SYNTHESIS OF INDOLO AND BENZO HEXAHYDROQUINOLIZINES VIA THE CYCLIZATION OF 1,4-DIHYDROPYRIDINE DERIVATIVES

JEROME HENRY SUPPLE

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SYNTHESIS OF INDOLO- AND BENZOHEXAHYDROQUINOLIZINES

VIA

THE CYCLIZATION OF 1,4-DIHYDROPYRIDINE DERIVATIVES

BY

JEROME HENRY SUPPLE

B. S., Boston College, 1957
M. S., Boston College, 1959

A THESIS

Submitted to the University of New Hampshire

In Partial Fulfillment of

The Requirements for the Degree of

Doctor of Philosophy

Graduate School
Department of Chemistry

June, 1963

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[Signatures]

February 6, 1963
Date
ACKNOWLEDGMENT

The author wishes to express his gratitude to the University of New Hampshire for granting a Teaching Assistantship for the period 1959-1960 and a Research Assistantship for the period 1960-1961 and to Eastman Kodak Company for the award of a Research Fellowship for the period 1961-1962.

Appreciation is also due to the faculty, staff and graduate students of the Department of Chemistry for their friendliness and helpfulness. In particular, Dr. G. G. Lyle, Mr. P. S. Anderson, and Mr. J. A. Verdone deserve appreciation for many hours of enjoyable and fruitful discussion.

Finally, the author wishes to express grateful appreciation to Dr. R. E. Lyle, Jr., for his instruction, unending patience, and friendly guidance during the course of this work.
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INTRODUCTION

The various indole alkaloids have been the subject of intensive investigation over the years.\textsuperscript{1} Recently, the formation of the C ring in the pentacyclic indoloisoquinoline series and the tetracyclic series, by way of a cyclization involving the highly nucleophilic indole ring, has received particular attention. In 1949, Julian and Magnani\textsuperscript{2} reported that palladium on charcoal dehydrogenation of the oxindoyl-tetrahydroisoquinoline derivative 1 yielded the dihydroisoquinoline 2 which underwent reductive cyclization to 4 on treatment with lithium aluminum hydride. It was later shown\textsuperscript{3} that the actual product of the dehydrogenation was the condensed material 3 rather than 2, and that 3 yielded the indole 4 on treatment with lithium aluminum hydride.
Subsequently, Potts and Robinson demonstrated that the indolylethylisoquinolinium salt was reduced with spontaneous cyclization to 7. These workers postulated the dihydroisoquinoline as an intermediate and suggested that the inorganic salts in the reaction medium caused the cyclization by Lewis acid catalysis. It was felt that the olefinic double bond in the dihydroisoquinoline would be attacked by acid (A) at the carbon atom to the nitrogen. The highly electrophilic center thus established at the carbon (A- \overset{\oplus}{\text{C}} - \overset{\ominus}{\text{N}} \leftrightarrow A- \overset{\oplus}{\text{C}} - \overset{\ominus}{\text{N}}) would then attack the indole ring. Elderfield employed a reductive cyclization of this type as the key step in the total synthesis of alstonilinol.

Huffman isolated an unstable product from the lithium aluminum hydride reduction of 5, in which the excess hydride was decomposed under basic conditions. This material appeared to be the dihydroisoquinoline and afforded 7 on treatment with dilute acid. This suggested to Huffman that the cyclization reported by Potts and Robinson may have occurred during the work up of the reaction mixture and does not require the postulate of Lewis acid catalysis. Otherwise, he did not disagree with the proposed mechanism, except to point out that initial cyclization of 6 to the indolenine 9, by way of the Schiff's base 8, followed by rearrangement to 7 should be considered as a possible alternate mechanism.
Elderfield reported\(^7\) that the analogous \(\beta\)-indolyl-

ethylpyridinium salts, on reduction with lithium aluminum

hydride or sodium borohydride, gave no cyclized products but

only the 1,2,5,6-tetrahydropyridine derivatives. Thesing

and Festag\(^8\), however, catalytically reduced the pyridinium

salt \(10\) to the piperidine \(11\) and brought about cyclization

in dilute acid. Other cyclizations to form the C ring in

similar cyclic indole systems have also been reported.\(^9\)–\(^12\)
In a recent publication, Wenkert and co-workers describe the reductive cyclization of the pyridinium salt $13^*$. Reduction with lithium aluminum hydride or with sodium borohydride in diglyme, followed by acidification, yielded a mixture of the cyclized $14a$ and unicycled $15a$ $1,2,5,6$-tetrahydropyridines.

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It is assumed that the 1,2-dihydropyridine 16a is intermediate to the formation of both products 11a and 15a. Protonation of the 1,2-dihydropyridine 16a at the 5-position of the pyridine ring, perhaps by the slightly acidic hydrogen on the indole nitrogen, followed by rapid reduction of the protonated material 17a in the reducing medium, would account for the formation of the uncyclized 1,2,5,6-tetrahydropyridine in this case and in the case reported by Elderfield. However, acidification of 16a in the absence of any reducing agent would account for the formation of the cyclic product 11a.

Wenkert suggests that an indolylaluminohydride complex, formed by the abstraction of the proton on the indole nitrogen, may account for the reduction of the dihydropyridine 16a to the tetrahydropyridine 15a. Indeed, reduction of the salt 13b, with a methyl group on the indole nitrogen, followed by acidification, yielded only the cyclized product 14b and no 15b.

The fact that the attempted cyclization of the 2-methylindole derivative 13a did not yield the indolenine 18c cannot be taken as proof that the indolenines 18a and 18b are not intermediate to the formation of 11a and 14b respectively, since only 15c could be isolated from this reaction.

The cyclization reported by van Tamelen, on heating the piperidinol 19 in the presence of acetic acid and sodium acetate, is sufficient reason for considering cyclic indolenines of the type 18 as intermediates in the formation of tetracyclic indole derivatives through a reductive cyclization of the corresponding N-(β-indol-3-yl)ethylpyridinium salts.
That the 3-position on the indole nucleus is more susceptible to electrophilic attack than the 2-position has long been known and is to be expected on the basis of electron density calculations.\textsuperscript{16} Hinman showed\textsuperscript{17}, using proton magnetic resonance data, that protonation of the indole nucleus in acid occurs predominantly at the 3-position. He also showed, however, that in strong deuterium acid a slow exchange of the hydrogen on the 2-position of the indole ring takes place. Indeed, the electron density calculations\textsuperscript{16} would suggest that the 2-position should also show some nucleophilic character. This has apparently been borne out in some reactions of 3-substituted indoles\textsuperscript{18,19} and one of these\textsuperscript{18} suggests that the determining factor in the position of attack by an electrophile on a 3-substituted indole is a steric one. Thus a small electrophilic species, such as a proton, will attack the 3-position. A larger electrophilic species, however, may encounter hindrance at the 3-position of sufficient energy to offset the difference in reactivity and attack takes place at the 2-position. This is the situation encountered.
in the dimerization of skatole. In normal electrophilic substitution of 3-substituted indoles, wherein the resultant product is a 2,3-disubstituted indole, the position of initial attack of the electrophile cannot be inferred directly from the structure of the product, since initial attack may have occurred at the 3-position to give a 3,3-disubstituted indolenine, which then can undergo rearrangement to the 2,3-disubstituted indole.

Subsequent to the work of Huffman, Nelson, as part of a study of the properties of partially reduced pyridines, caused the cyclization of the 3-benzoyl-1,4-dihydropyridine derivative to the corresponding quinolizine derivative in glacial acetic acid.

\[ \text{CH}_3\text{COOH} \]

\[ \text{C}_6\text{H}_5 \]

The present work is concerned with a study of the cyclization of a 1,4-dihydropyridine to a quinolizine derivative in an attempt to determine its general utility as a synthetic procedure and to shed light on the mechanism of the cyclization. Since the indole system, as tryptophan, and the 1,4-dihydropyridine system, in diphosphopyridine nucleotides, are generously dispersed in nature, this reaction assumes im-

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portance as a possible biogenetic pathway for the formation of the indole alkaloids.
DISCUSSION AND RESULTS

Selection of the 1,4-dihydropyridine System

Westheimer has shown\(^{21}\) that the reduction with sodium dithionite of pyridinium salts, bearing an electron withdrawing group on the 3-position, leads exclusively to the formation of the corresponding 1,4-dihydropyridine. In some preliminary studies, we found that the sodium dithionite reduction of \(\text{N}-\text{benzyl}-3\)-cyanopyridinium bromide \(^{23}\), according to the method of Anderson and Berkelhammer\(^{22}\), gave a mustard colored solid whose infrared spectrum exhibited very strong absorption at 2195 cm\(^{-1}\), 1680 cm\(^{-1}\), and 1605 cm\(^{-1}\) (of Table I). This material also showed absorption in the ultraviolet region at 340 m\(\mu\). On addition of a small amount of hydrochloric acid, this band disappeared with the formation of a new band at 273 m\(\mu\). A larger sample of the product from the dithionite reduction, on treatment with acid, gave a light brown unstable solid whose infrared spectrum had strong absorption at 2200 cm\(^{-1}\) and 1630 cm\(^{-1}\) but no absorption at 1680 cm\(^{-1}\).
At this time a publication by Druey and Schenker\textsuperscript{23} appeared which described the preparation of N-methyl-3-cyano-1,4-dihydropyridine \textsuperscript{26} and listed infrared bands for this material at 2190 cm\textsuperscript{-1}, 1685 cm\textsuperscript{-1}, and 1605 cm\textsuperscript{-1} and an ultraviolet maximum at 340 m\textmu. On addition of hydrochloric acid to a methanolic solution of \textsuperscript{26}, the band at 340 m\textmu disappeared and a new band at 268 m\textmu was formed. Catalytic reduction of \textsuperscript{26} afforded the 1,4,5,6-tetrahydropyridine \textsuperscript{27} whose infrared spectrum had strong bands at 2180 cm\textsuperscript{-1} and 1630 cm\textsuperscript{-1} and whose maximum in the ultraviolet region appeared at 276 m\textmu.

In our work, catalytic reduction of the quaternary salt \textsuperscript{23} yielded the 1,4,5,6-tetrahydropyridine \textsuperscript{25} which had a maximum at 274 m\textmu in its ultraviolet spectrum and bands at 2190 cm\textsuperscript{-1} and 1630 cm\textsuperscript{-1} in the infrared region. The results of Druey and Schenker confirm the structure \textsuperscript{24} as the product of the dithionite reduction of \textsuperscript{23}.

The spectral data show that in a 1,4-dihydropyridine of the type \textsuperscript{24}, the conjugated 2,3-double bond is quite stable, whereas the unconjugated 5,6-double bond comprises a highly reactive enamine system.\textsuperscript{24,25} This enamine double bond, in acid, would be protonated at the 5-position rendering the 6-position highly electrophilic. This is precisely the situation required for electrophilic attack of the indole nucleus. This fact, along with the relatively high stability of the dihydropyridine \textsuperscript{24} and the characteristic spectral properties of both the dihydropyridine \textsuperscript{24} and the tetrahydropyridine \textsuperscript{25}, led to the selection of the 3-cyano-1,4-dihydropyridine system.
for the study of the cyclization reaction.

The first step in this study was to determine whether or not the parent compound, \(N-\left[\theta-(\text{indol-3-yl})\text{ethyl}\right]-3\)-cyanopyridinium bromide (28) could be made to cyclize to the quinolizine derivative 30. Having attained this end, the next step would be to obtain evidence for, or against, the presence of the indolenine 31 as an intermediate in this reaction.

It was hoped that an indolenine, if one is intermediate in the cyclization, could be isolated either by extending the side chain linking the indole nucleus to the pyridine ring by one carbon atom or by blocking the 2-position on the indole ring with a substituent. It was thought that the indolenine resulting from the lengthened side chain might be more stable, due to the six-membered spiro-ring, than the indolenine 31 with the five-membered spiro-ring. The indolenine formed from the compound with the 2-position of the indole nucleus blocked would be unable to rearrange to yield an indole derivative.
Demonstration of the Feasibility of the Cyclization of a 1,4-dihydropyridine to an Indoloquinolinizine.

Preparation and Reductive Cyclization of N-(indol-3-yl)ethyl-3-cyanopyridinium Bromide (28). The scheme for the preparation of the desired quaternary salt 28 is outlined in Figure 1.

Initially the acid 32 was obtained from gramine (54) or 3-piperidinomethylindole (55). These Mannich bases were prepared according to the method of Kuhn and Stein and, after treatment with sodium cyanide and hydrolysis, the acid 32 was obtained. This procedure was quite lengthy and, for the sake of expediency, commercial indoleacetic acid 32 (Matheson) was employed in most instances.

Lithium aluminum hydride reduction of the acid 32 afforded tryptophol (33) in good yield. Bromination of tryptophol (33) with phosphorous tribromide, followed by treatment...
of the resultant bromide 34 with 3-cyanopyridine, according to the method of Nelson 20, gave the desired salt 28.

The pyridinium salt 28, in unbuffered aqueous methanol, was treated with sodium dithionite. The solid reduction product exhibited infrared and ultraviolet absorption indicative of a 3-cyano-1,4,5,6-tetrahydropyridine, rather than the expected 1,4-dihydropyridine (cf. Tables I and II). The analytical data showed that the product was the desired cyclized material 30. Later it was shown that the reaction mixture was actually slightly acidic due to the liberation of sulfur dioxide from the oxidation of the dithionite ion. Thus, it was assumed that the 1,4-dihydropyridine 29 was protonated as it was formed and underwent cyclization immediately to the quinolizine 30. In fact, when the reduction was carried out in an aqueous slurry under a layer of ether, impure dihydropyridine 29 was obtained.

Thus the desired cyclization of the enamine portion of a 1,4-dihydropyridine with an indole nucleus occurs readily. The indoloquinolizine 30 was obtained in 75% yield. The high yield of this reaction emphasizes the possible synthetic utility of such a reaction.
Cyclization of a 1,4-dihydropyridine to yield a benzoquinoline.

Preparation and Reductive Cyclization of \( N\-\left[\overset{\oplus}{\text{C}}\right]-(3,4-\text{dimethoxyphenyl})\text{ethyl}\] -3-cyanopyridinium Bromide (38). In order to study the scope of this cyclization and to eliminate the possibility that the indole system may be a necessary prerequisite for this reaction, reductive cyclization employing a different aromatic moiety was attempted. The 3,4-dimethoxyphenyl system was chosen because it was readily available and possessed the required susceptibility to electrophilic attack.

This proved to be a fortunate choice, since a successful study of the reduction and cyclization of the quaternary salt 38 would also be of biogenetic significance. A search of the literature revealed that Battersby and Binks had reported that papaverine (43), on treatment with tin and hydrochloric acid, yielded pavine (44). These workers felt that the reaction proceeded via a reduction of the hydrochloride salt of papaverine to the corresponding 1,2-dihydroisoquinoline derivative followed by acid catalyzed cyclization to pavine (44). In support of this postulate they prepared the N-methyl-1,2-dihydroisoquinoline derivative 45 and found that it gave N-methyl-pavine (46) on treatment with acid.
Similarly, Huffman and Miller\textsuperscript{38} synthesized 2,3-dimethoxyberbine (43) from a lithium aluminum hydride reduction of the isoquinolinium salt 47 followed by acidification of the resultant 1,2-dihydroisoquinoline 48.

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The preparation of 3,4-dimethoxy-β-phenylethanol (36) had previously been reported. Huffman reported a 30% yield of the alcohol on lithium aluminum hydride reduction of 3,4-dimethoxyphenylacetic acid 35. This was probably due to the insolubility of the acid 35 in diethyl ether. Nearly quantitative yields of the alcohol 36 were obtained when tetrahydrofuran was employed as the solvent. The bromide 37,38,41-43 was prepared by heating the alcohol 36 in ether, on the steam cone with an excess of phosphorous tribromide or by allowing the reactants to heat at reflux temperature in benzene to which a few drops of pyridine had been added. The latter method required less phosphorous tribromide and seemed to give a product of better purity. The yields were essentially the same in both cases. The desired quaternary salt 38 was obtained in good yield by heating the bromide 37 with 3-cyanopyridine in the absence of solvent.

Several attempted reductions of unbuffered aqueous solutions of the salt 38 with sodium dithionite resulted in a small amount of dihydropyridine 39, which appeared from its infrared spectrum to be contaminated with a tetrahydropyridine and water. In these reactions the amount of material obtained was quite small relative to the amount of starting material employed. It was assumed that a large amount of the starting material remained in the aqueous solution.

After one dithionite reduction the reaction mixture was extracted with chloroform and the extract dried with an—
hydrous potassium carbonate. When the chloroform was removed a nearly white solid, mixed with some water, was obtained. This material was no longer soluble in chloroform and had an infrared spectrum indicative of a 1,4,5,6-tetrahydropyridine. When the aqueous portion of the reaction mixture was saturated with potassium carbonate, an oil separated which solidified on contact with chloroform. This material was shown by its infrared spectrum and melting point to be identical with that isolated from the chloroform extract. The analytical and spectral data indicated that this material was the potassium sulfinate 40.

After this work was completed, a paper was published by Wallenfels and Hofmann 45 describing the reaction of the 1,4-dihydropyridine 51 with sulfurous acid. These workers suggested that the initial product of this reaction is the adduct 52, which can be rearranged to the sulphonic acid 53.

\[
\begin{align*}
\text{CONH}_2 & \quad \text{CONH}_2 \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

It does not seem that a mechanism of this type is operative in the present situation. An adduct similar to 52 would not be expected to be reduced to a stable material and, if a sulphonic acid is the initial product, it should be stable and resistant to further reduction. 46 Since the reac—
tion mixture was acidic to litmus paper, a reasonable mechanism for the production of the sulfinate 40 would involve protonation of the 1,4-dihydropyridine 39 at the 5-position of the pyridine ring followed by nucleophilic attack of dithionite ion on the 6-position to yield the sulfinate 40 and sulfur dioxide. Since the sulfur atoms in dithionite ion bear most of the negative charge and since the sulfur-sulfur bond is extraordinarily long (corresponding to a Pauling bond order of about one third) 61 , a reaction of this type is not surprising.

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

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

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

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

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

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

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
\text{N} & \quad \text{CN} \\
\text{N} & \quad \text{CN} \\
\end{align*}
\]
When the sodium dithionite reduction of the salt 38 was carried out in the presence of sodium bicarbonate and/or in contact with an immiscible solvent such as ether or chloroform, the dihydropyridine 39 did not come in contact with acid and could be isolated. Treatment of the dihydropyridine 39 with anhydrous hydrogen chloride in chloroform or with hydrochloric acid in methanol afforded the cyclic product 41. The nuclear magnetic resonance spectrum showed this to be the symmetrical product 41 rather than the isomeric product 42 (cf. Figure 4). Thus the scope of the cyclization has been extended and the intermediacy of the dihydropyridine firmly established. The successful formation of the benzoquinolizine further supported the possible biogenic importance of the reaction.

The remainder of this work was focused primarily on an attempt to gain evidence for, or against, the intermediacy of the indolenine (31) in the cyclization of the 1,4-dihydropyridine (29).
Attempted Isolation of an Indolenine by Lengthening the Side Chain

Preparation and Reductive Cyclization of \( \text{N}-(\text{indole-3-yl})\text{propyl}-3\)-cyanopyridinium Bromide (56). The study of the reductive cyclization of the indolylpropylpyridinium salt 56 was initiated since, by extending the chain connecting the indole and pyridine moieties by one carbon atom, the indolenine might be isolable, due to the sterically more favorable six-membered spiro-ring. The scheme for the preparation of the quaternary salt 56 started with indolepropionic acid (57) and followed the same route as in the preparation of the lower homolog 28. The acid 57 was synthesized from indole and acrylic acid according to the method of Johnson and Crosby.\(^{31}\) The acid 57 underwent reduction readily to the corresponding alcohol 58 with lithium aluminum hydride; however, the bromination with phosphorous tribromide gave only a dark red oil which was very unstable and could not be purified easily. This oil was assumed to be the bromide 59 on the basis of a positive Beilstein flame test for halogen and the lack of oxygen-hydrogen stretching absorption in the infrared spectrum.

Heating the bromide 59 with 3-cyanopyridine gave what appeared to be the desired salt 56 as an unstable oil which resisted all attempts at purification. Reduction of this material with sodium dithionite gave, after extensive purification, a small amount of material which appeared to be the
cyclic indole 62, rather than the cyclic indolenine 61 on the basis of the infrared and ultraviolet spectra (cf. Tables II and IV). No satisfactory carbon and hydrogen analyses for this material were obtained but the spectral data and a satisfactory analysis for the nitrogen content allow the assignment of the indole structure 62.

The fact that cyclization occurred is not surprising, since the reduction was again carried out under conditions which allowed the intermediate dihydropyridine 60 to come in contact with acid. That the indole product 62, rather than the corresponding indolenine 61, was isolated does not rule out the intermediacy of such an indolenine. The possibility of rearrangement of the indolenine 61 to the indole 62 must be considered. Thus, due to the experimental difficulties encountered in this series, it was decided to continue the study with a series containing a substituent on the 2-position of the indole ring.

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Blocking of the 2-position on the Indole Ring with a Phenyl Substituent

Preparation and Reduction of N-(2-phenylindol-3-yl)propyl-3-cyanopyridinium Bromide (63). The phenyl group was chosen as the blocking substituent with the hope of increasing the stability of the quaternary salt and its precursors. The phenylhydrazone of acetophenone, on treatment with polyphosphoric acid in the manner employed by Witkop\textsuperscript{32}, afforded 2-phenylindole (64). For large scale preparations, the yield of this reaction could be improved by treating acetophenone and phenylhydrazine directly with polyphosphoric acid without isolating the phenylhydrazone. Although the product from the latter method was quite impure, recrystallization of the product from high boiling ligroin gave the 2-phenylindole (64) of sufficient purity to make this method practical.

The Mannich base 68 was prepared according to the method of Kuhn and Stein.\textsuperscript{27} When running this reaction on a larger scale than reported, the acetic acid solvent must be increased nearly twice as much as the other reagents to avoid extensive dimerization. When a methanolic solution of the Mannich base 68 was allowed to stand with methyl iodide, a quantitative yield of tetramethylammonium iodide was isolated. The indole portion of the starting material was obtained as a viscous red oil which was not identified.

Madinaveitia\textsuperscript{33} obtained similar results on treating
gramine (54) with methyl iodide. He suggested that the indole product was the 3-hydroxymethylindole (70). The Mannich base 68 is odorless in the solid state, but in solution the pungent odor of dimethylamine is evident. This suggests that the Mannich base in solution is in equilibrium with its precursors and that the dimethylamine is preferentially quaternized upon addition of methyl iodide. The oily indole product may be the diindolylmethane 69 resulting from the reaction of 2-phenylindole and formaldehyde.34

\[
\text{\begin{align*}
\text{64} & \quad \text{+ CH}_2\text{O} + (\text{CH}_3)_2\text{NH} \quad \rightleftharpoons \quad \text{68} \\
\text{+ CH}_3\text{I} & \quad \text{69}
\end{align*}}
\]

Treatment of the Mannich base 68 with sodium cyanide, in the same manner used in the preparation of indole acetic acid (32), gave26 only a very small yield of what appeared, from the infrared spectrum, to be 2-phenylindol-3-yl acetamide (71). This material was quite resistant to hydrolysis and was recovered unchanged after treatment with lithium aluminum hydride for two hours.

Snyder and coworkers35 had prepared indol-3-ylpropionic

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acid (57) by alkylating malonic ester with gramine (54) in the presence of potassium hydroxide, followed by hydrolysis and decarboxylation. Thus ethyl cyanoacetate was alkylated with 2-phenylgramine (58). However, the alkylation product, after hydrolysis, was unstable and decomposed on attempted decarboxylation.

The 2-phenylindol-3-ylpropionic acid (65) was prepared by treating 2-phenylindole (64) with acrylic acid and acetic anhydride. Recrystallization of the acid 65 from alcohol caused esterification. Reduction of the acid 65 with lithium aluminum hydride afforded the alcohol 66 in good yield. When a sample of the alcohol 66 was recrystallized by allowing a benzene solution of it to evaporate at room temperature, the product exhibited no oxygen-hydrogen absorption in the infrared spectrum. Carbon and hydrogen analyses also indicated that the alcohol 66 had undergone transformation but the product was not characterized. Molecular models of the acid 65 and the alcohol 66 indicate that, when the phenyl ring is nearly coplanar with the indole ring, a condition required for maximum resonance stabilization of the system, strong steric interaction is encountered between the ortho-hydrogen of the phenyl substituent and the substituent on the 3-position of the indole ring. Kamlet and Dacons found, from a comparative study of the ultraviolet absorption spectra of 2-arylindoles, that in 2-phenyltryptophan (73), the phenyl ring is forced 36° out of the plane of the indole ring.
Further inspection of the models indicates that a favorable conformation of the side chain on the 3-position of the indole ring, due to the steric requirement of the phenyl ring, is one in which the terminal group lies over the plane of the five-membered ring of the indole nucleus. Thus, the unusually facile esterification of the acid 65 and the transformation of the alcohol may be due to some intramolecular catalytic action by the pyrrole part of the indole nucleus.

The large steric requirements of the phenyl ring may also account for the instability of the bromide 67 and the salt 63. Several attempted preparations of the bromide 67, in the manner used in the previous two cases, resulted in recovery of the starting alcohol 66 or in total decomposition. Finally, by heating a benzene solution of the alcohol 66 and phosphorous tribromide with a few drops of pyridine, a good yield of the bromide 67 was obtained.

\[ \text{Further reaction equations and structures are shown here.} \]
No attempted quaternization of 3-cyanopyridine with the bromide 67, however, was successful. In every case only a dark, heat-sensitive, ether-insoluble oil was obtained. This material resisted all attempts at purification. Reduction of the crude oil with sodium dithionite, in the presence of a small amount of sodium bicarbonate, resulted in a crude oily product which appeared, from its infrared spectrum, to be a mixture of the 1,4-dihydropyridine 74 and unreacted salt 63. This mixture was quite unstable and could not be separated.

Thus it seems that the phenyl substituent on the 2-position does not confer the desired stability on the indole system, but actually contributes to the instability of the system due to the steric interference at the 3-position of the indole ring. For this reason the 2-phenylindole series was abandoned.
Preparation and Reductive Cyclization of N-(β-(2-methylindol-3-yl)ethyl)-3-cyanopyridinium Bromide (77).

Since the phenyl substituent on the 2-position of the indole ring proved unfavorable, due to its large steric requirement, the smaller methyl group was employed as the blocking substituent. The synthesis of ethyl 2-methylindol-3-ylpropionate (78) has previously been reported. This material was converted in good yield to the alcohol 79. However, due to previous synthetic difficulties involving the propyl side chain, it was decided to attempt the preparation of the salt with the ethyl side chain, 77. Although the product of the cyclization of 77 would be the indolenine 84 with a spiro-5-membered ring, if an indolenine were formed, 84 was expected to be isolable. The 2-methyl-3-spiro-pentanoidolenine 85 is a known compound and is quite stable.

The reaction scheme for the preparation and reductive cyclization of the salt 77 is outlined in Figure 2. The method reported for the preparation of the propionate ester 78 was readily extended to the preparation of the acetate ester 80. Reduction to the alcohol 81, followed by bromination, afforded the halide 82. The alcohol 81 and the bromide 82 had previously been prepared. Quaternization of 3-cyanopyridine with the bromide 82 in the usual manner gave the desired salt 77.
\[
\text{CH}_3\text{CCH}_2\text{CH}_2\text{COOH} + \text{C}_6\text{H}_5\text{NNH}_2\cdot\text{HCl} \rightarrow \text{H}_2\text{SO}_4 \rightarrow \text{C}_6\text{H}_5\text{OH}(\text{abs.}) \rightarrow \text{C}_6\text{H}_5\text{CNH}_2 \rightarrow \text{LiAlH}_4 \rightarrow \text{PBr}_3 \rightarrow \text{Na}_2\text{S}_2\text{O}_4 \rightarrow \text{NaHCO}_3 \rightarrow \text{H}^+ \rightarrow
\]

Fig. 2

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A suspension of the salt 77 in aqueous sodium bicarbonate, over a layer of chloroform, was treated with sodium dithionite. The product, as evidenced by its infrared spectrum (cf. Table I), was the dihydropyridine 83. Treatment of this dihydropyridine with anhydrous hydrogen chloride in chloroform, or better, with aqueous hydrochloric acid added to a methanolic solution with a steam of nitrogen bubbling through, afforded a solid, the infrared and ultraviolet spectra of which indicated the 1,4,5,6-tetrahydropyridine system. Quantitative analyses for carbon, hydrogen, and nitrogen showed this material to be isomeric with the dihydropyridine 83. Thus this material must be a cyclization product of the dihydropyridine 83.

There are four reasonable products which may result from electrophilic attack on the indole ring by the 6-carbon atom of the pyridine system. The first of these is the indolenine 84 resulting directly from attack at the 3-position of the indole ring. The second, the indolenine 87, would result from acid catalyzed rearrangement of the indolenine 84 or from initial attack at the 2-position of the indole nucleus, followed by a 1,2-shift of the methyl group. The other two possible structures both retain the indole nucleus. One of these, 88, could arise from electrophilic attack at the 4-position of the indole ring and the other, 86, from attack directly on the 2-methyl group.

There are several obvious differences between an indole and an indolenine. The most marked, of course, is the
presence of a hydrogen on the nitrogen in the indole system. The presence of absorption in the nitrogen—hydrogen stretching region of the infrared spectrum of the cyclization product at 3470 cm⁻¹ and 3340 cm⁻¹ (cf. Table II) is good evidence for the presence of the indole system rather than the indolenine system. A second difference between the two systems lies in the relative basicities of the nitrogen atoms. The nitrogen in the indole ring system is very weakly basic, whereas the indolenine system contains a strongly basic nitrogen. The spiro-pentanoindolenine readily forms a salt on treatment with hydrochloric acid. Thus, if the cyclization product were an indolenine, it should have been isolated from the reaction mixture as a hydrochloride salt. That this was not the case was apparent from the analytical data and the lack of absorption in the stretching region of the infrared spectrum.

The presence of a carbon—nitrogen double bond in the indolenine structures, constitutes another means of eliminating these structures from consideration. The indolenine carbon—nitrogen double bond should be reduced by sodium borohydride; however, a sample of the cyclization product, when treated with sodium borohydride, showed no change in its ultraviolet spectrum.

Thus, it appears that the cyclization product is not an indolenine and, further, that an indolenine is not intermediate in the cyclization of 1,4-dihydropyridines to the
corresponding indoloquinolizine derivatives.

The distinction between the two possible indole products is less apparent. The fact that a methyl group on the 2-position of an indole ring is active has been demonstrated. Szmuszkovicz isolated the carbazole by warming 2-methylindole (90) with methylvinylketone and oxidizing the product with hydroquinone.

\[
\begin{align*}
\text{Indole} & \quad + \quad \text{CH}_2=\text{C} & \xrightarrow{\text{Hydroquinone}} & \text{Carbazole} \\
\text{(90)} & \quad & & \text{(89)}
\end{align*}
\]

The 4-position of the indole nucleus is the position of lowest electron density and electrophilic attack at that site seems unlikely under the conditions of the cyclization. An analogy for a cyclization of this type may be drawn from the work of Ager and May. These workers reported the successful cyclization of the tetrahydropyridine to the bicyclic system. Although the site of cyclization in the case reported by these workers may be more receptive toward electrophilic attack than the 4-position of the indole nucleus, the fact that the electrophile is a hindered olefinic double bond, rather than an unhindered enamine double bond, makes this a poor analogy. It is worth comparing the conditions employed in both instances, however. In the work herein reported, the
cyclization took place almost instantaneously at room temperature, while the cyclization of 91 required twenty hours at 135–140° in the presence of 48% hydrobromic acid. It would be most surprising, if electrophilic attack at the 4-position of the indole ring occurred under such mild conditions as reported here.

The nuclear magnetic resonance spectrum of the cyclization product, although it did not allow unequivocal assignment of the structure 86 (cf. Figure 6) was inconsistent with structure 88. The relative integrated intensities of the bands require four aromatic hydrogens on the indole nucleus. This fact, along with the loss of absorption due to the methyl group in the infrared spectrum, allows assignment of the structure 86 to the product from the cyclization of the dihydropyridine 83.

91

92

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Spectral Studies of 1,4-Dihydro- and 1,4,5,6-tetra-
hydropyridines. During the course of this investigation,
due to the instability of several of the materials obtained,
spectral techniques were necessary for analytical purposes.
In two cases nuclear magnetic resonance was employed as an
aid in structural elucidation. Ultraviolet spectroscopy
proved useful in distinguishing between dihydropyridines and
tetrahydropyridines and in studying reactions from which no
stable material could be isolated. By far, however, the
major portion of the spectral evidence was obtained with an
infrared spectrophotometer.

a. Infrared spectra

Two infrared spectrophotometers were employed in
this work. Most of the spectra determined in the earlier
part of this investigation were recorded on a Perkin-Elmer
Model 21 Infrared Spectrophotometer. The spectra determined
in the later work were obtained from a Perkin-Elmer Model
137B Infracord. The Infracord afforded better resolution
and, once it became available, was preferable for routine
analytical spectra. The major disadvantage of this instru-
ment, and the only one encountered in the present investi-
gation, is the small size of the chart paper on which the
spectrum is recorded. This makes precise readings of the
positions of the bands difficult (an error of 10 cm\(^{-1}\) is
possible in the carbon-hydrogen stretching region). This
difficulty was compounded by the fact that, in several in-
stances, spectra determined with one instrument were com-
pared with spectra obtained with the other. Also, most spectra of the pyridinium salts and the tetrahydropyridines were determined as halocarbon mulls in the region from 4000 cm\(^{-1}\) to 1300 cm\(^{-1}\) and Nujol mulls from 1300 cm\(^{-1}\) to 650 cm\(^{-1}\), whereas most spectra of the corresponding dihydropyridines were determined in the liquid phase as films. The dihydropyridines were generally obtained as oils which did not crystallize. These problems obviate any meaningful discussion of small changes in intensity or minor shifts in wavelength of absorption involved in the transition from pyridinium salt to dihydropyridine or from dihydropyridine to tetrahydropyridine. Consequently, the bands discussed in this section and those listed in Tables I and II are only those bands which represent gross changes involved in the transition from one system to another and may be said to be truly characteristic of the given system. An error of 10 cm\(^{-1}\) in the oxygen–hydrogen, nitrogen–hydrogen, and carbon–hydrogen stretching regions and 5 cm\(^{-1}\) in other regions should be allowed for the spectra obtained with the Infraord.

The spectra are listed in Tables I and II according to the number of the compound and the number of the spectrum. The spectrum number is preceded by the number "21", indicating that it was obtained with the Model 21 spectrophotometer, or by the letters "In", referring to the Infraord spectrophotometer. All infrared spectra are on file at the University of New Hampshire.

Nelson\(^{20}\) has studied the changes exhibited in the
infrared spectra of various 3-substituted pyridines on conversion to the quaternary salt. This study was quite complete and the spectra of the pyridinium salts obtained in the present investigation correlate well with the characteristic absorption reported. Nelson also reported the infrared spectra of several dihydropyridines and indicated the characteristic changes involved in the transition from quaternary salt to dihydropyridine. However, in every case reported, the 3-substituent on the pyridine ring contained a carbonyl group. Since the 3-substituent markedly affects the spectral properties of the 1,4-dihydropyridines, it is not surprising that the spectra of the 3-cyano-1,4-dihydropyridines are quite different from those reported. Thus in Table I are listed bands which represent gross differences between the spectrum of the particular 3-cyano-1,4-dihydropyridine and the spectrum of the salt from which it was obtained.

The dihydropyridine 21 was obtained as a solid. The other dihydropyridines, 22, 23, 24, 25, and 26, were obtained as oils. These oils bound polar solvents rather tenaciously as evidenced by the appearance of absorption at 3500–3400 cm⁻¹. This absorption is assigned to water and is present even in the absence of nitrogen–hydrogen stretching absorption. In fact, the dihydropyridine 24, which was stable enough to be sent for analysis, contained a molecule of water.

Generally, a consideration of the structural differences between a pyridinium salt and a 1,4-dihydropyridine, suggests several differences which should be present in the
carbon-hydrogen stretching region. A single vinyl hydrogen at the 2-position of the dihydropyridine ring along with the cis vinyl hydrogens at the 5- and 6-positions should show absorption between 3040 and 3010 cm\(^{-1}\); the methylene group generated at the 4-position would be expected to absorb near 2930 cm\(^{-1}\) and 2850 cm\(^{-1}\). In every case, however, the substituent on the pyridine nitrogen contained aromatic hydrogens and at least one methylene group. Consequently, absorption in these regions is not obviously characteristic of the dihydropyridine system.

The 2200 cm\(^{-1}\) region, on the other hand, is much more useful. The nitrile absorption in 3-cyanopyridine appears as a strong, sharp band at 2245 cm\(^{-1}\). In all cases, on quaternization of 3-cyanopyridine, the nitrile absorption appears between 2255 cm\(^{-1}\) and 2235 cm\(^{-1}\). In the salts, however, the band is extremely weak and is not seen unless the spectrum is determined as a concentrated mull. After reduction to the corresponding 1,4-dihydropyridine, this band appears as a very strong, sharp peak between 2210 cm\(^{-1}\) and 2195 cm\(^{-1}\).

Bellamy\(^{53}\) lists the limits for nitrile absorption as 2260 to 2215 cm\(^{-1}\) with few examples in the lower range. The remarkably low absorption in the case of the dihydropyridines suggests a unique structural effect. Druy and Schenker\(^{23}\) in their discussion of the spectrum of N-methyl-1,4-dihydro-3-cyanopyridine (26), suggest that the dihydropyridine is actually a resonance hybrid. Considering the dihydropyridine system as a resonance hybrid of the canonical forms shown in
Figure 3, an explanation of the absorption at 2200 cm$^{-1}$ is available.

![Diagram of molecular structures](image)

**Fig. 3**

One compound with the C=C=N bond system is known, and it absorbs at 2045 cm$^{-1}$. That diazomethane (H$_2$C=N=N) and carbodiimides (R–N=C=N–R) show absorption at 2110 cm$^{-1}$ and 2150 cm$^{-1}$ respectively, also argues for a large contribution of the dipolar canonical form B to the resonance hybrid. The stability conferred on the nitrile group in this system is considerable. The nitrile is quite unreactive and resisted all attempts at hydrolysis.

In addition to the strong absorption near 2200 cm$^{-1}$, there are two other bands which allow identification of the 3-cyano-1,4-dihydropyridines. These bands occur at 1680–1675 cm$^{-1}$ and 1605–1595 cm$^{-1}$ and are both very strong. Druey and Schenker assigned these bands to C=C and/or C=N stretching vibrations but made no attempt to distinguish between them.

Nelson$^{20}$ found that the strong band at 1603–1592 cm$^{-1}$ in the infrared absorption of various pyridines is shifted to 1662–1625 cm$^{-1}$ on quaternization, accompanied by a decrease
in intensity. This band, in the pyridinium salts, was assigned to the C=N# stretching vibration. The spectra of the 3-cyano-pyridinium salts all contain a band at 1637–1627 cm\(^{-1}\) of medium to strong intensity.

An assignment of the 1680 cm\(^{-1}\) band to the C=C stretching vibration of the 5,6-double bond and the 1605 cm\(^{-1}\) band to the C=N# vibration can be made. This suggests a high contribution of the canonical form B to the resonance hybrid. The high energy absorption of the 5,6-double bond suggests that there is very little conjugative effect and that the canonical form C makes little contribution to the ground state resonance hybrid.

These assignments are supported by a consideration of the spectra of the corresponding 3-cyano-1,4,5,6-tetrahydropyridine derivatives. In the tetrahydropyridines the absorption at 1680 cm\(^{-1}\) disappears and the 1605 cm\(^{-1}\) band shifts to 1630 cm\(^{-1}\). The 1630 cm\(^{-1}\) absorption is in the region of the C=N# stretching vibration seen in the quaternary salts and suggests that the canonical form analogous to B, with a saturated 5,6-bond, makes an even greater contribution to the resonance hybrid of the tetrahydropyridine than does B to the resonance hybrid of the dihydropyridine. The large contribution of the polar form is reflected in the high melting points of the tetrahydropyridines and their general insolubility in non-polar solvents.

The enamines resulting from the reaction of pyrroliidine or morpholine with cyclohexanone and N-methyl-4-piperi-
done exhibit strong absorption near 1650 cm\(^{-1}\) in their infra-red spectra. In these cases the p-electrons on the nitrogen atom are free to overlap with the \(\pi\) electrons of the double bond and hence, the absorption occurs at lower frequency than that of the relatively unconjugated 5,6-double bond of the dihydropyridine system.

The remaining bands in the dihydropyridine spectra are less useful for purposes of identification. As mentioned before, the main structural differences between the pyridinium salts and corresponding 1,4-dihydropyridines are the methylene group at the 4-position, the \textit{cis} vinyl hydrogens at the 5,6-positions, and the single vinyl hydrogen on the 2-position of the dihydropyridine ring. The absorption due to the methylene group is of little use in the cases studied. The characteristic absorption due to the out of plane deformation of the \textit{cis} vinyl hydrogens at 824-700 cm\(^{-1}\) is generally obfuscated by absorption of the aromatic nuclei. Medium to weak absorption at 715-705 cm\(^{-1}\) appears in all spectra of dihydropyridines which may be attributed to these hydrogens.\textsuperscript{53} The spectra of all of the dihydropyridines examined have a strong to medium band at 1418-1407 cm\(^{-1}\) which can be assigned to the in-plane bending mode of the \textit{cis} vinyl hydrogens.

The other bands which appear to be characteristic of the dihydropyridine system are not readily assigned. Several spectra show a strong to medium band at 1360 cm\(^{-1}\) where only weak absorption was apparent in the corresponding quaternary salts. Strong to medium absorption appeared in all spectra,
except those of the cyanide addition products, 92 and 94, at 1315–1320 cm\(^{-1}\) and in every case at 1180–1145 cm\(^{-1}\). Two other bands of variable intensity, which appeared to be characteristic of the dihydropyridine system, were seen at 1050–1012 cm\(^{-1}\) and 1000–970 cm\(^{-1}\). By and large, however, the most characteristic absorption of the 3-cyano-1,4-dihydropyridine is that occurring near 2200 cm\(^{-1}\), 1660 cm\(^{-1}\), and 1605 cm\(^{-1}\).

The transformation of a 1,4-dihydropyridine to a 1,4,5,6-tetrahydropyridine is readily indicated by a comparison of the infrared spectra. Baldwin, in a study of the infrared and ultraviolet spectra of enammonitriles of the type H\(_2\)N–C=C–CN, assigned the bands occurring in the 1616–1608 cm\(^{-1}\) region to a C=C stretching vibration. This is not consistent with the data obtained from the tetrahydropyridines. As mentioned above, the physical properties of the tetrahydropyridines suggest that the charge-separated resonance form makes a larger contribution to the resonance hybrid in the case of the tetrahydropyridines than in the case of the dihydropyridines. Thus, for example, the dihydropyridines are insoluble. One would, therefore, expect the 2,3-carbon–carbon bond to have greater single bond character in the tetrahydropyridine. If the absorption at 1605 cm\(^{-1}\) in the dihydropyridines is assigned to the 2,3-carbon–carbon bond, a shift to lower frequency would be expected on conversion to the tetrahydropyridines. All of the tetrahydropyridines examined showed strong absorption at 1630 cm\(^{-1}\) as the most characteristic band in the spectrum. This shift to higher frequency on
going from dihydro- to tetrahydropyridines is better explained by assigning this absorption to the C=N⁺ vibration.

As may be expected, there was a slight shift to lower frequency in the 2200 cm⁻¹ region in the tetrahydropyridines. This shift, however, must be viewed skeptically since the spectra were determined in different states and this region of the spectrum is difficult to read with accuracy.

Except for the lack of absorption at 1680 cm⁻¹ and the presence of strong absorption at 1630 cm⁻¹, differences between the spectra of dihydro- and tetrahydropyridines are manifest by changes in intensity and shifts in the wavelength of absorption of various bands. Without rigid experimental control meaningful interpretations of these changes cannot be made. One change that is noticeable is the loss of absorption near 1420 cm⁻¹ and 705 cm⁻¹. These bands were assigned to the cis-olefinic hydrogens in the dihydropyridine system. New bands appear in the tetrahydropyridines near 1220 cm⁻¹, 1190 cm⁻¹, and 1060 cm⁻¹ but no assignment can be made for them.

A comparison of the infrared spectrum (In—73) of N-[γ-(2-phenylindol-3-yl)propyl]-3-cyanopyridinium bromide (63) with that (In—95) of the crude product of the reduction of this salt indicated that the reduction product was a mixture of the dihydropyridine 74 and unreacted salt 62. This was probably due to the insolubility of the material in the reaction medium.

The sulfinic acid salt 40 (21-3557) has the characteristic band at 1630 cm⁻¹ indicative of the tetrahydropyridine system. The strong absorption expected 44 near 1250 cm⁻¹ and
1150 cm\(^{-1}\) for the S-O bond is obscured. The cyclic dimethoxybenzoquinolizine \(\mathbf{11}\) also has strong absorption in this region and as a result, the spectrum of \(\mathbf{10}\) exhibits broad, poorly resolved absorption extending from 1235 cm\(^{-1}\) to 1135 cm\(^{-1}\).

Heating a methanolic solution of the sulfinate \(\mathbf{10}\) with methyl iodide in an attempt to make the methyl sulfone gave a product whose infrared spectrum (In-1237) showed it to be identical with the cyclic material \(\mathbf{11}\). Thus the sulfinate group must be readily displaced.

The infrared spectrum (In-2032) of the dihydropyridine bearing a methyl group on the 2-position of the indole nucleus, \(\mathbf{81}\), along with the spectra of its precursors, \(\mathbf{77}, \mathbf{80}, \mathbf{81},\) and \(\mathbf{82}\), has a strong band at 1460 cm\(^{-1}\) which may be assigned to the asymmetrical deformation vibration of the methyl group. This band is not present in the cyclization product giving strong evidence in support of the structure \(\mathbf{86}\).

b. Ultraviolet spectra

Druey and Schenker\(^{23}\) reported that the ultraviolet absorption spectrum of N-methyl-1,4-dihydro-3-cyanopyridine (26) showed a single maximum at 340 m\(\mu\) (\(\epsilon\) 5,600), and that the corresponding 1,4,5,6-tetrahydropyridine 27 absorbed at 278 m\(\mu\) (\(\epsilon\) 18,300). All of the dihydro- and tetrahydropyridines examined in the present investigation had maxima corresponding to those reported. N-Benzyl-1,4-dihydro-3-cyanopyridine (24) exhibited a maximum at 339 m\(\mu\) (\(\epsilon\) 6,600) and the corresponding tetrahydropyridine 25 had a maximum at 274 m\(\mu\). In many cases the dihydro- and tetrahydropyridines
were generated in solution and the spectra were determined on these solutions. Thus it was not possible to determine the extinction coefficients. The maxima determined for various dihydro- and tetrahydropyridines are listed in Tables III and IV and extinctions are listed only in those cases in which the spectra were determined with isolated samples of good purity.

The wavelength of absorption of the tetrahydropyridine chromophore, 270–280 m\(\mu\), on first consideration seems quite high. Wheeler\(^56\) reported absorption at 212 m\(\mu\) (\(\varepsilon = 11,200\)) for 1-cyanocyclohexene and a bathochromic shift of nearly 60 m\(\mu\) due to a \(\beta\)-amino substituent is quite large. This shift is best explained by considering a large amount of \(p-\pi\) conjugation involving the electron pair of the amino nitrogen atom and the \(\Pi\)-electrons of the \(\alpha,\beta\)-unsaturated nitrile system. This is essentially the same argument used in the interpretation of the absorption at 2200 cm\(^{-1}\) in the infrared spectra of these compounds (\textit{vide supra}).

The wavelength of absorption of the dihydropyridines at 340 m\(\mu\) is a result of the conjugative effect of the 5,6-double bond present in the dihydropyridine system. It will be recalled that lack of ground state overlap of the 5,6-double bond was invoked as an argument for the assignment, in the infrared spectra of the dihydropyridines, of the 1680 cm\(^{-1}\) band. The ultraviolet data do not negate the interpretation of the infrared data. The long wavelength absorption of the dihydropyridine system suggests that the overlap of the \(\Pi\)-electrons
of the 5,6-double bond with the β-amino-α,β-unsaturated nitrile system stabilizes the excited state of the dihydro-
pyridine chromophore. Similar overlap in the ground state is not required in order to explain this absorption. Thus over-
lap of the π-electrons of the 5,6-double bond appears to be of major importance in the excited state but not in the ground state.

Apart from the obvious analytical application, ultra-
violet spectroscopy was used to advantage in determining the feasibility of several reactions. Thus, the spectra of the salts 23, 28, 38, 63, and 77 were determined and a small amount of sodium dithionite was added directly to the sample cell. In each case an extremely strong band at 310 μm, due to the di-
thionite ion, formed immediately. This absorption decreased rapidly giving rise to absorption at 340 μm, indicative of the formation of the 1,4-dihydopyridine chromophore. This 340 μm band was masked in the spectrum of the reduction product of 63 due to the strong absorption of the 2-phenylindole chro-
mophore at 303 μm. The band at 340 μm diminished slowly on standing and rapidly on addition of a small amount of hydro-
chloric acid with concomitant increase of absorption in the 270 μm region, indicating the formation of the tetrahydropyri-
dine chromophore. If sodium bicarbonate was added to the cell before the addition of dithionite, the dihydropyridine band was quite stable until acid was added.

When the spectrum of the salt 77 was determined in sodium bicarbonate solution, weak absorption at 335 μm was
apparent. San Pietro\textsuperscript{57} suggested that cyanide ion attacks
the 4-position of the pyridinium ring in DPN and Karrer et al.\textsuperscript{58}
isolated a crystalline cyanide addition product of N-methyl-
nicotinamide. Anderson and Berkelhammer reported\textsuperscript{59} the action
of ethoxide, hydroxide, and cyanide ions on several 1-alkyl-
pyridinium salts having an electron withdrawing group on the 3-
position. These workers suggested that the hydroxide and
ethoxide ions reversibly attacked the 6-position of the pyri-
dinium ring on the basis of the ultraviolet data. The effect
of bicarbonate ion on the ultraviolet spectrum of 77 may be
similarly explained.

Addition of ethoxide ion to the indolylethylpyridinium
salt 28 resulted in weak absorption at 348 mp and an inflex-
tion at 240 mp in addition to absorption due to the salt. Al-
though these effects were very slight, it is worth mentioning
that N-methyl-1,6-dihydro-3-cyanopyridine absorbs at 349 mp
and at 240 mp.\textsuperscript{23} No effect was noticeable on addition of
hydroxide ion to a solution of 28 but these spectra were de-
termined on very dilute aqueous-methanolic solutions and an
equilibrium would lie in favor of the salt rather than a di-
hydropyridine. Addition of cyanide to a solution of the
quaternary salt 28 caused definite absorption at 335 mp. In
fact the crude cyanide addition products, 23 and 24, resulting
from attack of cyanide ion on the salts 23 and 28 respectively,
were isolable. Both of these adducts were unstable but gave
infrared and ultraviolet spectra indicative of the 1,4-dihydro-
pyridine system. A single attempt to cyclize the 3,4-dicyano-
1,4-dihydropyridine 94, resulting from the attack of cyanide ion on the salt 28, was unsuccessful.

\[ \text{\includegraphics[width=0.4\textwidth]{chemical Structures.png}} \]

\[ \text{\includegraphics[width=0.3\textwidth]{chemical Structures.png}} \]

93 94

c. **Nuclear magnetic resonance spectra.**

Nuclear magnetic resonance spectroscopy was employed in two cases as an aid in elucidating the structure of a cyclization product. In the first case there was some question as to the product from the cyclization of N-β -(3,4-di-methoxyphenyl)ethyl -1,4-dihydro-3-cyanopyridine (29). The infrared spectrum of this material was difficult to interpret in the 800–650 cm⁻¹ region and an unequivocal distinction between the symmetrical isomer \( \text{\includegraphics[width=0.2\textwidth]{symmetrical.png}} \), resulting from attack at the 6-position of the aromatic ring, and the unsymmetrical isomer \( \text{\includegraphics[width=0.2\textwidth]{unsymmetrical.png}} \), resulting from attack at the 2-position, could not be made. The nuclear magnetic resonance spectrum of this material is shown in Figure 5. Of particular interest is the aromatic portion of the spectrum between 6.67 and 6.90 ppm relative to tetramethylsilane. The absorption of the six methoxyl protons is readily seen as a strong sharp singlet at 3.90 ppm.

Relative to this peak for the methoxyl hydrogens, the three

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peaks at 6.67, 6.75, and 6.90 ppm represent the absorption of one proton each and are, therefore, three unsplit bands. It is apparent that any uncyclized material or the unsymmetrical cyclic isomer \( \text{II} \) would have a more complex splitting pattern in the aromatic region of the spectrum. The only structure which is consistent with this spectrum is the symmetrical cyclization product \( \text{I} \). Two of the bands in the aromatic region are due to the para-hydrogens on the aromatic ring and the third may be assigned to the vinyl hydrogen on the 2-position of the tetrahydropyridine ring. That this hydrogen appears at such low field is further reason for considering the \( \beta - \text{amino-} \alpha , \beta - \text{unsaturated nitrile system as a resonance hybrid.} \)

The nuclear magnetic resonance spectrum of the cyclization product of the dihydropyridine \( \text{83} \), with the methyl group on the 2-position of the indole ring, was much more difficult to interpret. Since the cyclization product was not soluble in the usual solvents employed in nuclear magnetic resonance studies, spectra were determined in dioxane and in pyridine. The bands which were not obscured by the particular solvent employed are shown in Figures 6 and 7.

Consideration of the possible structures for the cyclization product, \( \text{84, 86, 87, and 88} \), suggests significant differences in the nuclear magnetic resonance spectra. The indolenines \( \text{84} \) and \( \text{87} \) and the indole \( \text{88} \) should exhibit strong, unsplit absorption due to the methyl group present in these structures whereas the cyclic indole, \( \text{86} \), should have no un-
split absorption. The cyclic indoles \( \text{86} \) and \( \text{88} \) would be expected to show a difference in intensity of absorption in the aromatic region, \( \text{86} \) containing four aromatic hydrogens plus the hydrogen on the 2-position of the tetrahydropyridine ring and \( \text{88} \) having three aromatic hydrogens in addition to the tetrahydropyridine hydrogen.

The spectrum obtained in dioxane (cf. Fig. 6) distinguished readily between the cyclic indole isomers, \( \text{86} \) and \( \text{88} \). Assuming that the absorption appearing at 9.43 ppm is due to the single hydrogen on the indole nitrogen or that the multiplet at 1.91 ppm is due to two hydrogens (the only assumptions which give results consistent with the analytical data) the multiplet at 7.12 ppm may be said to represent the absorption of five hydrogen atoms. Thus the indole structure \( \text{88} \), resulting from electrophilic attack at the 4-position of the indole nucleus, was eliminated from consideration.

The presence of absorption at 9.43 ppm assigned to the hydrogen on the indole nitrogen is evidence against the indolenine structures \( \text{84} \) and \( \text{87} \). The point of ambiguity in the interpretation of these spectra is the presence of unsplit absorption at 2.58 ppm in dioxane and at 2.93 ppm in pyridine. This unsplit band is not explicable on the basis of the structure \( \text{86} \). The relative integrated intensity of this band, however, indicated that it represented slightly less than two hydrogens. This is not consistent with the presence of a methyl group. A possible explanation for the presence of this band is available on closer inspection of
the two spectra. The position of the bands in the pyridine spectrum are seen to be at higher field than the same bands in dioxane. This shift is due to the diamagnetic shielding effect of the \( \Pi \)-electrons in the pyridine. The magnitude of the shift varies with the particular band since the amount of shielding depends on the steric approach of the solvent molecules. The sharp, unsplit peak at 2.58 ppm in dioxane, however, appears at 2.93 ppm in pyridine. A shift of a band to lower field in pyridine solution is generally considered to be due to bonding of the given proton to the basic nitrogen of the solvent. This suggests that the band at 2.93 ppm in pyridine and at 2.58 ppm in dioxane is spurious and is probably due to an impurity such as water. Indeed, Mavel has studied the effect of solvent on the chemical shift of water and his results are consistent with this interpretation.

Disregarding the absorption at 2.93 ppm a tentative assignment of the bands in the pyridine spectrum (cf. Fig. 7) be made on the basis of the structure 86. The multiplet at 1.67 ppm, including the band at 1.88 ppm, is assigned to the 

![Diagram](image_url)
hydrogens at A split by the B hydrogens and the C hydrogen. The hydrogens at B appear as a finely split doublet centered at 2.15 ppm. The single hydrogen C, finely split by the A and D hydrogens, appears near 3.31 ppm and the multiplet centered near 3.55 ppm is assigned to the methylene group adjacent to the nitrogen atom. C appears at higher field than the D hydrogens due to the diamagnetic shielding effect of the indole nucleus. Inspection of models shows this to be reasonable. The absorption due to the E protons of the two methylene groups adjacent to the indole nucleus is centered near 2.98 ppm.

The position of the methylene protons, D, is lower than that expected for methylene protons adjacent to an amino-nitrogen atom and is further evidence for the representation of the \( \beta \)-amino-\( \alpha,\beta \)-unsaturated nitrile system as a resonance hybrid. The partial positive charge conferred on the nitrogen atom in the resonance hybrid would cause a shift of the absorption of the adjacent methylene hydrogens to lower field. That the absorption of the hydrogen on the 2-position of the tetrahydropyridine ring appears in the aromatic region also supports this. Some idea of the magnitude of the contribution of the polarized form to the resonance hybrid of the \( \beta \)-amino-\( \alpha,\beta \)-unsaturated nitrile system may be drawn from a comparison of the chemical shift of the hydrogen on the 2-position of the tetrahydropyridine ring, near 7.0 ppm, with the indole derivatives reported by Witkop and Daly and the 1,4-dihydropyridine reported by Kosower and Sorensen. These
are shown in Figure 4.

Fig. 4
### TABLE I

**Characteristic Infrared Absorption Bands of the 1,4-dihydro-3-oxanopyridine System**

<table>
<thead>
<tr>
<th>Sample Spectrum Number</th>
<th>Bands</th>
</tr>
</thead>
<tbody>
<tr>
<td>21^b</td>
<td>2198(S) 1680(S) 1605(S) 1407(S) 1320(S) 1175(S) 1160(M) 985(S) 710(M)</td>
</tr>
<tr>
<td>29^b</td>
<td>In-1662 3500(M) 2205(S) 1675(S) 1605(S) 1410(S) 1315(M) 1170(M) 1040(M) 995(M) 715(M)</td>
</tr>
<tr>
<td>39^c</td>
<td>In-1565 3550(M) 2200(S) 1680(S) 1605(S) 1418(S) 1320(M) 1175(M) 1030(M) 970(W) 705(W)</td>
</tr>
<tr>
<td>83^c</td>
<td>In-2032 3500 (S-B) 2210(S) 1675(S) 1605(S) 1415(S) 1318(M) 1175(S) 1140(M) 1050(M) 1000(M) 715(M)</td>
</tr>
<tr>
<td>93^c</td>
<td>In-2294 3440(M-B) 2230(W) 1675(S) 1580(S) 1415(S) 1180(S) 1120(S)</td>
</tr>
<tr>
<td>94^d</td>
<td>In-2579 3470(S) 2205(S) 1675(S) 1592(S) 1412(S) 1195(S) 1125(M) 1012(M)</td>
</tr>
</tbody>
</table>

^aBands are listed in cm⁻¹; S = strong, M = medium, W = weak, and B = broad.

^bDouble mull

^cFilm

^dChloroform solution
TABLE II

Characteristic Infrared Absorption Bands of the 1,4,5,6-tetrahydro-3-cyanopyridine System

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>Spectrum Number</th>
<th>2200(S)</th>
<th>1630(S)</th>
<th>1420(M)</th>
<th>1066(M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(^b)</td>
<td>In-1749</td>
<td>3250(S-B)</td>
<td>2195(S)</td>
<td>1630(S)</td>
<td>1433(M)</td>
</tr>
<tr>
<td>30(^c)</td>
<td>21-1669</td>
<td>32470(W)</td>
<td>2200(S)</td>
<td>1630(S)</td>
<td>1470(M)</td>
</tr>
<tr>
<td>41(^c)</td>
<td>In-2509</td>
<td>3340(M)</td>
<td>2200(S)</td>
<td>1630(S)</td>
<td>1470(M)</td>
</tr>
<tr>
<td>66(^c)</td>
<td>In-2061</td>
<td>3340(M)</td>
<td>2200(S)</td>
<td>1630(S)</td>
<td>1470(M)</td>
</tr>
<tr>
<td>62(^c)</td>
<td>21-2039</td>
<td>3340(M)</td>
<td>2180(S)</td>
<td>1615(S)</td>
<td>1463(M)</td>
</tr>
<tr>
<td>40(^c)</td>
<td>21-3557</td>
<td>3450(W-B)</td>
<td>2175(S)</td>
<td>1625(S)</td>
<td>1420(S)</td>
</tr>
</tbody>
</table>

\(^a\) Bands are listed in cm\(^{-1}\); S = strong, M = medium, W = weak, B = broad, and Sh = shoulder.

\(^b\) Film

\(^c\) Double null

\(^d\) Unresolved
### TABLE III

**Ultraviolet Absorption of Pyridinium Salts and Their Transformation Products**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Absorption maxima in m u</th>
</tr>
</thead>
<tbody>
<tr>
<td>63&lt;sup&gt;a&lt;/sup&gt;</td>
<td>300; 278&lt;sup&gt;b&lt;/sup&gt;; 223</td>
</tr>
<tr>
<td>63&lt;sup&gt;a&lt;/sup&gt; + Na&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>350&lt;sup&gt;c&lt;/sup&gt;; 300</td>
</tr>
<tr>
<td>28&lt;sup&gt;a&lt;/sup&gt;</td>
<td>287&lt;sup&gt;b&lt;/sup&gt; (5,600); 270 (6,200); 218 (31,000)</td>
</tr>
<tr>
<td>28&lt;sup&gt;a&lt;/sup&gt; + Na&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>340; 288&lt;sup&gt;b&lt;/sup&gt;; 280</td>
</tr>
<tr>
<td>28&lt;sup&gt;a&lt;/sup&gt; + NaCN</td>
<td>335; 289; 280; 240&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>28&lt;sup&gt;a&lt;/sup&gt; + NaCN + HCl</td>
<td>287&lt;sup&gt;b&lt;/sup&gt;; 268</td>
</tr>
<tr>
<td>28&lt;sup&gt;a&lt;/sup&gt; + NaOCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>348&lt;sup&gt;a&lt;/sup&gt;; 288&lt;sup&gt;b&lt;/sup&gt;; 270; 240&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>28&lt;sup&gt;a&lt;/sup&gt; + NaOCH&lt;sub&gt;3&lt;/sub&gt; + HCl</td>
<td>287&lt;sup&gt;b&lt;/sup&gt;; 280&lt;sup&gt;b&lt;/sup&gt;; 266</td>
</tr>
<tr>
<td>18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>284&lt;sup&gt;b&lt;/sup&gt; (4,700); 270 (8,600); 224 (20,400)</td>
</tr>
<tr>
<td>18&lt;sup&gt;a&lt;/sup&gt; + Na&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>340; 273</td>
</tr>
<tr>
<td>77&lt;sup&gt;d&lt;/sup&gt;</td>
<td>286 (5,800); 271 (10,100)</td>
</tr>
<tr>
<td>77&lt;sup&gt;a&lt;/sup&gt; + Na&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>340; 287; 272</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined in 60% methanol  
<sup>b</sup>Shoulder  
<sup>c</sup>Inflection  
<sup>d</sup>Determined in methanol

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### TABLE IV

**Ultraviolet Absorption Maxima of Dihydro- and Tetrahydropyridines**

<table>
<thead>
<tr>
<th>Compound Number</th>
<th>Wavelength of Absorption in Millimicrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>340 (6,600)</td>
</tr>
<tr>
<td>25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>274</td>
</tr>
<tr>
<td>26&lt;sup&gt;b&lt;/sup&gt;</td>
<td>340 (5,600)</td>
</tr>
<tr>
<td>27&lt;sup&gt;b&lt;/sup&gt;</td>
<td>278 (18,300)</td>
</tr>
<tr>
<td>30&lt;sup&gt;a&lt;/sup&gt;</td>
<td>289&lt;sup&gt;c&lt;/sup&gt;; 278 (20,460); 223 (20,830)</td>
</tr>
<tr>
<td>62&lt;sup&gt;a&lt;/sup&gt;</td>
<td>276 (22,400); 224 (31,400)</td>
</tr>
<tr>
<td>40&lt;sup&gt;a&lt;/sup&gt;</td>
<td>276 (20,000); 230 (8,330)</td>
</tr>
<tr>
<td>41&lt;sup&gt;a&lt;/sup&gt;</td>
<td>280; 231</td>
</tr>
<tr>
<td>86&lt;sup&gt;a&lt;/sup&gt;</td>
<td>289&lt;sup&gt;c&lt;/sup&gt;; 279; 223</td>
</tr>
<tr>
<td>93&lt;sup&gt;d&lt;/sup&gt;</td>
<td>327</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined in methanol solution

<sup>b</sup> Determined in 95% ethanol

<sup>c</sup> Shoulder

<sup>d</sup> Determined in ether solution
Fig. 5 — Nuclear Magnetic Resonance Spectrum of 47

The author is indebted to the Central Research Laboratories of E. I. DuPont de Nemours for determining and interpreting this spectrum.
The author is indebted to Dr. Francis J. Evans for obtaining this spectrum.

b The bands are listed in parts per million relative to tetramethyldisilane.
EXPERIMENTAL

GENERAL

Melting points were determined on a Kofler hot stage equipped with a polarizing microscope and are uncorrected.

Infrared spectra were determined on a Perkin-Elmer Model 21 Infrared Spectrophotometer and on a Perkin-Elmer Model 137B Infracord Spectrophotometer equipped with sodium chloride optics. All infrared spectra are on file at the University of New Hampshire and are listed by number. The spectra determined on the Model 21 Spectrophotometer are indicated by the number "21", whereas those spectra determined on the Infracord are indicated by the letters "In", preceding the spectrum number.

Infrared spectra determined on liquid samples were run neat, as films. Spectra of solid samples were generally determined as mulls in Halocarbon oil (from 4000 cm\(^{-1}\) to 1300 cm\(^{-1}\)) and Nujol (from 1300 cm\(^{-1}\) to 600 cm\(^{-1}\)). Specific mention is made of the solvent employed for those few infrared spectra determined in solution.

Ultraviolet spectra were determined on a Perkin-Elmer Model 4000 Spectracord Recording Spectrophotometer. The spectra of most quaternary salts were determined in 60% methanol. All other spectra were determined in anhydrous methanol solution unless otherwise mentioned.
The nuclear magnetic resonance spectrum of **41** was determined with a Varian Model A—60 proton resonance spectrometer in deuterochloroform solution. The nuclear magnetic resonance spectra of **86** were determined with a Varian Model HR—60 spectrometer.

Elemental analyses were by Schwartzkopf Microanalytical Laboratories, Woodside, New York.
Preparation of 2-phenylindole (64). A mixture of 60 g. (0.5 mole) of acetophenone and 54 g. (0.5 mole) of phenylhydrazine was heated on a steam cone for 1 hr. and poured into water. The light yellow solid (21-1883) was removed by filtration and washed with petroleum ether. Half of this material was added to 100 ml. of polyphosphoric acid and warmed on the steam cone. The temperature rose to 130° and the mixture was poured into ice water. The light yellow solid, m.p. 181-183° (lit. a, m.p. 186°) (21-1662), which was removed by filtration, amounted to 20 g. (42%). Yields of up to 80% were obtained by mixing the same amounts of acetophenone and phenylhydrazine with polyphosphoric acid and heating on the steam cone to initiate the reaction. The temperature was kept below 200° by cooling in a water bath when necessary. The 2-phenylindole (64) obtained in this manner was less pure, m.p. 170-177°, and more highly colored but it was readily purified by recrystallization from ligroin (b.p. 100-115°).

Preparation of 3-piperidinomethyl-2-phenylindole. The method used was essentially that of Kuhn and Stein 27, wherein 70 g. of acetic acid was added to a 7.2 g. of piperidine cooled to 5°. The mixture was cooled to 5° and 6.1 g. of 40% Formalin solution was added. The mixture was shaken and poured into a flask containing 15 g. of 2-phenylindole (64). The flask was shaken until solution was complete. After standing overnight, the mixture was poured slowly into
a stirred solution of 23 g. of sodium hydroxide in 170 ml. of water. The mixture was cooled, and the solid which separated was removed by filtration. Recrystallization from methanol afforded 7 g. (34%) of the Mannich base, m.p. 75–77° (21-1704).

Preparation of 3-dimethylaminomethyl-2-phenylindole

(68). 27 A 54 g. sample of 25% dimethylamine, 10.24 ml. of 37% formaldehyde, and 40 ml. of glacial acetic acid, all at 5°, were mixed. The mixture was cooled to 5° and poured into a flask containing 28.9 g. of 2-phenylindole (6). The flask was shaken until most of the solid had dissolved and was allowed to stand overnight. The mixture was poured into 800 ml. of water, filtered to remove any insoluble material, and made basic with 10% sodium hydroxide. The solid which separated was removed by filtration. After recrystallization from alcohol, the Mannich base 68 was obtained as a white solid, m.p. 124.5–125° (lit.34, m.p. 128–129°) in 60% yield (21-1949).

Anal. calcd. for C_{17}H_{18}N_{2}: C, 81.55; H, 7.24.
Found: C, 81.84; H, 7.47.

Reaction of 2-phenylgramine(68) with methyl iodide.

A 4 g. sample of the Mannich base 68 was dissolved in alcohol and 3 g. of methyl iodide was added. The flask was stoppered and allowed to stand overnight. A light solid separated which had an infrared spectrum (21–2199) identical with that (21–2177) of a known sample of tetramethylammonium...
iodide. This reaction was not studied further.

Preparation of 3-piperidinomethylindole(55). To 7.5 g. (0.088 mole) of piperidine at 5° was added 12 g. of glacial acetic acid. The mixture was cooled to 5° and 6.5 g. of 40% Formalin, also at 5°, was added. This mixture was shaken and poured into a flask containing 10 g. (0.086 mole) of indole. After standing for two days the mixture was worked up as before yielding, after recrystallization from ethyl acetate, 15 g. (81%) of the Mannich base 55, m.p. 160-161° (21-1700).

Preparation of indol-3-ylacetic acid(32). The preparation of the acid 32 was carried out according to the method of Kuhn and Stein.27 In this instance a mixture of 15 g. of gramine (54), 21 g. of sodium cyanide, 167 ml. of alcohol, and 70 ml. of water was heated under reflux for 80 hrs. The mixture was cooled and 200 ml. of water was added. After treatment with activated charcoal, the solution was concentrated to remove all the alcohol and cooled to 5°. The indoleacetaminde which precipitated amounted to 1 g. and was removed by filtration. The filtrate was concentrated to about 150 ml., cooled to 10°, and acidified by slow addition of concentrated hydrochloric acid to the stirred mixture to yield a pink solid. Care must be taken to have adequate ventilation during the acidification due to the liberation of hydrogen cyanide. The indoleacetamide was hydrolyzed in boiling sodium hydroxide solution for 4 hrs. A solid was
obtained after acidification. The combined solids, after recrystallization from chloroform, afforded 8 g. (53%) of the acid 32, m.p. 160–161° (21–1395) (Lit. m.p. 160–161°).

Preparation of 2-phenylindole-3-ylpropionic Acid (65).31

A 9.8 g. sample (0.051 mole) of 2-phenylindole (64), m.p. 176–177°, was heated in a hot water bath for 4 hrs. with 30 ml. of acetic acid, 11 ml. (1.0 mole) of acetic anhydride, and 8.0 g. (8.5 ml.; 1.1 moles) of acrylic acid. The mixture was allowed to stand at room temperature overnight. The volatile materials were removed by distillation at reduced pressure leaving a shiny green solid. This material turned tan in 10% sodium hydroxide solution but was not soluble. A suspension of this material in 10% sodium hydroxide solution was extracted with ether, chloroform, and benzene and acidified with concentrated hydrochloric acid to give a green solid. One recrystallization of this material from alcohol afforded 5.8 g. (54.2%) of the acid 65 as shiny green platelets, m.p. 153–156°. The structure was confirmed by infrared analysis (21–2129).

A sample of the acid 65 was recrystallized again from alcohol and gave a white solid, m.p. 95.5–97°. The infrared spectrum of this material (21–3186) and the carbon and hydrogen analyses indicated that the acid 65 had been converted to the ethyl ester during recrystallization.

Anal. calcd. for C19H19NO2: C, 78.0; H, 6.53.
Found: C, 78.58, 78.55; H, 6.67, 6.74.

The ester was hydrolyzed in boiling 10% sodium hydrox—
ide solution to yield, after acidification, the acid \(65\), m.p. 153-157° (In-208).

**Attempted preparation of 2-phenylindol-3-ylpropionic acid**\(^{(16)}\). In a 500 ml. 3-necked flask fitted with a ball and socket stirrer, Friedrichs condenser, and nitrogen inlet tube was placed 200 ml. of dry xylene, four crushed pellets of potassium hydroxide, 6 g. of 2-phenylgramine \(^{(19)}\), and 2.7 g. of ethyl cyanoacetate. The mixture was heated under reflux for 5 hrs. with a steady stream of nitrogen bubbling through. The mixture was filtered, concentrated, and allowed to stand overnight, after which time a light orange oil had separated. The xylene was removed by decantation from the oil and the oil crystallized on addition of methanol yielding a light yellow solid, m.p. 110-122°. One recrystallization of the solid from methanol gave what appeared to be ethyl 2-cyano-3-(2-phenylindol-3-yl)propionate \(^{(72)}\). Without further purification, this compound was heated under reflux for 7 hrs. in a 30% sodium hydroxide solution. The brown reaction mixture was cooled, filtered, and acidified with concentrated hydrochloric acid. The acidic material was extracted into ether and dried with anhydrous magnesium sulfate. The oil \((\text{In-442})\), which remained after removing the ether at reduced pressure, was heated in a Wood's metal bath at 180° until the evolution of gas ceased. This heating caused extensive decomposition and no identifiable material was obtained from the reaction mixture \((\text{In-542})\).
Preparation of ethyl 2-methylindol-3-ylpropionate(78).

This preparation was carried out according to the method of Mndzhoian, Terzian and Tatevosian, except that twice the amount of reactants was used. The yield after distillation was 44 g. (73%) of the ester 78, b.p. 183-190° at 0.5 mm. The ester was identified by the boiling point and the infrared spectrum (In-792).

Preparation of ethyl 2-methylindol-3-ylacetate(80).

The procedure used for the preparation of the ester 80 was precisely that of Mndzhoian, Terzian and Tatevosian. In this method a mixture of 11.6 g. (0.1 mole) of levulinic acid (In-798), 14.5 g. (0.1 mole) of phenylhydrazine hydrochloride, 65 ml. of absolute alcohol, and 10 ml. of sulfuric acid was allowed to reflux for 3.5 hrs. The dark brown solution was poured into 300 ml. of ice water. The oil which formed was separated from the water with the aid of 100 ml. of ether and the water was extracted with two 100-ml. portions of ether. The ether solution was washed with 10% sodium hydroxide solution and with water and was dried over anhydrous potassium carbonate. The solution was filtered and the ether removed at reduced pressure, leaving 18.8 g. (88%) of a dark red oil (In-709). A small amount of this oil, when mixed with a 10% solution of picric acid in alcohol, gave a red picrate, m.p. 120.5-121° (lit. m.p. 121°)(In-471). The oil was distilled to give 15.6 g. of the light colored ester 80, b.p. 183-190° at 0.3-0.5 mm.
Preparation of tryptophol(33). Indole-3-acetic acid (32) (5 g.; 0.028 mole) was dissolved in 300 ml. of dry ether and the solution was added dropwise to a slurry of 1.4 g. of lithium aluminum hydride in 100 ml. of dry ether at a rate sufficient to maintain gentle reflux. After addition was completed, the mixture was allowed to stir for 15 min. and a few drops of water were added followed by dropwise addition of 60 ml. of 10% sodium hydroxide solution. The ether layer was separated and the water layer and the insoluble material were extracted with two 100-ml. portions of hot chloroform. The combined chloroform and ether solutions were dried over anhydrous potassium carbonate and the solvents were removed on a steam cone. The tryptophol (33) obtained in this manner was a light-colored oil (3.4 g.; 81%) which was converted to the bromide without further purification.

When the reaction was run on a larger scale, employing tetrahydrofuran as the solvent, the alcohol 33 was obtained in 52% yield as a nearly white solid. After one re-crystallization from benzene, the solid melted at 52-53° (lit. 5, m.p. 57-58°). The infrared spectrum was consistent with that expected (21-1394; In-1663).

Preparation of γ-(indol-3-yl)propanol(58). A solution of 5 g. of the acid 57 in 300 ml. of dry ether was added dropwise, with stirring, to a slurry of 1.45 g. of lithium
aluminum hydride in 75 ml. of dry ether. The mixture was allowed to stir for 12 hrs. The excess hydride was decomposed by acutious addition of a few drops of water, followed by dropwise addition of 50 ml. of 10% sodium hydroxide solution. Workup in the same manner employed for tryptophol (23) afforded 4 g. (89%) of 58 as an oil which could not be caused to crystallize. Identification was based on the absence of absorption at 1695 cm\(^{-1}\) in the infrared spectrum (21–1853) and the presence of absorption bands due to the oxygen–hydrogen stretching vibration at 3520 cm\(^{-1}\) and 3200 cm\(^{-1}\) and the carbon–oxygen stretching vibration at 1025 cm\(^{-1}\).

Preparation of \(\gamma\)-(2-phenylindol-3-yl)propanol (66).

A 9.4 g. sample of impure acid \(65\) in dry ether was added dropwise to a slurry of 2.7 g. of lithium aluminum hydride in ether. The mixture was stirred with a magnetic stirrer for 5 hrs. and worked up as before. The product was isolated as a yellow oil which crystallized when scratched with a glass rod. One recrystallization of the crude solid from chloroform afforded 7.29 (81%) of the alcohol \(47\), m.p. 97.5–98° (Ir–113). Recrystallization of a small amount of this alcohol from benzene gave a solid which melted at 125.8–127.5° and exhibits no oxygen–hydrogen stretching absorption in the infrared spectrum (21–3096). This material retained the absorption due to the 2-phenylindole chromophore in the ultraviolet spectrum at 228 m u and 310 m u, yet its analysis did not correspond to those of the alcohol \(47\). This solid was not further characterized.
Anal. calcd. for C$_{17}$H$_{17}$NO: C, 79.9; H, 6.83; N, 5.60.

Found: C, 74.54; 74.58; H, 6.35, 6.42; N, 4.17.

The alcohol 47 obtained after recrystallization from chloroform was used in subsequent steps.

Preparation of (2-methylindol-3-yl)ethanol (81).

A 38.5 g. sample of the ester 80, dissolved in 400 ml. of tetrahydrofuran, was added dropwise to a stirred slurry of 10 g. of lithium aluminum hydride in 100 ml. of tetrahydrofuran. After the addition was complete, the mixture was stirred for 2 hrs. and allowed to stand for 13 hrs. more. The excess hydride was decomposed with water and the solid residue was removed by filtration. This solid was extracted with hot chloroform and the extract was combined with the filtrate and dried over anhydrous potassium carbonate. After removal of the solvents at reduced pressure, 26.5 g. (81%) of the alcohol 81 was obtained. The infrared spectrum of this material (In-717) was consistent with that expected for 81. The alcohol 81 formed a red picrate melting at 129–131° (lit. 129, 134.5°).

Preparation of (3,4-dimethoxyphenyl)ethanol (36).

A 10 g. sample of 3,4-dimethoxyphenylacetic acid (35) (In-818) in tetrahydrofuran was added to a slurry of 4 g. of lithium aluminum hydride in tetrahydrofuran. The mixture was allowed to stir for 2 hrs. and was worked up in the usual manner. The alcohol 36 was obtained in essentially quantitative yield as an oil (In-995). The oil crystallized when cooled and scratched
with a glass rod to give 6.8 g. (92%) of 36 as a nearly white solid, m.p. 35-42° (lit. 40, 47-48°).

Preparation of \( \beta \)-(2-methylindol-3-yl)propanol (79).
A 11 g. sample of the ester 78 was reduced with 11 g. of lithium aluminum hydride in the usual manner, employing tetrahydrofuran as the solvent. The alcohol was obtained as a light-orange oil, (b.p. 209-210° at 0.8 mm.), in 80% yield. The structure was based on the lack of carbon-oxygen double bond stretching absorption in the infrared spectrum (21-3409) and the presence of bands due to the oxygen-hydrogen stretching vibration at 3530 cm\(^{-1}\) and 3300 cm\(^{-1}\).

Anal. calcd. for C\(_{12}\)H\(_{15}\)NO: C, 76.2; H, 7.99.
Found: C, 76.54; H, 8.13.

Phosphorous Tribromide Brominations

Preparation of \( \beta \)-(indol-3-yl)ethyl bromide (34).
To a dry ethereal solution of 12 g. of tryptophol (13) was added a solution of 25 g. of phosphorous tribromide in dry ether. Immediately a light colored gum coated the flask. The mixture, after standing for 7 hrs., was poured into cold water and neutralized with sodium bicarbonate. The ether layer was separated and the water and insoluble residue were extracted with ether and chloroform. The combined solutions were dried over anhydrous potassium carbonate and the solvents were removed under reduced pressure without heating. The
light solid (10.8 g., 64.5%) obtained in this manner melted at 94–100° (lit.30, 98–99°). The lack of oxygen–hydrogen stretching absorption in the infrared spectrum (In–1681) of this material and a strongly positive Beilstein flame test for halogen confirmed the presence of the bromide 34.

Preparation of \(\gamma\)–(indol–3–yl)propyl bromide (59).

Several attempts to prepare the bromide 59 analogous to the method used for \(\beta\)–(indol–3–yl)ethyl bromide (34), gave only a dark red oil. Lengthy attempts to purify this oil were unsuccessful and generally resulted in decomposition to a black tar. The oil, which gave a positive Beilstein flame test for halogen and an infrared spectrum (21–1825) consistent with that expected, was treated with 3–cyanopyridine without further purification.

Preparation of \(\gamma\)–(2–phenylindol–3–yl)propyl bromide (67). A 9 g. sample of the alcohol 66 was dissolved in dry benzene and a few drops of pyridine and 3 ml. of phosphorous tribromide were added. The mixture was heated under reflux overnight. After cooling, the reaction mixture was poured onto cold water and was neutralized with sodium bicarbonate. The benzene layer was separated from the water layer, and the insoluble material was extracted with ether and chloroform. The benzene, ether, and chloroform solutions were combined and dried over anhydrous potassium carbonate. The solvents were removed under reduced pressure without the application of heat and a tan oil was obtained which crystallized
when scratched with a glass rod. The solid was dissolved in alcohol and the hot solution was treated with water until just turbid. On standing, a resinous material separated. The supernatant liquid was decanted and chilled. The solid which separated from the cold solution was removed by filtration and recrystallized from aqueous alcohol affording 7.6 g. (67.5%) of the bromide 67, m.p. 97.2–100.5°. This material exhibited only nitrogen-hydrogen stretching absorption in the infrared region above 3100 cm⁻¹ and gave a strong Beilstein flame test for halogen. A small amount of the bromide 67 was recrystallized from ligroin (b.p. 100–115°) and melted at 99.2–101° (21–3185).

**Anal. calcd. for C₁₇H₁₆NBr: C, 65.01; H, 5.23. **
**Found: C, 65.33; H, 5.18.**

**Preparation of 7-(2-methylindol-3-yl)ethyl bromide (82).** A 21.3 g. sample of the alcohol 81 was dissolved in dry ether and the solution was divided into five nearly equal portions. To each portion was added an ethereal solution of 3 g. of phosphorous tribromide. After standing for 15 min. the samples were combined, poured onto cold water and neutralized with sodium bicarbonate. The ether layer was separated and the water layer was extracted with ether and chloroform. After drying the combined solutions and removing the solvents at reduced pressure without heating, the bromide 82 was obtained as a nearly colorless oil (In-511) which was not further purified.
Preparation of \( \beta -(3,4\text{-dimethoxyphenyl})\text{ethyl bromide} \) (37). A 35.4 g. sample of the alcohol 36 was dissolved in dry benzene and a few drops of pyridine were added. To this solution was added 54 g. of phosphorous tribromide and the mixture was heated under reflux for 3 hrs. After standing overnight at room temperature, the mixture was poured into ice water and neutralized with sodium bicarbonate. Work-up in the usual manner afforded 37.99 (78.5\%) of 37 as a nearly colorless oil. This material gave a strongly positive Beilstein flame test for halogen and the infrared spectrum (In-1697) was consistent with that expected. The bromide 37 was not purified further.

Quaternization Reactions of 3-Cyanopyridine

Preparation of \( 1\text{-benzyl-3-cyanopyridinium bromide} \) (23). Benzyl bromide (8.55 g., 0.05 mole) and 3-cyanopyridine (5.08 g., 0.05 mole) were dissolved in acetone and the solution was heated under reflux for 4 hrs. The solid which separated was removed by filtration and washed with cold acetone. The filtrate and washings were combined and concentrated. The solvent was decanted from the oil which separated and the oil was caused to crystallize by warming under acetone. This solid was removed by filtration and washed with cold acetone. The combined solids were recrystallized from isopropyl alcohol yielding 7.2 g. (52\%) of 23 as light tan crystals, m.p. 147.5-151° dec. (21-1084).
Preparation of $N-\beta-(\text{indol-3-yl})$ethyl-3-cyano-
pyridinium bromide (28). The bromide 34 and 3-cyanopyridine,
in a 1:3 ratio, were heated on a steam cone in the absence
of solvent. After 30 min., the yellow solid which separated
was removed by filtration and washed with acetone. The fil-
trate and washings were returned to the steam cone, and the
process was repeated until no more solid separated. The
quaternary salt 28, after two recrystallizations from methanol,
melted at $222-222.5^\circ$ (21-1660).

Anal. calcd. for $C_{16}H_{14}N_{3}Br$: $C$, 58.5; $H$, 4.28.
Found: $C$, 58.95, $H$, 4.57.

Preparation of $N-\gamma-(\text{indol-3-yl})$propyl-3-cyano-
pyridinium bromide (56). Attempted quaternizations of 3-
cyanopyridine with the crude bromide 59 in ether and in
methanol at room temperature resulted in the formation of
black tars. Quaternization in the manner employed for the
preparation of the salt 28 was attempted, and an ether in-
soluble oil was obtained. This material contained absorption
due to the indole system and the pyridine system in the in-
frared spectrum (21-1839). All attempts to cause it to
crystallize met with failure and, since further attempts at
purification resulted in decomposition, the crude salt 56
was employed in the dithionite reduction.

Preparation of $N-\gamma-(2$-phenylindol-3-yl)$propyl-3-
cyanopyridinium bromide (63). Attempts to prepare the
quaternary salt 63 by heating a mixture of the bromide 67 and 3-cyanopyridine on the steam cone, yielded an ether insoluble oil which could not be crystallized. The ultraviolet spectrum, with bands at 300 μν and 220 μν, and the infrared spectrum (In-73) of this crude material, were consistent with that expected for the salt 63. This oil was reduced without further purification.

Preparation of N-(3-(2-methylindol-3-yl)ethyl)-3-cyanopyridinium bromide (77). A solution of 24 g. of the bromide 82 and 8.59 of 3-cyanopyridine in acetone was allowed to stand, and a yellow solid separated after two days. The solid was removed by filtration and recrystallized from methanol yielding 12.5 g. (36.5%) of the salt 77, m.p. 194–197°. Some more material could be isolated from the mother-liquor but it was contaminated. A small sample of the initial precipitate was recrystallized twice more from methanol and once from water, giving pure 77, m.p. 197–198° dec. (21–3420).

Anal. calcd. for C_{17}H_{16}BrN_{3}:  C, 58.7;  H, 4.71.
Calcd. for C_{17}H_{16}BrN_{3} + H_{2}O:  C, 56.8;  H, 5.03. Found:  
C, 56.67, 56.60;  H, 5.49, 5.46.

Preparation of N-(3-(3,4-dimethoxyphenyl)ethyl)-3-cyanopyridinium bromide (38). A 37.9 g. sample of the bromide 37 was heated on the steam cone with 17 g. of 3-cyanopyridine. The solid which separated was removed by filtration and washed with acetone. The process was repeated as in the preparation of 28 until no more solid could be obtained. This

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method afforded 44.3 g. (82.4%) of the salt as a nearly white solid, m.p. 229–230°. After three recrystallizations from acetone with a small amount of methanol added to aid solution, the salt melted at 233–237° (21–3419).

Anal. calcd. for C_{16}H_{17}BrN_{2}O_{2}: C, 54.8; H, 4.91.
Found: C, 54.58; H, 5.01.

Dithionite Reductions of Pyridinium Salts and Acidification of the Products.

Dithionite Reduction of N-[(3-indol-3-yl)ethyl]-3-cyanopyridinium bromide (28). a) A 4 g. sample of the quaternary salt 28 was dissolved in a minimum amount of methanol at room temperature. Water was added until the mixture became slightly turbid and excess sodium dithionite was added in small portions with stirring. Immediately the orange-yellow solution turned light yellow and turbid, and soon a solid began to separate. The solid was removed by filtration and one recrystallization from methanol afforded 2.3 g. (75%) of 3,4,5,8,9,9a-hexahydro-7-cyanoindolo [2,3-a] quinolizine (30) as tan needles, m.p. 223–225°. The infrared spectrum (21–1669), with bands at 2190 cm$^{-1}$ and 1630 cm$^{-1}$, and the ultraviolet absorption at 280 μ (20460) and 223 μ (20830) were consistent with that expected for the cyclic product 30.

Anal. calcd. for C_{16}H_{15}N_{3}: C, 77.1; H, 6.07; N, 16.86.
Found: C, 77.94; H, 6.33; N, 16.93.

b) A small amount of the salt, as a slurry in water...
under a layer of ether, was treated with sodium dithionite until the ether layer no longer became colored. The ether solution was dried with anhydrous potassium carbonate and the ether was removed at reduced pressure without heating. An oil was obtained which could not be caused to crystallize. The infrared spectrum (In-1648) of this material had bands at $2190 \text{ cm}^{-1}$, $1680 \text{ cm}^{-1}$, and $1600 \text{ cm}^{-1}$ indicating the presence of $N$- $\beta$ -(indol-3-yl)ethyl -1,4-dihydro-3-cyanopyridine (29). A band also appeared at $3500 \text{ cm}^{-1}$ which was not diminished on further drying. This dihydropyridine was unstable and decomposed on further attempted purification.

Dithionite reduction of $N$-$\gamma$ -(indol-3-yl)propyl -3-cyanopyridinium bromide(56). The crude quaternary salt was dissolved in aqueous methanol and sodium dithionite was added in small portions until no further color change could be observed, then a few more portions of dithionite were added. After stirring for 15 min., a gummy residue separated. Addition of water to the methanol solution caused more material to separate. The supernatant liquid was decanted and the gummy residue was dissolved in acetone. Water was added until the mixture became slightly turbid. After standing a few days, a viscous oil separated with a few crystals on top. The crystals were removed by decanting a suspension of them in the supernatant liquid. The residual oil was redissolved in acetone, water was added, and the process was repeated until no more crystalline material was obtained.
The solid thus obtained was recrystallized several times from acetone to yield about 100 mg. of a nearly white solid melting at 125–128°. The infrared spectrum (21–2039) of this material exhibited two nitrogen–hydrogen stretching bands at 3340 cm⁻¹ and 3360 cm⁻¹, nitrile absorption at 2180 cm⁻¹, and absorption indicative of a tetrahydropyridine at 1615 cm⁻¹. The ultraviolet absorption at 224 μm (31,400) and 276 μm (22,400), was also consistent with that expected for 1,2,6,7,8,10a-hexahydro-3-cyanonindolo [2,3-1]-5H-pyrido 1,2-α-azepine (62).

A sample was sent for analysis but a portion which was kept behind decomposed after a few days. The nitrogen analytical value is correct but the carbon and hydrogen values are not consistent with the structure 62 or any other reasonable product of this reaction.

**Anal. calcd. for C₁₇H₁₇N₃:** C, 77.53; H, 6.57; N, 15.96. **Found:** C, 71.95, 72.05; H, 7.58, 7.41; N, 15.57.

Dithionite reduction of N-(2-phenylindolyl)-propyl-3-cyanopyridinium bromide (63). A sample of the crude salt 63 was dissolved in 50% methanol. A small amount of sodium bicarbonate was added to the stirred solution followed by addition of sodium dithionite. After 15 min., the mixture was extracted with chloroform, and the extract was dried with anhydrous potassium carbonate. The carbonate was removed by filtration, and the chloroform was distilled at reduced pressure. The brownish semi-solid obtained in this manner seemed from its infrared spectrum (In-95) to be a
mixture of \( \text{N-} \ (2\text{-phenylindol-3-yl})\text{propyl} -1,4\text{-dihydro-3-cyanopyridine} (74) \) and the starting salt 63. This mixture resisted all attempts at purification and decomposed readily.

Dithionite reduction of \( \text{N-} \ (3\text{-}(3,4\text{-dimethoxyphenyl})\text{ethyl} -3\text{-cyanopyridinium bromide}(38). \)

a) A 5 g. sample of the quaternary salt 38 was dissolved in 200 ml. of methanol and 50 ml. of water was added. A three-fold excess of sodium dithionite was added, and the mixture was stirred for 6 hrs. with a stream of nitrogen bubbling through it. The reaction mixture was extracted with ether and chloroform. After drying both extracts separately with anhydrous potassium carbonate, the ether extract was concentrated under reduced pressure. The dark oil which was obtained appeared to be the result of decomposition. The chloroform extract, after standing overnight in contact with the drying agent, was concentrated under reduced pressure without heating. An attempt was made to redissolve the semi-solid material which was obtained and a white, chloroform insoluble solid remained. This solid was separated by filtration and melted at 205–215° with decomposition. The infrared spectrum (In-1916) of this material indicated the presence of the tetrahydropyridine system. The water layer from the original reaction mixture was heated to remove organic solvents and was saturated with potassium carbonate. The oil which separated was removed and, when treated with chloroform, crystallized. The infrared spectrum of this material (21–3557) showed it to be identical with the solid obtained from the chloroform extract. The combined solids,
2.3 g., after three recrystallizations from methanol afforded a white solid, m.p. 225–229° dec.

Anal. calcd. for C_{16}H_{18}N_2O_2 (64): C, 71.1; H, 6.70; N, 10.35. Found: C, 48.12; H, 4.86; N, 8.50.

The solid was dissolved in methanol and anhydrous hydrogen chloride was bubbled into the solution. A strong mercaptan-like odor was noticeable, and extensive decomposition was evident. A solution of the solid in methanol was heated under reflux for 10 hrs. with methyl iodide. After standing for 2 days at room temperature, the solvent was removed under reduced pressure and a white solid was obtained. After recrystallization from methanol and from isopropanol, the solid melted at 171–174° (In–1237). This material was unstable in benzene and decomposed on attempted recrystallization from that solvent.

The original solid, m.p. 225–229° dec., was soluble in water and burned with a red flame. The presence of sulfur was confirmed by elemental analysis, and the strong absorption at 1250 cm⁻¹ in the infrared spectrum of this material (In–1916) suggested the potassium sulfinate as the correct structure. Sulfinic acid salts generally crystallize with water of crystallization:

Anal. calcd. for C_{16}H_{17}N_2SO_4K·H_2O: C, 48.9; H, 5.36; N, 7.15. Found: C, 49.07, 49.04; H, 5.24, 5.22; N, 6.74.

b) A 10 g. sample of the salt in water under a layer of ether, was treated with 7 g. of sodium dithionite. The reaction mixture was stirred for 10 min., the ether layer
was separated, and more ether was added. This process was continued until the ether layer no longer became colored. The material in the ether layer decomposed on workup probably due to the application of heat. The water layer, which was acidic, was treated with potassium carbonate and turned a very dark brown. After acidification with concentrated hydrochloric acid, the water layer lightened and a solid separated. The solid was extracted into chloroform, and the solution was dried with anhydrous potassium carbonate. The chloroform was removed at reduced pressure leaving a solid which melted, after one recrystallization from methanol, at 166—167° with decomposition. The infrared spectrum (In—l491), indicative of the tetrahydropyridine system, was identical to that of the solid isolated from heating the potassium sulfinate \textsuperscript{40} in methanol in the presence of methyliodide. Elemental analyses indicated the absence of sulfur and halogen. After recrystallization from isopropanol, this material melted at 171.5—174° with decomposition.

Anal. calcd. for C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}: C, 71.1; H, 6.70; N, 10.35. Found: C, 71.29, 71.35; H, 6.89, 6.97; N, 10.44, 10.54.

The nuclear magnetic resonance spectrum of this material, with three bands, representing three hydrogens, at 6.90, 6.75, and 6.68 ppm from tetramethylsilane, confirmed the product as 3,4,5,8,9,9a-hexahydro-7-cyano-4',5'-dimethoxybenzo 1,2-a'-quinolizine (441).
c) A 2 g. sample of the salt $\text{Na}_2\text{SO}_4$ was dissolved in water under a layer of ether. A small amount of sodium bicarbonate was added followed by addition of sodium dithionite. As before, the ether was changed at intervals and dithionite was added until the ether layer remained colorless. The combined ether extracts were dried with potassium carbonate. After filtering the solution, the ether was removed under reduced pressure without applying heat. The dark oil which was obtained had bands in the infrared spectrum (In-1561) at 2205 cm$^{-1}$, 1680 cm$^{-1}$ and 1605 cm$^{-1}$ consistent with that expected for $N_{-}\left[\text{P}(-3,4\text{-dimethoxyphenyl})\text{ethyl}\right]\text{1,4-dihydro-3-cyano-pyridine (39)}$ and a band near 3600 cm$^{-1}$ which suggested the presence of water. The oil was redissolved in ether, dried again with anhydrous potassium carbonate, and recovered as before but the water band at 3600 cm$^{-1}$ in the infrared spectrum (In-1565) was not diminished.

Anal. calcd. for $C_{16}H_{18}N_2O_2$: C, 71.1; H, 6.70. Calcd. for $C_{16}H_{18}N_2O_2\cdot H_2O$: C, 66.7; H, 7.02. Found: C, 66.49; H, 7.17.

Cyclization of the dihydropyridine(39). The oily dihydropyridine 39 was dissolved in methanol and concentrated hydrochloric acid was added. Water was added to the mixture after a few minutes and a solid, m.p. 156–166°, separated. This material was identical with the cyclization product 41 as evidenced by the infrared spectrum (In-1574).
Dithionite reduction of $N\beta -(2\text{-methylindol}3\text{-yl})$-ethyl-3-cyanopyridinium bromide (77) and cyclization of the product. A 1 g. sample of the salt 77 in water was treated under ether with sodium dithionite in the usual manner. After drying the extracts and removing the solvent under reduced pressure without heating, a dark oil was obtained. The infrared spectrum of this oil (In-2023) exhibited bands at 2190 cm$^{-1}$, 1685 cm$^{-1}$, and 1605 cm$^{-1}$ indicative of $N\beta -(2\text{-methylindol}-3\text{-yl})$-ethyl-1,4-dihydro-3-cyanopyridine (82). Acidification of a turbid mixture of the dihydropyridine 83 in aqueous methanol with concentrated hydrochloric acid caused initial clearing of the solution which reclouded on addition of potassium carbonate. Acidification of a second portion of 83 in the same manner again resulted in initial clearing of the mixture; however, the mixture reclouded on standing without basification.

A small amount of semi-solid material was isolated from both mixtures (In-1957). Both samples had identical ultraviolet spectra with maxima at 223 μm and 275 μm and shoulders at 288 μm. Acidification of the sample from the basic mixture caused no change in the ultraviolet spectrum. Addition of sodium borohydride to either sample caused no change in the ultraviolet spectra.

A second sample of the dihydropyridine 83 was dissolved in ether and treated with anhydrous hydrogen chloride. After standing overnight, an oil separated. The ether was removed by decantation and the oil crystallized when washed with water. The orange solid, m.p. 122–132° dec., was removed by filtration.
The infrared spectrum (In—2038) with bands at 2200 cm⁻¹ and 1630 cm⁻¹ was indicative of a tetrahydropyridine. Several attempted recrystallizations of this material from acetone, from methanol, and from isopropanol caused considerable decomposition as evidenced by the formation of a dark oil. A small amount of light orange solid was obtained by adding water to an isopropanol solution of the original material. This solid was recrystallized from acetone, removed by filtration, and washed with cold isopropanol to yield a nearly white solid, m.p. 210–213.5°. The infrared spectrum (In—2061) retained the characteristic bands of a 1,4,5,6-tetrahydropyridine and exhibited two bands due to the nitrogen-hydrogen stretching vibration at 3470 cm⁻¹ and 3340 cm⁻¹.

When a methanolic solution of the dihydropyridine 83, with a steady stream of nitrogen bubbling through, was treated with 6 N hydrochloric acid and, after a few minutes, poured into cold water, the cyclization product, 1,2,6,7,10,10α-hexahydro-3-cyanoindolo [2,3-b] -5H-pyrido [1,2-a] -azepine (86), was obtained in better purity. Several recrystallizations from isopropanol and aqueous acetone afforded 86 as a light colored solid, m.p. 213–215°.


Dithionite reduction of 1-benzyl-3-cyanopyridinium bromide(23). The procedure was essentially that of Anderson and Berkelhammer.22 The pyridinium bromide 23 (5 g., 0.18
mole) and sodium bicarbonate (8.2 g., 0.08 mole) were stirred in 60 ml. of water. After heating in order to dissolve the bicarbonate, the mixture became bright yellow. The small amount of red oil which separated was removed by filtration. Sodium dithionite (86.7%, 11.7 g., 0.059 mole) was added in small portions. The mixture turned dark orange initially and then lightened. A small amount of dark oil began to separate above the water. After stirring for 30 min., a yellow precipitate began to form. The mixture was allowed to stand overnight. The yellow solid which separated was removed by filtration and washed with water. This material was re-crystallized from alcohol, affording 1-benzyl-1,4-dihydro-3-cyanopyridine (2k) as golden needles, m.p. 54-55° dec. (3.2 g., 91%). The infrared spectrum (21-1076), with bands at 2190 cm\(^{-1}\), 1680 cm\(^{-1}\), and 1605 cm\(^{-1}\), was consistent with that expected.

**Addition of acid to 1-benzyl-1,4-dihydro-3-cyanopyridine (2k).** Addition of a drop of concentrated hydrochloric acid to a methanolic solution of the dihydropyridine 2k in an ultraviolet cell caused the destruction of the band at 338 mu with the formation of a new band at 273 mu. Addition of hydrochloric acid to a small amount of 2k in methanol, afforded a tan solid which was unstable and could not be purified. This material gave bands in the infrared spectrum (21-1223) at 2195 cm\(^{-1}\) and 1633 cm\(^{-1}\) with no absorption at 1680 cm\(^{-1}\). The material can thus be assumed to have the 1,4,
5,6-tetrahydropyridine structure.

**Attempted hydrolysis of the dihydropyridine (24).**

Treatment of the dihydropyridine 24 with ammonium hydroxide in aqueous methanol on the steam cone, yielded a solid, m.p. 55°, the infrared spectrum of which (21–1196) showed it to be the starting material 24. Starting material was also obtained after heating 24 under reflux with potassium hydroxide in diethylene glycol for 15 min. Longer heating in diethylene glycol caused decomposition of the starting material and no solid product was isolated. Treatment of the dihydropyridine 24 with potassium hydroxide in boiling methanol for 15 min, also gave starting material, while only benzoic acid could be isolated from the attempted hydrolysis of 24 with potassium hydroxide in boiling benzyl alcohol.

The dihydropyridine (24) was also recovered unaltered, m.p. 55–56°, after treatment with sodium borohydride in methanol.

**Addition of potassium cyanide to 1-benzyl-3-cyano-pyridinium bromide (23).** An aqueous solution of 1 g. of 1-benzyl-3-cyano pyridinium bromide (23) was treated with solid potassium cyanide and allowed to stand. The orange–red oil which separated was extracted into ether and the extract was dried with anhydrous potassium carbonate. The solution was filtered and the ether was removed under reduced pressure. The oil which remained showed evidence of the 1,4-dihydro-
pyridine structure 93 in the infrared spectrum (21–2294) but was unstable and decomposed before it was further characterized.

**Reaction of N-[3-(indol-3-yl)ethyl]-3-cyano-pyridinium bromide (28) with potassium cyanide.** An aqueous-methanolic solution of 1 g. of the salt 28 was treated with potassium cyanide. After a few minutes the pea-green mixture was poured into cold water and extracted with ether. The ether solution was dried over sodium sulfate and the ether was removed leaving a light brown semi-solid. This material was quite unstable and further purification was unsuccessful. The infrared spectrum (21–2579) of this material with strong absorption at 2200 cm⁻¹, 1675 cm⁻¹, and 1593 cm⁻¹, and the ultraviolet maximum at 327 mu, were consistent with the dihydropyridine structure 94 resulting from attack of the cyanide ion at the 4-poison of the pyridinium ring. Treatment of a chloroform solution of this material with acetic acid gave no identifiable material.
SUMMARY

The intramolecular cyclization of N-arylalkyl-1,4-dihydro-3-cyanopyridines has been demonstrated. The 1,4-dihydropyridine system in the presence of acid undergoes protonation at the 5-position rendering the 6-position highly electrophilic. This 6-position may then intramolecularly attack an available aromatic system or react with an available nucleophile such as dithionite ion.

The cyclization reaction, when the aryl group is the indole nucleus, proceeds directly to the cyclic indole without intermediate formation of the corresponding cyclic indolenine. The facility of the formation of the indoloquinolizine 30 and the benzoquinolizine 44 emphasizes the synthetic potential of this reaction and lends credence to the proposal that such a reaction may be important in the biosynthesis of various alkaloids.
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