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A SYNTHETIC APPROACH TO THE IBOGA ALKALOIDS:
A NEW SYNTHESIS OF ISOQUINUCLIDINES

DISSERTATION
Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By
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The Ohio State University
1964

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I wish to acknowledge the guidance and inspiration afforded me by Dr. M. P. Cava during the course of this research and to extend thanks to my colleague Keith Buck for his helpful discussions.
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INTRODUCTION

THE IBOGA ALKALOIDS:

The iboga alkaloids consist of a group of eighteen compounds isolated from plants of the family Apocynaceae (see page 2). Ibogaine, the first to be isolated, was found in *Tabernanthe iboga* by Dybowski and Landrin\(^1\) and Heller and Heckel\(^2\) in 1901. Except for a few related oxidized compounds which may be formed during the isolation procedures, these alkaloids possess a 2-azabicyclo[2.2.2]octane (isoquinuclidine) system (I) fused to a 3-ethyl indole nucleus. The structure proof of these compounds was completed only in 1958 by a research group at CIBA\(^3\). Extracts from *Tabernanthe iboga* have been reported to increase man's resistance to fatigue\(^4\). In rabbits ibogaine has been found to reinforce the hypotensive effect of adrenaline but decrease the hypertension produced by constriction of the arteries\(^5\). Ibogaine also produced strong contractions in the uterus of rabbits.

\(^1\) J. Dybrowski and Ed. Landrin, Compt. Rend., 133, 748 (1901).
\(^2\) A. Heller and Ed. Heckel, Compt. Rend., 133, 850 (1901).
TABLE 1
THE IBOGA ALKALOIDS

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>Structural Formula</th>
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<tbody>
<tr>
<td>Ibogamine</td>
<td>R = R^1 = R^2 = R^3 = H</td>
</tr>
<tr>
<td>Ibogaine</td>
<td>R = OCH₃, R^1 = R^2 = R^3 = H</td>
</tr>
<tr>
<td>Iboxygaine</td>
<td>R = OCH₃, R^1 = R^2 = H, R^3 = OH</td>
</tr>
<tr>
<td>Tabernanthine</td>
<td>R = R^2 = R^3 = H, R^1 = OCH₃</td>
</tr>
<tr>
<td>Ibogaline</td>
<td>R = R^1 = OCH₃, R^2 = R^3 = H</td>
</tr>
<tr>
<td>Coronaridine</td>
<td>R = R^1 = R^3 = H, R^2 = O_C-OCH₃</td>
</tr>
<tr>
<td>Voacangine</td>
<td>R = OCH₃, R^1 = R^3 = H, R^2 = O_C-OCH₃</td>
</tr>
<tr>
<td>Voacristine</td>
<td>R = OCH₃, R^1 = H, R^2 = O_C-OCH₃, R^3 = OH</td>
</tr>
<tr>
<td>Isovoacangine</td>
<td>R = R^3 = H, R^1 = OCH₃, R^2 = O_C-OCH₃</td>
</tr>
<tr>
<td>Conopharyngine</td>
<td>R = R^1 = OCH₃, R^2 = O_C-OCH₃, R^3 = H</td>
</tr>
<tr>
<td>Isovoacristine</td>
<td>R = H, R^1 = OCH₃, R^2 = O_C-OCH₃, R^3 = OH</td>
</tr>
</tbody>
</table>

Hydroxyindolenines
- C₁₉H₂₄ON₂  R = H
- C₂₀H₂₆O₂N₂  R = OCH₃

Desmethoxyiboluteine
- R = H
- Iboluteine
  - R = OCH₃
TABLE 1 (Cont d.)

\[
\text{Iboquine} \quad \text{Voacriptine}
\]

\[
\text{Catharanthine}^9
\]

Recently a group of four compounds found in *Voacanga africana*, also a member of the Apocynaceae, have been shown to contain an iboga system and a vobasine system (see II a-d).

![Chemical Structures]

**II**

a) Voacamine  
\[ R_1 \quad R_2 \quad R_3 \quad R_4 \]
\[ \text{H} \quad \text{OCH}_3 \quad \text{Vob} \quad \text{H} \]

b) Voacamidine  
\[ \text{Vob} \quad \text{OCH}_3 \quad \text{H} \quad \text{H} \]

c) Conodurine  
\[ \text{H} \quad \text{H} \quad \text{OCH}_3 \quad \text{Vob} \]

d) Conoduramine  
\[ \text{H} \quad \text{Vob} \quad \text{OCH}_3 \quad \text{H} \]

The only other naturally occurring compound possessing an iso-quinuclidine system is dioscorine (III)\(^\text{11}\) isolated from *Dioscorea hirsuta* and *hispida*, members of the family Dioscoraceae.

![Chemical Structure]

**III**

---


Vincaleucoblastine (IVa) and leurocristine (IVb),\textsuperscript{12} which are useful in the treatment of Hodgkins' disease and choriocarcinoma, are dimeric alkaloids, one half of which consists of an iboga system in which one bond is missing. This partial iboga system could arise biogenetically via a catharanthine-cleavamine type of transformation (V).\textsuperscript{13} The fact that catharanthine is the major alkaloid of \textit{Vinca rosea} supports this hypothesis.

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


The synthesis of a naturally occurring compound in the iboga series would be the final link in the proof of structure of these alkaloids. Since it is unlikely that the ethyl group is important to the biological activity of the iboga alkaloids, the synthesis of desethylibogamine (VI), which is equivalent to the basic iboga system,

\[ \text{VI} \]

\[ \text{VII} \]

\[ \text{VIII} \]

would be of great interest to medicinal chemistry.

An attempt to synthesize the partial iboga system (VII) from 2(3 pyridyl) indole (VIII) failed.\(^\text{14}\)

Since the isoquinuclidine ring is the most complex part of the iboga system, the approach taken in the work described here has been the initial synthesis of an isoquinuclidine, functionalized on one of the two carbon bridges, followed by attachment of the indole nucleus. Existing syntheses of isoquinuclidine were found to lack generality; i.e., no derivatives simply functionalized on one of the two carbon bridges are known.

The Reduction of p-Aminobenzoic Acids

Historical. The first synthesis of isoquinuclidine, reported by Ferber and Bruchner in 1942 consisted of the reduction of p-aminobenzoic acid to a mixture containing cis-4-aminocyclohexanecarboxylic acid, cyclization to 3-isoquinuclidone and subsequent reduction to isoquinuclidine\(^{15}\) (see IX). This synthetic scheme has been modified to produce only 2 and 6 alkyl derivatives.\(^{16,17}\) Attempts to hydrogenate appropriately substituted di- and tricarboxylic acids have been unsuccessful. Attempted hydrogenation of aminotrimesic acid (X) or its trimethyl ester with ruthenium or platinum oxide at 40 lbs. of hydrogen pressure at room temperature gave only starting material.

\[ \text{NH}_2 \quad \text{COOH} \xrightarrow{\text{H}_2/\text{PtO}_2} \quad \text{NH}_2 \quad \text{COOH} \quad \xrightarrow{\Delta} \quad \text{N} \quad \text{COO} \xrightarrow{\text{H}_2/CuCr}_2O_4 \quad \text{N} \quad \text{COO} \]

IX

\[ \text{HOOC} \quad \text{NH}_2 \quad \text{COOH} \]

X

\(^{15}\) E. Ferber and H. Bruchner, Ber., 75B, 425 (1942); \textit{ibid.}, 76B, 1019 (1943).

\(^{16}\) W. Schneider and R. Dillmann, Ber., 96, 2377 (1963).

Hydrogenation of it using the same catalysts at 150°C and 100 atmospheres of hydrogen gave products which readily lost ammonia. 4-Aminoisophthalic acid failed to absorb hydrogen at room temperature at 40 lbs. pressure with platinum oxide. 18

Discussion and results. The failure of these di- and tricarboxylic acids to hydrogenate under mild conditions may be due to the reduced electron density of the benzene ring caused by the additional electron withdrawing substituents. Presumably this effect could be avoided by using p-aminobenzoic acids substituted with electron donating substituents. The reduction of 4-aminosalicylic acid with platinum oxide with 40 lbs. of hydrogen in dilute acid did not, however, proceed to completion. Cyclization of the crude hydrogenated product gave a very poor overall yield of a product with a melting range of 25°C presumed to be a mixture of exo- and endo-3-oxo-5-hydroxy-2-azabicyclo[2.2.2]octane (XI). The failure of the hydrogenation to proceed to completion seems to be due to poisoning of the catalyst by the product. Recrystallization of the starting material did not alter this result. Neither oxidation nor acetylation of crude XI produced a crystalline derivative.

The reported synthesis of ketone (XII) by alkylation of the p-tosyl derivative of methyl anthranilate with methyl 4-bromobutyrate

18 E. Lipinsky, unpublished results. The Ohio State University.
followed by a Dieckman cyclization and subsequent hydrolysis, suggested a combination of this reaction sequence with a modified p-aminobenzoic acid synthesis of isoquinuclidine. The following sequence of reactions was proposed:

Ketone (XIV) could be converted to desethylibogamine via the Fischer indole synthesis.

The tosyl derivative (XIII) was prepared in 70% yield from dimethyl 4-aminoisophthalate and p-toluenesulfonyl chloride. All attempts to alkylate XIII with ethyl 4-bromobutyrate under a variety of conditions gave only starting material.

---

\[ \text{Ts} \]

XII

19 \( \text{p-Toluenesulfonyl} = \text{Tosyl} = \text{Ts} \).

The Diels-Alder Reaction of 1,2-Dihydropyridines as Dienes

**Historical.** The other general synthesis of isoquinuclidines involves the Diels-Alder reaction using 1,2-dihydropyridines, \(^{21-24}\) which are produced by nucleophilic attack of pyridinium salts, \(^{21-25}\) as dienes. The general reaction scheme is:

![Reaction Scheme](image)

The synthesis of dihydropyridines is most successful when \(R\) or \(R^1\) are electron withdrawing groups. Thus the following Diels-Alder adducts are known:

![Adducts](image)

---

A related type of reaction, the 1,4 dimerization of 2-pyridones is known:\textsuperscript{26}

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

Since the 1,3 "dienel system of 2-pyridones is reactive in dimerization, a photolytic Diels-Alder reaction using a suitably substituted 2-pyridone was proposed.

Discussion and results. Since the dihydropyridine derivatives where \( R \) is indolylethyl could undergo facile ring closure, an unreactive and easily removable alkyl group attached to nitrogen was necessary. The benzyl group was chosen since it can be easily removed by hydrogenation and should be generally inert. An attractive method of synthesis of dihydropyridines was the reduction of pyridinium salts with sodium borohydride. 1-Benzyl-3-cyanopyridinium chloride was prepared by reacting benzyl chloride with 3-cyanopyridine. Reduction with sodium borohydride gave an oil which could not be crystallized. Reaction of the oil with N-phenylmaleimide afforded only a minute quantity of a crystalline product tentatively assigned structure XV. The infrared spectrum was consistent with the assigned structure.
The reaction of Grignard reagents with pyridinium salts is known to produce 1,2-dihydropyridine derivatives.\textsuperscript{25} 1-Methylpyridinium iodide gave on treatment with methyl magnesium bromide a yellow oil

\[
\text{R} + \text{R'}\text{MgX} \rightarrow \text{R}_1 \text{N} \text{R'} + \text{MgX}_2
\]

which on further reaction with N-phenylmaleimide yielded a second oil which has been tentatively assigned structure XVI. This assignment is supported by the infrared spectrum, but the material was not obtained crystalline.

\[
\text{CH}_3
\]

\[
\text{CH}_3
\]

\[
\text{XVI}
\]

Irradiation of N-benzyl-2-pyridone in acrylonitrile solution produced only the pyridone dimer (presumably XVII) and no products resulting from a Diels-Alder reaction. This result has been substantiated by another investigator.\textsuperscript{27}

\[
\text{XVII}
\]

\textsuperscript{27} E. C. Taylor, private communication.
The Diels-Alder Reactions of Imines as Dienophiles

Historical. An alternative method of synthesis of the isoquinuclidine system by a Diels-Alder reaction involves the use of an imine moiety as a dienophile. The literature concerning reactions of this type is indeed scant and indicates that this reaction is not very general. Oximes,28 imino chlorides29 diethyl chloromethyl amine30 and dimethyl anilinomaleate reacting as an imine31 are known to undergo the Diels-Alder reaction.

Sulfuryl chloroisocyanate (XVIII) undergoes cyclo-addition reactions with alkenes32 and dienes33 to give products of type XIX.

\[ C\{-SO_2\}N \]

\[ C\{-SO_2\}N = C=O \]

XVIII XIX

These examples indicate that imines which have polar substituents on either the carbon or the nitrogen atom are most active in Diels-Alder or cyclo-addition reactions.

30 H. Bohme, K. Hartke, and A. Muller, Ber., 96, 607 (1960).
The synthesis of several tetrahydropyridine derivatives has been reported to result from the reaction of methylene diurethanes with boron trifluoride etherate in the presence of dienes:\(^{34}\)

\[
+ \text{CH}_2\text{(NHOC}_2\text{CH}_3)_2\text{BF}_3\text{(CH}_3\text{CH}_2)_2}\rightarrow \text{N}^\circ\text{C}_2\text{OCH}_2\text{CH}_3
\]

This reaction must proceed through intermediate XX or its equivalent which may lose a proton to give imine (XXI) which may be

\[
\begin{array}{c}
\text{CH}_2\text{N}^\circ\text{C}_2\text{OCH}_2\text{CH}_3 \\
\text{XX}
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_2\text{N}^\circ\text{C}_2\text{OCH}_2\text{CH}_3 \\
\text{XXI}
\end{array}
\]

stabilized by a molecule of boron trifluoride. Either intermediate XX or XXI or their equivalents may be attacked by dienes to give tetrahydropyridines. Isolation of telomers of the type XXII supports the attack of intermediate XX by the diene.

\[
\begin{array}{c}
\text{CH}_3\text{=CH}_2\text{O}^\circ\text{C}^\circ\text{N}\text{-(CH}_2\text{=CH}=\text{CH}_2\text{)}^\circ\text{N}\text{=CH}_2\text{=N}^\circ\text{C}_2\text{OCH}_2\text{CH}_3 \\
\text{XXII}
\end{array}
\]

**Discussion and results.** Reaction of the imino chloride derived from acetamide (XXIII) with 1,3-cyclohexadiene gave only tars. Probably cyclohexadiene is polymerized under the reaction conditions.

\[
\begin{array}{c}
\text{CH}_3\text{C}=\text{NH} \\
\text{XXIII}
\end{array}
\]

\[
\begin{array}{c}
\text{S}^\circ\text{C}^\circ\text{N}\text{=C}-\text{OCH}_2\text{CH}_3 \\
\text{XXIV}
\end{array}
\]

\(^{34}\) R. Merten and G. Muller, Angew. Chem., **74**, 866 (1962).
Carbethoxyisothiocyanate (XXIV) failed to react with 1,3-cyclohexadiene even at 80°C.

1,3-Cyclohexadiene reacted with methylene diurethane in the presence of boron trifluoride etherate to give a 30% yield of 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (XXV) as a colorless oil. The yield of this reaction seemed to decrease with increasing scale until it was found that the reflux time was critical. It was found that the optimum reflux period, one hour, gave a 27% yield of adduct.

Benzaldiurethane (XXVI) affords a 50% yield of 2-carbethoxy-3-phenyl-2-azabicyclo[2.2.2]oct-5-ene (XXVII) under the same conditions.

Adduct (XXV) was hydrogenated in the presence of palladium on carbon to give 2-carbethoxy-2-azabicyclo[2.2.2]octane (XXVIII), which on hydrolysis with potassium hydroxide yielded isoquinuclidine, isolated as the picrate and its N-benzoyl derivative. Hydrolysis of XXV with potassium hydroxide gave 2-azabicyclo[2.2.2]oct-5-ene (XXIX)
(dehydroisoquinuclidine) isolated as the picrate and as its tosyl derivative. Lithium aluminum hydride reduction of XXV and XXVII gave 2-methyl-2-azabicyclo[2.2.2]oct-5-ene (XXX) and 2-methyl-3-phenyl-2-azabicyclo[2.2.2]oct-5-ene (XXXI), respectively, both isolated as crystalline picrates.

After completion of the work described here the reaction of fluoral N-benzenesulfonylimine (XXXII) with 1,3-cyclohexadiene was reported to give adduct XXXIII. This reaction supports the hypothesis that electron deficient imines are most reactive in Diels-

\[
\text{XXXII} \quad \text{XXXIII}
\]

Alder reactions but the substituents present in XXXIII make this particular reaction unattractive as a general synthesis of simple isoquinuclidines.

The Attempted Syntheses of Desethylibogamine

Discussion and results. The only published synthetic work in this area is the attempted synthesis of the partial iboga system which was mentioned in the introduction. (see page 6). Since a simply functionalized isoquinuclidine was now available, the problem which remained was the attachment and cyclization of an appropriate indole system to form desethylibogamine (VI). Dehydroisoquinuclidine (XXIX) reacted with indole 3-glyoxyl chloride and 5-methoxy indole 3-glyoxyl chloride to yield the crystalline glyoxylamides XXXIVa and XXXIVb, respectively. The glyoxylamides were reduced to the corresponding amines (XXXVa and b) by lithium aluminum hydride. XXXIVa was also reduced by sodium borohydride to give the glycolamide XXXVI. It was hoped that treatment of either the amine (XXXVa) or the glycolamide (XXXVI) with acid would induce the desired cyclization to the iboga ring system. Cyclizations involving the α-position of indole

XXXIVa, R = H
b, R = OCH₃

XXXV a, R = H
b, R = OCH₃

XXXVI

with activated double bonds are well known. Although the double bond in neither XXXVa nor XXXVI bears an exact formal analogy to that used in known cyclizations, there is a reasonable mechanistic possibility that the desired ring closure could occur in both cases. Amine (XXXVa) could be protonated at the double bond to yield intermediate XXXVII which by an aromatic substitution mechanism could yield desethylibogamine, (VI).
The same mechanism could operate in the case of the glycolamide (XXXVI) or the following reaction sequence could occur to produce cyclization:

When amine (XXXVa) was treated with hydrochloric acid only polymer and starting material were recovered. Glycolamide (XXXVI) when treated with strong acid gave a purple substance which did not melt below 280°C and which had the properties of an indicator.

It was postulated that a molecule without a basic nitrogen or a labile hydroxyl group might give the desired ring closure. The molecule of choice was the acetamide (XXXVIII). Reduction of the glycolamide (XXXVI) with zinc and acetic acid, conditions which reduce benzoin to desoxybenzoin and glycolic acid to acetic acid, gave an amorphous material with an indefinite melting point.

   b) A. Claus, Ann., 145, 256 (1868).
Here it was deemed desirable to use the model system (XXXIX) for further reactions since the acetamide (XL) had been previously prepared by the reaction of piperidine with methyl 3-indoleacetate. Reduction of glyoxylamide (XXXIX) with zinc and hydrochloric acid gave non-crystalline gums which showed no spot corresponding to the desired product by thin layer chromatography. The failure of this type of reduction may be due to simultaneous reduction of the indole to the indoline, a known reaction. Attempted reduction of the glyoxylamide (XXXIX) with stannous chloride gave only starting material. Glyoxylamide (XXXIX) failed to react with hydrazine even at elevated temperatures, ruling out the use of the Wolf-Kishner reduction. It is known that indole 3-aldehyde fails to give carbonyl tests such as reaction with Schiff's reagent and Tollens' and Fehling's tests. This compound also does not give the Cannizzaro reaction and the benzoin condensation. In addition, indole 3-aldehyde is easily acetylated.

39 O. R. Jackson, Ber., 14, 879 (1881); J. v. Braun, and W. Sobecki, ibid., 44, 2158 (1911).
41 R. Majima and M. Kotake, Ber., 58, 2037 (1925).
These results may be due to the facile formation of the resonance stabilized anion (XLI). The existence of the anion of glyoxylamide (XXXIX) as (XLII) may well explain its failure to react with hydrazine. Indeed, glyoxylamide (XXXIX) readily gave crystalline N-acetyl and N-benzyl derivatives (XLIII and XLIV) on treatment with acetic anhydride and benzyl chloride, respectively.

The acetyl group of (XLIII) was labile and was removed when the compound was treated with hydrazine, regenerating glyoxylamide (XXXIX). The benzyl derivative (XLIV) failed to react with hydrazine indicating that it may exist as the resonance hybrid (XLV).
The commercial availability of 3-indoleacetic acid suggested that the synthesis of the acetamide (XXXVIII) could be achieved by standard methods.

Reaction of dehydroisoquinuclidine (XXIX) with methyl indole 3-acetate yielded a very small quantity of non-crystalline material. The amine apparently decomposed under the reaction conditions.

Using another standard amide preparation, indole 3-acetic acid reacted with dehydroisoquinuclidine in the presence of dicyclohexyl-carbodiimide to give a crystalline product of unknown structure. Using a different standard amide preparation, indole 3-acetic acid reacted with dehydroisoquinuclidine in the presence of dicyclohexyl-carbodiimide to give a crystalline product of unknown structure. This compound was not 3-indoleacetic acid, dicyclohexylurea, which is usually formed as a by-product, or acetamide (XXXVIII) which was subsequently prepared by another method.

Availability of the piperidine indoleacetamide (XL) prompted the use of piperidine in further attempts to find a good synthesis of the acetamide (XL) which could be carried out at low temperatures and thus could be applied to the synthesis of the desired acetamide (XXXVIII).

The reaction of ethoxyacetylene with indole 3-acetic acid gave a mixture of the acid and its anhydride. Reaction of the anhydride with piperidine gave a low yield of an acetamide identical to the authentic material. Use of ethyl chloroformate in the mixed anhydride method of amide synthesis yielded 30% of acetamide (XL). Using the same procedure with amine (XXIX) produced a 50% yield of an oil.

which crystallized partially over a two month period. Clearly this was the desired acetamide (XXXVIII) since lithium aluminum hydride reduction of a portion of the crude oil produced the amine (XXXVa) in 40% yield. Treatment of the crude acetamide with acid followed by lithium aluminum hydride reduction gave no spots with an \( R_f \) close to that of ibogamine.

Since it was clear that the double bond in these indole derivatives does not permit facile cyclization to desethylibogamine, conversion of the double bond into a function more suitable for cyclization was attempted. It was thought that alcohol (XLVI) on treatment with acid might give desethylibogamine (VI) through carbonium (XXXVII). Hydroboration\(^{45}\) of amine (XXXVa) gave an oil clearly different from (XXXVb), presumably (XLVII). Treatment of the oil with polyphosphoric acid afforded a mixture which contained no component in the \( R_f \) range of ibogamine on thin layer chromatography. The oil did not yield a crystalline p-nitrobenzoate on treatment with p-nitrobenzoyl chloride, and therefore could not be better characterized.

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\text{XLVI} \quad \text{XLVII}
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EXPERIMENTAL

All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured in potassium bromide pellets or on sodium chloride plates with a Perkin-Elmer model 237 recording spectrophotometer unless otherwise noted. Elemental analyses were carried out by Dr. A. Bernhardt, Mulheim, Germany, and by Midwest Microlab Inc., Indianapolis, Indiana. All chromatography was carried out on Woelm Neutral alumina. All starting materials are commercial samples used without further purification unless otherwise noted.

Hydrogenation of p-aminosalicylic acid. p-Aminosalicylic acid (1.0 g.) was dissolved in glacial acetic acid (35 ml.) and platinum oxide (150 mg.) was added. The mixture absorbed 1.0 lb. hydrogen on hydrogenation in a Parr shaker in 6 hours. (Theoretical absorption was 3.2 lbs. based on p-aminobenzoic acid as a standard.) Additional catalyst (150 mg.) was added and hydrogenation was resumed. Additional hydrogen (0.9 lb.) was absorbed in 12 additional hours. The mixture was filtered and evaporated to a green syrupy residue. Addition of acetone gave on filtration 210 mg. of a yellow crystalline material which decomposed above 270° and a dark green filtrate.

Infrared spectrum: 2.96, 6.11, 6.44-6.52, 7.12, 9.15, 13.44 μ.
Hydrogenation and ring closure of p-aminosalicylic acid.

p-Aminosalicylic acid (4.5 g.) in glacial acetic acid (150 ml.) was hydrogenated as above with platinum oxide (0.87 g.). The mixture absorbed 4.0 lbs. of hydrogen initially. On addition of more catalyst (0.3 g.) an additional 2.6 lbs. of hydrogen was absorbed. (Theoretical hydrogen absorption was 14.4 lbs.) Filtration and evaporation of the resulting solution yielded a brown gum which was heated to 280-320° for 10-15 minutes. The dark tarry residue was extracted with chloroform and the extracts after concentration were chromatographed on activity grade I alumina. A blue fluorescent oil was the first and major fraction. This oil was extracted with benzene, the extracts treated with activated charcoal and the solvent evaporated. A semi-crystalline oil which weighed 300 mg. was obtained from which 65 mg. (6.7%) of tan crystals, m.p. 100-125° was isolated.

Infrared spectrum: 2.88 μ (hydroxyl group), 3.13 μ, 5.98 μ and 9.08 μ.

Dimethyl 4-aminoisophthalate. Crude 4-nitroisophthalic acid (30 g.) was dissolved in tetrahydrofuran (250 ml.) and palladium on carbon (1.5 g.) was added. The mixture on hydrogenation on a Parr shaker absorbed 37.2 lbs. of hydrogen. After filtration the solvent was evaporated and methanol (200 ml.) and concentrated sulfuric acid

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(8 ml.) were added. The resulting solution was refluxed 12 hours, filtered and evaporated to one third volume. Saturated sodium bicarbonate (200 ml.) was added and a light brown solid was precipitated. The mixture was extracted with ether and the ether extracts evaporated to give a quantitative yield of crude diester (37.0 g.) as a brown solid, m.p. 115-122° (lit., m.p. 131°).

Infrared spectrum: 3.03, 5.90, 6.14, 6.98, 8.90, 10.16, 11.94 and 14.16 μ.

**Dimethyl 4(p-toluenesulfonamido)isophthalate (XIII).** Crude dimethyl 4-aminoisophthalate (40.0 g., 0.191 mole) was dissolved in pyridine (50 ml.) and tosyl chloride (36.8 g., 0.193 mole) added. Heat was evolved and after several hours the product crystallized as white prisms. The crude yield of yellow prisms was 56 g., (70%), m.p. 175-180°. Recrystallization from ethyl acetate gave white prisms, m.p. 180.5-181.5°.

Infrared spectrum: 3.12, 6.01, 6.14, 8.24, 9.40, 10.99 and 13.28 μ.

Anal. Calcd. for C_{17}H_{17}NO_{6}S: C, 56.20; H, 4.72; N, 3.86; S, 8.81.

Found: C, 56.46; H, 4.79; N, 3.70; S, 8.73.

**Attempted alkylation of dimethyl 4-(p-toluenesulfonamido)isophthalate XIII with ethyl 4-bromobutyrate.** (1) Dimethyl 4-(p-toluenesulfonamido)isophthalate (XIII) (3.0 g., 0.0091 mole) was dissolved in acetone (18 ml.) and ethyl 4-bromobutyrate 49 (1.64 g., 0.0084 mole)

and 3.6 g. anhydrous potassium carbonate were added. The mixture was refluxed 24 hours and 40 ml. water was added with cooling. A white solid precipitated, m.p. 178-180°. Its infrared spectrum indicated that it was starting material. (2) Dimethyl 4-(p-toluenesulfonamido)-isophthalate (XIII) (1.0 g., 0.0030 mole) was dissolved in methanol (30 ml.) and ethyl 4-bromobutyrate (0.55 g., 0.0028 mole) and sodium methoxide (0.2 g., 0.0037 mole) were added. The mixture was treated as in (1). White crystals were obtained as in (1), m.p. 174-179°. Recrystallization from ethyl acetate gave white prisms, m.p. 177-179°. The infrared spectrum of this substance was practically identical with that of the starting material.

N-Benzyl 3-cyanopyridinium chloride. 3-Cyanopyridine (3.0 g.) was added to benzyl chloride (25 ml.) and the mixture was heated on the steam bath overnight. The colorless solution slowly changed to a mass of light pink needles. The crystals were washed well with benzene and dried. The yield of pink solid was 3.7 g., (55%), m.p. 205-210° with decomposition.

Infrared spectrum: 4.48, 6.73, 11.09, and 14.76 μ.

Anal. Calcd. for C_{13}H_{11}N_{2}Cl: C, 67.68; H, 4.70; N, 12.14.

Found: C, 67.61; H, 5.02; N, 12.17.

Reduction of N-benzyl 3-cyanopyridinium chloride with sodium borohydride and the Diels-Alder reaction of the 1,2-dihydropyridine. N-Benzyl-3-cyanopyridinium chloride (1.0 g., 0.0043 mole) was dissolved in methanol-water 1:1, (30 ml.). The solution was cooled to 5° and sodium borohydride (0.41 g., 0.011 mole) was added slowly with stirring.
The solution, which was originally light pink, precipitated a yellow oil on addition of the borohydride. After the borohydride had been added, 25 ml. of water was added and the resulting suspension of yellow oil was extracted with four 10-ml. portions of benzene. The combined extracts, which were yellow, were dried for 5 minutes over sodium sulfate and N-phenylmaleimide (0.75 g., 0.0023 mole) was added after separation of the solution from the drying agent. The yellow solution which resulted was refluxed overnight. The solution, which turned brown on refluxing, was extracted with dilute hydrochloric acid and the extracts in turn extracted with ether and neutralized. The resulting brown suspension was extracted with chloroform and the extracts dried and evaporated to dryness. The brown residue was redissolved in methylene chloride and chromatographed on activity grade III alumina. A blue fluorescent band, which moved off the column quickly, crystalized on addition of methanol to tan needles. The solid was recrystallized from methanol-water to give a few mg. of tan needles, m.p. 223-224.5°.

Infrared spectrum: 4.53, 5.68, 7.28, 8.08, 13.63 and 14.35 μ.

Reaction of N-Methyl pyridinium iodide with methyl magnesium bromide and the Diels-Alder reaction of the 1,2-dihydropyridine.

N-Methyl pyridinium iodide (6.0 g., 0.027 mole) was dissolved in dry tetrahydrofuran (30 ml.) in a flask fitted with a dropping funnel and a drying tube. Methyl magnesium bromide (20 ml. of 3 N solution, 0.06 mole) was added and the mixture was stirred 15 minutes. Ice water was added and the mixture was extracted with ether. The ether extracts were extracted with dilute acid. The acid extracts were
neutralized and the resulting suspension extracted with ether. 4.0 g. of a light brown oil remained after drying and evaporating the ether extracts. This residue was redissolved in benzene and refluxed with N-phenylmaleimide (4.7 g., 0.027 mole) overnight. On chromatography on activity grade III alumina in benzene 200 mg. of a yellow oil was isolated. The oil was not crystallized.

Infrared spectrum: 5.66, 5.85, 6.20, 6.63, 10.06, and 10.87 μ.

N-Benzyl pyridone. Pyridine (40.0 g., 0.506 mole) and benzyl chloride (64.0 g., 0.506 mole) were dissolved in benzene (150 ml.) and refluxed overnight. The solution became yellow and 82.3 g. of yellow oil separated. The oil was dissolved in 80 ml. water and the solution cooled to 0°. Potassium ferricyanide (264.0 g., 0.80 mole) in 500 ml. water and sodium hydroxide (64 g., 1.6 mole) in 120 ml. water were added dropwise so the reaction temperature never rose above 15°. The addition was regulated so all the base had been added when half of the oxidizing agent had been added. After several hours standing at room temperature, the reaction mixture, which was brown in color, was extracted with ether and on drying and evaporating the ether extracts 37 g. crude pyridone was obtained. Recrystallization from cyclohexane gave 30 g. (40%), m.p. 71-72° (lit. 75-76°50).

Infrared spectrum: 6.02, 8.56, 12.89, 13.71, and 14.42 μ.

N-Benzyl pyridone dimer. N-Benzyl pyridone (2.9 g.) was irradiated in 95% ethanol (210 ml.) with the full spectrum (quartz probe) of a

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50 O. Fischer, Ber., 32, 1297 (1899).
Hanovia 450 watt medium pressure mercury vapor lamp for 19.5 hours. 140 mg. of a white solid was filtered from the resulting brown solution. Recrystallization from glacial acetic acid-water gave white plates, m.p. 207-215° with decomposition.


Anal. Calcd. for C$_{12}$H$_{11}$NO: C, 77.81; H, 5.99; N, 7.56.

Found: C, 77.64; H, 6.09; N, 7.54.

**Irradiation of N-benzyl pyridone in acrylonitrile.** N-Benzyl pyridone (0.5 g.) was dissolved in acrylonitrile (20 ml.) and the solution irradiated with the full spectrum of a low pressure mercury vapor lamp for 15 hours. 30 mg. of a tan solid was filtered from the resulting brown solution. Recrystallization gave white needles, m.p. 205-213° with decomposition. The infrared spectrum of this material was identical with that of N-benzyl pyridone dimer.

**Attempted Diels-Alder reaction of an imino chloride and 1,3-cyclohexadiene.** Acetamide (0.75 g., 0.0125 mole) was dissolved in nitrobenzene (3.2 ml.). Phosphorous oxychloride (1.92 g., 0.0125 mole) was added and the mixture refluxed 10 minutes. 1,3-Cyclohexadiene (1.0 g., 0.0125 mole) was added dropwise. The solution, which was originally yellow, turned purple, blue, and finally black. A large quantity of black gum formed at the bottom of the flask during 13 hours of refluxing. The mixture was neutralized and extracted with ether. The yellow ether extracts, after drying and evaporation of the solvent, yielded 20 mg. of a yellow oil which had a basic odor.
Attempted reaction of carbethoxyisothiocyanate with 1,3-cyclohexadiene. Carbethoxyisothiocyanate was prepared by refluxing ethyl chloroformate (2.5 g., 0.023 mole) with potassium thiocyanate (2.4 g., 0.025 mole) in dry acetone for 10 minutes. The solvent was evaporated under reduced pressure and 1,3-cyclohexadiene (1.9 g., 0.023 mole) was added with carbon tetrachloride (20 ml.). The mixture was allowed to stand at room temperature overnight. The reaction was monitored periodically by the removal of several ml. of the mixture and subjecting the sample to infrared analysis. No change occurred on standing. No change in the infrared spectrum was noted after 3 hours at reflux.

Infrared spectrum: 5.05-5.22 μ.

Methylene diurethane. Urethane (178 g., 2.0 moles) was dissolved in cold water (1.0 l.) and 37% formaldehyde (81 g., 1.0 mole) and concentrated hydrochloric acid (2-3 ml.) were added. The mixture was allowed to stand 3 days at room temperature. 140 g. (65%) of white needles was obtained, m.p. 127-30° (lit.131°52).

Benzal diurethane. Benzaldehyde (26.5 g., 0.25 mole), urethane (49.9 g., 0.50 mole) and boron trifluoride etherate (1.42 g., 0.01 mole) were added to benzene (250 ml.). The mixture was refluxed overnight in a flask fitted with a water separator. On cooling 31.0 g. of fluffy white solid precipitated. Concentration of the mother liquors yielded 18.0 g. second crop. The crude yield of white solid was 64%, m.p. 177-184°. Recrystallization from benzene chloroform gave white fluffy crystals with m.p. 182-184° (lit., m.p. 178-179°53).

52 M. Conrad and K. Hock, Ber., 36, 2206 (1903).
53 F. Lehmann, Ber., 34, 366 (1901).
2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene XXV. Boron trifluoride etherate (5.0 g., 0.035 mole) and crude methylene diurethane (24 g., 0.126 mole) were added to benzene (200 ml.). The mixture was brought to reflux and 1,3-cyclohexadiene \(^{54}\) (12.5 g., 0.125 mole) was added dropwise over a period of 30 minutes. The resulting mixture was refluxed 1 hour and cooled to room temperature. Saturated sodium bicarbonate was added and the brown organic phase was washed till the acid was neutralized. The organic layer was washed several times with water, dried over sodium sulfate and the solvent evaporated under reduced pressure. The yellow residue was distilled under reduced pressure to give 6.0-6.5 g. (27\%) of a colorless oil, b.p. 58-64° (3 mm.).

Infrared spectrum: 5.98, 7.16, 9.96, 13.11, and 14.20 μ.

Anal. Calcd. for C\(_{10}\)H\(_{15}\)NO\(_2\): C, 66.27; H, 8.34; N, 7.73.

Found: C, 66.33; H, 8.40; N, 7.71.

2-Carbethoxy-3-phenyl-2-azabicyclo[2.2.2]oct-5-ene XXVII. Boron trifluoride etherate (5.9 g., 0.042 mole) and phenyl methylene diurethane (39.5 g., 0.148 mole) were added to benzene (240 ml.) and the solution heated to reflux. 1,3-Cyclohexadiene (16.8 g., 0.167 mole) was added and the reaction was treated as described above. The yield of colorless oil was 18.6 g. (50\%) b.p. 118.5-121° (3 mm.).

Infrared spectrum: 5.90, 7.33, 8.59, and 12.97 μ.

Anal. Calcd. for C\(_{16}\)H\(_{19}\)NO\(_2\): C, 74.68; H, 7.44; N, 5.44.

Found: C, 74.61; H, 7.55; N, 5.44.

2-Carbethoxy-2-azabicyclo[2.2.2]octane XXVIII. Redistilled 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (XXV) (5.0 g.) was dissolved in cyclohexane (55 ml.) and palladium on carbon (60 mg.) was added. The mixture absorbed 2.0 lb. (theoretical, 2.2 lb.) of hydrogen in

30 minutes on hydrogenation on a Parr shaker. After filtration and evaporation of the solvent the solution yielded 3.7 g. (74%) of colorless oil, b.p. 87-90° (5 mm.).

Infrared spectrum: 5.89, 7.62, 7.98, 10.07, and 12.97 μ.

Anal. Calcd. for C_{10}H_{17}NO_{2}: C, 65.54; H, 9.35; N, 7.64.
Found: C, 65.24; H, 9.40; N, 7.62.

Isoquinuclidine I. 2-Carbethoxy-2-azabicyclo[2.2.2]octane XXVIII (2.55 g.) was heated strongly with potassium hydroxide (12 g.) in triethylene glycol (50 ml.) in a flask fitted with a distilling head. A colorless liquid with a basic odor was collected between 150 and 240° (reaction temperature) when the distillate became yellow. The distillate was treated with solid potassium carbonate until two layers were formed when the mixture was extracted with benzene. The benzene extracts were treated with a saturated solution of picric acid in benzene yielding 3.0 g. (52%) of a yellow picrate, m.p. 240-243°. Recrystallization from ethanol gave yellow needles, m.p. 244-247° with decomposition above 220° (lit., m.p. 247-249°).

Benzoyl isoquinuclidine. 2-Carbethoxy-2-azabicyclo[2.2.2]octane (2 g.) was hydrolyzed with potassium hydroxide (10 g.) and triethylene glycol (40 ml.) as above. The distillate was added to sodium hydroxide (200 mg.) and benzoyl chloride (4 ml.) and stirred overnight. A yellow oil separated and solidified on standing. Recrystallization gave 0.7 g., m.p. 115-118° and 0.4 g., m.p. 105-115°, a total yield of 47%. The authentic material had a melting point of 118-120°. The mixed melting point was 114.5-118.5°. Infrared spectra of the two samples were identical.

Infrared spectrum: 6.17, 9.00, 11.51, 12.72, and 13.47 μ.
2-Azabicyclo[2.2.2]oct-5-ene (dehydroisoquinalidine) XXIX.

2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (1 g.) was hydrolyzed as above with potassium hydroxide (5 g.) and triethylene glycol. The distillate was treated with potassium carbonate and the amine extracted into benzene. Saturated picric acid in benzene was added to give 1.5 g. crude picrate. Recrystallization from ethanol gave 0.8 g. (44%) of yellow needles, m.p. 222-223.5°.

Anal. Calcd. for C_{14}H_{14}N_{4}O: C, 44.16; H, 4.17; N, 16.56.

Found: C, 44.24; H, 4.44; N, 16.36.

The tosyl derivative of 2-azabicyclo[2.2.2]oct-5-ene XXIX, which had a melting point of 107-108°, was prepared by reacting the amine with tosyl chloride.

Infrared spectrum: 7.55, 8.63, 10.99, 12.18, and 14.06 μ.

Anal. Calcd. for C_{14}H_{17}NO_2S: C, 63.86; H, 6.51; N, 5.32; S, 12.15.

Found: C, 64.01; H, 6.75; N, 5.53; S, 12.11.

2-Methyl-2-azabicyclo[2.2.2]oct-5-ene XXX. 2-Carbethoxy-2-aza-
bicyclo[2.2.2]oct-5-ene (628 mg.) was reduced with lithium aluminum hydride (200 mg.) in dry tetrahydrofuran (20 ml.) by refluxing overnight. Saturated sodium sulfate was added and the solvent filtered from the hydroxides. The hydroxides were extracted several times with hot solvent and the extracts combined. The extracts were evaporated to dryness, the residue dissolved in a few ml. of ether and a saturated picric acid solution (in ether) was added to give 0.5 g. picrates as a yellow solid. Recrystallization from ethanol gave 0.4 g. (33%) of yellow needles, m.p. 248-250°.
Anal. Calcd. for C_{14}H_{16}N_{4}O_{7}: C, 47.73; H, 4.58; N, 15.90.  
Found: C, 47.80; H, 4.75; N, 15.95.

2-Methyl-3-phenyl-2-azabicyclo[2.2.2]oct-5-ene XXXI. 2-Carbethoxy-3-phenyl-2-azabicyclo[2.2.2]oct-5-ene XXVII (628 mg.) was reduced as above with lithium aluminum hydride (200 mg.) to yield 0.6 g. crude picrates. Recrystallization from ethanol gave 0.45 g. (43%) of yellow needles, m.p. 190-193°.

Anal. Calcd. for C_{25}H_{21}N_{4}O_{7}: C, 56.07; H, 4.71; N, 13.08.  
Found: C, 55.98; H, 4.89; N, 13.11.

3-Indoleglyoxylic chloride. Oxalyl chloride (0.8 ml.) was added to a solution of indole (1.0 g.) in dry ether (25 ml.) at 0°. The mixture changed from colorless to orange and after a few minutes 1.3 g. (73%) yellow crystals precipitated, m.p. 135-138° (lit., m.p. 139°55).

5-Methoxy-3-indoleglyoxylic chloride. Oxalyl chloride (1.6 ml.) was added to 5-methoxyindole (2.0 g.) in 30 ml. dry ether at 0°. The mixture changed from colorless to red and on standing 3.6 g., a quantitative yield, of orange crystals precipitated, m.p. 133-142° with decomposition (lit., m.p. 130°56).

Glyoxylicamide. XXIVa. The dehydroquinuclidine derived from the hydrolysis of adduct XXV was dissolved in chloroform (30 ml.) and normal  

sodium hydroxide (5 ml.) was added. 3-Indoleglyoxyl chloride and normal sodium hydroxide was added alternately such that the pH of the aqueous phase is maintained at about 10, about 6 g. 3-indoleglyoxyl chloride was added. When the aqueous phase became notably yellow and base was rapidly consumed, the additions were stopped and the organic phase was dried over sodium sulfate. Evaporation of the solvent gave a yellow oil which was crystallized on addition of benzene and scratching, yielding 3.5 g. of a yellow solid, m.p. 185-195°. Recrystallization from methanol gave 2.0 g. (24%), of white crystals, m.p. 201.5-203°.

Infrared spectrum: 3.16, 6.11, 6.23, 8.06, 12.95 and 13.55 μ.

Anal. Calcd. for C_{17}H_{16}N_{2}O_{2}: C, 72.84; H, 5.75; N, 9.99.

Found: C, 72.98; H, 5.95; N, 10.28.

**Amine XXXV**. Glyoxylandide (XXXIVa) (1.5 g.) was reduced with lithium aluminum hydride (2.0 g.) in dry tetrahydrofuran (100 ml.) by refluxing the mixture 5 hours. Saturated sodium sulfate was added and the hydroxides extracted several times with hot solvent. After the combined extracts were dried and evaporated, 1.2 g. of a yellow solid was isolated. Recrystallization from cyclohexane gave 1.0 g. (74%), of white crystals, m.p. 124-126°.

Infrared spectrum: 3.3, 6.91, 8.16, 9.33, 10.94, and 14.15 μ.

Anal. Calcd. for C_{17}H_{20}N_{2}: C, 80.91; H, 7.99; N, 11.10

Found: C, 80.90; H, 8.10; N, 11.15.
Glycolamide XXXVI. Glyoxylamide (XXXIVa) (1.0 g.) was dissolved in ethanol (50 ml.) and sodium borohydride (0.7 g.) was added with stirring. The mixture was stirred for 2 hours and 100 ml. water was added. The resulting suspension was extracted with chloroform and the extracts were dried and evaporated. The milky, oily residue was crystallized from methanol to yield 0.66 g. (66%) of white prisms; m.p. 185-186°. Recrystallization from methanol gave white prisms, m.p. 190-193°.

Infrared spectrum: 3.09, 6.15, 6.49, 9.60, 11.46, and 13.46 μ.

Anal. Calcd. for C\textsubscript{17}H\textsubscript{16}N\textsubscript{2}O\textsubscript{2}: C, 72.32; H, 6.43; N, 9.92.

Found: C, 72.17; H, 6.61; N, 9.92.

Glyoxylamide XXXIVb and amine XXXVb. The dehydroisoquinuclidine from the hydrolysis of 24.5 g. of adduct XXV was reacted with 5-methoxy-3-indoleglyoxylchloride (19 g.) as above to give 12.5 g. of crude glyoxylamide. Recrystallization from glacial acetic acid gave 9.5 g. (22%) of white crystals, m.p. 239-242°.

Infrared spectrum: 3.30, 6.20, 6.33, 6.43, 8.36, 9.82, 11.94, and 13.05 μ.

Anal. Calcd. for C\textsubscript{18}H\textsubscript{16}N\textsubscript{2}O\textsubscript{3}: C, 69.66; H, 5.85; N, 9.03.

Found: C, 69.82; H, 5.86; N, 9.11.

Glyoxylamide (XXXIVb) (15.2 g.) was reduced with lithium aluminum hydride (15.0 g.) as above to yield 12.0 g. crude amine. Recrystallization from benzene-cyclohexane gave 8.0 g. (58%) of a light tan solid, m.p. 117-119°.

Anal. Calcd. for C_{18}H_{20}N_{2}: C, 76.56; H, 7.85; N, 9.92.

Found: C, 76.59; H, 7.80; N, 10.00.

**Attempted cyclization of amine (XXXVa).** Amine (XXXVa) (200 mg.) was dissolved in concentrated hydrochloric acid and the solution refluxed for 1 hour. Sodium bicarbonate was added to neutralize the acid and the resulting mixture was extracted with ether. The light yellow ether extracts were dried over sodium sulfate, the solvent evaporated and the residue chromatographed on activity grade II alumina in benzene. A yellow solid (100 mg.), m.p. 115-122°, was isolated and some dark colored material was adsorbed at the top of the chromatographic column. The infrared spectrum of the solid was virtually identical with that of amine (XXXVa).

**Attempted cyclization of glycolamide (XXXVI).** Glycolamide (XXXVI) (200 mg.) was dissolved in methanol (10 ml.) and concentrated hydrochloric acid (2 ml.) was added. After the mixture was refluxed 30 minutes saturated sodium bicarbonate was added. The solution, which was colorless before heating, changed to a deep purple while refluxing. A yellow solid which did not melt precipitated on addition of bicarbonate.

**Attempted reduction of glycolamide (XXXVI) with zinc.** Glycolamide (XXXVI) (0.5 g.) was added to glacial acetic acid (20 ml.) and water (4 ml.). Most of the solid dissolved to give a colorless solution. Powdered zinc and concentrated hydrochloric acid were added alternately in order to minimize the formation of the purple color which formed when the strong acid was added. Zinc dispelled the purple color.
When the formation of the purple color ceased on addition of acid, the mixture was allowed to stir 2 hours. The reaction mixture gave a suspension on treatment with saturated sodium bicarbonate. The suspension was extracted with benzene and the extracts dried and evaporated to dryness yielding an orange solid, m.p. 150-260°. The melting range was not significantly altered on recrystallization from methanol-water.

Glyoxylamide (XXXIX). 3-Indoleglyoxyl chloride (22 g.) was added to piperidine (20 g.) in benzene (200 ml.). The mixture precipitated 29 g. crude glyoxylamide while stirring for 3 hours. Recrystallization from benzene-chloroform gave 13.5 g. (54%) of white needles, m.p. 178-182°, and 3.5 g. crude material (lit., m.p. 179-180°\textsuperscript{57}).

Infrared spectrum: 3.46, 6.14, 6.23, 7.88, 8.90, 10.46, 11.75 and 13.56 μ.

Attempted reduction of glyoxylamide (XXXIX) with zinc and acid. Glyoxylamide (XXXIX) (0.1 g.) was dissolved in methanol (10 ml.) and concentrated hydrochloric acid (2 ml.) was added. Zinc dust (0.1 g.) was added slowly with stirring. After the solution was stirred 2 hours saturated sodium bicarbonate was added and the resulting suspension extracted with chloroform. The chloroform extracts were dried over sodium sulfate and evaporated to yield a brown oil which was not crystallized. Comparison of the oil with acetamide (XL) on thin layer chromatography showed that the oil contained none of acetamide (XL).

\textsuperscript{57} T. Nogradi, Monatsh., 88, 768 (1957).
Attempted reduction of glyoxylamide (XXXIX) with stannous chloride. Glyoxylamide (XXXIX) (50 mg.) was dissolved in methanol (5 ml.) and concentrated hydrochloric acid (1 ml.) was added. Stannous chloride (0.1 g.) was added slowly with stirring. After the solution was stirred 2 hours saturated sodium bicarbonate was added and the resulting suspension extracted with chloroform. The chloroform extracts were dried and concentrated. Thin layer chromatography indicated that only starting material was recovered.

Attempted reaction of glyoxylamide (XXXIX) with hydrazine. Glyoxylamide (XXXIX) (50 mg.) was dissolved in ethanol (10 ml.) and hydrazine (0.1 ml.) was added with 1 drop N-hydrochloric acid. The mixture was refluxed an hour and poured into water. The white crystals which precipitated had an identical infrared spectrum with that of the starting material and a melting point of 174-178°.

Acetylglyoxylamide (XLIII). Glyoxylamide (XXXIX) (2.0 g.) was added to acetic anhydride (4 ml.) and pyridine (10 drops). The mixture was heated on the steam bath 70 minutes and poured into cold water. A light yellow oil separated which crystallized on standing to 2.2 g. light yellow prisms, m.p. 133-134°. Recrystallization from benzene-cyclohexane gave white prisms, m.p. 136-5-137.5°.

Infrared spectrum: 5.76, 6.08-6.22, 7.57, 8.47, 10.43, 11.74 and 12.89 µ.

Found: C, 68.59; H, 6.09; N, 9.41.
Benzylglyoxylamide (XLIV). To glyoxylamide (XXXIX) (5.0 g.) in acetone (50 ml.) was added benzylchloride (5 ml.) and powdered potassium carbonate (5 g.). After the mixture was refluxed one and one-half hours, benzylchloride (4.5 ml.) and potassium carbonate (3 g.) were added and the mixture was refluxed an additional 3 hours. The reaction mixture was poured into water, yielding a yellow oil. The mixture was extracted with ether and the extracts dried over sodium sulfate and concentrated. The yellow oil remaining crystallized overnight to give 3.9 g. of light yellow prisms, m.p. 101-102.5°. The filtrate was chromatographed on activity grade IV alumina in benzene to give an additional 1.1 g. The total crude yield was 70%. Recrystallization from benzene-cyclohexane gave white prisms, m.p. 99-101°.

Infrared spectrum: 3.09, 6.09, 6.16, 7.26, 8.83, 10.53, 12.84, and 14.34 μ.

Anal. Calcd. for C$_{22}$H$_{22}$N$_2$O$_2$: C, 76.27; H, 6.40; N, 8.09.

Found: C, 76.29; H, 6.57; N, 77.90.

Treatment of neither the acetylglyoxylamide (XLIII) nor benzylglyoxylamide (XLIV) with hydrazine as was described for glyoxylamide (XXXIX) afforded a hydrazone.

Methyl-3-indoleacetate. A mixture of indole-3-acetic acid (3.5 g.) dissolved in methanol (25 ml.) with anhydrous hydrogen chloride (2.0 g.) was refluxed 10 hours. The volume was reduced to 10 ml. and saturated sodium bicarbonate was added. The resulting suspension was extracted into ether and the extracts dried over sodium sulfate and evaporated. A brown oil resulted which was dissolved in benzene and chromatographed on
activity grade II alumina to yield 2.3 g. (60%) of a yellow oil which solidified. The melting point was 45-47° (lit. 49-50.5°5).

Infrared spectrum: 3.01, 5.83, 7.01, 8.53, 10.06, and 13.35 μ.

Acetamide (XL). Methyl-3-indoleacetate (0.5 g.) was refluxed overnight in piperidine (3 ml.). The resulting brown solution was dissolved in chloroform, the chloroform extracts were washed with dilute hydrochloric acid and sodium bicarbonate, and the extracts were dried over sodium sulfate. Evaporation of the solvent yielded a brown oil. Chromatography on activity grade II alumina in benzene gave a light brown oil which solidified on standing to 0.4 g. (64%) of a brown solid, m.p. 80-90°.

Attempted preparation of acetamide (XXXVIII). Methyl-3-indoleacetate (1 g.) was refluxed with the dehydroisoquinuclidine derived from the cleavage of 10.0 g. adduct (XXV) dissolved in 15 ml. toluene for 10 hours. The resulting brown solution was extracted with dilute hydrochloric acid and sodium bicarbonate and dried over sodium sulfate. The brown solution yielded about 20 mg. of an oil on evaporation which had a nondescript infrared spectrum.

Attempted synthesis of acetamide (XXXVIII) using dicyclohexylcarbodiimide. The dihydroisoquinuclidine derived from the hydrolysis of adduct (XXV) (1.35 g., 0.0075 mole) extracted into tetrahydrofuran, was added to 3-indoleacetic acid (650 mg., 0.0037 mole) and dicyclohexylcarbodiimide (770 mg., 0.0037 mole) in tetrahydrofuran with

stirring. The clear solution became slightly warm and was stirred 2 hours. After extraction with dilute hydrochloric acid and saturated sodium bicarbonate, dicyclohexylurea crystallized and was filtered from the yellow solution. Evaporation of the solvent gave 400 mg. of tan crystals, m.p. 171-175°. This was found not to be identical with acetamide (XIX).  

Infrared spectrum: 3.07, 6.00, 6.08, 8.17, 9.93, 11.61, and 13.64 μ.

Analytical found: C, 73.11; H, 9.23; N, 10.00. This corresponds to C₂₆H₃₉O₂N₃.

Preparation of acetamide (XL) using ethoxyacetylene(1). 3-Indoleacetic acid (0.5 g., 0.0029 mole) was dissolved in dry tetrahydrofuran (2 ml.) and ethoxyacetylene (0.5 ml.) was added. The mixture was allowed to stand at 25° for 2 days when an additional 0.5 ml. ethoxyacetylene was added. After 3 more days at 25° the solvent was evaporated to yield a brown oil which showed strong infrared absorption at 5.49 and 5.75 μ, the anhydride region.⁵⁹ Piperidine (1 ml.) and pyridine (2 drops) were added and the mixture heated on the steam bath 15 minutes. The brown solution was allowed to stand 2 hours at room temperature when it was dissolved in ether. The solution was washed with dilute hydrochloric acid and sodium bicarbonate, dried over sodium sulfate and evaporated to a brown oil. After chromatography on activity grade III alumina in benzene the oil crystallized to 100 mg. (17%) of a brown solid, m.p. 95-100°. The infrared spectrum of this solid was virtually identical.

with that of the authentic material. (2) Using the mixed anhydride. 3-Indoleacetic acid (175 mg., 0.001 mole) was dissolved in dry tetrahydrofuran (1 ml.) and triethylamine (85 mg., 0.001 mole) was added. The solution was cooled to 0° and ethyl chloroformate (109 mg., 0.001 mole) was added. After ten minutes piperidine (85 mg., 0.001 mole) was added in 3 ml. of tetrahydrofuran-water (2:1). Two layers appeared and the mixture was stirred 2 hours at 25°. The mixture was extracted with ether and the ether extracts washed with dilute hydrochloric acid, saturated sodium bicarbonate and water. The extracts were dried over sodium sulfate and evaporated yielding a yellow oil. Chromatography as in (1) gave 88 mg. (48%) crude acetamide identical to that previously prepared and melting at 97-103°.

Infrared spectrum: 3.07, 6.16, 8.00, 9.90, and 13.46 μ.

Preparation of acetamide (XXXVIII). 3-Indoleacetic acid (10.6 g., 0.06 mole), ethyl chloroformate (6.75 g., 0.06 mole) and triethylamine (6.25 g., 0.06 mole) were reacted as in the preceding experiments. The dehydroisoquinucllicine derived from 25 g. adduct XXV in tetrahydrofuran was added. The work up yielded several grams of a brown oil which gave six fractions of brown oil on chromatography on activity grade III alumina in benzene. The first fraction was primarily unreacted ethyl chloroformate and was discarded. The weights of the remaining ones were: #2, 1.8 g.; #3, 3.0 g.; #4, 3.2 g.; #5, 0.7 g.; and #6, 0.6 g. The total weight was 8.3 g. Fraction #5 was rechromatographed on activity grade II alumina in benzene to give three fractions of oil.

Infrared spectrum: 3.11, 6.10, 6.95, 8.02, 9.83, and 13.49 μ.
An amount of 100 mg. of fraction #3 was reduced with 60 mg. of lithium aluminum hydride by refluxing in 50 ml. dry tetrahydrofuran to yield 40 mg. crude amine (XXXVa).

After standing several weeks all fractions crystallized partially after seeding and/or scratching. The crude crystalline product was recrystallized from benzene-cyclohexane to yield 0.4 g. white prisms, m.p. 113-115\(^\circ\).

**Analytical.** Calcd. for C\(_{17}\)H\(_{18}\)N\(_2\)O: C, 76.66; H, 6.81; N, 10.52.

Found: C, 76.80; H, 6.62; N, 10.45.

**Attempted cyclization of acetamide (XXXVIII).** 150 mg. of fraction #3 from the preceding experiment was dissolved in methanol (5 ml.) and concentrated hydrochloric acid was added. The mixture was refluxed 15 minutes and allowed to stand overnight. The color of the reaction mixture changed from brown to purple on standing. Saturated sodium bicarbonate was added and the resulting suspension extracted with chloroform. The extracts were dried and evaporated leaving a brown oily residue. The oily residue was reduced with lithium aluminum hydride (80 mg.) in refluxing tetrahydrofuran (5 ml.) to yield 40 mg. of a yellow oil. Comparison of the oil with ibogamine on thin layer chromatography (silica gel-methanol) showed no material in the R\(_f\) region of ibogamine.

**Hydroboration of amine (XXXVa) and attempted cyclization of the product.** Amine (XXXVa) (1.2 g., 0.0005 mole) dissolved in tetrahydrofuran (50 ml.) was treated with the diborane generated from boron.

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A generous donation of ibogamine was made by Dr. S. K. Tala-patra, The Ohio State University.
trifluoride etherate (20 g., 0.139 mole) and sodium borohydride (2.3 g., 0.06 mole) in diglyme. The organoborane was treated with hydrogen peroxide (13.6 g., 0.06 mole) and 3 N sodium hydroxide (20 ml., 0.06 mole). After evaporation of the solvent, the residue was treated with concentrated hydrochloric acid. Saturated sodium bicarbonate was added and the resulting suspension was extracted with chloroform. After the extracts were dried, evaporation of the solvent gave 1.0 g. of a brown oil which did not crystallize. Chromatography on activity grade I alumina in methylene chloride gave several fractions of oil none of which crystallized on standing several weeks.


The oily product (200 mg.) was added to 2 g. polyphosphoric acid and the mixture heated 24 hours on the steam bath. Addition to saturated sodium bicarbonate, extraction of the resulting suspension with ether, drying of the ether extracts and evaporation of the extracts gave a brown oil. This oil showed no spots in the Rf region of ibogamine on thin layer chromatography.
APPENDIX

Infrared Spectra

Except where specifically noted, the following spectra were taken in potassium bromide disks or on sodium chloride plates with a Perkin-Elmer Infracord using a three minute scan, or a Baird Associates Model B spectrophotometer in which case they are labeled "Baird." Most of the spectra have been calibrated at 6.238 μ with polystyrene.
Product of cyclohexyloarbodiimide reaction
Product of \( \text{B}_2\text{H}_6 \) on amine XXXVa after chromatography
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