) After the addition was complete, the mixture was allowed to slowly warm to -20° ± 5°C for one hour. Dry-ice was added to the solution and the mixture was subsequently hydrolyzed by adding 5N hydrochloric acid (30 ml). The organic solvent was removed at reduced pressure and the aqueous slurry was extracted with chloroform (10 x 50 ml). The combined extracts were dried over anhydrous sodium sulfate and the solvent was removed in vacuo to afford 63 mg of a beige solid. Purification via chromatographic methods (silica gel PF, 2.0 mm, 50% cyclohexane-ethyl acetate) afforded 20 mg (32%) of the pyridone (106) identical in all respects to the compound obtained by the independent synthesis described on page 107, along with 34 mg (34%) of the unchanged 2,2-bis-2'-(6-bromopyridyl)-1,3-dioxolane.
**Reaction B.** The reaction was repeated in an identical manner as in Reaction A except that the solvent utilized was tetrahydrofuran [similar results were obtained with dimethoxyethane in the place of diethyl ether or tetrahydrofuran] instead of diethyl ether. The carboxylation step was omitted in favor of merely quenching the reaction with methanol (10 ml) and 5N hydrochloric acid (10 ml). Chromatographic procedures (same conditions as in Reaction A) allowed isolation of 51 mg (51%) of unaltered ketal (46) and 24 mg (42%) 2,2-bis-(2'pyridyl)-1,3-dioxolane (93): mp 164-165°.

**Reaction C.** In order to identify more precisely the nature of the metallated intermediate, Reaction A was repeated except that a mixture of deuterated sulfuric acid (98%, 1 ml) and deuterium oxide (10 ml) was substituted in place of the carbon dioxide and hydrochloric acid utilized in the former work-up. Purification in the same manner as previously described afforded 13.5 mg (21%) of the pyridone (170): nmr (CDCl$_3$, 100 MHz) δ 4.16 (-OCH$_2$CH$_2$O-, s, 4H), 6.49 (H$_5$, d, J = 8.0 Hz), 7.35 (H$_4$, d, J = 8.0 Hz), 7.2-7.4 (H$_5''$, m, J = 7.2, 1.6 Hz), 7.65-7.8 (m; H$_3''$, J = 8.0, 1.6; H$_4''$, J = 8.0, 7.2 Hz).

**Reaction D.** The reaction was re-run as described in Reaction A. The sequence was changed such that reaction temperatures were lowered
to the range -40° to 35°. After three hours, the reaction was quenched as described in Reaction C and the subsequent purification afforded only a trace (detected via tlc compared to an authentic sample) of the pyridone product (107) along with 33 mg (30%) recovered (108) and 31 mg (52%) trideuterated ketal (110): mp 164-166° (needles, petroleum ether A); nmr (CDCl₃, 100 MHz) δ 4.14 (−OCH₂CH₂O−, s, 4H), 7.12-7.23 (H₅, ₅'), m, J = 7.1, 1.5 Hz, 2H), 7.61-7.89 (m, 3H, H₃, J = 8.0, 1.5 Hz; H₄, ₄', J = 8.0, 7.2 Hz). See Table I for a compilation of mass spectral data on these deuterated products.

**Reaction E.** Finally, the sequence described in Reaction A was repeated at -78° to -60° for thirty minutes. Work-up as in Reaction C afforded only ketal (110) in ca. 50% yield along with unreacted starting material. No pyridone product was detected under these conditions!

**Treatment of 2,2-Bis-(2'-pyridyl)-1,3-dioxolane (93) with n-Butyllithium. Reaction A.** A solution of 2,2-bis-(2'-pyridyl)-1,3-dioxolane (0.18 g, 0.8 mmol) in diethyl ether (50 ml) was cooled to...
-80°C and n-butyllithium (1.0 ml, 2M in hexane; 2.0 mmol) was slowly added. After three hours at temperatures below -70°, methyl iodide (1.4 g, 10 mmol) was added to "trap" the intermediate anions formed and, after a final hour at -78°, 5N hydrochloric acid (20 ml) was added. The suspension was neutralized with sodium bicarbonate and extracted with chloroform (5 x 50 ml). The combined extracts were concentrated in vacuo to afford 0.4 g of an amber oil which was separated via chromatographic methods (plc, silica gel PF, 2.0 mm, diethyl ether, 2 elutions) to yield three distinct components: 100 mg (62%) unchanged 2,2-bis-(2'-pyridyl)-1,3-dioxolane; 20 mg (8.7%) ketal (III). R = 0.3, [bp 100° (0.1 mm) temperature of oil-bath for micro-distillation apparatus], nmr (CDCl₃, 60 MHz) δ 1.0-1.7 (CH₂, m, 7H), 2.8 (Py-CH₂-C₆H₅, t, J = 8.0 Hz, 2H) 4.18 (-O-CH₂-CH₂-, s, 4H), 7.0-7.8 (pyr-H, m, 6H), 8.65 (6-pyr-H, dd, J = 4.5 Hz, 1H); and 31 mg (12%) of a third component, ketal (II), R = 0.4, [bp 110° (0.05 mm) temperature of oil-bath for micro-distillation apparatus], nmr (CDCl₃, 100 MHz) δ 0.88 (CH₃, t, J = 6.8 Hz, 3H), 1.14-1.90 (Pyr-CH₂-(CH₂)₂-C₆H₅, m 4H), 2.23 (CH₃-Pyr, s, 3H), 2.77 (Pyr-CH₂-C₆H₅, t, J = 7.1 Hz, 3H), 4.18 (-OCH₂CH₂O-, s, 4H), 6.95 (H₅-Pyr, d, J = 7.6Hz, 1H), 7.06-7.20 (H₅-Pyr, m, 1H), 7.28 (H₄-Pyr, d, J = 7.6 Hz, 1H), 7.54-7.56 (H₃-Pyr, m, 2H),
8.64 (H$_6$-Pyr, m, 1H). A 10% nuclear overhauser effect was recorded for the H$_5$ doublet when the sample was irradiated at 275 MHz. Irradiation at 225 MHz produced a 100% NOE for the H$_4$ doublet.

**Reaction B.** The reaction was repeated in an identical manner as in **Reaction A** except that the trapping agent was a mixture of deuterated sulfuric acid (98%, 1 ml) and deuterium oxide (10 ml) instead of methyl iodide. The suspension was extracted with chloroform (5 x 50 ml), the organic phase was dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure to yield 60% recovery of 2,2-bis-(2'-pyridyl)-1,3-dioxolane. Mass spectral analysis indicated a substantial incorporation of at least one deuterium and nmr integration indicated the product to be ketal (113). Apparently a further exchange of H- for D- also occurs after prolonged reaction times. See Table I for collected relative intensities of the ion fragments of (113).
Table I. Collected Values for Selective Metallation Product Mass Spectra.

\[
\begin{array}{cccccccc}
\text{Mass} & 93 & 113 & 110 & 46 & 108 & 109 \\
76 & \text{---} & \text{---} & \text{---} & 50.0 & 28.5 & 20.7 \\
77 & 0.2 & 7.6 & 1.5 & 31.0 & 22.8 & 16.9 \\
78 & 8.4 & 97.2 & 7.6 & 6.4 & 34.2 & 28.3 \\
79 & 0.8 & 25.0 & 80.7 & 2.8 & 97.0 & 79.2 \\
80 & 0.1 & 5.5 & 15.3 & 1.7 & 17.1 & 13.2 \\
104 & \text{---} & \text{---} & \text{---} & 4.3 & 3.9 & \text{---} \\
105 & 0.1 & 4.6 & 0.9 & 11.2 & 6.8 & 11.3 \\
106 & 3.3 & 48.8 & 3.8 & 4.2 & 10.8 & 13.2 \\
107 & 0.3 & 8.3 & 30.7 & 2.1 & 57.0 & 28.3 \\
108 & 0.1 & 2.7 & 4.0 & 2.1 & 5.1 & 8.6 \\
109 & 0.1 & 8.3 & 0.7 & 1.4 & 1.1 & 11.3 \\
149 & \text{---} & \text{---} & \text{---} & 25.7 & 3.4 & 26.4 \\
150 & 100.0 & 100.0 & 8.4 & 5.7 & 37.1 & 33.9 \\
151 & 0.9 & 18.0 & 100.0 & 2.5 & 91.3 & 100.0 \\
152 & 0.1 & 4.4 & 13.0 & 1.0 & 20.0 & 15.4 \\
153 & 0.1 & 1.0 & 0.9 & 4.8 & 3.4 & 5.6 \\
154 & 0.1 & 0.8 & 0.3 & 3.9 & \text{---} & \text{---} \\
155 & 0.2 & 2.2 & 0.1 & 2.5 & 2.2 & 6.7 \\
156 & 0.2 & 3.3 & 0.7 & 100.0 & 9.1 & 22.6 \\
157 & 0.1 & 1.1 & 1.0 & 9.0 & 6.2 & 5.6 \\
158 & \text{---} & 0.6 & 2.4 & 98.0 & 34.2 & 17.7 \\
159 & \text{---} & 0.3 & 0.9 & 7.9 & 3.4 & 3.7 \\
184 & 0.9 & 8.3 & 0.6 & 71.0 & 91.3 & 32.0 \\
185 & 1.5 & 9.7 & 1.6 & 7.1 & 17.1 & 9.4 \\
186 & 0.2 & 2.7 & 9.2 & 60.0 & 42.8 & 16.9 \\
187 & 0.1 & 1.1 & 10.0 & 5.1 & 5.1 & 5.6 \\
188 & \text{---} & 0.5 & 1.6 & \text{---} & 1.1 & 1.8 \\
\end{array}
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Formation of Dibromodiketal (51). Method A. Ketalization via 2-Bromoethanol under Basic Conditions. A mixture of diketone (50b) (2.0 g, 4.4 mmol) and anhydrous lithium carbonate (15.0 g, 200 mmol) was suspended in excess 2-bromoethanol (30 ml). After 5 hours of gentle reflux, the reaction mixture was poured into 10% aqueous sodium carbonate and extracted with dichloromethane (5 x 50 ml). The organic phase was dried over anhydrous sodium sulfate and distilled at reduced pressure almost to dryness. The residue was purified via chromatographic techniques [silica gel PF, 2.0 mm, cyclohexane-ethyl acetate (1:1)] affording 560 mg (24%) of the diketal: mp 190-190.5° (rhombohedral prisms from chloroform-dichloromethane); tlc Rf 0.11 [cyclohexane-ethyl acetate (1:1)]; nmr (CDCl₃-1% TMS) δ 4.12 (s, 8H, -OCH₂-), 7.30-7.80 (m, 9H, pyr-H); ir (KBr) 2900, 2800, 1602, 1559, 1460, 1395, 1272, 1230, 1157, 1131 (ketal), 1107, 1085, 1042, 1020, 1005 cm⁻¹; Mw_calcd. = 535; Mw_osmotic (Benzene) = 510, 529—average = 519.

Anal. Calcd. for C₂₁H₁₇N₃O₄Br₂: C, 47.2; H, 3.2; N, 7.9; Found: C, 48.5; H, 3.2; N, 8.1%.

Formation of Dibromodiketal (51). Method B. Ketalization via 2-Chloroethanol under Basic Conditions. A slurry of diketone (19.0 g,
42 mmol), lithium carbonate (50 g), and 2-chloroethanol (200 ml) was refluxed for 30 hours. The reaction mixture was worked up as described above and after removal of the solvent, the pasty residue was chromatographed by "dry-column" techniques [silica gel, activity III, 2" x 20"; 1% methanol in chloroform] affording (37%) the expected diketone diketal (8.3 g), identical to known sample, as well as 1.8 g (9.6%) of a crystalline macrocycle (114): Rf 0.20; nmr (CDCl₃-1% TMS) δ 4.25 (d, 4H, J = 5.0 Hz, O-CH₂), 4.6 (s, 8H, O-CH₂), 7.12-7.80 (m, 9H, pyr-H).

Diketal (114) (1.8 g) was hydrolyzed with 5N hydrochloric acid (20 ml) in methanol (20 ml) at reflux conditions for 24 hours. After neutralization with sodium carbonate and extraction with dichloromethane, the organic solvent was removed at reduced pressure to afford 1.3 g (8.5%) of a white prismatic ketonic macrocycle (115): mp 122-4°; nmr (100 MHz, CDCl₃) δ 4.23 (-OCH₂CH₂O-, s, 4H), 5.93 (4,4'-pyr, ddd, J = 6.5, 6.5, 1.5 Hz, 2H), 6.44 (2,2'-pyr, ddd, J = 9.0, 1.5, 0.7 Hz, 2H), 6.93 (5,5'-pyr, ddd, J = 6.5, 2.0, 0.7 Hz, 2H), 7.12-7.30 (m, 3H; 1-pyr, J = 9.0, 1.5 Hz; 3,3'-pyr, J = 6.5, 2.0, 1.5 Hz). A decoupling experiment was performed with the irradiation frequency set at 644 MHz: δ 4.23 (-OCH₂CH₂O-,...
s, 4H), 5.93 (4,4'-pyr, dd, J = 6.5, 6.5 Hz), 6.93 (5,5′-pyr, dd, J = 6.5, 2.0 Hz), 7.30–7.48 (m; 1-pyr, J = 1.5 Hz; 3,3'-pyr, J = 6.5, 2.0 Hz); ir (KBr) 3040, 1680 (C=O), 1575, 1425, 1300, 1025 cm⁻¹.

MW calcd. = 359, MW osmotic (benzene) 362, 368—average = 365.

Anal. Calc. for C₁₉H₁₃N₃O₄: C, 65.7; H, 3.7; N, 12.1. Found: C, 65.9; H, 3.7; N, 12.3.

1,3,5-Tri[2,6]pyridacyclohexaphane-2,4,6-trione (40). Cyclization of Dilithiodiketal via Ethyl Chloroformate. A solution of dibromo diketal (51) (530 mg, 1.0 mmol) in anhydrous tetrahydrofuran (150 ml, redistilled from lithium aluminum hydride) was cooled to -90° and n-butyllithium [2.0 M in hexane, 1 ml] suspended in THF (50 ml) was slowly added with vigorous stirring and rigorous temperature control below -80° at all times. The mixture was maintained at -90° for one hour at which point ethyl chloroformate (110 mg, 1.0 mmol) was quickly added. After complete addition, then the solution was allowed to warm slowly to -40°. After 30 minutes at -40°, the reaction was quenched with methanol (50 ml) followed by 5N hydrochloric acid (50 ml). The ether was removed at reduced pressure and the acidic solution was diluted with an equal volume of methanol and heated to a gentle reflux for 6 hours. The hydrolysate was concentrated in vacuo to remove the alcohol and the aqueous layer was neutralized with 10% aqueous sodium bicarbonate. The resultant solution was extracted with chloroform for 24 hours via a liquid-liquid continuous extraction apparatus. The organic extract was dried over anhydrous sodium sulfate and concentrated at reduced pressure to afford a beige solid, which
was separated via chromatographic procedures [silica gel PF, 2.0 mm, 1% MeOH in CHCl₃] affording 11 mg (3.5%) of 1,3,5-tri[2,6]pyridacyclohexaphane-2,4,6-trione (40): Rₚ 0.90; mp 134.5-135° (chloroform); nmr (CDCl₃-1% TMS) δ 7.35 (t, 1H, J = 9.2 Hz, 4-pyr-H), 7.60 (d, 2H, J = 9.2 Hz; 3,5-pyr-H); ir (KBr) 3040, 1685 (C=O), 1575, 1550, 1425, 1330, 1155, 1080, 992, 950 cm⁻¹; MW calcd. = 3.15, osmotic (Benzene) 320, 327—average 324.

Further elution afforded 220 mg (49%) of diketone (50b):

Rₚ 0.75; mp 140-142° [from hydrolysis of unreacted starting material].

A third component was collected affording 98 mg (26%) dibromo-hexapyridyl-pentaone (116): Rₚ = 0.5; mp 184-6° (dec.); nmr (CDCl₃) δ 6.40-7.47 (m, pyr-H); ir (KBr) 3040, 3000, 1685 (C=O), 1660, 1575, 1550, 1427, 1395, 1295, 1260, 1170, 1130, 1125, 1025 cm⁻¹. MW calcd. = 762, Osmotic (Benzene) 735, 751—average 743.

Anal. Calcd. for C₂₃H₁₈N₆O₆Br₂: C, 55.1; H, 2.4; N, 11.0.
Found: C, 54.9; H, 2.3; N, 10.8.
Reaction of \textit{Di}(6-lithio-2-pyridyl)ketone Ketal with Ethyl Chloroformate. The same procedure and work-up used in the analogous reaction with methyl 2,6-pyridinedicarboxylate coupling reagent was used in this reaction. The dilithio ketal was generated from \textit{di}(6-bromo-2-pyridyl)ketone ketal (2.6 mmol, 1.0 g) and \textit{n}-butyl-lithium (6.0 mmol) in tetrahydrofuran (110 ml) at -90\textdegree. Ethyl chloroformate (2.6 mmol, 276 mg) was added quickly and, after subsequent work-up and hydrolysis, chromatographic procedures [silica gel PF, 2.0 mm, petroleum ether A-ethyl acetate (5:1)] afforded 230 mg (16\%) of dibromotetrapyridyl trione (\ref{eq:17}): mp 164-6\textdegree;
**Reaction of Di(6-lithio-2-pyridyl)ketone Ketal with Methyl 2,6-Pyridinedicarboxylate.** A mixture of di(6-bromo-2-pyridyl)ketone ketal (1.0 g, 2.6 mmol) in anhydrous tetrahydrofuran (200 ml) was cooled to -90° and n-butyllithium (3 ml, 2M in hexane; 6.0 mmol) in THF (10 ml) was slowly added. After one hour at temperatures below -80°, solid methyl 2,6-pyridinedicarboxylate (350 mg, 3 mmol) was added quickly with vigorous stirring and the reaction was maintained below -70° for an additional hour. The reaction was quenched by adding a mixture of methanol (30 ml) and 5N hydrochloric acid (30 ml). The organic solvent was removed at reduced pressure and the aqueous solution was dissolved in an equal volume of methanol. This acidic mixture was refluxed for 8 hours then neutralized with 10% aqueous sodium bicarbonate. The solution was extracted with dichloromethane (10 x 50 ml), then the combined extract was dried over anhydrous sodium sulfate, and concentrated in vacuo to afford 720 mg of a pale yellow solid. Purification via chromatographic methods (silica gel PF, 2.0 mm, 5% ethyl acetate in chloroform) afforded 260 mg (31%) of the dibromo-penta-pyridyl-tetraone (118): mp 170-172° (dec.); nmr (CDCl₃-1% TMS) δ 7.44-8.15 (m, pyr-H); ir (KBr) 3000, 1687 (C=O), 1570, 1555, 1320, 995, 822 cm⁻¹; MW calcd. = 657, MW osmotic (Benzene) 649, 693—average = 671.
2,6-Dipicolinoyl chloride (119). A slurry of 2,6-pyridinedicarboxylic acid (100 g, 0.60 mol) in thionyl chloride (300 ml) was gently refluxed for 36 hours. The excess thionyl chloride was removed via reduced pressure to afford a red gum which was recrystallized from petroleum ether B to give 97 g (79.5%) of the colorless prisms of 2,6-dipicolinoyl chloride: mp 54-56° (lit. 56 mp 56-58°). No further purification was attempted due to the high degree of chemical reactivity.

2,6-Dicyanopyridine (48a). 2,6-Pyridinedicarboxylic acid (20.0 g, 0.12 mol) and thionyl chloride (100 ml) was refluxed for three hours. The thionyl chloride was fractionally distilled and then the residual diacid chloride was cautiously added to cold, concentrated ammonium hydroxide. The resultant solid diamide was removed via filtration and dried in a vacuum dessicator overnight. The crude dipicolyl diamide was suspended in phosphorous oxychloride (30 ml), then refluxed for one hour. After neutralization with 10% aqueous sodium carbonate, the
suspension was extracted with chloroform, the organic layer was dried over anhydrous sulfate, and concentrated at reduced pressure to afford a beige solid, which was recrystallized from methanol affording 5.0 g (30.0%) of 2,6-dicyanopyridine: mp 125-126° (lit. 57 mp 126-127°); nmr (CDCl$_3$) δ 7.86-8.32 (pyr-H, m); ir (KBr pellet) 3050, 2240 (C=N), 1570, 1440, 1090, 990, 834 cm$^{-1}$.

**2,6-Dibenzoylpyridine (120).** A mixture of 2,6-pyridinedicarboxylic acid (16.7 g, 0.10 mol) and excess thionyl chloride was refluxed for 24 hours under nitrogen. Excess thionyl chloride was removed in vacuo and the residue was suspended in a mixture of benzene (200 ml) and carbon disulfide (100 ml). Aluminum trichloride (66.0 g, 0.495 mol) was gradually added via a solid addition funnel and the resulting mixture was refluxed for six hours. The solvents were removed at reduced pressure and ice water was added to hydrolyze any unreacted acid chloride. The aqueous suspension was made basic with 5N NaOH and extracted with ether (10 x 100 ml). The combined organic phase was dried over anhydrous sodium sulfate and concentrated to give a solid residue, which was recrystallized from 95% ethanol to afford 16.0 g (55.8%) of pure 2,6-dibenzoylpyridine: mp 106-107° (lit. 58 mp 108°); nmr (CDCl$_3$) δ 7.28-8.47 (Ph-H and pyr-H, m); ir (KBr pellet) 3110, 2930, 1670 (C=O), 1630, 1580, 1445, 1400, 1325, 1320, 1300, 1240, 1175, 1170, 1085 cm$^{-1}$.

**Methyl 2,6-Pyridinedicarboxylate (48b).** 2,6-Pyridinedicarboxylic acid (167.0 g, 1 mol) was dissolved in absolute methanol (1 l) and anhydrous HCl was passed through the mixture until a saturated solution

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was obtained. The reaction mixture was refluxed for 24 hours, then concentrated via reduced pressure. The residue was suspended in aqueous 10% sodium bicarbonate and extracted with chloroform. The combined chloroform extracts dried over anhydrous sodium sulfate, and upon concentration in vacuo afforded 192.0 grams (98%) of methyl 2,6-pyridinedicarboxylate: mp 121-122.5° (lit. mp 124-125°); nmr (CDCl₃) δ 4.00 (-CO₂CH₃, s, 6H), 7.85-8.45 (pyr-H, m, 3H); ir (nujol) 1740 (C=O, ester), 1570, 1285, 1245, 1195, 1140 cm⁻¹.

2,6-Di(hydroxymethyl)pyridine (121). Methyl 2,6-pyridinedicarboxylate (39.0 g, 0.2 mol) was stirred in 300 ml absolute methanol while sodium borohydride (38.0 g, 1.0 mol) was added via a solid addition funnel over two hours. Intermittent cooling by immersion in an ice-water bath maintained the temperature at 40° ± 5°. After the addition was complete, the reaction was stirred at 40° for one hour, followed by reflux for 12 hours. To quench the reaction, the solution was cooled and 80 ml acetone was added. Concentration afforded a solid residue, which was warmed in 10% sodium carbonate (80 ml) on a steam bath for one hour. After re-evaporating to dryness, the residue was extracted with chloroform for 12 hours using a Soxhlet extractor affording 26.0 g (98%) of crude 2,6-di(hydroxymethyl)pyridine: mp 113-115°. Recrystallization from methanol-ethyl acetate produced 19.1 g (71%) of the pure diol: mp 112-113° (lit. mp 113°).

2,6-Di(chloromethyl)pyridine (122). 2,6-Di(hydroxymethyl)pyridine (13.9 g, 0.1 mol) in chloroform (500 ml) was refluxed under a nitrogen atmosphere. Thionyl chloride (30 ml, 0.42 mol) in chloroform (60 ml)
was added over two hours while maintaining a gentle reflux for an additional 12 hours. Upon cooling, solvent and unreacted thionyl chloride were removed under reduced pressure to obtain a beige solid [DERMATACTIC! Caution while manipulating is required!] which was suspended in 10% aqueous sodium carbonate and extracted with several portions of diethyl ether. The combined ether extracts were dried over magnesium sulfate and concentrated. The residue was recrystallized from petroleum ether to afford 14.0 g (80%) of 2,6-di(chloro-methyl)pyridine: mp 74.5-76° (lit. mp 74-75°); nmr (CDCl₃) δ 4.68 (pyr-CH₂-Cl, s, 4H), 7.25-7.95 (pyr-H, m, 3H); ir (nujol) 1590, 1250, 1085, 752, 688, and 674 cm⁻¹.

8-Bromoquinoline (123). Method A. Bromination of Quinoline. To a stirred suspension of quinoline (65.0 g, 0.5 mol) dissolved in sulfuric acid (98%, 100 ml), and silver sulfate (17.0 g, 0.05 mol), elemental bromine (8.0 g, 0.05 mol) was added slowly at 0° under nitrogen. After 8 hours, the mixture was filtered to remove the silver bromide and the filtrate was poured into ice-cold aqueous sodium sulfite to remove unreacted bromine. The pH was adjusted to ca. 11 with sodium carbonate and the entire mixture was steam distilled until the distillate was clear. The distillate was extracted with ether and the combined organic extract was dried over sodium sulfate, then fractionally distilled to afford 10.5 g of a pale amber oil: bp 85° (0.5 mm).

This residue was treated with an excess of oxalic acid in ethanol. 5-Bromoquinoline oxalate precipitated [white plates; mp 150-151° (lit. mp 152°)], while 8-bromoquinoline remained in solution. On
concentration, 1.1 g (10.6%) of crude 8-bromoquinoline was isolated as a beige oil, bp 300° (lit. 62 bp 302-303°). A sample of this compound was treated with picric acid in alcohol to afford a yellow-orange picrate, which was recrystallized from ethanol to afford a sharp-melting solid: mp 168-168.5° (lit. 62 mp 169°).

Since the 8-bromoquinoline afforded by this preparation is contaminated with 5-bromoquinoline, it was not judged feasible to continue with this procedure.

8-Aminoquinoline (124). A mixture of 8-hydroxyquinoline (30.0 g, 0.21 mol), ammonium sulfite (30.0 g, 0.31 mol), and 28% ammonium hydroxide (80 ml) was sealed in a 250 cm³ stainless steel bomb and heated to 150°C for 24 hours. After cooling, the bomb was opened and the slurry poured into ice-water (500 ml). This mixture was heated to 70°, cooled to 25°, filtered, and the solids washed with water (1 l), followed by washing with 5N sodium hydroxide. The remaining solid was washed with water until the washings were non-alkaline, and then steam distilled to afford 21 g (71.3%) of an amber oil, which crystallized on cooling to afford pure 8-aminoquinoline: mp 66-66.5° (lit. 63 mp 65-65.5°); nmr (CDCl₃) δ 4.75 (-NH₂, broad s, 2H), 6.70-7.37 (H₃, H₅, H₆, H₇, m, 4H) 7.90 (H₈, m, 1H), 8.65 (H₂, m, 1H).

8-Bromoquinoline (123). Method B. Sandmeyer Reaction with 8-Aminoquinoline. To a mixture of 8-aminoquinoline (25 g, 0.176 mol) and 48% HBr (52.8 ml, 0.44 mol) cooled to 0°C, a solution of sodium nitrite (12.3 g, 0.176 mol) slurried in ice water (22.0 ml) was added, followed by enough solid sodium nitrite to afford a solution

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that gave an immediate black spot on starch-iodide test paper. The resultant cold mixture was slowly added to a mixture of cuprous bromide (12.96 g, 0.09 mol) and 48% HBr (13.33 ml, 0.10 mol), then refluxed. After the addition was complete, the solution was cooled and neutralized with 5N sodium hydroxide. Extraction with chloroform and concentration yielded 23 g of a brown oil, which was chromatographed (silica gel, column: 3" x 20"; chloroform) affording 18.1 g (49.6%) of 8-bromoquinoline: bp 301-303° (760 mm) [lit.62 bp 302-303°]. Picrate: mp 167-169° (lit.62 mp 169°).

**Reaction of 8-Bromoquinoline with n-Butyllithium.** 8-Bromoquinoline (5.0 g, 0.024 mol) was dissolved in dimethoxyethane (100 ml) and cooled to -40°C. An excess of n-butyllithium in diethyl ether (25.0 ml, 2.2N, 0.055 mol) was slowly added and the reaction was refluxed for 2 hours, then hydrolyzed with 5N H₂SO₄ (150 ml). The pH was adjusted to 7.0 with 5N NaOH and the solution was extracted with chloroform. Concentration in vacuo afforded 3.2 g of a red-brown oil. Upon chromatographic separation (plc, 2.0 mm silica gel, 3X, 80% cyclohexane-ethyl acetate), the only identifiable products were quinoline: [Rf 0.68; bp 235-236° (lit. bp 237°); nmr (CDCl₃) δ 7.13-8.30 (H₃ to H₉, m, 6H), 8.80 (H₂, dd, 1H)], and 8-bromoquinoline: [Rf 0.53; bp 301-303° (760 mm)]. Although a product balance was not obtainable, all other isolable material resembled polymeric, ill-defined semi-solids.

**2,2'-Dipyridyl (125).** Photochemical Induced Coupling of 2-Bromo-pyridine. 2-Bromopyridine (5.0 g, 0.032 mol), iron powder (1.5 g, 0.027 mol), and elemental bromine (30 g, 0.38 mol) were mixed carefully.
at 0°C, in a flask which can be sealed. The system was flushed thoroughly with nitrogen, sealed, and placed in the sunlight. After six hours at 0°C, the reaction was poured into 5N H₂SO₄ (150 ml) and steam distillation removed all the unreacted bromine. The residue was made alkaline with solid sodium hydroxide and again steam-distilled until the distillate was clear. The organic phase from the distillate was dried over sodium sulfate and separated via standard chromatographic methods [plc, 2.0 mm silica gel, cyclohexane-ethyl acetate (4:1)] to afford 3.2 g (64%) of unreacted 2-bromopyridine (Rf 0.47); bp 190° (lit. bp 192-194°) and 130 mg (27.4%) of pure 2,2'-dipyridyl (Rf 0.27); mp 69-70° (lit. 64 70-73°); nmr (CDCl₃) δ 7.1-8.6 (pyr-H, m, 3H); 8.65-8.75 (6-pyr-H, dd, 1H). The 2,2'-dipyridyl was identical to a commercial sample.

2,2'-Bipyridyl Sulfur Dichloride (126). 2,2'-Bipyridyl (15.6 g, 0.10 mol) was suspended in anhydrous diethyl ether (500 ml) and sulfur dichloride (10.3 g, 0.10 mol) was added with vigorous stirring. After maintaining efficient agitation of the mixture for 24 hours, the suspended solid was filtered affording 22.0 g (85%) of 2,2'-bipyridyl sulfur dichloride: mp 198-200° (dec., sealed tube).

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\text{Cl}^- & \text{\}} \\
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This compound reacts vigorously when added to H₂O, HMPA, DMSO; it is insoluble in CHCl₃, pyridine, benzene, CH₂Cl₂, etc., thus no NMR data are available. Furthermore the sample chars and decomposes when
pressure was applied subsequent to the formation of a KBr pellet!

Anal. Calcd. for C₁₀H₆N₂SCl₂:  C, 46.3; H, 3.1; N, 10.8. Found:  
C, 44.2; H, 3.7; N, 10.3.

Sublimation attempts affected neither a substantial improvement  
in purification nor any evidence for a rearrangement to 6,6'-dichloro-
2,2'-bipyridyl. DTA-TGA studies do show decomposition of the compound  
but no loss of hydrogen sulfide. Instead a slow loss of 85% of the 
weight is shown---probably due to both sublimation and decomposition.  
No additional studies have been carried out on this adduct.

Reaction of Bis(6-bromo-2-pyridyl)mercury with K₂Ni(CN)₆ in 
the Presence of CO. Method A. Anhydrous Solvent. Potassium  
hexacyanodinickelate (2.5 g, 7.0 mmol) was suspended in anhydrous  
dimethylformamide and carbon monoxide was bubbled into the mixture  
for 2 hours. Bis(6-bromo-2-pyridyl)mercury (3.6 g, 7.0 mmol,  
mp 88-9°) dissolved in dimethylformamide (50 ml) was added main-
taining efficient agitation. The reaction was stirred to 25°  
for 18 hours, followed by warming to 70° for an additional two  
hours. The suspension was filtered through a celite pad to remove  
the elemental mercury, then the filtrate was concentrated in vacuo.  
The yellow-green residue was suspended in water (200 ml) and extracted  
with chloroform (5 x 50 ml). The combined extract was dried over  
anhydrous sodium sulfate and concentrated. Chromatographic techniques  
(plc, silica gel, 2.0 mm, 3X, 80% cyclohexane-ethyl acetate) afforded  
320 mg (14.5%) crystals (Rf 0.30) of 6,6'-dibromo-2,2'-bipyridyl:  
mp 216-217° (lit.⁶⁺ mp 218°); nmr (CDCl₃) δ 7.14, 7.78 (pyr-H, m);
ms (70 eV) m/e (relative intensity) 316 (0.3), 314 (1.0), 312 (0.3),
236, (8.1), 235 (70.4), 234 (8.4), 233 (73), 159 (7.0), 158 (97.4),
157 (7.7), 156 (100), 155 (1.7), 154 (7.6), 153 (8.1), 149 (1.4),
131 (3.4), 129 (3.4), 127 (1.7), 126 (2.5), 112 (1.1), 108 (1.8),
107, (1.3), 106 (2.4), 105 (1.4), 79 (1.1), 78 (4.0), 77 (29.5),
76 (67.5), 75 (4.8), 50 (2.3), 49 (9.7), 48 (24.3), 47 (1.5).

Reaction of Bis(6-bromo-2-pyridyl)mercury with K₂Ni₂(CN)₆ in
Dimethylformamide under Ultraviolet Light. Method B. Bis(6-bromo-
2-pyridyl)mercury (5.0 g, 9.7 mmol) was dissolved in degassed dimethyl-
formamide (50 ml) and the solution was blanket ed with argon. After
four days in sunlight, chromatographic analysis (tlc., 0.25 mm silica
gel, 50% cyclohexane-ethyl acetate) indicated the presence of only
unchanged bis(6-bromo-2-pyridyl)mercury. Potassium hexacyanodi-
nikelate (1.5 g, 4.0 mmol) was added and the flask was reexposed to
sunlight. After 2 days, elemental mercury had been deposited.
Chromatographic separation (plc, 2.0 mm silica gel, 3X, 80% cyclo-
hexane-ethyl acetate) afforded 87 mg (29%) of colorless crystals of
6,6'-dibromo-2,2'-bipyridyl: mp 216-217° (lit.65 mp 218°).

6,6'-Dibromo-2,2'-bipyridyl (127). Method C. via Cupric Chloride
Coupling of 2-Bromo-6-lithiopyridine. A solution of 2-bromo-6-lithio-
pyridine [prepared from 2,6-dibromopyridine (10.0 g, 0.042 mol) and
n-butyllithium (2.23 M in hexane, 18.9 ml, 0.042 mol)] in diethyl
ether (150 ml) was cooled via liquid nitrogen/petroleum ether bath
to -90° and powdered cupric chloride (2.18 g, 0.022 mol) was added.
The mixture was allowed to warm to -70° C with efficient stirring.
[Caution: Reaction exothermic at this point!] At no point should the temperature rise above -50° C. After one hour, dry compressed air was bubbled through the solution until the solution turned pale green (ca. 30 minutes) and 5N HCl (100 ml) was added to stop the reaction. The solution was filtered, the ether layer was concentrated in vacuo, and the residue was recrystallized from benzene to afford 3.7 g (56.2%) of the white crystalline 6,6'-dibromo-2,2'-bipyridyl: mp 219-220° (lit. mp 218°); nmr (CDCl₃) δ 7.42-8.65 (Py-H, m); ir (KBr pellet) 3300, 1570, 1530, 1420, 1400, 1365, 1160, 1135, 1120, 1070, 990, 790, 708.

6,6'-Dipicolinoyl-2,2'-bipyridyl (128). A solution of 6,6'-dibromo-2,2'-bipyridyl (1.0 g, 3.1 mmol) in freshly distilled tetrahydrofuran (50 ml) was cooled to -90° and a solution of n-butyllithium (3.0 ml, 2.2N; 6.6 mmol) dissolved in THF (5.0 ml) was cautiously added with vigorous stirring. The temperature was maintained below -70° for one hour then a solution of 2-cyanopyridine (644 mg, 6.2 mmol) in THF (25 mol) was slowly added over 45 minutes. The deep-red solution was stirred at -70° for an additional hour, then hydrolyzed with 5N HCl (20 ml). The slurry was heated on a steam-bath for three hours and the resulting aqueous suspension was extracted with benzene. The organic phase was dried over anhydrous magnesium sulfate and concentrated affording 800 mg of a tan solid, which was recrystallized from benzene affording 530 mg (45.1%) of 6,6'-dipicolinoyl-2,2'-bipyridyl: white needles, mp 217-218.5° (lit. mp 218-219°); nmr (CDCl₃-1% TMS) δ 7.0-8.0 (m, 12H, pyr-H), 8.5 (m, 2H, 6-pyr-H); ir (KBr) 3490, 3300, 1680 (C=O), 1580, 1550,
Reaction of 6,6'-Dilithio-2,2'-bipyridyl with Ethyl Chloroformate.

To a solution of n-butyllithium (6.0 mmol) in anhydrous tetrahydrofuran (50 ml) cooled to -90°, a solution of 6,6'-dibromo-2,2'-bipyridyl (4.0 g, 3.0 mmol) in THF (100 ml) was slowly added, always maintaining the temperature below -78°. The resultant orange-gold solution was stirred at -90° for 30 minutes, then ethyl chloroformate (650 mg, 6.0 mmol) dissolved in THF (30 ml) was added over 30 minutes. The mixture was stirred at -90° for 90 minutes, then allowed to warm to -30° for 30 minutes and the reaction was quenched with methanol (30 ml) and 5N hydrochloric acid (30 ml).

The ethereal solvent was removed at reduced pressure, the aqueous slurry was neutralized with 10% aqueous sodium carbonate extracted with chloroform (5 x 50 ml), dried with anhydrous sodium sulfate, and concentrated in vacuo to afford 740 mg of a pale yellow solid, which was chromatographed (plc, silica gel, 2mm; CHCl₃, 5X) affording 84 mg (7.6%) of the bipyridylketone macrocycle (n = 2): Rf 0.62;
mp 176-8° (dec.); nmr (CDCl₃) δ 7.1 7.1-8.05 (PyOH, m); ir (KBr) 3490, 3300, 1740, 1730, 1680, (C=O), 1660, 1580, 1560, 1450, 1430, 1320, 1260, 1190, 1130, 1120, 995 cm⁻¹. MWCalcd. = 364, MWOsmotic (Benzene) = 360, 371---average = 365.

Anal. Calcd. for C₂₂H₁₂N₄O₂: C, 72.5; H, 3.3; N, 15.4. Found: C, 72.4; H, 3.1; N, 15.2.

A second band contained 68 mg (4.1%) of macrocycle (n = 3): Rf 0.46; mp 185-187° (dec.); nmr identical to that of cyclic bipyridylketone (n = 2); MWCalcd. = 547, MWOsmotic (Benzene); 3 run average = 567.

Anal. Calcd. for C₃₃H₁₆N₆O₃: C, 72.5; H, 3.3; N, 15.4. Found: C, 72.3; H, 3.1; N, 15.3.

A third band contained 52 mg (2.3%) macrocycle (n = 4): Rf 0.30; mp 196-199° (dec.); nmr identical to that of cyclic bipyridyl ketone (n = 2); MWCalcd. = 729, MWOsmotic (Benzene); 3 run average = 709.

Further elution afforded 60 mg (2.2%) macrocycle (n = 5): Rf 0.15; mp 218-221° (dec.); nmr identical to that of cyclic bipyridyl ketone (n = 2); MWCalcd. = 911, MWOsmotic (Benzene); 3 run average 901.
These compounds become less soluble as the molecular weight increases. Even with the smallest macrocycle, solubility is so low as to render it very difficult to work with the material and to obtain an analytically pure sample.

**Methyltriphenylphosphonium Bromide (129).** Triphenylphosphine (25.0 g, 0.11 mol) and anhydrous benzene (25 ml) were placed in a 100 cm\(^3\) stainless steel bomb, which was cooled to 0\(^\circ\) C. Methyl bromide (15 g, 0.16 mol) was added to the solution and the apparatus was sealed and allowed to warm to 25\(^\circ\) C. After 24 hours, the bomb was heated to 80\(^\circ\) C for an additional 12 hours. After recooling to 0\(^\circ\) C, the cylinder was opened carefully and the solid material was collected via filtration. The crude methyltriphenylphosphonium bromide was washed with cold, anhydrous benzene (300 ml) and dried in a vacuum dessicator. Total yield was 30.0 g (76.3\%) of a white powder: mp 228-230\(^\circ\) C (lit.\(^{66}\) mp 227-231\(^\circ\) C).

**1,2-Bis(triphenylphosphonium)ethane Dibromide (130).** To triphenylphosphine (25 g, 0.11 mol) dissolved in anhydrous benzene (100 ml), 1,2-dibromoethane (11.3 g, 0.06 mol) was added. The mixture was refluxed for twenty-four hours. The suspension was cooled and the white crystalline powder was collected by filtration and washed with cold benzene affording 31.2 g (73.1\%) of the desired diphosphonium salt: mp 349\(^\circ\) (via Differential Thermal Analysis; chromel/alumel thermocouple, temperature corrected for deviation via standard curves; experimental uncorrective value mp 356\(^\circ\).

**Anal.** Calc. for C\(_{30}\)H\(_{34}\)P\(_2\)Br\(_2\): C, 64.04; H, 4.77. Found: C, 64.06; H, 4.70.
1-Phenyl-1-(2'-pyridyl)ethene (131). A suspension of methyl-triphenylphosphonium bromide (5.0 g, 14.0 mmol) in anhydrous diethyl ether (70.0 ml) was stirred vigorously while n-butyllithium (14.0 mmol; 2.26N, hexane) was added. After 12 hours at room temperature, phenyl(2-pyridyl)ketone (1.4 g, 7.65 mmol) dissolved in diethyl ether (150 ml) was added gradually and, after another 12 hours at 25°, the mixture was refluxed for an additional 2 days. Ice water was added and the mixture was extracted with ether (4 x 50 ml). The combined extract was concentrated at reduced pressure, the residue was suspended in 5N hydrochloric acid, and washed with benzene (50 ml). The aqueous phase was neutralized and re-extracted with benzene (5 x 50 ml) after which the organic phase was dried with anhydrous sodium sulfate then concentrated to afford a red-orange syrup, which was chromatographed (plc 2.0 mm silica gel, 80% cyclohexane-ethyl acetate, 4X) affording 850 mg (9.4%) of 1-phenyl-1-(2-pyridyl)ethene: bp 118-120° (0.5 mm), lit. ²⁷ bp 120-122° (0.5 mm); nmr (CDCl₃) δ 5.25 (H, s, 1H), 5.76 (H₆, s, 1H), 6.92-7.67 (ph- and pyr-H, m, 8H), 8.37-8.54 (6-pyr-H, m, 1H).

1,1-Bis(2'-pyridyl)ethene (132). Methyltriphenylphosphonium bromide (0.70 g, 1.96 mmol) was suspended in anhydrous diethyl ether (10 ml) and phenyllithium (2 mmol) was added. After 4 hours of vigorous stirring at ambient temperature, bis(2-pyridyl)ketone (200 mg, 1.09 mmol) dissolved in diethyl ether (20 ml) was added. The reaction was stirred at room temperature for two days followed by refluxing for an additional six hours. The reaction was quenched
by adding ice water and the resultant suspension was extracted with ether (4 x 50 ml). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was suspended in 5% HCl and washed with benzene (2 x 50 ml). The aqueous layer was neutralized with 5% NaOH then extracted with benzene (3 x 50 ml). These organic extracts were combined, dried over sodium sulfate, and concentrated at reduced pressure to afford 70 mg of a beige oil, which was subjected to chromatography (plc, 2 mm, 1X, 50% ethyl acetate-cyclohexane) affording 50 mg (25.2%) of 1,1-bis(2-pyridyl)ethene: bp 100-102° (0.2 mm) [lit. 68 bp 98-100 (0.1 mm)] nr (CDCl₃) δ 6.35 (=CH₂, s, 1H), 7.20-7.85 (Py-H, m, 3H), 8.6 (6-Py-H, m, J = 5.0 Hz, 1H); (Rf 0.20); uv (ethanol) λ_max 227 (ε = 1 x 10⁴), 272 (8 x 10³).

Anal. Calcd. for C₁₂ ᵃ₁₂ ᵈ₁₂ ᵇ₁₂ ᵈ₁₂ ᵇ₁₂ : C, 79.1; H, 5.5; N, 15.4. Found: C, 78.9; H, 5.7; N, 15.4.

2-Bis(methylthio)methylpyridine S-Oxide (134). Precursor to 2-Pyridinecarboxaldehyde. Method A. via 2-Bromopyridine. Sodium hydride (50 mg, 1.1 mmol) was suspended in dimethoxyethane (25 ml) and methyl methylsulphinylmethyl sulphide (Aldrich Chemical, 62 mg, 5.0 mmol) was added carefully; the mixture was stirred for an additional 30 minutes. 2-Bromopyridine (40 mg, 2.5 mmol) was added and the mixture was maintained at ambient temperature for 24 hours. The suspension was poured into cold water (75 ml) and extracted with chloroform (5 x 50 ml). The combined extracts were dried over anhydrous sodium sulfate and concentrated to yield an amber syrup, of which 500 mg was chromatographed [plc, 2.0 mm silica gel, cyclo-
hexane-ethyl acetate (1:1) affording 2-bis(methylthio)methylpyridine S-oxide: Rf 0.20; nmr (CDCl₃) δ 2.28 and 2.32 (MeS-, s, 6H), 5.10 (CHSO-, d, J = 6.0 Hz, 1H), 7.1-7.8 (Py-H, m, 3H), 8.6 (6-Py-H, dd, 1H); ir (neat film) 3500, 3000, 2980, 2900, 1600, 1580, 1470, 1430, 1425, 1420, 1300, 1060, 1000, 950, 815, 780, 755, 733, 700 cm⁻¹.

The bulk of the sample was distilled [bp 200° (1.5 mm) (short-path)] to afford 197 mg (74%) of 2-pyridinecarboxaldehyde [tlc: 0.25 mm silica gel, cyclohexane-ethyl acetate (4:1), Rf 0.45; bp 180-181° (760 mm) [lit. 69 bp 181° (760 mm)]; nmr (CDCl₃) δ 7.3-8.05 (Py-H, m, 3H), 8.86 (6 Py-H, dd, 1H), 10.08 (CHO, s, 1H); ir (neat film) 3070, 2990, 2830, 1725 (-CHO), 1680, 1600, 1580, 1480, 1450, 1370, 1340, 1320, 1310, 1270, 1230, 1140, 1090, 1050, 1000, 965, 840, 775, 755 cm⁻¹] and 0.16 g of dimethyl disulphide: bp 106-107° (lit. 70 bp 109°): nmr (CCl₄) δ 2.39 (Me-S, s).

2-Pyridinecarboxaldehyde (135). Method B. via 2-Chloropyridine as Precursor to Intermediate 2-Bis(methylthio)methylpyridine S-Oxide.
Sodium hydride (1.44 g, 30 mmol) and methyl methylsulphinylmethyl sulphide (3.5 g, 30 mmol) were placed in dimethoxyethane (50 ml) and stirred for 30 minutes. 2-Chloropyridine (3.75 g, 33 mmol) was added and the mixture was maintained at ambient temperature for 48 hours. The suspension was poured into cold water and extracted with chloroform (5 x 50 ml). The combined extracts were dried over anhydrous sodium sulfate, concentrated and distilled [200° (1.5 mm)] affording, after purification by a standard chromatographic method (plc 2.0 mm silica gel, cyclohexane-ethyl acetate
of 2-pyridinecarboxaldehyde: bp 180-181°;
Rf 0.45.

2-[Bis(methylthio)methyl]-6-chloropyridine S-oxide (136).
Sodium hydride (1.5 g, 30 mmol) and methyl methylsulphinylmethyl sulphide (3.5 g, 30 mmol) were suspended in anhydrous dimethoxy-ethane (50 ml) and stirred for 30 minutes. 2,6-Dichloropyridine (5.0 g, 33 mmol) was added and the mixture was maintained at ambient temperature for 24 hours. The reaction mixture was poured into cold water (100 ml) and the ethereal solvent was removed at reduced pressure. The aqueous slurry was extracted with chloroform (5 x 50 ml) and the organic phase was dried over anhydrous sodium sulfate then concentrated in vacuo to yield a red-orange syrup, which was purified by dry-column chromatography [200 g, activity 3 silica gel, cyclohexane-ethyl acetate (4:1)] affording 4.1 g (58.3%) of 2-bis(methylthio)methyl 2-pyridine) S-oxide: Rf 0.25;
nmr (CDCl₃) δ 2.38 and 2.42 (MeS-, s, 6H), 5.09 (CHSO-, d, J = 6.0Hz, 1H), 7.25-8.0 (Py-H, m, 3H); ir (neat film) 3500, 3100, 3000, 2950, 1590, 1570, 1440, 1425, 1330, 1300, 1180, 1160, 1140, 1050 (broad), 1000, 960, 915, 820 cm⁻¹.

6-Chloro-2-pyridinecarboxaldehyde (137). Method A. Acid Hydrolysis of 2-[Bis(methylthio)methyl]-6-chloropyridine S-oxide.
2-Bis(methylthio)methyl-6-chloropyridine S-oxide (1.0 g, 4.25 mmol), tetrahydrofuran (4 ml), and 12 M HCl (0.5 ml) were refluxed for 15 minutes, then stirred for another two hours at 25° C. The ph was adjusted to 10 with solid sodium carbonate and the aqueous...
layer was extracted with dichloromethane (10 × 25 ml). The combined extracts were dried over anhydrous sodium sulfate and concentrated affording 340 mg (60%) of crude 6-chloro-2-pyridine-carboxaldehyde, which was recrystallized from dichloromethane/diethyl ether to afford a dense crop of pale yellow needles: mp 69-70°; nmr (CDCl$_3$) δ 7.50-8.18 (Py-H, m, 3H), 10.08 (-CHO, s, 1H); ir (CHCl$_3$) 3345, 3000, 2830, 1760, 1730, 1600, 1580, 1440, 1350, 1280, 1120 (broad), 1160, 1150, 1140, 1080, 995, 880 cm$^{-1}$.


6-Chloro-2-pyridinecarboxaldehyde (137). Method B. Pyrolysis of 2-[Bis(methylthio)methyl]-6-chloropyridine S-oxide. 2-[Bis-(methylthio)methyl]-6-chloropyridine S-oxide (1.8 g, 7.67 mmol) was distilled [210° (1.5 mm)] affording 1.05 g (95.4%) of yellow-green oil which crystallized on cooling. The solid was recrystallized from dichloromethane/diethyl ether yielding 910 mg (84%) of pure 6-chloro-2-pyridinecarboxaldehyde: mp 69-70°; nmr (CDCl$_3$) δ 7.50-8.18 (Pyr-H, m, 3H), 10.08 (-CHO, s, 1H). This sample was identical in all respects to the aldehyde prepared via Method A.

6-Bromo-2-pyridinecarboxaldehyde (139). Sodium hydride (500 mg, 11.0 mmol) and methyl methylsulphinylmethyl sulphide (620 mg, 5.0 mmol) were placed in dimethoxethane (25 ml) and stirred for 30 minutes. 2,6-Dibromopyridine (590 mg, 2.5 mmol) was added and the mixture was maintained at ambient temperatures for 36 hours, followed by refluxing for 30 minutes. After cooling, the suspension was
hydrolyzed with ice-water (75 ml), neutralized with 5N HCl, and extracted with chloroform (5 x 50 ml). The combined extracts were dried over anhydrous sodium sulfate and concentrated to afford a red oil, which was chromatographed [plc 2.0 mm silica gel, cyclohexane-ethyl acetate (1:1)] affording 450 mg (63.4%) of the crude S-oxide (Rf 0.20). Pyrolysis [150° (1.5 mm)] of this S-oxide afforded 284 mg (61.0% based on 2,6-dibromopyridine) of a pale yellow oil, which crystallized affording pure 6-bromo-2-pyridine-carboxaldehyde: mp 77-78°; nmr (CDCl₃) δ 7.68-8.01, (Pyr-H, m, 3H), 10.06 (CHO, s, 1H); ir (CHCl₃) 3345, 3000, 2830, 1758, 1730, 1600, 1580, 1440, 1345, 1280, 1115 (broad), 1160, 1150, 1140, 1080, 995, 880 cm⁻¹.

Anal. Calcd. for C₆H₄NOBr: C, 38.75; H, 2.17; N, 7.53. Found: C, 38.81; H, 2.30; N, 7.50.

3-Pyridinecarboxaldehyde (139). Sodium hydride (1.0 g, 22 mmol) and methyl methylsulphinylmethyl sulphide (1.2 g, 10 mmol) were suspended in dimethoxyethane (25 ml) and agitated for 10 minutes. 3-Bromopyridine (1.6 g, 10 mmol) was added and the suspension was stirred at ambient temperature for 48 hours. The mixture was hydrolyzed in a 50% mixture of alcohol/water (50 ml) and all organic solvents were removed in vacuo. The aqueous solution was extracted with chloroform (5 x 50 ml) and dried over anhydrous sodium sulfate. Concentration at reduced pressure, followed by pyrolysis at 240° (1.5 mm) afforded a mixture of starting 3-bromopyridine and traces (ca. 10% by nmr integration) of the desired 3-pyridine carboxaldehyde.
bp 200° (760 mm) [lit.71 bp 95-97° (15 mm) corrected bp 199-201° (760 mm)] ir (neat film) 1725 (C=O) cm⁻¹.

4-Pyridinecarboxaldehyde (140). Sodium hydride (1.0 g, 22 mmol) and methyl methylsulphenylmethyl sulphide (1.2 g, 10 mmol) were placed in anhydrous dimethoxyethane (25 ml) and stirred for 10 minutes. After addition of 4-chloropyridine (1.25 g, 10 mmol) the suspension was stirred at ambient temperatures for 48 hours. The resulting slurry was poured carefully into a 50% mixture of ethanol/-water (50 ml) and the organic solvent was removed at reduced pressure. The aqueous residue was extracted with chloroform (5 x 50 ml), dried over anhydrous sodium sulfate, and concentrated in vacuo to afford the crude 4-bis(methylthio)methylpyridine S-oxide, which was pyrolyzed at 200° (1.5 mm) without further purification. This procedure yielded the crude aldehyde, which was purified via vacuum distillation to yield 460 mg (43%) of pure 4-pyridinecarboxaldehyde: bp 75-77° (12 mm) [lit. 72 77-78° (12 mm); nmr (CCl₄) δ 7.64 (3,5-Py-H, dd, J = 6.0, 2.0 Hz, 2H), 8.82 (2,6-Py-H, dd, J = 6.0, 2.0 Hz), 10.06 (CHO, s, 1H); ir (neat film) 3200, 3000, 2850, 2750, 1720 (CHO), 1670, 1600, 1590, 1470, 1430, 1390, 1330, 1300, 1240, 1220, 1180, 1100, 1078, 1035, 1025 cm⁻¹.

Attempted Preparation of p-Nitrobenzaldehyde via Methyl Methyl-sulfinylmethyl Sulphide. A mixture of sodium hydride (50 mg, 1.0 mmol), methyl methylsulfinyl methyl sulfide (620 mg, 5.0 mmol), and dimethoxyethane (25 ml) was stirred at 25° for 10 minutes. Solid p-nitrobromobenzene (1.0 g, 4.95 mmol) was added and the solution

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was stirred at room temperatures for 24 hours. The residual sodium hydride was destroyed with isopropyl alcohol (ca. 5 ml) and then shaken with water (30 ml) and extracted with chloroform (5 x 50 ml). The combined extract was dried and concentrated in vacuo. An aliquot of the residue was heated to 250° (1.0 mm) in an attempt to either distill the desired intermediate S-oxide or p-nitrobenzaldehyde. The distillate obtained in this fashion contained neither the aldehyde product nor the intermediate, but on chromatographic analysis (tlc, 0.25 mm silica gel, 80% cyclohexane-ethyl acetate) only components having a retention time corresponding to either p-nitrobromobenzene (Rf 0.78) or the methyl methylsulfinyl methyl sulfide (Rf 0.47) were found. Since ir analysis showed the absence of any aldehydic carbonyl absorption, this reaction sequence was discontinued.

Acetylenebismagnesium bromide\(^{25}\) (141). Magnesium metal turnings (10.0 g, 0.417 mol) were placed in a three neck reaction vessel equipped with a true-bore mechanical stirrer, a reflux condensor, a nitrogen atmosphere, a gas inlet to an open tube, [no fritted glass-tends to "plug" up during course of reaction], and an addition funnel. The equipment was heated while a heavy nitrogen stream purged the interior of the reaction vessel and, when cool, anhydrous diethyl ether (300 ml) was added. A solution of methyl iodide (47.5 g, 0.50 mol) in diethyl ether (50 ml) was dripped into the stirred mixture at a rate to maintain a gentle reflux. One hour after the completion of the halide addition, a slow stream of acetylene [passed through (1) dry-ice/acetone cold trap, (2) Conc.
H₂SO₄ trap, (3) Soda-lime drying tower] was bubbled into the methyl magnesium bromide solution for ca. 12 hours. The resultant acetylene-bismagnesium bromide was insoluble in diethyl ether and appeared as a deep purple layer at the bottom of the reaction flask. This suspension was immediately utilized in subsequent synthesis of substituted acetylene diols.

1,1,4,4-Tetraphenyl-2-butyne-1,4-diol (6lc). Acetylenebis-
magnesium bromide [prepared from methylmagnesium bromide (0.10 mol)] in diethyl ether (100 ml) was treated with a solution of benzophenone (36.5 g, 0.20 mol) in diethyl ether (100 ml). The mixture was stirred at ambient temperature for six hours and poured into cold 5N hydrochloric acid (250 ml). The aqueous solution was neutralized with 5N sodium hydroxide and extracted with diethyl ether. The organic phase was dried over anhydrous magnesium sulfate and concentrated to afford a solid mass, which was recrystallized from toluene to give 30.8 g (79.0%) of 1,1,4,4-tetraphenyl-2-butyne-
1,4-diol as white needles: mp 191-192° (lit. 25,26 mp 192-193°); nmr (Pyridine-d$_5$) δ 4.78 (-O-H, s, 1H), 7.06-8.03 (ph-H, m, 10H); ir (KBr pellet) 3500, 3400, 3000, 2990, 2360, 1595, 1480, 1445, 1337, 1220, 1195, 1170, 1065, 1030, 1005 cm$^{-1}$.

1,4-Diphenyl-1,4-di(2′-pyridyl)-2-butyne-1,4-diol (6la,b). Acetylenebismagnesium bromide [prepared from methylmagnesium bromide (0.05 mol)] in diethyl ether (100 ml) was cooled in an ice bath and a solution of phenyl(2-pyridyl)ketone (18.3 g, 0.10 mol) in diethyl ether (50 ml) was added rapidly with vigorous stirring.
The mixture was stirred at ambient conditions for six hours then hydrolyzed with 2N ice-cold hydrochloric acid. The pH was rapidly adjusted to \( \text{ca. 8} \) with chilled 5N sodium hydroxide and the precipitate was collected by filtration. This crude diol was recrystallized from toluene to afford 6.4 g (32%) of 1,4-diphenyl-1,4-di(2'-pyridyl)-2-butyne-1,4-diol: mp 180-180.5\(^\circ\) (sealed tube, dec.), (lit.\(^{25,26}\) mp 179\(^\circ\)); nmr (Pyridine-\(d_5\)) \( \delta \) 4.74 (-O-H, s, 1H), 6.88-8.71 (ph- and pyr-H, m, 9H); ir (KBr pellet) 3400, 3050, 1590, 1580, 1485, 1450, 1430, 1285, 1195, 1095, 1070, 1035 cm\(^{-1}\).

1,1,4,4-Tetra(2'-pyridyl)-2-butyne-1,4-diol (61d). Phenyl(2'-pyridyl)ketone (10.0 g, 0.055 mol) dissolved in diethyl ether (50.0 ml) was rapidly added to a cooled solution of acetylenebismagnesium bromide [prepared from methylmagnesium bromide (0.03 mol)] suspended in diethyl ether (150 ml). The resulting slurry was stirred at ambient conditions for six hours then poured into 5N ammonium chloride (200 ml). The solution was filtered and the solid recrystallized from toluene to afford 3.5 g (33%) of 1,1,4,4-tetra(2'-pyridyl)-2-butyne-1,4-diol: mp 173-173.5\(^\circ\); nmr (Pyridine-\(d_5\)) \( \delta \) 6.49 (-O-H, s, 1H), 6.95-8.15 (pyr-H, m, 6H), 8.47 (6-pyr-H, dd, 1H); ir (KBr pellet) 3280, 3030, 1590, 1565, 1454, 1300, 1220, 1195, 1090, 1085, 1065, 1037 cm\(^{-1}\).

Anal. Calc. for C\(_{24}\)H\(_{16}\)N\(_4\)O\(_2\): C, 73.0; H, 4.6; N, 14.2. Found: C, 73.1; H, 4.6; N, 14.3.

Diphosphorous Tetraiodide (142). A slurry of potassium iodide (99.6 g, 0.60 mol) and diethyl ether (160.0 ml) was stirred vigorously.
under an argon atmosphere while phosphorous trichloride (27.4 g, 0.2 mol) was added cautiously. The mixture was refluxed for twelve hours and the solvent was removed at reduced pressure. The residue was extracted with boiling dichloromethane (2 x 500 ml). The combined extract subsequently concentrated to a volume of ca. 100 ml and upon cooling, 85.0 g (74.7%) of diphosphorous tetraiodide crystallized as long, orange needles: mp 123-125° (sealed tube), [lit. 73 mp 126-127° (other melting points range from 122-124°)]. [Caution: store under Argon, in freezer. Reasonable care must be exercised when handling this reagent!]

\[ 1,1,4,4\text{-Tetraphenylbuta-1,2,3-triene (62c).} \]

1,1,4,4-Tetraphenylbuta-1,2,3-triene (62c). 1,1,4,4-Tetraphenyl-2-butyn-1,4-diol (0.20 g, 0.513 mmol) was dissolved in pyridine (5.0 ml) and cooled to 0° C. Solid diphosphorous tetraiodide (0.30 g, 0.527 mmol) was added with vigorous stirring and the reaction was maintained at 0° for one hour. The solution was poured into cold 10% sodium thiosulfate and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated to afford a brilliant yellow solid, which was chromatographed (plc: 2.0 mm silica gel, 80% cyclohexane-ethyl acetate) to give 80 mg (43%) of 1,1,4,4-tetraphenylbutatriene (Rf 0.95) as yellow needles: mp 235-236° (lit. 25,26 mp 236-236°); nmr (Pyridine-d$_5$) δ 7.20-7.68 (ph-H, m); ir (CHCl$_3$) 3050, 1700, 1520, 1480, 1435, 1360, 1260, 1160, 1110, 1080, 1040, 1030, 1020, 880 cm$^{-1}$; uv (benzene) $\lambda_{max}$ 420 μm ($ε = 2.74 \times 10^4$), 277 (2.26 $\times 10^4$).

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(E)- and (Z)-1,4-Diphenyl-1,4-di(2′-pyridyl)buta-1,2,3-
triene (62a,b). 1,4-Diphenyl-1,4-di(2′-pyridyl)-2-butyne-1,4-diol
(0.25 g, 0.64 mmol) was dissolved in 50% pyridine/benzene and cooled
to 0° C. Solid diphosphorous tetraiodide (0.4 g, 0.70 mmol) was
added and the mixture was rigorously stirred for one hour at 0°.
The solution was quenched in 10% aqueous sodium thiosulfate (50 ml)
and extracted with dichloromethane. The organic phase was dried
over anhydrous sodium sulfate and concentrated to afford a bright
yellow-orange oil, which was chromatographed (plc: 2.0 mm silica
gel, 80% cyclohexane-ethyl acetate) affording two components: (Z)-
1,4-diphenyl-1,4-di(2′-pyridyl)butatriene: yellow needles: 80 mg
(34.9%); (dec. sealed tube; color change noted at 131-135° yellow
to red); Rf 0.30; nmr (CDCl₃) δ 7.10-7.87 (ph- and pyr-H, m, 8H)
8.62-8.78 (6-pyr-H, m, J = 5.0 Hz, 1H); ir (CHCl₃) 3000, 1720, (w),
1580, 1520, 1460, 1430, 1420, 1380, 1330, 1280, 1160, 1120, 1080,
1050, 1025, 930, 880, 856 cm⁻¹; uv (benzene) λmax 430 μν (ε = 3.06
x 10⁴), 276 (2.12 x 10⁴); and (E)-1,4-diphenyl-1,4-di(2′-pyridyl)-
butatriene: orange powder: 30 mg (13.1%); mp 142-143° (dec.,
sealed tube); Rf 0.35; nmr (CDCl₃) δ 7.10-7.87 (ph- and pyr-H, m,
8H) 8.62-8.78 (6-pyr-H, m, J = 5.0 Hz, 1H); ir (CHCl₃) 3000, 1720
(cumulated olefin), 1580, 1520, 1460, 1435, 1360, 1260, 1160,
1120, 1080, 1050, 1025, 880 cm⁻¹; uv (benzene) λmax 430 μν (ε =
2.59 x 10⁴), 276 (3.54 x 10⁴).

Anal. Calc. for C₂₆H₁₆N₂:  C, 87.15; H, 5.16; N, 7.82. Found
(Z-isomer):  C, 87.30; H, 4.92; N, 7.71.

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Attempted Catalytic Reduction of 1,4-Diphenyl-1,4-(2'-pyridyl)buta-1,2,3-triene. A mixture of (Z)- and (E)-1,4-diphenyl-1,4-(2-pyridyl)-butatrienes (25 mg, 0.07 mmol) was dissolved in benzene (4 ml) and this solution was added via syringe to a previously prepared catalyst [10% Palladium on carbon; the catalyst had been stirred in a hydrogen atmosphere for thirty minutes in preparation for the reduction step] suspended in additional benzene (5 ml). The mixture was stirred for thirty minutes during which time a three mole excess of hydrogen was consumed. The suspension was filtered through a celite pad and the filtrate was concentrated at reduced pressure to afford 26 mg of a beige oil. Nmr (100 MHz) studies indicated hydrogenation had been exhaustive and the product was 1,4-diphenyl-1,4-di(2'-pyridyl)butane and not the desired butadiene.

1,4-Diphenyl-1,4-di(2'-pyridyl)butane: nmr (CDCl₃ δ 0.9-1.75 (-CH₂-, m, 6H), 7.15-7.81 (ph- and pyr-H, m, 16H), 8.17-8.28 (6-pyr-H, m, J = 5.0 Hz, 2H); ir (CHCl₃) 3000, 1610, 1590, 1520, 1430, 1420, 1320, 1280, 1050, 880 cm⁻¹.

1,1,4,4-Tetra(2'-pyridyl)buta-1,2,3-triene (62d). A solution of 1,1,4,4-tetra(2'-pyridyl)-2-butyne-1,4-diol (200 mg, 0.51 mmol) in 50% pyridine/benzene (10 ml) was cooled to 0°C and diphosphorous tetraiodide (300 mg, 0.53 mmol) was added with rapid stirring. After 5 hours, the reaction mixture was poured into cold 10% sodium thiosulfate (50 ml) and the suspension extracted with benzene. The combined extract was dried over anhydrous sodium sulfate and concentrated to afford a yellow-red oil, which was chromatographed (plc:...
2.0 mm silica gel, 80% cyclohexane-ethyl acetate) yielding ca. 75 mg (40%) of 1,1,4,4-tetra(2’-pyridyl)butatriene as a yellow-orange oil*: Rf 0.05; nmr (CDCl₃) δ 7.02-8.80 (pyr-H, m, 3H) 8.61-8.78 (6-pyr-H, m, J = 5.0 Hz, 1H); ir (CHCl₃) 3000, 1590, 1520, 1475, 1430, 1380, 1280, 1160, 1120, 1070, 1050, 1030, 880 cm⁻¹; uv (benzene) λmax 430 nm (ε = 6.00 x 10²), 330 (6.06 x 10³), 275 (6.56 x 10³).

*Although this compound is apparently relatively stable in dilute benzene solution, upon concentration the color alters rapidly from a characteristic deep yellow to a green-black semi-solid. Analysis by tlc indicates the presence of a new component (Rf 0.01), that has not been characterizable along with decreased yields of the desired 1,1,4,4-tetra(2’-pyridyl)butatriene. Due to this difficulty, an elemental analysis and a melting point have not been obtained.
The goal set-forth in this research problem was the synthesis of hetero-macrocyclus containing the 2,6-pyridino moiety. The first macrocyclic system dealt with in this fashion was the class possessing a skeleton of the type represented by (III). Although related systems (15)\textsuperscript{11} and (41)\textsuperscript{20} had been synthesized, these macrocycles all possessed non-planar conformations and, as such, are limited in their effectiveness as specific chelates. The introduction of the \textit{sp}\textsuperscript{2} bridge, however, will force these compounds to exist as rigid, planar ligands. The chelating ability of these molecules will be enhanced by the structural rigidity in two ways. First, the electron pairs of the pyridine nitrogen atoms will be directed into the central cavity of the planar macrocycles, whereas the non-planar systems can exist as conformers having the electron-pair directed orthogonally to this central region (Figure V). Secondly, in the planar system, small changes in the dimensions of the macrocyclic perimeter...
will be directly felt by any internally located cation. This rigidity should allow maximum optimization of chelate specificity toward single cationic species. This capability to "tailor" the cavity of the cyclic ligand for a "custom-fit" of the cation is greatly diminished in the corresponding non-rigid ligands since they have the ability to re-locate portions of the ring via simple conformational changes at the linking sp\(^3\) atoms.

Therefore, although non-planar macrocycles can easily form complexes with metal ions, it is doubtful whether these systems can be coerced into being specific for a single metal. In principle at least, the geometry of planar chelates could allow for extreme specificity in their chelating ability. While it was recognized that actual application of "custom-designed" heteromacrocycles in specific metal complexation was a very long-range goal probably beyond the scope of this dissertation, it was still a powerful impetus in the initial outline of synthetic procedures.

The carbonyl functionality was selected as the initial connective unit to capitalize on the diverse range of synthetic alterations possible for this chromophore. It was felt, for example, that the ketonic system could easily be converted into an exocyclic-polyene via a typical Wittig reaction. Simple reactions should also be possible to effect transformations into aliphatic or carbinol-functional-ality (albeit these alterations would yield the less desirable sp\(^3\) linked macrocycle).

The initial over-all Scheme for the production of the carbonyl-bridged macrocycle (40) is re-illustrated below. This route will be
subdivided and discussed by steps in order to allow a logical progression for the total synthesis. In this manner, the over-all production of the desired novel macrocycles can be discussed from the standpoint of individual, previously documented model reactions. The subdivisions utilized in this discussion follow exactly the important segments of the total scheme already illustrated and are (in order) (a) Substituted Lithiopyridines; (b) Substituted Pyridyl Ketones; (c) Substituted Pyridyl Ketone Ketals; (d) Metallation of Protected Ketones; and finally (e) Cyclization to Form Macrocyclic Ketones.
**Substituted Lithiopyridines.** The initial step in the proposed reaction sequence required a dihalogenated pyridine molecule to undergo a single transmetallation reaction to afford the reactive intermediate (30). Early work reported by Wibaut et al.\(^7\) indicated that treatment of 2,6-dibromopyridine with an alkylmagnesium halide via an entrainment procedure yielded the bis(2,6-pyridyl)magnesium bromide (144). In subsequent work by Gilman and Spatz,\(^{33}\) however, the same substrate (2,6-dibromopyridine) was demonstrated to undergo a specific transmetallation reaction only one time upon treatment with alkyllithium reagents in ethereal solvents at low (less than -20° C) temperatures. This specific reactivity would allow production of the desired unsymmetrical 2,6-disubstituted pyridines.

Following this procedure, 2,6-dibromopyridine was treated with alkyllithium reagents (alkyl groups were either methyl or n-butyl) to generate 2-bromo-6-lithiopyridine (30) which afforded, upon carboxylation and acidification, ca. 50% of 6-bromo-2-picolinic acid.
It was observed that allowing reaction temperatures to rise above the noted -20°C resulted in a marked decrease in desired product formation. Although products arising from competing reaction routes operable at >-20°C were not isolated and identified in this work, previous researchers\(^\text{33,75}\) indicate a predilection of substituted pyridines to undergo a facile alkyl lithium addition at the -N=C- linkage with these reaction conditions. This addition is suppressed to allow a successful substitution mode of reaction only when low temperatures and short reaction times are utilized.

**Substituted Pyridyl Ketones.** The 6-bromo-2-picolinic acid (75) was an easily characterizable, crystalline solid that was readily converted to 6-bromo-2-picolyl chloride (76) via reaction with thionyl chloride. Ammonolysis of 76 produced picolinamide (42) and subsequent dehydration in the presence of thionyl chloride afforded the corresponding picolinonitrile (43) in an overall yield (dibromide to nitrile) of approximately 40%. Elemental analysis on the supposed 6-bromo-2-picolinonitrile (43) was not consistent with the calculated
values and subsequent mass-spectral data indicated that the bromine substituent had been exchanged with a chlorine atom to afford a mixture of 6-bromo-2-picolinonitrile and 6-chloro-2-picolinonitrile with variable and unpredictable ratios. Studies of this exchange were undertaken utilizing either 6-bromo-2-picolinic acid or 2,6-dichloropyridine as model substrates and it was determined that the transhalogenation became effective only at low pH with high concentrations of halide ion. No successful method for quantitatively replacing one halogen with another was forthcoming in this work.

This halogen exchange was unexpected, but not totally unprecedented. For example, Graf\textsuperscript{76} reported that treatment of 5-chloro-4-iodopicolinic acid (147) with thionyl chloride afforded 4,5-dichloropicolinic acid and other workers\textsuperscript{77} have demonstrated that 3-amino-2-bromo-5-chloropyridine (149) gives 3-amino-2,5-dichloropyridine when treated with refluxing hydrochloric acid for prolonged
periods of time. Since metallation of 2-chloropyridine is extremely slow, this preparative sequence was unacceptable in light of the necessary subsequent metallation cyclization step.

Although the source of 6-bromo-2-picolinic acid was a metallation followed by carboxylation, 2-picolinic acid itself was commercially available. A model system with 2-picolinic acid was utilized to establish the reaction parameters for picolinonitrile production without interference of unwanted side reactions. Although treatment of picolinic acid with thionyl bromide did afford the desired acyl bromide, the initial reaction yields were low. To bypass this problem, phosphorous tribromide was substituted for the unstable thionyl bromide, thus permitting an efficient production of the desired picolybromide. As in the original attempt, simple ammonolysis of the acyl bromide yielded picolinamide in essentially quantitative amounts. Since Levelt and Wibaut\textsuperscript{78} had reported that dehydration of 2,6-dibromoisonicotinamide (15\textsubscript{0}) via thionyl chloride resulted in the production of 2,6-dichloroisonicotinonitrile (15\textsubscript{1}) and, since

\[
\begin{align*}
\text{CONH}_2 & \xrightarrow{\text{SOCl}_2} \text{CN} \\
\begin{array}{c}
\text{Br} \\
\text{Br}
\end{array} & \rightarrow \\
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\end{align*}
\]

our early work on bromopicolinic acid had given evidence for susceptibility to halogen exchange, an alternate procedure was necessary to dehydrate the picolinamide thus far synthesized.

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Teague and Short\textsuperscript{79} reported the facile conversion of nicotinamide (153) into nicotinonitrile via heating with phosphorous pentoxide.

$$\text{CONH}_2 \xrightarrow{P_2O_5} \text{CN}$$

A modification of this experimental technique was utilized for the analogous transformation of our model picolinamide into the desired picolinonitrile in approximately 50% yield. This procedure shown in Scheme XIV, when applied to 6-bromo-2-picolinic acid, met with reasonable success as demonstrated by a total isolated yield (from acid to nitrile) of over 60%. Thus to circumvent facile halide exchange in halopyridines, the reagents must utilize the same halide ions as the substrate.

Scheme (XIV)

With a viable pathway to 6-bromo-2-picolinonitrile in hand, model studies were undertaken to develop a high-yield synthesis of the bis(2-pyridyl)ketones. In order to learn the eccentricities of the chemistry of this class of material, a series of model and necessary ketones were synthesized; see Table II.
Table (II): 2-Pyridyl Ketones

<table>
<thead>
<tr>
<th>Compound</th>
<th>Method</th>
<th>R-</th>
<th>R'-</th>
<th>mp (°C)</th>
<th>% Yield</th>
<th>IR (C=O)a</th>
<th>NMR, δb</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>A</td>
<td>H</td>
<td>2-Pyr</td>
<td>55-56</td>
<td>40</td>
<td>1680</td>
<td>7.44-8.15 (6H); 8.70-8.75 (2H)</td>
</tr>
<tr>
<td>82</td>
<td>B</td>
<td>H</td>
<td>2-Pyr</td>
<td>&quot;</td>
<td>36</td>
<td>1680</td>
<td>&quot;</td>
</tr>
<tr>
<td>85</td>
<td>A</td>
<td>H</td>
<td>Ph</td>
<td>43-44</td>
<td>28</td>
<td>1670</td>
<td>7.33-8.15 (8H); 8.65-8.7 (1H)</td>
</tr>
<tr>
<td>86</td>
<td>A</td>
<td>Br</td>
<td>CH₃</td>
<td>54.5-55</td>
<td>41</td>
<td>1700</td>
<td>2.60 (3H); 7.6-8.0 (3H)</td>
</tr>
<tr>
<td>87</td>
<td>A</td>
<td>Br</td>
<td>Ph</td>
<td>64.5-65.5</td>
<td>45</td>
<td>1690</td>
<td>7.27-8.20</td>
</tr>
<tr>
<td>88</td>
<td>A</td>
<td>Br</td>
<td>2-Pyr</td>
<td>85-86</td>
<td>42</td>
<td>1687</td>
<td>7.27-8.20 (6H); 8.67-8.73 (1H)</td>
</tr>
<tr>
<td>45</td>
<td>A</td>
<td>Br</td>
<td>2-(6-Br-Pyr)</td>
<td>155-156</td>
<td>14</td>
<td>1690</td>
<td>7.69-8.05</td>
</tr>
<tr>
<td>45</td>
<td>B</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>24</td>
<td>1690</td>
<td>&quot;</td>
</tr>
<tr>
<td>45</td>
<td>C</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>48</td>
<td>1690</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

aKBr Pellet; bDeuterio-chloroform, ca. 10% wt/vol, 1% TMS.
The most general synthetic path (Method A) was by way of a nucleophilic addition of a lithiopyridine to the proper nitrile to give first the intermediate substituted ketimine (155) which, upon acid hydrolysis, yielded the desired carbonyl product. For comparisons sake, alternate methods B and C for symmetrical ketones are listed in this Table immediately following the entry describing the individual ketone of interest.

A short cut to the desired ketones, outlined by R. H. Holm and co-workers in 1973, provided a very efficient method for the preparation of symmetrical pyridyl ketones. When a lithiopyridine was reacted with ethyl chloroformate, the latter reagent underwent two nucleophilic attacks as illustrated in Scheme (XV) to give a symmetrical ketone (156) as the terminal product. This sequence has the very obvious twin advantages of simplicity and brevity!

The overall reaction efficiency for this method was severely impaired when the reaction temperatures were allowed to rise above
-40° C. At these "elevated" temperatures, undesirable side-reactions caused a decrease in the final yield of isolated ketone. This route was readily applicable to the formation of both bis(2-pyridyl)ketone (82; R = H) and bis(6-bromo-2-pyridyl)ketone (45; R = 6-Br) in 50% yield.

Modifications of this route were attempted by substituting cyanogen bromide and pyrocatechol dichloromethylene ether (84), respectively, for the ethyl chloroformate coupling reagent. In the case of cyanogen bromide, the reaction pathway should have been exactly analogous to the ethyl chloroformate reaction. The inter-

mediate di-imine (155) would, on acid hydrolysis, afford the symmetrical ketone (156). In actual practice, the major product obtained from this reaction was the substituted picolinonitrile (157), and only traces of the desired ketone were observed. This reaction modification had no particular advantage over the reaction
with ethyl chloroformate and, from a practical point of view, cyanogen bromide is a more noxious reagent to work with (ethyl chloroformate tends to induce a lachrimatory reaction with most people; but BrCN had a frightening, intense choking effect on this experimenter). No effort was applied to maximize product yields with the cyanogen bromide reagent.

The modification utilizing pyrocatechol dichloromethylene ether (84) was particularly intriguing due to the fact that the product would be a protected ketone, thus eliminating the need to perform an additional ketalization step. The reagent needed for this step was not readily available and, in fact, was prepared by the reaction sequence shown in Scheme (XVI). This work was originally done by Hanslick, Bruce, and Mascitti where pyrocatechol was reacted with phosphorus pentachloride to give pyrocatechol carbonate\(^\text{37}\) (83). A subsequent "bomb" reaction with phosphorous pentachloride afforded pyrocatechol dichloromethylene ether\(^\text{38}\) (84) in fair (ca. 40%) yields.

Work done by Gross, Busche, and Bornowski\(^\text{80}\) indicated that pyrocatechol dichloromethylene ether would undergo the nucleophilic
displacement of both chloride ions when treated with ethoxide to afford 2,2-diethoxy-1,3-benzodioxole (159). In the hope of extending this reaction to the pyridyl compounds dealt with in this dissertation, the dichloromethylene ether (84) was reacted with an ethereal solution of 2-bromo-6-lithiopyridine at -40°C. In order to simplify the analysis of the reaction mixture, the entire solution was acidified and subjected to reflux conditions for several hours. The resulting mixture was examined for the net production of bis(6-bromo-2-pyridyl)ketone and it was observed that only traces (<1%) of the desired carbonyl product was obtained. Although the reaction appeared to be possible, the current method produced such low yields as to be synthetically unfeasible. Further work to improve the efficiency of this scheme should be expended, since this method allows a novel incorporation of a carbonyl "synthon" already protected against nucleophilic addition reaction conditions.

Whitesides and co-workers\textsuperscript{81} demonstrated that mixtures of phenyl-lithium in ethereal solvents could be carbonylated in medium yields (40\%) via simply imposing a carbon monoxide atmosphere over the reaction solution. Other examples are also known where modified aryl- or alkyl- substrates can be carbonylated in the presence of
metal catalysts. Tri-iron dodecarbonyl reacts with iodobenzene\textsuperscript{82} in refluxing toluene to produce benzophenone in 53% yield. Although this does represent a modest improvement in yield of ketonic product, it also requires the formation of an aryl-iodide and the metal complex $\text{Fe}_3(\text{CO})_{12}$. Seyforth and Spohn introduced the reaction between organomercuric halides (160) and dicobalt octacarbonyl to afford symmetrical ketones in high yields (60%).\textsuperscript{83} Although this reaction required stoichiometric amounts of dicobalt octacarbonyl, a subsequent communication by the same researchers reported a novel synthesis of symmetrical ketones wherein only carbon monoxide was
used in stochiometric amounts and the expensive \( \text{Co}_2(\text{CO})_8 \) was employed in only catalytic quantities.\(^8\) The procedure for this reaction

\[
\text{Co}_2(\text{CO})_8 + \text{R}-\text{Hg}-\text{R} \xrightarrow{\text{CO}} \text{R}-\text{C} = \text{O}-\text{R} + \text{Hg}^+ 
\]

involved simply stirring the di-aryl-mercury compound in tetrahydrofuran in the presence of 0.05 equivalent \( \text{Co}_2(\text{CO})_8 \) and 1.0 atmosphere of carbon monoxide for ca. 200 hours. The reaction required continuous irradiation via a u.v. lamp and yields were in the neighborhood of 90\% for the desired diaryl ketones.

Other metal complexes had also been used in related reactions and an excellent review of this work was recently published by Ryang and Tsutami.\(^8\) These modified approaches utilize the complexes shown in Table III.
Table (III): Carbonyl Insertion via Various Metal Complexes

<table>
<thead>
<tr>
<th>Metal Complex</th>
<th>Reaction Mode</th>
<th>Organic Substrate</th>
<th>Solvent</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Fe}<em>3(\text{CO})</em>{12}$</td>
<td>non-catalytic</td>
<td>Aryl-I</td>
<td>toluene</td>
<td>$\sim$50</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>Benzyl-X</td>
<td>benzene</td>
<td>50</td>
</tr>
<tr>
<td>$\text{Ni(CO)}_4$</td>
<td>&quot;</td>
<td>&quot;</td>
<td>DMF</td>
<td>90</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>R-Hg-X</td>
<td>DMF</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>DMSO</td>
<td>85-95</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>CH$_3$CN</td>
<td></td>
</tr>
<tr>
<td>$\text{Co}_2(\text{CO})_8$</td>
<td>&quot;</td>
<td>&quot;</td>
<td>THF</td>
<td>$\sim$85</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>R-Hg-R</td>
<td>THF</td>
<td>85</td>
</tr>
<tr>
<td>&quot;</td>
<td>catalytic$^\dagger$</td>
<td>&quot;</td>
<td>THF</td>
<td>$&gt;90$</td>
</tr>
<tr>
<td>$\text{Hg}[\text{Co(CO)}_4]_2$</td>
<td>&quot;</td>
<td>$^\dagger$</td>
<td>THF</td>
<td>$&gt;80$</td>
</tr>
<tr>
<td>$\text{K}_2[\text{Ni}_2(\text{CN})_6]$</td>
<td>non-catalytic$^\dagger$</td>
<td>Benzyl-X</td>
<td>H$_2$O/acetone</td>
<td>$\sim$90</td>
</tr>
</tbody>
</table>

$^\dagger$Reaction run with a carbon monoxide atmosphere.
Hashimoto, et al. had observed that a reaction of potassium hexacyanodinickelate(I) (89) with various benzyl halides in the presence of carbon monoxide had proceeded via a carbonylation step to produce symmetrical dibenzyl ketones in high yields. Other researchers reported that potassium hexacyanodinickelate(I) underwent a disproportionation reaction in the presence of carbon monoxide to afford the yellow, carbonylcyanonickel(I) complex (161). In the acetone/water solvent system, this reaction occurs readily as:

\[
K_2[Ni_2(CN)_6] + 2CO \rightarrow K_2[Ni(CN)_4]^+ + K_2[Ni(CO)_2(CN)_2]^- \]

evidenced by the rapid discoloration (brick red fades to yellow-green) of the solution of complex. The reactive species is the carbonyl complex (161) which was postulated to perform the role shown in Scheme (XVII).

\[
K_2[Ni(CO)_2(CN)_2]^+ + R-X \rightarrow K_2[R-Ni(CO)_2(CN)_2]^+ + X \cdot CO
\]

\[
R-CO-R \rightarrow K_2[R-CO-Ni(CO)_{x+1}(CN)_2]^+
\]

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The principle disadvantage involved in these carbonyl insertion reactions lay in the fact that either the metal complex was consumed (i.e., non-catalytic) during the carbonylation or the reaction involved the transfer and manipulation of extremely dangerous (in terms of toxicological properties) reagents (e.g. nickel carbonyl). These problems notwithstanding, this class of reactions seemed to hold promise as an efficient mode of production for the symmetrical pyridyl ketones pertinent to this research.

In the hopes of utilizing and extending a carbonylation reaction in the ultimate synthesis of pyridyl ketones, a modified combination of reaction conditions and metal complex was designed. Since the reactions that were catalytic with respect to metal complex usually involved in aryl-mercury substrate as the source of the aryl groups in the ketonic product, the proposed modification would start with an appropriate bis(pyridyl)mercury compound. The problem of extreme toxicity could be at least tempered by reducing the physiological activity of any material that had to be transferred in setting up the reaction equipment. With potassium hexacyanodinickelate(I), the active "carbonyl-reagent" is generated in situ and no special precautions would be necessary for the handling of the starting materials. In the reported form, however, this reaction was non-catalytic, but it was hoped that the alteration of the starting aryl-halide to an aryl-mercury species would overcome this handicap. The overall postulated synthesis is shown in Scheme (XVIII).
Although the eventual intermediate needed was bis(6-bromo-2-pyridyl)mercury (91), Gilman et al. had reported previously the facile synthesis of bis(2-pyridyl)mercury. Their original procedure was repeated in order to gain practical knowledge of the reaction conditions necessary. When 2-pyridyllithium was treated with solid mercuric chloride at -20° C., bis(2-pyridyl)mercury was obtained in 40% yield. This reaction sequence was modified to our needs by using 2-bromo-6-lithiopyridine in place of the 2-pyridyllithium to afford the desired bis(6-bromo-2-pyridyl)mercury (91) as a stable intermediate. The carbonyl insertion reaction via potassium hexacyanodinickelate was carried out by bubbling carbon-monoxide through a stirred solution of bis(6-bromo-2-pyridyl)mercury (91) and potassium hexacyanodinickelate(I) (89) in acetone/water. The labile carbon-mercury bond allowed a relatively smooth carbonylation reaction to occur, albeit the over-all yield of desired ketone was
comparatively low (24%). In view of the moderate yield of the intermediate bis(6-bromo-2-pyridyl)mercury (91) combined with the relatively low conversion to the desired ketone, this sequence was not felt capable of competing with the methodology of ethyl chloroformate coupling. It did seem, nevertheless, to be a step toward improving the nature of typical carbonylation reaction procedures.

In order to have the materials available for the proposed synthetic approach through fragment \( \text{iii} \), the reaction sequence shown in Scheme XIX was carried out. As in the production of the symmetrical bis(pyridyl)ketones, the approach utilized involved the preliminary generation of 2-bromo-6-lithiopyridine (30) at low (-40° C) temperatures, followed by reaction with either 2,6-dicyanopyridine (48a), 2,6-dipicolinoyl chloride, or methyl 2,6-

Scheme (XIX)
pyridinedicarboxylate (48b). In the case of 2,6-dicyanopyridine, an acid hydrolysis of the intermediate bisimine (50a) is a necessary step; whereas, this procedure is unnecessary for 48b and 119. The di-imine (50a) hydrolysis step, surprisingly enough, requires rather vigorous and prolonged treatment with 5N mineral acid (usually HCl) to yield the final di-ketone (50b). Although product yield is comparable in all three of these reactions, the one chosen for routine use was the method involving the di-methyl ester as the coupling reagent since the synthesis of 48a was a time consuming process as illustrated in Scheme (XX), whereas the diester is stable and is not plagued with a later difficult hydrolysis step. These synthetic reasons are very obvious disadvantages compared to the preparation of the diester. Although the reagent dipicolinoyl chloride can be prepared in high yield from 162 and excess thionyl chloride, this reagent suffers from the practical aspects of working with corrosive, noxious acid chlorides. Especially since there is

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no advantage accrued from utilization of 48a, only a token trial of this pathway was carried out.

Pyridyl Ketone Ketals. At this stage, the ground-work was complete on the synthesis of pyridyl ketones in linear systems. The next step, however, was just as crucial in terms of the total project. This step involved the "simple" modification of the carbonyl moiety in such a manner as to protect this functional point of the substrate from nucleophilic attack during the necessary upcoming transmetallation step. The typical method for protection of the ketone was a standard ketalization via ethylene glycol and an acid catalyst. Although this procedure is only a simple "text-book", sophomore-level reaction, a literature survey afforded procedures which could be applied to our model systems. Bradsher and Parham

\[
\begin{align*}
\text{163} & \quad \text{CH}_3 \quad \rightarrow \quad \text{CH}_3 \\
\end{align*}
\]

had successfully made the transformation from 2-acetylpyridine (163) to methyl(2-pyridyl)ketone ketal (92). This work was repeated with only minor modifications and it was determined that the ketal could be prepared in approximately 30% yield by slowly distilling a mixture of 2-acetylpyridine, ethylene glycol, 2,2-dimethoxypropane, benzene, and p-toluenesulfonic acid through a Vigreaux column for several hours. With this comfortable glow of success lighting the way, analogous reactions were run on bis(2-pyridyl)ketone in order
to ascertain the necessary conditions for the eventual ketalization of the substituted pyridyl ketones.

To our dismay and consternation, no ketal was formed utilizing there reaction conditions. Not to be daunted, however, by bad tidings, the reaction was repeated with slight modifications (time for reaction, solvent/temperature, acid catalysts, methods of water removal) all to no avail! At this junction, alternate routes were examined and work by Lorette and Howard\textsuperscript{48} was modified to attempt the conversion, (Scheme XXI) where the protecting group was an acyclic ketal. These conditions were no more successful than the previous attempts with ethylene glycol and only un-reacted starting bis(2-pyridyl)ketone could be isolated.

Since sulfur compounds are often more nucleophilic than their oxygen relatives, mixtures of bis(2-pyridyl)ketone and propane-1,3-dithiol dissolved in toluene were treated with anhydrous hydrogen chloride. The only noticable result from this attempt was a marked

\[ \text{Scheme (XXI)} \]

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olefactory paralysis on the part of the experimenter! The ketone, on the other hand, was remarkably unimpressed by this alteration and, as before, was simply returned undaunted!

Since early efforts concentrated on protecting the pyridyl ketone group had run aground, the approach was altered in the direction of removal of the \( sp^2 \) carbonyl moiety and substituting in its place a \( sp^3 \) carbon. The and Peterson, in a preliminary communication, reported the reaction of dipyrazol-1-yl ketone (163) with acetone and metal catalysts to produce 2,2-dipyrazolypropane (165). Although no mechanism was given, mention was made that the metal complex (164) was readily isolable and, in fact, the reaction would not proceed in the absence of the metal salt. Furthermore, labeling experiments demonstrated conclusively that the "propane" backbone of the product was derived from the acetone solvent (other ketonic solvents afforded analogous aliphatic products).

This reaction sequence was adapted to the bis(2-pyridyl)ketone system in hopes of generating 1,3-bis(2'-pyridyl)propane (96), but
the reaction of the ketone with cobalt chloride and acetone afforded only unaltered bis(2-pyridyl)ketone after 24 hours at reflux conditions.

Some of the more notable modifications and synthetic procedures attempted in this search for a "protected" ketone are compiled in Table (IV). Some of these reactions were also attempted with phenyl-(2-pyridyl)ketone and bis(6-bromo-2-pyridyl)ketone as the reacting substrate in the forlorn hope that the failures previously discussed were unique to our model bis(2-pyridyl)ketone. Table (IV) reflects our total failure to effect this conversion under acidic conditions.

On the basis of this extraordinary refusal to react like sensible, normal ketonic materials, bis(2-pyridyl)ketone was treated with phenyllithium at -30° C. It was determined in this manner, that no matter how unlike normal ketones these pyridine substrates behaved with respect to ketalization-type reaction conditions, they were very willing to undergo nucleophilic additions of various organometallic reagents (Scheme XXII). This observation eliminated
<table>
<thead>
<tr>
<th>Method</th>
<th>Reference</th>
<th>R</th>
<th>Ketone (mmol)</th>
<th>Catalyst (mmol)</th>
<th>Protecting Reagent (mmol)</th>
<th>Solvent (ml)</th>
<th>Temp. (°C)</th>
<th>Time (hr)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td>H-</td>
<td>0.64</td>
<td>p-Toluenesulfonic acid (1.92)</td>
<td>Ethylene Glycol (1.84)</td>
<td>Benzene (70.0)</td>
<td>80</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>41</td>
<td>H-</td>
<td>0.64</td>
<td>p-Toluenesulfonic acid (1.92)</td>
<td>Ethylene Glycol (3.96)</td>
<td>Benzene (100)</td>
<td>80</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>45</td>
<td>H-</td>
<td>0.70</td>
<td>p-Toluenesulfonic acid (6.0)</td>
<td>Ethylene Glycol (100)</td>
<td>Toluene (70.0)</td>
<td>110</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>46</td>
<td>H-</td>
<td>0.64</td>
<td>p-Toluenesulfonic acid (6.0)</td>
<td>Ethylene Glycol (150)</td>
<td>Toluene (250)</td>
<td>110</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>E</td>
<td>45</td>
<td>H-</td>
<td>3.20</td>
<td>p-Toluenesulfonic acid (12.0)</td>
<td>Ethylene Glycol (150)</td>
<td>Xylene (50.0)</td>
<td>120</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>45</td>
<td>H-</td>
<td>3.20</td>
<td>p-Toluenesulfonic acid (12.0)</td>
<td>Ethylene Glycol (750)</td>
<td></td>
<td>195</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>E</td>
<td>47</td>
<td>H-</td>
<td>0.70</td>
<td>Anhydrous HCl</td>
<td>Ethylene Glycol (12.0)</td>
<td>Benzene (70.0)</td>
<td>90</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>E</td>
<td>47</td>
<td>H-</td>
<td>0.60</td>
<td>Anhydrous HCl</td>
<td>Ethylene Glycol (150)</td>
<td>Toluene (50.0)</td>
<td>110</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>48</td>
<td>H-</td>
<td>0.70</td>
<td>H₂SO₄ (10.0)</td>
<td>Ethylene Glycol (100)</td>
<td>p-Xylene (70.0)</td>
<td>130</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>F</td>
<td>48</td>
<td>H-</td>
<td>0.60</td>
<td>H₂SO₄ (10.0)</td>
<td>Ethylene Glycol (100)</td>
<td>Mesitylene</td>
<td>165</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>-</td>
<td>48</td>
<td>H-</td>
<td>0.60</td>
<td>p-Toluenesulfonic acid (4.0)</td>
<td>2,2-Dimethoxypropane (40)</td>
<td>Toluene (50.0)</td>
<td>110</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>-</td>
<td>48</td>
<td>H-</td>
<td>0.60</td>
<td>H₂SO₄ (10.0)</td>
<td>2,2-Dimethoxypropane (40)</td>
<td>Toluene (50.0)</td>
<td>110</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>-</td>
<td>48</td>
<td>H-</td>
<td>0.60</td>
<td>H₂SO₄ (10.0)</td>
<td>2,2-Dimethoxypropane (40)</td>
<td>Toluene (50.0)</td>
<td>110</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>-</td>
<td>48</td>
<td>H-</td>
<td>0.60</td>
<td>H₂SO₄ (10.0)</td>
<td>Triethyl orthoformate (30)</td>
<td>Ethanol (20)</td>
<td>110</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>-</td>
<td>49</td>
<td>H-</td>
<td>4.0</td>
<td>CaCl₂·6H₂O (5.0)</td>
<td>Acetone</td>
<td>Acetone (50.0)</td>
<td>60</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>46</td>
<td>Br-</td>
<td>0.05</td>
<td>p-Toluenesulfonic acid (4.0)</td>
<td>Ethylene Glycol (150)</td>
<td>Toluene (250)</td>
<td>110</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>46</td>
<td>Br-</td>
<td>0.20</td>
<td>p-Toluenesulfonic acid (6.0)</td>
<td>Ethylene Glycol (150)</td>
<td>p-Xylene (200)</td>
<td>130</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>48</td>
<td>Br-</td>
<td>0.30</td>
<td>H₂SO₄ (5.0)</td>
<td>Ethylene Glycol (75)</td>
<td>p-Xylene (100)</td>
<td>130</td>
<td>150</td>
<td>0</td>
</tr>
</tbody>
</table>
the possibility that these ketones could survive low-temperature treatments with alkyllithium reagents that could effect the transmetallation reaction needed for the cyclization sequence.

Scheme (XXII)

It was obvious that some alternate procedure was a prerequisite for the protection of the carbonyl moiety, therefore, a completely novel mode of reaction was attempted. In casting about for diverse reagents to affect this modification, the reagent 2-chloroethanol was visualized as a more reactive source than ethylene glycol itself. In experimental practice, prolonged treatment (ca. twenty hours) of bis(2-pyridyl)ketone with gently refluxing 2-chloroethanol in the presence of lithium carbonate (as an acid "trap" for the hydrogen chloride from the 2-chloroethanol) effected very respectable yields (45%) of the desired 2,2-bis(2^-pyridyl)-1,3-dioxolane (93). The product was readily characterizable via spectral methods and, in fact, was a highly crystalline, stable material. This reaction sequence was modified by substituting 2-bromoethanol as the reactive
reagent in order to enhance reactivity, shorten reaction times, and to safeguard against possible halogen exchange in the bromine-substituted analogues. With this simple modification, yields improved marginally to 50-55% and reaction times were decreased to a mere three to five hours. A list of related pyridyl ketone ketals prepared can be found in Table (V). This reaction sequence worked for all of the substrates containing a pyridine ring flanking the carbonyl group. Success was not forthcoming in systems lacking the nitrogen atom adjacent to the ketonic site (e.g., benzophenone, florenone).

To explain the reactivity (and lack of it in benzophenone, etc.) of these ketones with 2-haloethanol (Cl or Br) the following mechanism was proposed. (Scheme XXII). Apparently, the first step of the

Scheme (XXII)
Table (V); 2-Pyridyl Ketone Ketals

Prepared via Basic Conditions.

![Image of molecular structure]

<table>
<thead>
<tr>
<th>Compound</th>
<th>R-</th>
<th>Y</th>
<th>R'-</th>
<th>mp (°C)</th>
<th>% Yield</th>
<th>NMR, δ ppm; [-OCH₂CH₂O--; Pyr-H]</th>
</tr>
</thead>
<tbody>
<tr>
<td>93</td>
<td>H-</td>
<td>N</td>
<td>Pyr</td>
<td>164-166</td>
<td>50</td>
<td>4.10 (s); 7.0-8.0 (m, 6H),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.47-9.52 (m, 2H).</td>
</tr>
<tr>
<td>100</td>
<td>Br-</td>
<td>N</td>
<td>Pyr</td>
<td>117-117.5</td>
<td>13</td>
<td>4.12 (s); 7.0-7.85 (m, 6H),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.47-9.52 (m, 1H).</td>
</tr>
<tr>
<td>46</td>
<td>Br-</td>
<td>N</td>
<td>6-Br-Pyr</td>
<td>146-148</td>
<td>56</td>
<td>4.14 (s); 7.35-7.82 (m, 6H).</td>
</tr>
<tr>
<td>106</td>
<td>H-</td>
<td>N</td>
<td>6-Br-Pyr</td>
<td>190-190.5</td>
<td>48</td>
<td>4.12 (s); 7.30-7.80 (m, 9H).</td>
</tr>
<tr>
<td>169</td>
<td>H-</td>
<td>CH</td>
<td>Ph-</td>
<td>------</td>
<td>0</td>
<td>------</td>
</tr>
</tbody>
</table>

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reaction must involve a quaternization of the pyridine nitrogen with 2-haloethanol to afford the complex (166). The species should undergo an acid-base interaction with lithium carbonate to generate a zwitterion 167 which proceeds to effect a nucleophilic attack on the carbonyl group to yield intermediate (168). This intermediate can then cyclize via another nucleophilic displacement that generates the desired 1,3-dioxolane (93) and at the same time dequaternizes the pyridine ring. This proposed mechanism accounts for the lack of reactivity of the non-pyridyl type ketones, since no quaternization and subsequent orientation for the desired reaction sequence is possible with such substrates. To the best of my knowledge, this reaction is the first example of a base-catalyzed (at least non-acid catalyzed) ketalization.

The ketals prepared were then studied briefly for insight as to their reactivity and inclination toward hydrolysis in various media. By the expedient of merely varying temperatures, lengths of reactions, and acid strength it was qualitatively noted that these 1,3-dioxolanes were remarkably stable to mildly acidic conditions. In fact, concentrated mineral acid at refluxing conditions requires several hours before complete hydrolysis to the ketone is observed. This hydrolysis, although relatively vigorous, causes no apparent side reactions and the expected ketone is isolated in a quantitative yield.

**Metallation of the Protected Ketones.** The bis(6-bromo-2-pyridyl)-ketone ketal (46) was subjected to treatment with two equivalents of n-butyllithium in a diethyl ether solution at -20° C according to...
the procedure of Gilman and Spatz. Upon carboxylation and acid work-up, expected diacid (170) was not isolated but in fact only the pyridone product (106) was observed! The structure proof of (106) was achieved by reaction of picolinonitrile (80) and 2-bromo-

6-lithiopyridine (30) to afford, upon hydrolysis, (70%) 2-pyridyl-2-(6-bromopyridyl)ketone (88), which upon base-catalyzed ketallization gave ketal (100).

The next step of this independent synthesis involves the chemical transition from halide to pyridone. Several routes are available in the literature to allow this alteration. Rath, for example, in 1929, prepared 2-pyridones by subjecting the corresponding halo-pyridine to a rigorous treatment neat in alkali hydroxide. Wibaut and Haagman, in 1940, utilized strong mineral acids at elevated temperatures. Although normally only small amounts of the pyridones are isolated when the halopyridine is subjected to alcoholic hydroxide.
conditions, the corresponding pyridyl ethers are readily isolated as the predominant product from this reaction. Furthermore the same pyridyl ethers could undergo a subsequent cleavage to produce a pyridone product when treated with concentrated acid. Scheme (XXIV) summarizes the classical approaches for the desired transformation.

Scheme (XXIV)

Although the above routes had already been studied at great length by other researchers, all of these methods suffer from either being very vigorous (neat pyridyl halide—alkali hydroxide at elevated temperatures) and/or being necessary to subject the halide to prolonged, high temperature concentrated acid.

The transformation from halide (100) to suspected pyridone product, (106) however could not allow the functionality in the remainder of the molecule to be endangered (as it certainly would be under most of these cited reactions). Therefore, a modification was developed utilizing mild, basic conditions to allow the chemical transformation to occur.
Treatment of 2-halopyridines with potassium t-butoxide in refluxing t-butanol for twelve hours afforded not the t-butyl pyridyl ether as the isolated product, but the desired 2-pyridone was directly obtained in high yield (65-90%). A postulated mechanism for this transformation is illustrated in Scheme (XXV), wherein the reaction is envisioned as proceeding through the intermediary 2-pyridyl t-butyl ether (174), which undergoes a facile β-elimination to the pyridone (173). This reaction was attempted on several different halopyridines and the results are summarized in Table VI. As an additional point of interest, the reaction proceeds only with halopyridines in which the halogen is situated in the 2-position. This would be additional evidence supporting the mechanism proposed for this synthesis, since the ether forming at either the 3- or 4- position would not be able to undergo a concerted β-elimination to the pyridone.

When this new method was applied to the unsymmetrical ketal (100), the isolated product was in every respect identical to the product arising from the attempted carboxylation of bis(6-bromo-
### Table (VI)

**Improved Synthesis of 2-Pyridones**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Starting Halopyr.</th>
<th>R-X</th>
<th>mp(°C)</th>
<th>%Yield</th>
<th>nmr; δ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td>H- Br-</td>
<td></td>
<td>104-106</td>
<td>64</td>
<td>6.12-7.65 (m)</td>
</tr>
<tr>
<td>102</td>
<td>Cl- Cl-</td>
<td></td>
<td>127-128</td>
<td>66</td>
<td>6.62-7.58 (m)</td>
</tr>
<tr>
<td>103</td>
<td>Br- Br-</td>
<td></td>
<td>119-120</td>
<td>89</td>
<td>6.56-7.58 (m)</td>
</tr>
<tr>
<td>104</td>
<td>H- 3-Br-</td>
<td></td>
<td>-----</td>
<td>0</td>
<td>-----</td>
</tr>
<tr>
<td>105</td>
<td>H- 4-Cl-</td>
<td></td>
<td>-----</td>
<td>0</td>
<td>-----</td>
</tr>
<tr>
<td>106</td>
<td>4-[OCH₂CH₂O]</td>
<td>Br-</td>
<td>185-187</td>
<td>75</td>
<td>4.16 (OCH₂CH₂O, s, 4H), 6.38-8.65 (pyr-H, 7H).</td>
</tr>
</tbody>
</table>
2-pyridyl)ketone ketal. Thus the overall independent synthesis of this pyridone is illustrated in Scheme (XXVI).

Scheme (XXVI)

In order to understand the method of production of pyridone (106), a series of reactions were run in order to ascertain the method of formation. The conditions and reagents are summarized in Scheme (XXVII). Treatment of bis(6-bromo-2-pyridyl)ketone ketal (46) with n-butyllithium (10° mole excess) in diethyl ether at -20° for 1 hour, followed by carboxylation and hydrolysis, gave (20-40%) the single pyridone (106) along with starting ketal. The reaction was conducted under an argon atmosphere with complete exclusion of oxygen. Either utilization of better anion-stabilizing solvents, such as dimethoxyethane or tetrahydrofuran, or reduced reaction temperatures (-60° to -90°) suppressed formation of pyridone (106) in favor of the products arising from the lithiated ketal. In

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Scheme (XXVII)

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order to ascertain the position(s) of lithiation, ketal (46) was subjected to a five-fold excess of n-butyllithium in diethyl ether at -60°, then quenched with D\textsubscript{2}SO\textsubscript{4}/D\textsubscript{2}O. Isolation of ketal (1\textsubscript{179}) established the intermediacy of the trilithiated ketal (1\textsubscript{179}) and spectral analyses of the recovered starting dibromoketal indicated that deuterium had been incorporated specifically into the 3-position (i.e., 1\textsubscript{108}).

A possible mechanism that will explain the formation of the products arising from these tagging experiments is outlined in Scheme (XXVIII). It is apparent that the actual conformation preferred by the ketal is that shown by (466). In this orientation, one pyridine ring is situated such that a normal trans-metallation reaction occurs, but in the other, the lithium reagent is complexed by the 1,3-dioxolane ring and is situated at a location remote from the remaining bromine on the substrate. This pre-intermediate complex can then merely selectively abstract a hydrogen from the 3-position of the pyridine nucleus to give rise to the intermediate (1\textsubscript{175}). At warmer temperatures (ca. -20° C), this species undergoes a facile 1,4-elimination of lithium bromide to produce the yne-enenitrile intermediate (1\textsubscript{176}). Since related acyclic nitriles have been shown to cyclize under dilute acid conditions after only several minutes to afford dehydropyridines, it should not be surprising that under standard work-up procedures one would obtain the substituted hydroxypyridine (1\textsubscript{178}). In solution, this species would be expected to exist as the pyridone (1\textsubscript{106}) tautomer observed.
At reduced temperatures (-60° C), the intermediate (175) gives rise to the trilithiated ketal (179) by a subsequent normal metal-halogen exchange. This species will be hydrolyzed by H+/H₂O or D+/D₂O to afford the observed and isolated products (110). Although no exact analogies exist for this mechanism, similar fragmentation reactions of the pyrimidine nucleus have been studied (Scheme XXIX) by H. C. van der Plas, wherein not one but two fragmentation reactions complete with subsequent cyclizations occur. In this sequence, what appeared to be a simple nucleophilic displacement of halide via a primary amine (path a) does not account for the observed product. It was shown that this reaction proceeded by a preliminary addition of the amine at the 2-position of the pyrimidine nucleus to afford adduct (180) which undergoes a first ring fission to give

Scheme (XXIX)
the linear nitrile (181) that, upon ring closure, produces the nucleotide (182). This material readily adds an additional amine molecule to afford (183) which can participate in a reversible second ring opening to (184). Compound (184) finally recylizes to give the substituted pyrimidine (185).

More recently, Utimoto and co-workers have described a pyridine ring cleavage that results in dienenitriles. The highlights of this reaction sequence are displayed in Scheme (XXX) where 2-bromo-6-pyridyllithium (30) was treated with a trialkylborane (186) to give the trialkyl pyridylborate (187). The borate was proposed to undergo a concerted reaction wherein an alkyl shift produced an acyclic nitrile (188) with the loss of a bromide ion. This linear nitrile-diene-borane (188) was subjected to an acetolysis procedure which allowed the final isolation of the dienenitrile (189).
One final example of pyridine fragmentation reactions is given in Figure (VI) in which Kasai and McLeod reported in 1972 that they had successfully trapped the 3-pyridyl radical (190) in an argon matrix and, on subsequent uv. irradiation, generated the

Figure (VI)

\[
\begin{array}{c}
\text{190} \\
\text{\textbullet} \\
\text{\textbullet}
\end{array} \rightarrow
\begin{array}{c}
\text{191} \\
\text{\textbullet} \\
\text{\textbullet}
\end{array}
\]

ynene-imine radical (191). The studies on this system involved esr work and obviously did not involve isolation of the linear system.

To return momentarily to the proposed mechanism of the herein reported specific metallation, fragmentation, and rearrangement of a pyridyl ketal, Grob, in his excellent review of fragmentation reactions, lists "Nitrile-Forming Fragmentations" as a sub-heading. He further devides this sub-topic into two classes dealing with \(a-b-C=N-x\) and \(a-b-N=C-x\) type systems. The examples typifying these subclasses are various second order Beckmann reactions (more appropriately, a Beckmann fragmentation), and the general reaction is depicted in Scheme (XXXI). The substrates are generally modified ketoximes (192) where the hydroxyl group has been converted into a very good leaving group by protonation, esterification, etc. This reaction would seem to fit nicely into a modified \(a-b-C=N-x\) classification (really a \(b-C=N-x\)), but no examples were cited for the
alternate a-b-N=C-x sub-division. Figure (VII) illustrates how the mechanism of the pyridone formation could actually be considered a good illustration of this type of fragmentation.

Further work should be directed toward assigning rotational parameters for the bis(6-bromo-2-pyridyl)ketone ketal (46) and toward isolation and/or observation of the intermediate ynenenitrile (176) proposed in this mechanism. The scope of this research however was more directly involved in heteromacrocyle synthesis so attention was redirected along these lines.

Cyclization to macrocyclic ketones. The initial synthetic route to heteromacrocyclic ketones was designed in such a manner that the last step involved the dimetallation of bis(6-bromo-2-pyridyl)ketone ketal to form 47 which was allowed to condense with methyl 2,6-pyridine-decarboxylate (48b). This sequence was carried out at rigorously...
controlled temperatures (-90° C) in tetrahydrofuran in order to prevent the selective metallation reaction already discussed. After an

\[
\text{Br} \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{Br} \quad \text{nBuLi} \quad \text{THF} \quad -90^\circ \text{C} \quad \text{Li} \quad \text{N} \quad \text{O} \quad \text{Li} \quad 40
\]

acid hydrolysis, the desired macrocycle 40 was not forthcoming but instead the tetraketon (118) was isolated. This linear compound was identified and characterized by its spectral properties and especially by its analysis and molecular weight determination.

Since this problem had at least partially been foreseen, the precursor for an alternate route had been synthesized. The diketone diketal (51) had been prepared and this compound was treated under exactly analogous lithiation conditions to afford the di-metallated species (193). This intermediate was treated with ethyl chloroformate and worked-up as in the previous reaction. Although, as before, a sizable fraction of the product was a linear "dimer" (116), [as

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demonstrated by the molecular weight (vapor pressure osmometry), elemental analysis, and complex aromatic region of its pmr spectrum), a small amount (3.5%) of the desired 1,3,5-tri[2,6]pyridacyclohexaphane-2,4,6-trione (40) was isolated. This compound was identified by its characteristic pmr spectrum consisting of a doublet at $\delta$ 7.60 for the 3,5-pyridine hydrogens and a triplet at $\delta$ 7.35 corresponding to the 4-pyridine hydrogen. The simple line pattern unequivocally demonstrates the high degree of symmetry that would be expected for
a planar, cyclic molecule of this type! Further evidence for this assignment was collected by vapor pressure osmometry, which allowed the measurement of the molecular weight to within 2.8\% of the calculated value. The compound was sparingly soluble in benzene and chloroform and was a stable, crystalline solid. Studies will be continued on a larger scale in order to allow further experiments with this interesting ligand.

During the course of preparing the diketone diketal (51) for the former cyclization reaction, an interesting side reaction was observed. The reagent 2-bromoethanol was extremely difficult to remove after the desired ketalization process was completed. Since 2-chloroethanol is considerable more volatile, the reaction was repeated with this reagent to compare product ratios and ease of purification. This reaction had been neglected with the bromine-substituted pyridyl ketones due to the potential for undesirable halogen exchange.
Although the net reaction is the same for both 2-chloro- and 2-bromo-ethanol, reaction was completed in 3-5 hours, the former required 20-30 hours to obtain the same result. At the end of the much longer reaction time, not only the expected diketal (51) was isolated, but also, the macrocycle (114). This material possessed an extremely complex aromatic region in the nmr and two singlets assigned to the methylene hydrogens of the "dioxolane" chromophore. This initially created a good deal of consternation, since all of the other poly-pyridyl ketals thus far studied always exhibited a unique singlet for these protons! After a rigorous acid hydrolysis, there remained a singlet at δ 4.23, but i.r. analysis indicated the presence of a carbonyl group (1680 cm⁻¹) in the molecule. This spectral information may be explained (and in fact is complemented by vapor phase osmometry measurements, elemental analysis, etc.) by assigning the structure (115) to this compound. The "so-called" dioxolane moiety remaining after the hydrolysis [and the group accounting for the "extra" singlet in the ketal (114)] is actually the "ether" methylene protons and not a dioxolane-type signal at all. The diketone (115) is also planar, as evinced by the 8-bond coupling from H₁ to H₄ and from H₂ to H₅ as well as the 6-bond long-range coupling from H₂ to H₃. A first order analysis is possible for the 100 MHz pmr spectrum, but simple decoupling experiments were performed that showed unequivocally the extensive long-range coupling already discussed. The apparent reaction mechanism for this transformation would involve polymerization of the 2-chloroethanol to afford poly-ethyleneoxide (194). This low molecular weight polymer could fragment and produce ethylene glycol dianion (195) units which
would undergo a nucleophilic displacement reaction with the bromo-

\[
\begin{align*}
\text{Cl-CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}^- & \quad \text{Cl-CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}^- \\
\text{Cl-CH}_2\text{CH}_2^- & \quad \text{Cl-CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}^- \\
& \quad \text{O-CH}_2\text{CH}_2^-\text{O}^- \\
\end{align*}
\]

pyridyl units as shown in Scheme (XXXII).

An analogous reaction has been successfully carried out by

Scheme (XXXII)

Newkome, et al. to generate a diverse set of macrocycles and linear compounds. Treatment of 2,6-dibromopyridine with dianions of di-

\[\text{ethyleneglycol (196)}\] allowed the synthesis of the compounds shown in

Scheme (XXXIII)

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Another skeletal alteration envisioned was that of the 2,2'-bipyridyl macrocycles (54) illustrated in Figure (VIII). In order to ascertain reactivity and spectral parameters, model substituted bis-pyridyls were synthesized. Early attempts in this work were patterned after definitive publications by H. J. denHertog and B. Mulder, wherein the photochemical induced coupling of 2-bromopyridine (197) to generate 2,2'-bipyridyl was described. On attempts to repeat this work, this researcher was able to isolate only relatively low yields (<30%) of bipyridyl. It had been envisioned (Scheme XXXIV) that might allow facile halogenation of these bipyridyl systems, although

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no exact precedent had been set for this halogenation procedure. Complex (126) was readily prepared in 85% yield by treating the 2,2'-bipyridyl with sulfur dichloride. The desired salt precipitated and could be efficiently collected by a simple filtration. Although the preparative procedures to this stage had been easy, work with this complex proved very difficult. Solubility was very low in any solvent that did not react with the material, and pressure or heating decomposed the sample. Differential Thermal Analysis and Thermal Gravimetric Analysis indicated no evidence for the thermal loss of hydrogen sulfide even at extreme temperatures (>500° C). Instead, the sample sublimes and/or partially decomposes to unidentified products. Although no further direct work was attempted on this material, preliminary biological screening indicated potential fungicide properties.

Alternate routes were necessary for the production of halogenated bipyridyl. Early work by Burstall \(^{63}\) (Scheme XXXV) included the preparation of dibromobipyridyl (127) via a vapor-phase bromination procedure, which resulted in a mixture of mono- and di-brominated bipyridyl.

Scheme (XXXV)
This procedure was not attempted in light of the low yields, complex product distribution, and elevated temperature reaction conditions.

During the previously described experimental work on the pyridyl-ketone series, the reaction of substituted pyridyl mercury compounds with the carbonyl-complex of potassium hexacyanodinickelate was investigated in the hopes of eliciting a carbonyl insertion reaction to generate symmetrical ketones. During this work, various solvent combinations and physical conditions (Scheme XXXVI) were studied in the hope of optimizing the carbonyl insertion. In some of these reactions, small amounts of bipyridyl products were isolated and further studies were now aimed at increasing their product yields.

Scheme (XXXVI)

\[
\begin{align*}
\text{Br} & \quad \text{N} & \quad \text{Hg} & \quad \text{Br} \\
\text{Br} & \quad \text{N} & \quad \text{N} & \quad \text{Br} \\
\text{Br} & \quad \text{N} & \quad \text{O} & \quad \text{N} & \quad \text{Br} \\
\text{Br} & \quad \text{N} & \quad \text{N} & \quad \text{Br} & \quad \text{Br}
\end{align*}
\]

The observed product distribution is in accord with similar systems studied by Okamoto and Shimakawa. These researchers reported reactions between benzyl halides and the nickel complexes as illustrated in Scheme (XXXVII). The reaction can, however, proceed by the alternate pathway (b), when carried out in the absence of a carbon-monoxide atmosphere, to produce the coupled bibenzyl compounds shown. The
mechanism proposed to explain the formation of these products is illustrated below.

Scheme (XXXVII)

Although not strictly analogous to these systems, a similar mechanism can account for the product distribution observed in Scheme (XXXVI). The carbon-mercury bond in bis(6-bromo-2-pyridyl)mercury (\(\text{K}_2[\text{Ni} \text{II} \text{CN})_6]\)) is very labile (a necessary condition, since mention was made by Hashimoto, et al.,\(^{97}\) that alkyl halides reacted at a very reduced rate compared to their benzylic halides). This increased bond sensitivity allowed, in the case of the water/acetone solvent system, the carbonyl insertion reaction with subsequent formation of the observed pyridyl ketone. In DMF, the \(\text{K}_2[\text{Ni(CO)}_2\text{(CN)}_2]\) complex does not form readily due to low solubility of carbon monoxide (experimentally, one sees no appreciable fading of the brick-red color arising from \(\text{K}_2[\text{Ni} \text{II} \text{CN})_6]\)).
In this modification then, product must arise from the decomposition of the complex (199), and the material in our case would be a bipyridyl.

When the reaction mixture was exposed to u.v. irradiation (with no carbon monoxide), yields were slightly enhanced so that c. 30% of the theoretical amount of 6,6'-dibromo-2,2'-bipyridyl was isolated.

Although several methods for production of dibromobipyridyl have been outlined, synthetic yields have not been encouraging. While this work was underway, R. H. Holm and co-workers announced a new procedure wherein oxidative coupling of bromolithiopyridine by cupric chloride afforded the desired 6,6'-dibromo-2,2'-bipyridyl (127) in high yield. This work was repeated and afforded a 56% yield of the (127).

In order to study the lithiation of this species, the reaction between n-butyllithium and (127) was performed at -90°. Treatment of the dilithio intermediate (200) with picolinonitrile (80) afforded (45%) 6,6'-dipicolinoyl-2,2'-bipyridyl after acid hydrolysis of the diimine (201).

An analogous reaction utilizing ethyl chloroformate (202) in place of picolinonitrile was studied and a series of macrocyclic bipyridyl ketones was isolated. Although the pmr spectrum was complicated and a first-order analysis was not possible for these compounds---the chemical shifts measured corresponded exactly with the
values obtained for the model system 6,6'-dipicolinoyl-2,2'-bipyridyl (1,28). An obvious difference expected and observed was the absence of 6-pyridine hydrogen signals in the spectra of the cyclic compounds. The i.r. spectra again corresponded closely with the model compound with carbonyl absorptions being recorded at 1680 cm$^{-1}$ for both species. The molecular weights for these macrocycles were determined by vapor pressure osmometry on dilute benzene solutions. Due to insolvability, satisfactory elemental analyses for the $n = 4$ and $n = 5$ homologues were unobtainable although all other measureable information was as expected for the cyclic systems.
These compounds can be easily named via proposed methods of Th. Kaufmann (a group-substitution nomenclature) or Vogtle and Neumann (a "pane" nomenclature). The alternative system, of course, is the cumbersome IUPAC nomenclature; the specific nomenclature of each of these systems can be located in Appendix (I).

Alternate Macroyclic Systems Related to sp² Bridged Poly-2,6-pyridines. Since the observed yields of the triketone macrocycle (40) were low, an alternate route to a modified skeletal

\[
\text{structure (203) was envisioned (Scheme XXXVIII). All of the precursors involved in this pathway were well known, so little effort was required to prepare for the final cyclization step. Preliminary studies were directed toward the repetition of the work of deLaMare, et. al. where quinoline was brominated directly to afford 8-bromoquinoline (123). In the hands of this researcher, this pathway afforded a mixture of 5- and 8-bromoquinoline. Since this reagent was the direct precursor for the attempted cyclization, and since these two isomers are difficulty separable via a fractional crystallization sequence, an alternate synthesis to 8-bromoquinoline was utilized.}
\]
8-Hydroxyquinoline is commercially available and methods were known that would allow a net substitution of a bromine atom for the hydroxyl functionality (via 8-aminoquinoline and a subsequent Sandmeyer reaction), therefore this procedure was utilized. Woroshtzow and Kogan had successfully synthesized 8-aminoquinoline (123) from 8-hydroxyquinoline (204) via a high-pressure reaction with ammonium sulfite and ammonium hydroxide. Their work was repeated and 8-aminoquinoline was realized in 71% yield. A typical Sandmeyer reaction was utilized to transform 8-aminoquinoline to 8-bromoquinoline (123) in 50% yield and the resultant halogenated precursor (123) was lithiated at -40°C with n-butyllithium. This intermediate was warmed to reflux conditions to attempt to undergo addition of the organolithium reagent across the 1,2-CN bond followed by elimination of LiH and thus rearomatization of the heterocyclic ring. After hydrolysis, the only products isolable were quinoline and unreacted 8-bromoquinoline. A product balance was unobtainable and the re-
remainder of the material was an ill-defined, intractable resin. This sequence was abandoned for the present!

**Pyridyl olefins.** Preliminary studies were undertaken on the alteration of a carbonyl moiety in order to lay down the necessary ground-work for expansion of the macrocyclic ketone series. The alteration studies is illustrated in Scheme (XXXIX), where the carbonyl has been "exchanged" for an exocyclic methylene group. This modification was of importance not only because it would give a series of readily formed derivatives of the ketonic macrocycles, but even more due to the fact that this change would drastically alter the electronic nature of these compounds. Whereas the carbonyl group is an electron-withdrawing substituent, the alkene moiety would not exhibit this effect! The typical reagent for making such an alteration would be the Wittig reagent derived from methyltriphenylphosphonium bromide. A standard preparation of this onium salt was realized in 76%.

The model substrate selected for use in developing this technique was bis(2-pyridyl)ketone. The reaction proceeded in a routine manner and the only difficulty encountered was that of isolation of the final alkene. The purification method, that was suitable for all of the substrates attempted, was that of preparative
layer chromatography and multiple elution techniques. The over-all yields obtained were of the order of 15-20%. This was considered to be rather detrimental to this method, although optimization of reaction parameters was not attempted.

The structure assignment could readily be made on the strength of the characteristic pmr signal for the CH$_2=$ in these compounds. For 1-phenyl-1-(2'-pyridyl)ethene (131), two singlets were observed since the hydrogens are in fact diasteriotopic. In the other compounds [1,1-bis(2'-pyridyl)ethene (132) and 1,1-bis-2'-(6'-bromo-pyridyl)ethene (133)] the CH$_2=$ signal is observed as a simple singlet. The aromatic region of the nmr is similar to that observed in the related pyridyl ketone series.

This sequence should be expanded to the next logical step shown in Scheme (XL). For many of the macrocycles covered in this dissertation, this simple reaction should give an elegant series of derivatives.
Synthesis of Pyridinecarboxaldehydes. In conjunction with the work involved in the synthesis of pyridyl macrocycles, it was desirable to have a convenient method for the preparation of 2-pyridinecarboxaldehydes. Oguro and Tsuchihashi described the use of methyl methylsulfinyl methylsulfide (205) in preparation of alkyl aldehydes [Scheme (XLI)]. This method was adapted as shown in Scheme (XLI), where the anion of (205) was allowed to participate in a nucleophilic attack on simple halogenated pyridines in order
<table>
<thead>
<tr>
<th>2-Halogenopyridine</th>
<th>Reaction time (hr.)</th>
<th>Temp. (°C)</th>
<th>% yield</th>
<th>Compound m. p. (b.p.) (°C/min Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>24</td>
<td>30</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>2-Br</td>
<td>48</td>
<td>30</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>2-Cl</td>
<td>24</td>
<td>30</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>6-Br</td>
<td>24</td>
<td>30</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>6-Cl</td>
<td>1</td>
<td>reflux</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>48</td>
<td>30</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>3-Br</td>
<td>48</td>
<td>30</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE (VII).**

<table>
<thead>
<tr>
<th>Reaction time (hr.)</th>
<th>Temp. (°C)</th>
<th>% yield</th>
<th>Compound m. p. (b.p.) (°C/min Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Br</td>
<td>181-182/760</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Cl</td>
<td>&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Br</td>
<td>77-78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Cl</td>
<td>69-70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>95-97/15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-C1</td>
<td>77-78/12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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to generate the 2-bis(methylthio)methylpyridine S-oxide (206). Although the planned route involved an acid hydrolysis of (206), on purification (via distillation) the intermediate (206) decomposed to afford the aldehyde directly. [Scheme (XLII)] A series of halogenated pyridines [Table (VII)] was examined to determine the scope of this reaction and it was discovered that: (a) Br$^-$ was displaced more rapidly than Cl$^-$, (b) only one halogen per pyridyl ring was easily substituted, and (c) the 2- and 4- positions are more reactive than the 3-position.

A mechanism postulated to explain the over-all reaction is depicted in Scheme (XLIII). This mechanism requires a preliminary
formation of the S-oxide (206) which thermally rearranges to an unisolated intermediate (207) via a thermal sulfur to oxygen 1,2-
migration (probably an ionic decomposition). Finally, an elimination of dimethyl disulfide affords the isolated pyridyl carboxaldehyde (208). The prediction that dimethyl disulfide would be evolved was born out by experimental observation; this material was trapped and identified by comparison to an authentic sample!

The thio-acetal (206) can be hydrolyzed in acidic media but no particular advantage seemed to arise from this method of aldehyde generation. If acid hydrolysis were preferred in some special system, addition of mercuric chloride to the hydrolysis mixture facilitated the reaction.

**Macrocycles with Multiunsaturation.** Figure (IX) illustrates yet another class of pyridyl macrocycles. As mentioned in the introduction section, pyridyl cumulenes are currently unknown in the chemical literature. A common route to aryl cumulenes is the one through aryl acetylene diols.

![Figure (IX)](image_url)
The method of Nahon and Day,\textsuperscript{101} was utilized to prepare acetylene-bismagnesium bromide. The yields of this di-Grignard reagent were typically above 60%, although a fair amount of mechanical difficulty was encountered in this preparation. The acetylene had to be added to the prepared methyl magnesium iodide via an open tube and constant monitoring of the equipment was mandatory due to continual "plugging" of the gas inlet with the insoluble Grignard reagent. The acetylene-bismagnesium bromide was treated with benzophenone after the method of Sisenwine and Day\textsuperscript{26} to gain experience in making transformations in this series. The 1,1,4,4-tetraphenyl-2-butyne-1,4-diol (61c) (obtained in 79% yield) was a highly crystalline, easily handled material. This reaction was repeated with phenyl 2-pyridyl ketone (85) and bis(2-pyridyl)ketone (82) [Scheme (XLIV)] to afford (32.9%) 1,4-diphenyl-1,4-di(2-pyridyl)-2-butyne-1,4-diol (61a,b) and (33%) 1,1,4,4-tetra(2-pyridyl)-2-butyne-1,4-diol (61d), respectively. Extreme care in handling the two butyne-diols (61a,b) and (61d) must be exercised because both are extremely sensitive to acid-catalyzed rearrangements. This, no doubt, partially accounts for the relatively poor yields of these diols compared to that of 1,1,4,4-tetraphenyl-2-butyne-1,4-diol.

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Newkome and Martin\textsuperscript{27} demonstrated that diol (61) undergoes a facile rearrangement to 3-hydroxy-4,9a-diphenyl-4-\(2^{'-}\)-pyridyl-4H-quinolizin-1(9aH)-one (66) [Scheme (XLVI)]. This rearrangement was shown to occur in ca. 90\% even in gently refluxing ethanol. All previous attempts to convert this diol to the cumulene via reagents such as stannous chloride in ethereal hydrogen chloride or phosphorous tribromide in pyridine had given rise exclusively to the rearrangement product (66) along with traces of several proposed intermediates.

Preliminary work with diol (61d) [a new compound in its own right] suggested that an even more facile rearrangement process might be occurring to an analogous product.

Although easily rearranged, these precursors were tempting starting materials due to their ready availability via short synthetic pathways; therefore, a search was undertaken for a mild reagent that could affect this didehydrogenation step. Hanafusa, et. al.\textsuperscript{28} had recently used diphosphorous tetraiodide to generate 1,4-dienes by a homo-1,4-elimination. It was considered feasible, then, that this reagent might be utilizable for the reaction step to generate the pyridyl cumulenes.

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Historically, $P_2I_4$ was first prepared by Germann and Traxler from elemental white phosphorous and iodine in refluxing carbon disulfide. Since this preparation dealt with relatively large amounts of highly hazardous reagents, an alternate synthesis of $P_2I_4$ was utilized. Feschenko and Kirsanov indicated that the reaction between phosphorous tri-iodide and diethyl ether gave an unstable oxonium salt (209) which would disproportionate as shown in equation (I). Furthermore, the reaction between $PCl_3$ and $KI$ would afford $PI_3$ in situ. The total synthesis for $P_2I_4$ then is depicted in Scheme (XLVII). The purity of diphosphorous tetraiodide obtained is very good and the yield is ca. 75% when prepared in this manner. Note should be taken that the material isolated must be handled with reasonable caution and should be stored under argon and in a freezer!

Treatment of acetylene diols (61a,b), (61c), and (61d) with $P_2I_4$/pyridine resulted in an instantaneous conversion of the diol.
into the corresponding cumulenes (62a,b), (62c), and (62d). These compounds are readily identified by examination of the u.v. spectrum for the characteristic absorptions at ca. 420-430 nm. This absorption is absent in the quinilizinone system and allowed us to verify the formation of cumulenic systems with ease!

Scheme (XLVII) illustrates the compounds generated in this manner. This reagent allowed total exclusion of the previously discussed quinilizinone (66). The isomeric cumulenes (62a,b)
were separated by preparative thick-layer chromatography with exclusion of light to afford E- (62b) [Rf 0.35] and z-(62a) [Rf 0.30]. Thermally, z-(62a) was transformed into the thermodynamically more stable E- (62b); photochemically, either pure z- or E- (62) isomerized to ca. a 1:1 mixture. The assignments of configuration were based on the systems [Diagram (I)] bis-(2-nitrobiphenylene) (210) and 1,4-diphenyl-1,4-di(2-nitrophenyl)butatriene (211).

Diagram (I)

The tetrapyridyl butatriene (62d) was extremely difficult to handle. Although it can be carefully chromatographed in the dark and presence of an inert atmosphere, all attempts to isolate pure 62d have to date resulted in complex mixtures of decomposition products. This extreme lability of pyridyl cumulenes emphasizes the diminished central double bond character of butatrienes when multiple electron-withdrawing groups (i.e., pyridyl) are attached.

Preliminary studies have been carried out on the catalytic hydrogenation of these butatrienes [Scheme (XLVIII)] in an attempt to generate tetra-aryl 1,3-butadienes. Due to an injudicious choice

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Table (VIII)

Tetrasubstituted Butatrienes:
Geometric Isomerism and Physical Properties.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Geometric Isomer</th>
<th>Reference</th>
<th>m.p. (°C)</th>
<th>Color</th>
<th>U.V. (ε)</th>
<th>Rf</th>
</tr>
</thead>
<tbody>
<tr>
<td>62c</td>
<td>--</td>
<td>26</td>
<td>236-237</td>
<td>yellow</td>
<td>420 μm (2.74 x 10^4)</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>277 μm (2.26 x 10^4)</td>
<td></td>
</tr>
<tr>
<td>211a</td>
<td>Z</td>
<td>101</td>
<td>213-213.5</td>
<td>orange</td>
<td>426 μm</td>
<td>0.017</td>
</tr>
<tr>
<td>211b</td>
<td>E</td>
<td>101</td>
<td>212-212.5</td>
<td>red</td>
<td>426 μm</td>
<td>0.012</td>
</tr>
<tr>
<td>225a*</td>
<td>Z</td>
<td>102</td>
<td>142-143</td>
<td>---</td>
<td>332 μm (1.63 x 10^4)</td>
<td>-----</td>
</tr>
<tr>
<td>225b*</td>
<td>E</td>
<td>102</td>
<td>127-128</td>
<td>---</td>
<td>321 μm (2.02 x 10^4)</td>
<td>-----</td>
</tr>
<tr>
<td>62a</td>
<td>Z</td>
<td>---</td>
<td>143-144</td>
<td>yellow</td>
<td>430 μm (3.06 x 10^4)</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>276 μm (2.12 x 10^4)</td>
<td></td>
</tr>
<tr>
<td>62b</td>
<td>E</td>
<td>---</td>
<td>141-143</td>
<td>red</td>
<td>&quot;</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*1,4-di-t-butyl-1,4-diphenylbutatriene; a[cyclohexane/ethyl acetate (4:1)]; b[cyclohexane].
of catalysts (10% Palladium on carbon) a complete hydrogenation was apparently effected with the final product isolated being the completely saturated butane (212).

Scheme (XLVIII)

Work is continuing to expand this portion of the project in the direction of actually incorporating the cumulene moiety in the backbone of the previously mentioned heteromacrocycle (70).

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SUMMARY AND CONCLUSIONS

One of the long-range goals of this research project involved the ultimate fabrication of specific metal chelates capable of distinguishing a small, select group (or ultimately a unique species) of a cationic nature from all other possible cations. This goal was not attained, nor even seriously approached. Advances have been made, however, in the direction of increasing our synthetic capabilities and in the over-all understanding of the chemistry of multi-hetermacrocycles.

The initial short-range goals of the synthesis and structure elucidation of 2,6-pyridine containing carbonyl bridged macrocycles has been more satisfactorily attained. The approach to these systems originally involved the utilization of 2-bromo-6-lithio-pyridine to afford, after carboxylation, 6-bromo-2-picolinic acid. The standard methods to generate substituted nitriles (i.e. treatment with thionyl chloride to generate the 6-bromo-2-picolinoyl chloride; ammonolysis to give 6-bromo-2-picolinamide; and a second treatment with thionyl chloride to effect a dehydration to ultimately afford 6-bromo-2-picolinonitrile) was rendered unacceptable due to a halogen exchange occurring either during the acid chloride formation or during the dehydration step. This unfortunate trans-halogenation resulted in the production of a mixture of 6-bromo- and 6-chloro-2-picolinotrile. Since a subsequent step involved a lithiation reaction, and since pyridylchlorides undergo this transformation only slowly (if at all), this reaction sequence was abandoned as it stood.
An alteration consisting of substitution of phosphorous tribromide for the thionyl chloride in the preparation of the picolinoyl halide satisfactorily allowed the ultimate synthesis (after ammonolysis) of the intermediate 6-bromo-2-picolinamide. The final dehydration to 6-bromo-2-picolinonitrile was achieved via treatment with phosphoric anhydride.

The reaction between various 2-lithiopyridines and 2-picolinonitriles allowed a facile synthesis of bis(2-pyridyl)ketone, bis-2-(6-bromopicolinoyl)pyridine. By substituting various non-pyridyl-nitriles in this reaction sequence, the following ketones were also prepared: phenyl(2-pyridyl)ketone, phenyl-2(6-bromopyridyl)-ketone, and 6-bromo-2-acetylpyridine. This route, therefore, is very valuable for the synthesis of unsymmetrical as well as symmetrical pyridyl ketones.

A reaction sequence developed by R. H. Holm and co-workers allowed the efficient production of symmetrical pyridyl ketones. This technique involved a coupling reaction between two moles of a pyridyllithium reagent and ethyl chloroformate. This unaltered procedure was utilized to synthesize bis(2-pyridyl)ketone and bis-2-(6-bromopyridyl)ketone. Modifications were attempted wherein the ethyl chloroformate was replaced by cyanogen bromide and pyrocatechol dichloromethylene ether. After hydrolysis in acidic media, both of these modified reactions afforded traces of the desired symmetrical ketone. Although these modifications were not studied extensively enough to optimize the yields of ketone product, it was encouraging to note some product formation. This was
especially true in the case utilizing the pyrocatechol dichloromethylene ether as the active "coupling" reagent, since the immediate product (prior to hydrolysis) would be the "ketal". If yields could be improved, this could be advantageous when the ultimate goal is a carbonyl synthon that would be inert to nucleophilic additions! Further work will be expended to develop this potential synthetic tool.

It had been demonstrated that various transition metal carbonyl compounds (e.g. Ni(CO)$_4$, Co$_2$(CO)$_8$) would produce a carbonyl insertion reaction with some aryl halides to yield symmetrical aryl ketones. The complex $K_2[Ni(CO)_2(CN)]$ was studied in an attempt to produce similar results with pyridyl analogues. Although pyridyl-halides gave no reaction, bis(6-bromo-2-pyridyl)mercury was successfully carbonylated to afford bis(6-bromo-2-pyridyl)ketone in moderate yield.

All known methods for protection of the previously mentioned pyridyl ketones via acid catalyzed ketalization were unsuccessful. However, the ketones readily underwent nucleophilic addition, as shown by the synthesis of bis(2-pyridyl)phenylcarbinol and tris-(2-pyridyl)carbinol brom bis(2-pyridyl)ketone and either 2-pyridyl-lithium or phenyllithium, respectively.

A novel base-catalyzed ketalization procedure was developed whereby bis(2-pyridyl)ketone was gently refluxed in 2-chloroethanol in the presence of excess lithium carbonate to afford (45%) the desired 2,2-bis(2'-pyridyl)-1,3-dioxolane. Substitution of 2-bromoethanol in the place of 2-chloroethanol shortened reaction times from ca. 30 hours to five hours and safeguarded against possible
halogen exchange in the bromine-substituted ketones. The ketals synthesized via this technique include: \(2,2\text{-bis}(2^\prime\text{-pyridyl})-1,3\text{-dioxolane}\) \(98\), \(2-(2^\prime\text{-pyridyl})-2-(6^\prime\text{-bromopyridyl})-1,3\text{-dioxolane}\) \(100\), \(2,2\text{-bis}(2^\prime\text{-bromo-6}\prime\text{-pyridyl})-1,3\text{-dioxolane}\) \(46\), and \(2,6\text{-bis}[2-(6^\prime\text{-bromo-2}\prime^-\text{pyridyl})-1,3\text{-dioxolan-2-yl}]\text{pyridine} \).\(51\)

Treatment of ketone \(46\) with n-butyllithium at \(-20^\circ\text{C}\) produced, after hydrolysis, pyridone \(106\). The structure of \(106\) was established via an independent synthesis. This route necessitated the development of a new, gentle method for conversion of pyridyl-halides into pyridones. Treatment of 2-halopyridines with potassium \(t\)-butoxide in refluxing \(t\)-butanol for twelve hours culminates in the isolation of the corresponding 2-pyridone in 65-90% yields. Although the reaction is general for 2-chloro- and 2-bromopyridines, it apparently does not proceed for 3- or 4-halopyridine systems.

A series of low-temperature reactions involving deuterium incorporation indicated that the previously mentioned rearrangement on metallation of \(46\) probably involved first a specific metallation at the 3-position of one pyridine ring; second, a fragmentation to yield a ynenenitrile intermediate \(176\); and, finally, a recylization to give the pyridone product observed. It was noted that decreasing the temperature of the metallation reaction below \(-60^\circ\text{C}\) prevented pyridone formation. These conditions, however, give rise to a tri-metallated intermediate when the reaction solvent is diethyl ether. If, instead of diethyl ether, a good anion-stabilizing solvent (i.e., dimethoxyethane or tetrahydrofuran) was utilized, it was observed that the reaction proceeded via the normal metal-halogen exchange

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Further studies should be carried out to ascertain more about structural and rotational parameters in the 1,3-dioxolane series. One technique currently being exploited is that of low-temperature nmr studies. Effort will also be expended to attempt an isolation of the ynenenitrile intermediate postulated in the fragmentation reaction.

The macrocycle 19,20,21-briazatetracyclo[13.3.1.1^3,7,9,13]heneicosa-1(19),3,5,7(21),9,11,13(20),15,17-nonaene-2,8,14-trione was synthesized in 3.5% yield from 2,6-bis[2-(6'-lithio-2'-pyridyl)-1,3-dioxolan-2-yl]pyridine and ethyl chloroformate in tetrahydrofuran at -90° C. The majority of other product obtained was ill-defined high-molecular weight material (apparently linear).

During the preparation of bis-dioxolane, the by-product 14,17-dioxa-22,23,24-triazatetracyclo[16.3.1.1^3,7,9,13]tetracosa-1(22),3,5,7(24),9,11,13(23),18,20-nonaene-2,8-dione was produced. Work should be continued on macrocycles to collect data on complex formation with various cations. Other work pertinent to this segment of research might include the introduction of sulfur atoms in place of the oxygen atoms in these compounds—especially the "ether" bridges in.

During the work involving the transition metal complexes and carbonyl insertion, it was noted that treatment of bis(6-bromo-2-pyridyl)mercury with K$_2$[Ni(CN)$_6$] in dimethylformamide resulted in the formation of 6,6'-dibromo-2,2'-bipyridyl. A transmetallation reaction could be carried out on (127) via n-butyllithium at -90° C and the resulting 6,6'-dilithio-2,2'-bipyridyl was reacted with ethyl...
chloroformate to generate the macrocycle series \( n = 2,3,4,5, \ldots \),
the simplest being: \( \text{23,24,25,26-tetraazapentacyclo[17.3.1.1}^{2,6-\cdot 1^{8,12}1^{13,17}\text{]hexacosa-1(23),2,4,6(26),8,10,12(25),13,15,17(24),19,21-dodecaene-7,18-dione(54).} \)

Several of the linear pyridyl ketones were treated with a typical Wittig reagent generated from methylenetriphenylophosphine bromide. The corresponding substituted alkenes were prepared in this fashion in medium yields (15-20%). The compounds thus synthesized were: 1-phenyl-1-(2'-pyridyl)ethene, bis-1,1-(2'-pyridyl)ethene, and bis-1,1-(6'-bromo-2'-pyridyl)ethene.

Further work to be attempted would be the application of this reagent to the classes of macrocyclic ketones previously described. This should allow the facile preparation of entire classes of novel macrocycles having unique electronic properties. A more detailed description of these predicted systems is given in the section on results and discussion of this dissertation.

A convenient synthesis of pyridylcarboxaldehydes was developed utilizing methyl methylsulfinylmethyl sulfide anion. The reactive species was generated via the reaction of sodium hydride in dimethoxyethane on methyl methylsulfinylmethyl sulfide. Subsequent addition of a halopyridine produced the corresponding S-oxide via a nucleophilic displacement of the halide. The S-oxide intermediate is thermally labile and, after a rearrangement, loses dimethyl disulfide to generate the desired pyridylcarboxaldehyde. Compounds prepared in this manner were 2-pyridinecarboxaldehyde, 6-chloro-
2-pyridinecarboxaldehyde, 6-bromo-2-pyridinecarboxaldehyde, 3-pyridinecarboxaldehyde, and 4-pyridinecarboxaldehyde.

8-Bromoquinoline was synthesized by previously published methods in hopes of utilizing this compound in the simple synthesis of quinoline-macrocycles. Treatment of this monomer with n-butyl-lithium resulted in the isolation of complex, linear polymeric materials.

Reaction of phenyl(2-pyridyl)ketone or bis(2-pyridyl)ketone with acetylene bismagnesium bromide afforded good yields of 1,4-diphenyl-1,4-bis(2'-pyridyl)-2-butyne-1,4-diol and 1,1,4,4-tetra-(2'-pyridyl)-2-butyne-1,4-diol, respectively. Care must be exercised to prevent these diols from undergoing acid-catalyzed rearrangements to produce quinolizinone-type compounds.

Phosphorous trichloride, potassium iodide, and diethyl ether react smoothly to produce (>90%) diphosphorous tetraiodide. This reagent was sued to effect a "di-dehydroxylation" reaction on the two pyridyl-substituted bytyne-diols previously discussed to afford the corresponding butatrienes. 1,4-Diphenyl-1,4-bis(2'-pyridyl)buta-1,2,3-triene was prepared and isolated as the two geometrical isomers. The structural assignments and reactivities are discussed in the results and discussion chapter. 1,1,4,4-Tetra-(2'-pyridyl)-buta-1,2,3-triene was also isolated but this material was extremely reactive and difficult to purify. Initial attempts at catalytic hydrogenation of the cumulene systems were carried out to afford mixtures of butadiene-butane compounds.
The results and procedures developed with the linear substrates should be extended to attempts to prepare the novel class of hetero-
macrocycles illustrated in Figure IX, page 208. This class would be unique for its capabilities to undergo the previously described \( \pi \)-bonding with the central metal ions of any complexes formed.
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APPENDIX I

INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY NOMENCLATURE FOR SELECTED POLY-PYRIDYL SYSTEMS
I.U.P.A.C. NOMENCLATURE

(40b)

\[
\text{Dispiro}[1,3\text{-dioxolane}-2,2'\text{-}[19,20,21]\text{triazatetracyclo-}
[13.3.1.1^{3,7,1^{9,13}}]\text{heneicosa}[1(19),3,5,7(21),9,11,13-}
(20),15,17]\text{nonaene}-8',2'\text{-}[1,3]\text{dioxolan}-14'\text{-one}
\]

or

\[
19,20,21\text{-Triazatetracyclo}[13.3.1.1^{3,7,1^{9,13}}]\text{heneicosa-}
1(19),3,5,7(21),9,11,13(20),15,17\text{-nonaene}-2,8,14\text{-trione}
\text{cyclic bis(ethylene acetal)}
\]

(40)

\[
19,20,21\text{-Triazatetracyclo}[13.3.3.3^{3,7,1^{9,13}}]\text{heneicosa-}
1(19),3,5,7(21),9,11,13(20),15,17\text{-nonane}-2,8,14\text{-trione}
\]

(50b)

\[
2,6\text{-Bis(6-bromopicolinoyl)pyridine}
\]
2,6-Bis[2-(6-bromo-2-pyridyl)-1,3-dioxolan-2-yl]pyridine

or

2,6-Bis(6-bromopicolinoyl)pyridine cyclic bis(ethylen acetal)
34,35,36,37,38,39-Hexaaazaheptacyclo[28.3.1.1.8,12,13,17-.
119,23,124,28]nonatriaconta-1(34),2,4,6(39),8,10,12(38),-
13,15,17(37),19,21,23(36),24,26,28(35),30,32-octadecaene-
7,18,29-trione

(59b)

\[ \text{Dispiro}[1,3\text{-dioxolane}-2,2'\text{-}[14,17]\text{dioxa}[22,23,24]\text{triaza-}
\text{tracyclo}[16.3.1.1.3,19,13]\text{tetracosa}[1(22),3,5,7(24),-
9,11,13(23),18,20]\text{nonaene}-8',2'\text{-}[1,3\text{dioxolane}] \]

or

14,17-Dioxa-22,23,24-triazatetracyclo[16.3.1.1.3,7,19,13]-
tetracosa-1(22),3,5,7(24),9,11,13(23),18,20\text{nonaene}-2,8-
dione cyclic bis(ethylene acetal)
14,17-Dioxa-22,23,24-triazatetracyclo[16.3.1^3,7,1^9,13]-tetracosa-1(22),3,5,7(24),9,11,13(23),18,20-nonaene-2,-8-dione

or

Bis[6-[2-(6-bromo-2-pyridyl)-1,3-dioxolan-2-yl]-2-pyridyl]-1,3-dioxolan-2-yl]-2-pyridyl]ketone

or

Bis[6-[6-(6-bromopicolinoyl)picolinoyl]-2-pyridyl]ketone-cyclic 6,6^*,6^′,6^″-tetrakis(ethylene acetal)
Bis[6-((6-bromopicolinoyl)picolinoyl)-2-pyridyl]ketone

Bis[6-((6-bromopicolinoyl)-2-pyridyl) ketone

2,6-Bis[6-((6-bromopicolinoyl)picolinoyl)pyridine
APPENDIX II

ISOSUCROSE. DEFINITIVE STRUCTURAL ASSIGNMENT BY SPECTRAL CORRELATION TO α,β- AND α,α-SUCROSE OCTAACETATE

240
ISOSUCROSE. DEFINITIVE STRUCTURAL ASSIGNMENT BY SPECTRAL CORRELATION TO $\alpha,\beta$- and $\alpha,\alpha$-SUCROSE OCTAACETATES. *

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INTRODUCTION

Early attempts to synthesize sucrose octaacetate by either (a) dehydration of 1,3,4,6-tetraacetyl-D-fructofuranose (2) and 2,3,4,6-tetraacetyl-D-glucopyranose (3)\(^1\)-\(^5\) or (b) condensation of 2 with tetraacetyl-D-fructofuranosyl halide\(^2a,b\) were all unsuccessful. Although sucrose octaacetate was not realized, a new disaccharide octaacetate, namely "isosucrose" octaacetate (1), was isolated (<5%) along with numerous other components. [Crystalline components isolated\(^2b\) were: glucose pentaacetate and isotrehalose octaacetate; non-crystalline components: acetylated diglucoses and difructoses, hexose pentaacetates, and at least one additional glucofructose acetate.] "Saccharose D", isolated by Pictet and Vogel,\(^6\) as well as a compound, prepared by Schlubach and Middelhoff,\(^7\) are probably both impure samples of 1. Recently, isosucrose was isolated and characterized as the octaacetate (1) from similar condensation procedures.\(^8\)-\(^9\)

[Drawings of the compounds 2 and 3]

In view of the well-established structure of sucrose, i.e., \(\alpha\)-D-glucopyranosyl-\(\beta\)-D-fructofuranoside,\(^10\) isosucrose must therefore by one of the three remaining anomeric disaccharides: e.g. \(\alpha,\alpha\), \(\beta,\alpha\), or \(\beta,\beta\). The previously accepted structure of isosucrose,\(^11\) namely

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γ-D-glucopyranosyl-α-D-fructofuranoside (4), was assigned on the following information: (a) hydrolysis of the methylated isosucrose gave the same products as those obtained from octamethylsucrose\textsuperscript{2e}; [isosucrose was methylated with extreme difficulty; ordinary methods afforded predominantly heptamethyl-isosucrose, which can be further methylated by treatment of the potassium salt with methyl iodide in liquid ammonia.\textsuperscript{2e}] therefore, they must be isomeric disaccharides differing solely in configuration of the glycosideic-fructosidic bond. (b) Georg\textsuperscript{4} deduced the β-glycosidic linkage since higher isolated yields of 1 were obtained when β-3 (rather than α-3 or an equilibrium mixture) was used in the condensation. The α-fructosidic bond was rationalized\textsuperscript{4} by analogy with the reaction of tetraacetyl-D-fructopyranosyl chloride with methanol generating methyl tetraacetyl- -fructopyranoside rather than the usual β-isomer. (c) Isosucrose was unaffected by maltase, invertase, and all enzymes in fermenting yeast,\textsuperscript{4,12} therefore, ruling out the α-D-fructofuranoside linkages. (d) Evaluation of Hudson's isorotation rules for isosucrose as well as α,α-sucrose and their corresponding octa-acetates is in strong agreement with experimental values.\textsuperscript{13}

We herein offer direct evidence that the structure of isosucrose is indeed the β,α-isomer. [The β,β-configuration has also been proposed for isosucrose.\textsuperscript{2b,d,6} The n.m.r. spectral data for 1,\textsuperscript{4,6} and 5 have been correlated; thus the α,α-isomer has also been confirmed structurally. 

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EXPERIMENTAL

**General Methods.** Melting points were determined in closed capillaries in a Hoover-Thomas Unimelt apparatus and are uncorrected. Optical rotations were taken with a Schmidt-Haensch polarimeter. Optical rotatory dispersion (ORD) spectra were determined on a Durrum-Jasco spectropolarimeter, Model J-20. Thin layer chromatography was performed on Brinkmann silica gel-HF plates (250 μm, activated at 115° for six hours); the solvent system used was: 1-butanolacetic acid-diethyl ether-water (9:6:3:1). Nmr spectra were determined on a Varian Associates Model HR-300 spectrometer; chemical shifts are given in parts per million relative to TMS as an internal standard and lock signal. Mass-spectral measurements were obtained with a Finnigan F 1015-D Electron-impact Mass Spectrometer at an accelerating potential of 70e.V. and a source temperature of 110° C and with a Finnigan F 3200 Chemical-ionization Mass Spectrometer using methane as the reagent-gas at a pressure of 1 Torr. Microanalyses were determined by Mr. R. Seab in these laboratories.

**Starting Materials.** Inulin acetate \([\alpha]_D^{20-34°} (c = 1.6, \text{CHCl}_3)\); lit.\(^{14}\) \([\alpha]_D^{20-34°} (c = 1.5, \text{CHCl}_3)\) was prepared from inulin (Calibiochem, Los Angeles, California). 2,3,4,6-Tetraacetyl-D-glucopyranosyl bromide [m.p. 88-89° (isopropanol), lit.\(^{15}\) m.p. 88-89°] was prepared by the method of Redemann and Niemann.\(^{15}\)

\(\alpha,\beta\)-Sucrose octaacetate was prepared from sucrose by standard procedures\(^ {16}\): m.p. 87-88°, \([\alpha]_D^{20} = 60° (c 1.5, \text{CHCl}_3)\) (lit.\(^{16}\))

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m.p. 89°, \([\alpha]_D^{20} = 59.6°\) (CHCl\(_3\)); ORD see Fig. 1; NMR (300 MHz) see Table 1; selected MS data see Tables 2 and 3.

\(\alpha,\alpha\)-Sucrose octaacetate was generously supplied by Dr. Robert K. Ness of the National Institutes of Health: m.p. 110-112°, \([\alpha]_D^{20} + 83.5°\) (c = 1, CHCl\(_3\)); ORD see Fig. 1; NMR (300 MHz) see Table 1; selected MS data see Tables 2 and 3.

2,3,4,6-Tetraacetyl-D-glucopyranose (3). Water was added dropwise to a stirred solution of 2,3,4,6-tetraacetyl-D-glucopyranosyl bromide (10 g, 0.024 mol) in acetone (50 ml) until the solution became occluded. Dissolution was accomplished by addition of several drops of acetone, then freshly prepared silver oxide (7 g) was added and the suspension stirred for one hour at 0°. The resultant slurry was filtered with the aid of a Celite pad and washed with acetone. Upon concentration, the residual colorless syrup was extracted with benzene (2 X 100 ml) followed by back extraction with water. The combined aqueous extracts were extracted with chloroform (10 X 50 ml). The combined chloroform extracts were dried over anhydrous magnesium sulfate and concentrated to afford 8.4 g (99%) for the viscous tetraacetate 3: \([\alpha]_D^{20} + 134°\) (c = 1.2, CHCl\(_3\)) \{lit.\[17\] \([\alpha]_D^{20} + 135.6° \pm .4\) (CHCl\(_3\))\}.

1,3,4,6-Tetraacetyl-D-fructofuranose (2). To a stirred solution of inulin acetate (10 g), glacial acetic acid (100 ml), and acetyl bromide (20 ml), an HBr-acetic acid solution (32% HBr w/w) was added. The mixture was stirred at room temperature for
three hours, then poured onto ice (100 g). Addition of sodium acetate (10 g) and water (1.5 l) was followed by solid sodium bicarbonate (ca. 170 g) to assure a pH of 5.5. The aqueous solution was extracted with chloroform (10 X 100 ml), and the combined organic extracts were dried over anhydrous magnesium sulfate. Concentration in vacuo afforded an orange-red syrup, which was dissolved in benzene (100 ml) and extracted with water (20 X 100 ml). The combined water fractions were extracted with chloroform (10 X 100 ml), dried, and concentrated in vacuo to yield 7.2 g of the pale yellow tetraacetate (2): b.p. 115°C (0.001 mm), [α]₂₀ + 31.3° (c = 1.5, CHCl₃).

Both 2 and 3 were used directly in the preparation of β,α-sucrose without additional purification.

β,α-(iso)Sucrose Octaacetate (1). Method A. A suspension of 2 (2.5 g, 7 mmol), 3 (2.5 g, 7 mmol), and phosphorous pentoxide (1 g) in anhydrous benzene 150 ml) was vigorously agitated. Additional phosphorous pentoxide (0.5 g) was added and the agitation continued for 24 hours. The solvent was carefully decanted from the black residue and extracted with water (20 X 100 ml). The organic layer was washed with aqueous sodium hydroxide (1%, 2 X 50 ml), then water (2 X 50 ml), and dried over anhydrous sodium sulfate. Concentration in vacuo afforded a light yellow syrup (900 mg), which initially dissolved in ether. Upon cooling to -10°C, crystals slowly formed. Recrystallization from diethyl ether afforded 300 mg (5.7%) of isosucrose octaacetate: m.p. 129-130.5°C (diethyl ether); Rₚ 0.85;
[α]_D$^{20}$ + 20.0° (c = 1, CHCl$_3$), lit.$^5$ m.p. 131-132°; [α]_D$^{27}$ + 20.4° (c = 4.9, CHCl$_3$); NMR (300 MHz) see Table 1; ORD see Fig. 1; selected MS data see Tables 2 and 3.

**Method B.$^{18}$** A mixture of 1,3,4,6-tetraacetylfructose (3.2 g, 8.3 mmol), Linde 4A molecular sieve (10 g), silver(II) oxide$^{19}$ (3.05 g), and dichloromethane (15 ml) was placed in a black-coated flask. A single crystal of iodine was added then the mixture was stirred for one hour under nitrogen. A solution of 2,3,4,6-tetraacetyl-D-glucosyl bromide (4.1 g, 10 mmol) in dichloromethane (15 ml) was added over 15 minutes. The reaction mixture was stirred at 25° for 12 hours, then filtered through a celite pad. Upon concentration, the filtrate afforded a complex mixture (6.0 g) of predominately 2 and 3. Traces of β,α-(iso)sucrose octaacetate were isolated (<1%): m.p. 129-130° (diethyl ether); [α]_D$^{27}$ + 19.1° (c = 1.3, CHCl$_3$); R$_f$ 0.85.

**β,α-(iso)Sucrose.** β,α-(iso)sucrose octaacetate (204 mg, 0.299 mmol) was dissolved in 0.02N methanolic sodium methoxide (20 ml, 0.40 meq), then stirred at 25° for 24 hours.$^{20}$ The solution was neutralized with dry-ice (ca. 2.0 g) and the solvent removed in vacuo. The residue was dissolved in distilled water (3 ml) and passed through a mixed-bed ion-exchange column$^{20}$ (1 g each of Amberlite IR-120-H and Amberlite IR-4B). The column was washed with distilled water (100 ml) to elute the disaccharide, which was isolated after removal of solvent in vacuo affording 96 mg (94%) of pure β,α-(iso)sucrose: [α]_D$^{27}$ + 52.3° (c = 0.9, CH$_3$OH), lit.$^{2b}$ [α]_D$^{27}$ + 50.0° (c = 2.13, CH$_3$OH).

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DISCUSSION

Synthesis of $\beta_{\alpha}$-isosucrose. The general synthesis of the octaacetate of 1 followed a modified procedure described by Binkley and Wolfrom, in which 2 and 3 were condensed in the presence of phosphoric anhydride with exclusion of air (see Experimental Section). The yields of the octaacetate of isosucrose varied from 1 to 6% even under seemingly identical reaction conditions. Alternate procedures were attempted, however, 1 octaacetate was isolated in less than 1% yield with great difficulty from the myriad of side products. Hydrolysis of this octaacetate under standard conditions afforded nearly quantitative yields of isosucrose, which was identical to an original sample.

Acetylation of isosucrose with acetic anhydride in anhydrous pyridine regenerated 1 octaacetate, which was identical in every respect to the initial sample.

Spectral Studies of the Isomeric Sucrose Octaacetates. 1. N.M.R. Studies.

The n.m.r. spectra of the known isomeric sucrose octaacetates have been measured at 300 MHz (Table 1) and, in general, can be analyzed on a first-order basis. The 100 and 220 MHz spectral data of $(\alpha,\beta)$-sucrose octaacetate (4) have been reported and these previously reported data correspond well with the herein presented values.

A. $(\beta,\alpha)$-Isosucrose Octaacetate. The n.m.r. spectrum of 1 octaacetate in CDCl$_3$ shows the H-2 proton as an observed triplet...
at δ5.02 consisting of two 10 Hz couplings. This pattern is characteristic of two vicinal diaxial couplings, specifically H-1 and H-3. Confirmation of the axially disposed H-1 proton is shown by a doublet at δ4.96 with a 10 Hz spacing. The lowest-field doublet at δ5.40 (J = 2 Hz) is assigned to H-3' on the basis of signal simplicity. The remaining low-field signals are observed as three quartets at δ5.18, 4.98, and 4.84, which can be assigned to H-3, H-4, and H-4', respectively. The distereotopic H-1' protons are easily discernible as indicated by their sole large geminal coupling (J = 12 Hz).

B. α,α-Sucrose Octaacetate. The low-field region of the spectrum of 5 octaacetate in CDCl₃ can be analyzed on a first-order basis. The H-1 doublet (J = 3.6 Hz) at δ5.51, as well as the double (J = 1 Hz) at δ4.82 of H-3' are readily discernible. The H-2 quartet at δ5.03 consists of 3.6 and 10 Hz spacings, which is characteristic of an axial proton coupled to both a vicinal, axial and equatorial hydrogen. The remaining chemical shifts and coupling constants were easily recognized and are tabulated in Table 1.

Thus from the data shown in Table 1, the glucoside configuration of 1 (octaacetate) is firmly established as β by: (1) the observed large coupling constant (J₁-₂ = 10 Hz) for H-1 and (2) the strong up-field shifts (Δ = 0.5-0.7 p.p.m. and Δ = 0.3-0.4 p.p.m.) for the H-1 and H-3 protons, respectively, of 1 octaacetate vs either 4 or 5 octaacetates, which both possess the α-configuration. These comparative data also confirm the previous α,α-sucrose (5) octa-
acetate assignments, since the small coupling constant (J_1,2 = 3-4 Hz) for H-1 establishes the α-glucoside linkage, thus the fructoside linkage must be α.

The fructoside configuration of 1 (octaacetate) is established as α on the basis of the following n.m.r. data. The strong observed down-field shift (δ5.58) experienced by H-4' in sucrose (4) octaacetate is caused by the inter-ring close proximity of the glucopyranose oxygen to the H-4' proton. This shielding is only possible when the furanose possesses the β configuration in these sucrose isomers; thus, isosucrose must possess the α fructose linkage (Figure 2). In order to disprove the possible influence caused by the juxtaposition of the fructofuranose acetoxy groups to the H-4' proton as well as confirm the necessity of the glucopyranose moiety as the source of down-field shift of H-4', the n.m.r. spectrum of tetra-0-acetyl-2,5-anhydro-D-glucitol (7) and tetra-0-acetyl-2,5-anhydro-D-mannitol (8) was examined. The chemical shift of H-4' in 7 and 8 as well as 1 and 5 octaacetates remains constant (δ4.8-5.0); these data support the above rationale that the fructose configuration in isosucrose (1) is the same as in 5 and the opposite to that of sucrose (4).

Other solvents (e.g. C_6D_6, DMSO-d_6, and acetone-d_6) were used to attempt better resolution of the fructose portion of these sucrose acetates; little advantage was realized.

2. Mass Spectral Studies. Electron-impact mass spectrometry (e.i.m.s.) affords insight into predominately small fragmentation
ions; whereas, chemical-ionization mass spectrometry (c.i.m.s.) is a complimentary tool in that larger fragmentation ions are realized. Selected ions of relative intensity larger than 1% are tabulated for the sucrose octaacetates under both chemical- and electron-ionization conditions (Tables 2 and 3, respectively). Relative intensities of ions are referenced to the most abundant ion (base peak, 100%) within that spectrum and are expressed as a percent of that base peak. Figure 3 summarizes the mass spectral results.

In general, the isomeric sucrose octaacetates give essentially the same fragmentation pattern within experimental error; thus, this tool affords little insight into the stereochemical distinction between these isomers. The lack of stereochemical differentiation of anomers has also been demonstrated recently for methyl α- and α-D-glucopyranoside tetraacetates. The chemical-ionization mass spectrum (methane) of 1, 4, or 5 octaacetates exhibited a weak (<1%) peak for the parent ion (m/e 680) which eliminated a molecule of acetic acid to generate m/e 620. The c.i.m.s. of these octaacetates is uncomplicated, consisting of the base peak (m/e 331), which results from cleavage of the C1-0 or C2-0 linkages, and four less-prominent peaks at m/e 271, m/e 211, m/e 169, and m/e 109 corresponding to the sequential loss of molecules of acetic acid (2), ketene (1), and lastly acetic acid (1), respectively. This characteristic mode of decomposition of monosaccharide acids is well documented.

The electron-impact mass spectrum of 1, 4, and 5 octaacetates affords corroborative evidence for the interpretation of the major fragments; however, the base peak (100%) under these conditions is m/e 43 which is assigned to the acetyl ion.
Biochemical Aspects. Isosucrose was incubated with Neurospora Crassa β-D-fructofuranoside fructohydrolase under the assays conditions used for sucrose. The enzyme did not release glucose from the disaccharide. Isosucrose was also incubated with β-glucosidase from almonds and α-glucosidase from yeast. The enzyme assays were accomplished at the pH optimum of each enzyme. Neither of these enzymes released glucose from the disaccharide. The inability of the α-glucosidase to catalyze hydrolysis of the α-bond was expected, and the inability of the β-glucosidase to hydrolyze the bond is explained by the marked preference of this enzyme for aryl β-glucosides. Isosucrose was hydrolyzed by a crude extract of Neurospora crassa. This organism is known to contain both an aryl β-glucosidase and a cellobiase. The activities belong to two distinct proteins, hence the release of glucose from isosucrose is apparently by the β-glucosidase that has cellobiase activity. These enzymatic studies support the conclusions drawn from the spectral studies.
The authors express thanks to Dr. James N. Schoolery (Varian Associates) and Mr. Everett R. Santee (The University of Akron, Institute of Polymer Science) for the 300 MHz n.m.r. spectra, to Mr. C. Richard Weisenberger (The Ohio State University) for preliminary mass spectra, to Dr. Robert K. Ness (National Institutes of Health) for an authentic sample of "α,α-sucrose octaacetate," and to Professor Louis M. Trefonas (University of New Orleans) for his attempted x-ray analysis of isosucrose octaacetate.
REFERENCES


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23. T. A. W. Koerner, R. J. Voll, and E. S. Younathan, unpublished data.
### TABLE 1. Chemical Shifts (and Coupling Constants) of the methine and methylene protons of the isomeric sucrose octaacetates.

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α-Fru
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a 'Expressed as percentage of the intensity measured for the base peak.
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*Expressed as percentage of the intensity measured for the base peak.*
Figure 1. Rotatory dispersion curves of \( \lambda \) (---) and \( \frac{\lambda}{2} \) (-----) in CHCl₃.
Figure 2. Pertinent n.m.r. Data for the Fructofuranosyl Residues in CDCl₃ at 300 MHz.
Figure 3.

```
[MH + ] -> [M'] [CH₃CO] ± Gln

m/e 331 (C₁₄H₁₉O₉) + -AcOH m/e 271 (3-10) -AcOH m/e 211 (55-37) -CH₂CO m/e 169 (31-72) -AcOH m/e 109 (20-37)

m/e 43 [CH₃CO] ± (100) m/e 127 [Gln' - 204] (2-5)

m/e 331 [Gln' - 404] + 2AcOH m/e 211 -CH₂CO m/e 169 m/e 109

m/e 619 (1)
```

(1), (4), or (5)
VITA

Joe Dean Sauer was born May 31, 1948, in Thomas, Oklahoma. He attended public schools in the town of Clinton, Oklahoma and graduated from Clinton High School in 1966. That same year he entered Southwestern State College (now Southwestern State University) in Weatherford, Oklahoma and was awarded a B.S. in Chemistry in 1970. While pursuing this degree, he was an undergraduate research participant in a National Science Foundation program and was employed full-time as key-punch and computer operator for the Kellwood Corporation, Clinton, Oklahoma. He began graduate studies at Louisiana State University in Baton Rouge in 1970 and was employed as a Teaching Assistant from 1970 to 1973. He was awarded the Dupont Teaching Award for the best graduate Teaching Assistant in 1973, and was appointed to Research Assistant in 1973, under a National Institute of Health grant. He was employed in 1975 as a full-time Instructor at Louisiana State University and subsequently taught both freshman and undergraduate organic chemistry courses. Currently, he is a candidate for the Doctor of Philosophy degree with a major in Organic Chemistry and a minor in Inorganic Chemistry. He has accepted a renewal of his Instructorship at Louisiana State University Baton Rouge, Louisiana, to begin in the Fall of 1976.
EXAMINATION AND THESIS REPORT

Candidate: Joe Dean Sauer

Major Field: Chemistry

Title of Thesis: The Synthesis of Heteromacrocycles Containing the 2,6-Pyridine Moiety.

Approved:

George R. Newkome
Major Professor and Chairman

James E. Traeger
Dean of the Graduate School

EXAMINING COMMITTEE:

Joel Selbin

K. N. Hark

Date of Examination:

March 25, 1976