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The Synthesis and Photolysis of Kreysiginone and the Syntheses and Antibacterial Activity of 1-Vinyl-3,4-Dihydroisoquinoline Methiodides

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THE SYNTHESIS AND PHOTOLYSIS
OF KREYSIGINONE
AND
THE SYNTHESES AND ANTIBACTERIAL ACTIVITY
OF 1-VINYL-3,4-DIHYDROISOQUINOLINE METHIODIDES

by
Bruce L. Jensen

A Dissertation
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Bruce L. Jensen
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INTRODUCTION

This dissertation is divided into two parts. The first part deals with two new groups of alkaloids, namely the homoproaporphines and the homoaporphines, which have recently been isolated from Kreysigia multifora. The homoproaporphine, kreysiginone, was shown to possess a spiro-dienone D ring which, in the presence of acid, rearranged to a homoaporphine with a phenolic D ring.

In order to examine the possibility of a photochemical rearrangement of kreysiginone, an eleven step total synthesis of this naturally occurring product was carried out. The reaction sequence was chosen so that a minimum number of steps were used with the final step in the scheme being the oxidative phenolic coupling of a diphenol derivative of 1-phenethyltetrahydroisoquinoline, the type of reaction known to occur in the living plant. Each product in this scheme was carefully characterized by the use of nmr, ir, uv, and elemental analysis. Photolysis of this homoproaporphine was then studied in the absence of a proton source.

In addition, the synthesis of a benzazepine leading to a "bishomoaporphine" was also attempted.

In the second part, 1-styrylisoquinolines and their derivatives have been shown to possess analgetic activity. However, highly substituted 1-vinyl-3,4-dihydroisoquinolines have never been prepared, and consequently, nothing is known about their chemistry and pharmacology.

1

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In order to characterize such compounds and to test them for possible biological activity, a convenient method for the syntheses of these compounds was developed. The procedure involves the formation of disubstituted acrylamides of β-((3,4-dimethoxyphenyl)-ethylamine which were subsequently converted to the corresponding disubstituted 1-vinyl-3,4-dihydroisoquinolines through the Bischler-Napieralski reaction. These compounds were isolated and characterized as the methiodide salts.

During the course of this investigation, N-(3,4-dimethoxy-phenethyl)-cinnamamide failed to give the expected methiodide salt after treatment with phosphorus oxychloride and methyl iodide. However, when it was heated in the presence of polyphosphoric acid, it gave an anomalous compound, 8,9-diethoxy-6-phenyl-3-benzazocin-4-one, which was characterized by ir, nmr, uv and elemental analysis.
PART I

THE SYNTHESIS AND PHOTOLYSIS
OF
KREYSIGINONE
The aporphines comprise a group of about 90 alkaloids all of which are based upon the 4H-dibenzo[de,§]quinoline structure (1). This class of alkaloids is often divided into three groups depending upon the type of substitution at the nitrogen atom. These groups are: (a) the N-methyl aporphines, (b) the noraporphines which have a secondary nitrogen atom, and (c) the quaternary aporphine salts.

Since glaucine (2a) was discovered by Probst in 1839, much research has been devoted to the isolation, characterization, synthesis and pharmacology of new aporphine type alkaloids.

Until 1966, the only useful laboratory preparation of aporphines was from the corresponding 1-(2-aminobenzyl)-1,2,3,4-tetrahydroisoquinoline by way of a Pschorr type cyclization (I).
Gadamer's synthesis of glaucine in 1911 was the first successful application of the Pschorr reaction. In 1966, two photochemical routes to aporphines were reported. Cava, et al. and Yang, et al. employed, as the key step, the well known stilbene-phenanthrene photocyclization reaction. In this manner they prepared the aporphine alkaloids nuciferine (2b) and glaucine (2a) (II).

In that same year, Kupchan and Kanojia reported the photolytic conversion of 1-(2-iodobenzyl)-1,2,3,4-tetrahydrosinoquinolines to a number of substituted aporphines. In 1970, Cava and coworkers showed that the 2-chloro and 2-bromo derivatives also underwent such a reaction (III).

Since the aporphines are naturally occurring compounds, many groups have studied their synthesis based upon routes used, or thought to be used, in the living plant. The aporphine alkaloids are based upon a skeleton, which has long been considered to be derived oxidatively from the 1-benzyl-1,2,3,4-tetrahydrosinoquinoline.
system (2). Since aporphines are probably formed in nature by intramolecular phenolic coupling, several attempts\(^7\),\(^8\) have been made to achieve such an oxidation \textit{in vitro}. In 1962, Franck and coworkers\(^9\) reported the first synthesis of an aporphine salt by oxidative coupling. This same group also demonstrated that previous failures to synthesize aporphines oxidatively was due to the fact that N-acyl, secondary and tertiary bases of type 3 tend to undergo nitrogen cyclization instead of coupling, and that quaternary salts undergo the desired condensation in good yields.

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{N-R} \\
\text{R}_3 \\
\text{R}_4 \\
\text{R}_5 \\
2
\end{array}
\]

In 1957, Barton and Cohen\(^10\) published a now classical analysis of the biogenetic aspects of phenol oxidation in the formation of a wide variety of natural products. These authors noted that while some aporphines could be formed in the plant by direct oxidative coupling, others could be rationalized only if dienones such as 4 were assumed to be intermediates within the general biosynthetic scheme. If such a structure is possible, it could undergo a catalytic dienone-phenol or dienone-benzene rearrangement. Then depending upon the substituents on the dienone ring, various aporphines could be formed (Scheme I).

Support for this theory was obtained in 1963 when Haynes\(^11\)
and Bernauer\textsuperscript{12} discovered two naturally occurring alkaloids related to 4. After isolation and purification, these compounds were smoothly rearranged to aporphines by treatment with hot acid. Haynes\textsuperscript{13}, Barton\textsuperscript{\textsuperscript{4}}\textsuperscript{4} and Pfeifer\textsuperscript{45} later showed that the dienone structure was the precursor of the aporphine structure by the use of radioisotopically labeled compounds in some in vivo studies; thereby, completing the biosynthetic scheme. Dienone bases having the skeleton 4 are now considered as members of a new class of
alkaloids designated as the proaporphines.

Once the proaporphine class of alkaloids was discovered, active interest was undertaken to prepare such compounds in the laboratory. Since 1963, three different methods have been reported for the synthesis of proaporphine structures. In 1965, Battersby reported the first synthesis of orientalinone (4a) by intramolecular oxidative coupling of orientaline (3a) using potassium ferricyanide as the oxidizing agent (IV). This synthesis was of significant importance since orientaline is a naturally occurring product and its oxidative phenolic coupling to give the proaporphine, orientalinone, demonstrated the role of oxidative cyclization of 1-benzylisoquinolines in the production of proaporphine and aporphine alkaloids. Even though the yields are often very low in this reaction, several proaporphines have now been prepared by this method utilizing ferric chloride, potassium ferricyanide or manganese dioxide as the oxidizing agents.

Bernauer and Huffman have communicated syntheses involving the step by step construction of the two lower rings (C & D rings) using classical methods. However, these procedures have
not been shown to be easily adapted to preparative laboratory syntheses of a wide range of proaporphine structures.

In 1967, two new classes of alkaloids were discovered by Battersby\(^4\); both homologs of the aporphine and proaporphine series. These compounds represented new members of the 1-phenethyltetrahydroisoquinoline (5) class of alkaloids and were given the names homoproaporphines (6) and homoaporphines (7). Floramultine (7a),

\[
\text{Floramultine (7a),}
\]

\[
\text{7a, } R_1=R_3=R_5=\text{OCH}_3, \text{ } R_2=\text{OH, } R_4=\text{H}
\]

multifloramine (7b) and kreysigine (7c) are thus the first examples of homoaporphine alkaloids and their occurrence in *Kreysigia multiflora* is of taxonomic interest since colchicine has recently
been detected in this plant. By chromatographic examination of the minor alkaloids of *K. multifora*, Battersby\textsuperscript{20} isolated kreysiginone (6a); the first member of the homoproaporphine class of alkaloids. As in the aporphine series, Battersby showed that the biosynthetic pathway involves the dienone intermediate. Tracer studies are now being carried out to fully elucidate this scheme.

The acid catalyzed rearrangement of kreysiginone has also been studied by Kametani\textsuperscript{21}. Chromatographic workup of the reaction mixture afforded the homoaporphine 7d as well as two rearrangement products 8; R=CH\textsubscript{3} and R=H.

\[
\begin{array}{c}
\text{CH}_3\text{O} \\
\text{O} \\
\text{N-CH}_3 \\
\text{RO} \\
\text{O}
\end{array}
\]

Kametani\textsuperscript{21} also indicated that kreysiginone, unlike its proaporphine counterpart, can best be represented as 6a', in which the dienone ring is not at right angles to the benzene ring. Such a structural limitation also helps to explain the formation of the two acid-catalyzed rearrangements.

\[
\begin{array}{c}
\text{CH}_3\text{O} \\
\text{HO} \\
\text{N-CH}_3 \\
\text{CH}_3\text{O}
\end{array}
\]
DISCUSSION

Total Synthesis of Kreysiginone

The total synthesis of a naturally occurring homoproaporphine, kreysiginone, was carried out in this laboratory. Starting with vanillin (9) both phenolic moieties of the desired isoquinoline were synthesized.

The first step of the reaction sequence was the protection of the hydroxyl function of vanillin by formation of the benzyl ether under the conditions of the Williamson ether synthesis (V).

\[
\begin{align*}
\text{CHO} & + \phi \text{CH}_2 \text{Cl} \xrightarrow{\text{KOH}} \text{CHO} \\
\text{HO} & \phi \text{CH}_2 \text{O} \\
9 & \text{10}
\end{align*}
\]

Once \text{10} was obtained, two different Knoevenagel condensations were performed with this aldehyde. The unsaturated nitro compound \text{11} was obtained by the condensation of nitromethane with \text{10} in the presence of sodium hydroxide followed by hydrolysis in aqueous hydrochloric acid (VI). By condensing \text{10} with malonic acid, the corresponding cinnamic acid \text{12} was produced (VII).

\[
\begin{align*}
\phi \text{CH}_2 \text{O} \text{CHO} & + \text{CH}_3 \text{NO}_2 \xrightarrow{1/2 \text{NaOH}} \phi \text{CH}_2 \text{O} \text{CHO} \\
\phi \text{CH}_2 \text{O} & \phi \text{CH}_2 \text{O} \\
\text{10} & \text{11}
\end{align*}
\]

\[
\begin{align*}
\phi \text{CH}_2 \text{O} \text{CHO} & + \text{CH}_2 \text{(CO}_2\text{H})_2 \xrightarrow{} \phi \text{CH}_2 \text{O} \text{CHO} \\
\phi \text{CH}_2 \text{O} & \phi \text{CH}_2 \text{O} \\
\text{10} & \text{12}
\end{align*}
\]

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Both $11$ and $12$ were then reduced. However, the choice of the reduction method was extremely important because of the extreme lability of the benzyl ether moiety of these compounds. Lithium aluminum hydride in refluxing THF reduced the unsaturated nitro compound to the saturated amine $13$ in one step without affecting cleavage of the benzyloxy linkage (VIII).

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{CH} & \quad \text{NO}_2 \\
\phi\text{CH}_2\text{O} & \quad \text{CH} & \quad \text{LiAlH}_4 & \quad \text{CH}_3\text{O} & \quad \text{NH}_2 \\
11 & \quad \text{CH} & \quad \text{CH} & \quad \text{O} & \quad (\text{VIII})
\end{align*}
\]

The cinnamic acid $12$ was reduced to the corresponding phenylpropionic acid $14$ by means of a preparative electrolytic method or by using sodium amalgam. In both these methods the yields were high and the benzyloxy group was left intact (IX).

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{CH} & \quad \text{CO}_2\text{H} \\
\phi\text{CH}_2\text{O} & \quad \text{CH} & \quad \text{H} & \quad 2\text{H} & \quad \text{CH}_3\text{O} & \quad \text{CO}_2\text{H} \\
12 & \quad \text{CH} & \quad \text{CO}_2\text{H} & \quad (\text{IX})
\end{align*}
\]

Compounds $13$ and $14$ were then condensed using $N,N$-dicyclohexylcarbodiimide as the dehydrating agent to afford the amide $15$ (X).

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{NH}_2 & \quad \text{CH}_3\text{O} & \quad \text{CO}_2\text{H} \\
\phi\text{CH}_2\text{O} & \quad \text{CH}_3\text{O} & \quad \phi\text{CH}_2\text{O} & \quad \phi\text{CH}_2\text{O} & \quad \text{NH} & \quad \text{O} \\
13 & \quad \text{CH} & \quad \text{CH} & \quad \phi & \quad \text{OCH}_2\phi & \quad (\text{X})
\end{align*}
\]

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Cyclodehydration of the amide 15 by phosphorus oxychloride according to the Bischler-Napieralski reaction gave the dihydroisoquinoline 16 (XI).

The reaction of iodomethane with 16 resulted in the formation of 17 which was subsequently reduced to the 1,2,3,4-tetrahydroisoquinoline 18 by lithium aluminum hydride or sodium borohydride (XII).

Hydrogenolysis of the benzyl groups was accomplished by treating 18 with 10% palladium on charcoal in the presence of hydrochloric acid at 40 psi (XIII).

To complete the reaction sequence, 19 was subjected to a phenolic oxidative coupling reaction using ferric chloride. A lengthy workup yielded a small amount of kreyssignine (6a) (XIV).
Photolysis of kreysiginone

Numerous examples for the photochemical rearrangement of dienones have appeared in the literature\(^2\). One system which has been extensively studied by Zimmerman\(^3\) is represented by 4,4-diphenylcyclohexadienone (20). Irradiation of this compound afforded several products, but most notably, were the structures resulting from a dienone-phenol rearrangement (XV).

\[
\text{20}
\]

Kreysiginone (6a), which possesses a spiro-dienone D ring, has been shown to undergo a dienone-phenol rearrangement in an acidic media\(^2\) to yield a homoaporphine 21 with a phenolic D ring (XVI). Treatment of 21 with base gave 7d.

\[
\text{6a}
\]

\[
\text{21}
\]

Until now, no attempt has been made to study the photochemical rearrangement of kreysiginone, a naturally occurring product. After the total synthesis of kreysiginone, this compound was irradiated for 69 hr in the absence of acid. A lengthy workup of the reaction
mixture yielded a small amount of product which was characterized by spectral data and a possible structure was proposed.

The infrared spectra showed an intense carbonyl (C=O) stretching at 1690 cm\(^{-1}\) as compared to 1660 cm\(^{-1}\) for the starting material. However, no hydroxyl group absorption was noted in this spectra. A shift to shorter wavelength (276 m\(\mu\)) and a smaller molar extinction coefficient for this wavelength (e 1,510) was shown in the ultraviolet spectrum. The nuclear magnetic resonance spectrum showed that the following protons were present: N-CH\(_3\), 2 O-CH\(_3\), CH\(_3\), =CH, aromatic. Finally, gas chromatography in conjunction with mass spectrometry showed that the product contained two peaks (rel. intensity 1:2) with the following fragmentations: m/e 341 (M\(^+\)), (M\(+\)-1), (M\(+\)-17), (M\(+\)-28), (M\(+\)-29), and (M\(+\)-43). The product was, therefore, considered to be an isomeric mixture. On the basis of the spectral data, elemental analysis and the rearrangement products previously isolated\(^{21}\), the following structure is proposed for our photolysis product 22.

\[
\begin{align*}
\text{CH}_3\text{O} &- \text{N-CH}_3 \\
\text{CH}_3\text{O} &- \text{O} \\
\text{22}
\end{align*}
\]

Considering the reaction conditions and the mechanism for the photolytic rearrangement of dienones, the formation of 22 can be rationalized. Chapman\(^{22,23}\) has stated that excitation of the
$\alpha,\beta$-unsaturated ketone moiety of a molecule involves electron redistribution which can be represented as a dipolar system. Thus, the excited state of kreysiginone could be represented by structure 23. Subsequently, a 1,4-Michael type addition could take place giving rise to 24. By a rapid tautomeric shift, the keto-structure 22 would be formed from the enol 24. This is shown in Scheme II.

Scheme II

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Attempted route to a "bishomoaporphine".

The aporphine 1 and homoaporphine 7 structures have been shown to differ only by one methylene group (CH₂) in the C ring. By analogy, the addition of a methylene group to the B ring would give rise to a "bishomoaporphine" (eq 30). Such a structure would possibly be a new class of alkaloids. A reaction route was devised to prepare such a compound.

Kanaoka and coworkers²⁵ have reported that simple amides of \(\gamma-(3',4'-\text{dimethoxyphenyl})\)-propylamine 25 can be converted to the corresponding 3',4'-dihydro-\(J\)-2-benzazepine 26 derivatives by means of polyphosphate ester (PPE) (XVII).

\[
\text{CH}_3\text{C}-\text{H} \quad \text{PPE} \quad \text{CH}_3\text{O} \quad \text{CH}_3\text{O}
\]

It was thought that by preparing the appropriate amide this reaction could then be used as the key step in the synthesis of a "bishomoaporphine". To complete this route, reactions analogous to IX - XIV could be used.

The phenylpropylamine 27 was prepared by treating 14 with thionyl chloride and ammonia followed by reduction with lithium aluminum hydride. Compounds 14 and 27 were then condensed in the presence of DCC to give 28. However, this amide failed to undergo the expected cyclodehydration to give 29. Polyphosphate ester and phosphorus oxychloride were used under a variety of reaction
conditions, however, no benzazepine 29 was isolated. An impasse was therefore reached in this attempted synthesis (Scheme III).

Scheme III

\[
\begin{align*}
\text{14} & \xrightarrow{1) \text{SOCl}_2} \text{14 + DCC} \\
\text{28} & \xrightarrow{\text{PPE}} \text{29} \\
\end{align*}
\]

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EXPERIMENTAL

The melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. A Beckman IR-8 spectrophotometer was used to record the infrared (ir) spectra. The infrared spectra were taken for all compounds used in this work, however, only the spectra for new compounds have been reported in this section. The ultraviolet (uv) spectra were taken in 95% ethanol solution on a Cary 14 recording spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian-A-60 spectrometer using deuterio-chloroform (CHCl₃-d) or hexadeuterio-dimethyl sulfoxide (DMSO-d₆) as solvents with tetramethysilane (TMS) as an internal standard; resonances were measured in T values downfield from TMS standard. Mass spectral data were obtained on an Atlas CH-4 mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee and Midwest Microlab, Inc., Indianapolis, Indiana. The photolysis apparatus used in this experiment was a Rayonet Photochemical Reactor with a pyrex filter. A Sorensen DCR 150-15A power supply was used in the electrolytic reduction. A Hewlett-Packard gas chromatograph with a 6 ft 10% SE 30 column was used for glc analysis. Silica Gel G was used for thin-layer chromatography (tlc) either on glass slides or 6 x 20 cm glass plates. Silica Gel G was also used for preparative thin-layer chromatography on 20 x 20 cm glass plates. Spots on plates were detected by iodine vapor. Column chromatography was carried out on a 2 x 40 cm glass column packed with Baker chromatography
grade silica gel using chloroform containing 1% methanol as the eluting solvents. Dry tetrahydrofuran (THF) was obtained by distilling commercial grade THF from a lithium aluminum hydride solution. Dry benzene was obtained by storing analytical grade benzene over molecular sieve.

Preparation of 4-benzyloxy-3-methoxybenzaldehyde\textsuperscript{26}(10)

Vanillin (60.8 g, 0.4 mole) and potassium hydroxide (24.4 g, 0.44 mole) were dissolved in 95% ethanol (120 ml) and water (24 ml). After this solution was brought to reflux, benzyl chloride (50.6 g, 0.4 mole) was added dropwise over a period of 30 min and the mixture was refluxed for 5 hr. The precipitated potassium chloride was removed by filtration while the mixture was still hot and washed with a small amount of hot ethanol (50 ml). The filtrate was then refrigerated at 5° over night. The product separated as yellow platelets which after one recrystallization from 95% ethanol gave light yellow crystals (62.8 g, 65%) of mp 60-62°, Lit.\textsuperscript{26} mp 63-64°; nmr (CHCl\textsubscript{3}-d); \textit{\textsuperscript{1}}H 6.10 (s, 3, OCH\textsubscript{3}), 4.78 (s, 2, OCH\textsubscript{2}), 2.70 (m, 8, Ar-H), 0.10 (s, 1, O=CH).

Preparation of 4-benzyloxy-3-methoxy-\beta\textsuperscript{-}nitrostyrene\textsuperscript{27}(11)

4-Benzylloxy-3-methoxybenzaldehyde (10, 24.2 g, 0.1 mole) was dissolved in 95% ethanol (800 ml) and cooled to 5-10°. Nitromethane (12.2 g, 0.2 mole) was added with stirring to the resulting solution followed by a solution of sodium hydroxide (10.0 g, 0.25 mole) in 95% ethanol (200 ml). While maintaining the temperature of the solution below 15°, just enough ice water (~400 ml) was added to
dissolve the precipitated sodium salt. This solution was then poured into a solution of concentrated hydrochloric acid (120 ml) and water (180 ml) with rapid stirring. After cooling for 30 min, the product 11 was collected by filtration, washed and dried (20.4 g). Recrystallization from 95% ethanol yielded 4-benzyloxy-3-methoxy-β-nitrostyrene (18.8 g, 67%) as brilliant yellow needles, mp 122-123°, Lit.27 mp 122-123°; nmr (CHCl₃-d): 6 6.06 (s, 3, OCH₃), 4.76 (s, 2, OCH₂), 2.80 (m, 8, ArH, CH), 2.06 (d, 1, J=14.0 cps, CH).

Preparation of 4-benzyloxy-3-methoxycinnamic acid (12)

A mixture of 4-benzyloxy-3-methoxybenzaldehyde (10, 24.2 g, 0.1 mole), malonic acid (20.8 g, 0.2 mole), dry pyridine (120 ml) and piperidine (3 ml) was refluxed for 2.5 hr. After standing at room temperature over night, the mixture was poured into concentrated hydrochloric acid (130 ml) containing crushed ice (200 ml). The resulting precipitate was collected by filtration and washed successively with hydrochloric acid (100 ml, 5%) and water (100 ml). Recrystallization from 95% ethanol afforded 4-benzyloxy-3-methoxycinnamic acid (23.8 g, 84%) as fine white needles, mp 189-191°, Lit.28 mp 191°; nmr (DMSO-d₆): 6 6.14 (s, 3, OCH₃), 4.84 (s, 2, OCH₂), 3.54 (d, 1, J=16.5 cps, CH), 2.60 (m, 9, ArH, CH).

Preparation of 4-benzyloxy-3-methoxy-β-phenethylamine (13)

Under an atmosphere of nitrogen gas, dry tetrahydrofuran (500 ml) and lithium aluminum hydride (35.0 g, 0.9 mole) were placed in a 3-l three necked round bottom flask fitted with an addition funnel, stirrer and reflux condenser (protected from
moisture). 4-Benzylloxy-3-methoxy-β-nitrostyrene (11, 57.0 g, 0.2 mole) was dissolved in dry tetrahydrofuran (1500 ml) and added dropwise at such a rate as to maintain reflux. After the addition was complete (~2 hr), the solution was refluxed for another 24 hr. This mixture was then cooled in an ice-salt bath and to it was added successively water (35 ml), aqueous sodium hydroxide solution (40 ml, 15%) and water (105 ml) over a period of several hours under a continuous stream of nitrogen gas. The precipitated salts were then filtered and washed with tetrahydrofuran (500 ml). The combined filtrate and washings were concentrated under reduced pressure. The residue was cooled and hydrochloric acid (200 ml, 10%) and enough water to just dissolve the salt formed was added. Organic impurities were removed by extracting this water solution with ether (300 ml). The organic layer was discarded while the aqueous layer was cooled and made strongly alkaline with 40% aqueous sodium hydroxide solution. This mixture was then extracted with ether (1000 ml) and dried over potassium carbonate. Filtration and concentration by vacuum evaporation of this ethereal solution yielded 4-benzyloxy-3-methoxy-β-phenethylamine (13, 30.6 g, 60%) as a thick oil which was sufficiently pure for further reactions. Crystallization was induced by the addition of benzene-petroleum ether (bp 30-60°) to give white needles, mp 59-62°, Lit.* mp 65-80°. 4-Benzylloxy-3-methoxy-β-phenethylamine hydrochloride, mp 173-174°, Lit.* mp 173-175°. nmr (CHCl₃-d); δ 8.64 (s, 2, NH₂), 7.25 (m, 4, CH₂), 6.18 (s, 3, OCH₃), 4.92 (s, 2, OCH₂), 3.25 (m, 3, ArH), 2.66 (m, 5, ArH).
Preparation of 4-benzyloxy-3-methoxyphenylpropionic acid (14)

Electrolytic method

Apparatus- The reduction was carried out in a 4-l beaker immersed in cold water for cooling. The cathode for the reaction was a mercury pool at the bottom of the beaker, while a strip of lead sheet suspended in a porous cup served as the anode. The current used for this experiment was provided by a Sorensen power supply. The reaction was run in such a manner so that mechanical stirring was provided for the catholyte.

Reduction- After assembly of the apparatus, aqueous sodium sulfate solution (1000 ml, 7%) was placed in the beaker and porous cup. Stirring was started and 4-benzyloxy-3-methoxycinnamic acid (12, 100 g, 0.35 mole) was added to the catholyte. A solution of sodium hydroxide (15 g) in water (75 ml) was then added slowly until most of the acid had dissolved. The current was started and maintained at 8 amperes for 8 hr while the liquid in the porous cup was kept alkaline by frequent additions of a concentrated aqueous sodium hydroxide solution. When reduction was complete the catholyte was decanted from the mercury pool, filtered and acidified with concentrated sulfuric acid. The precipitate was collected by filtration, washed with water (200 ml) and dried. White crystals (90.0 g, 90%) of 4-benzyloxy-3-methoxyphenylpropionic acid (14) were obtained by recrystallization from benzene-petroleum ether (bp 30-60°), mp 93-95°, Lit. mp 98-99°; nmr (DMSO-d₆) δ 7.20 (m, 4, CH₃), 6.14 (s, 3, OCH₃), 4.88 (s, 2, OCH₃), 3.26 (m, 3, ArH), 2.60 (m, 5, ArH), -0.98 (s, 1, CO₂H).
Preparation of 4-benzyloxy-3-methoxyphenylpropionic acid (14)
using sodium amalgam

4-Benzylxox-3-methoxycinnamic acid (12, 23.0 g, 81 mmole) and sodium hydroxide (7.0 g, 175 mmole) were dissolved in water (200 ml). While this solution was stirred and heated on a steam bath, 2.5% sodium amalgam (400 g) was added in small portions. Stirring and heating were continued for 16 hr. After which, the solution was decanted from the mercury pool, filtered and cooled. This solution was then acidified with concentrated hydrochloric acid and extracted with chloroform (200 ml). Drying (Na₂SO₄) and vacuum evaporation gave 4-benzyloxy-3-methoxyphenylpropionic acid (20.8 g, 90%) as a white solid. Recrystallization from benzene-petroleum ether (bp 30-60°) gave white needles, mp 93-95°, Lit. mp 98-99°; nmr (DMSO-d₆): 7 7.20 (m, 4, CH₃), 6.14 (s, 3, OCH₃), 4.88 (s, 2, OCH₃), 3.26 (m, 3, ArH), 2.60 (m, 5, ArH), -0.98 (s, 1, CO₂H).

Preparation of N-(4-benzyloxy-3-methoxyphenethyl)-4-benzyloxy-3-
methoxyphenylpropionamide (15)

4-Benzylxox-3-methoxy-β-phenethylamine (13, 10.3 g, 40 mmole) and 4-benzyloxy-3-methoxyphenylpropionic acid (14, 11.4 g, 40 mmole) were dissolved in methylene chloride (200 ml) and cooled to 0°. To this stirred and cold solution was added, N,N-dicyclohexyl-
carbodiimide (8.3 g, 42 mmole) in methylene chloride (50 ml) over a period of 30 min. The reaction mixture was allowed to stir at 0° for 20 hr. Filtration of the precipitated urea and vacuum evaporation of the solvent afforded a tan product which after recrystal-
lization from 95% ethanol gave colorless crystals (11.7 g, 56%) of 15, mp 133-135°. The analytical sample was obtained by four recrystallizations from 95% ethanol, mp 136-137°. \( \nu_{\text{max}} \text{(cm}^{-1} \text{)} \) 3310 (N-H), 1650 (C=O); nmr (CHCl\(_3\)-d): \( \tau \) 7.00 (m, 8, CH\(_2\)), 6.18 (s, 6, OCH\(_3\)), 4.88 (s, 4, OCH\(_2\)), 4.32 (s, 1, NH), 3.30 (m, 6, ArH), 2.60 (m, 10, ArH); \( \lambda_{\text{EtOH}} \) max 229 mp (c 14,500).

*Anal. calcd. for Cu_{33}H_{35}NO_{51}: C, 75.40; H, 6.71; N, 2.66.*

Found: C, 75.51; H, 6.56; N, 2.58.

**Preparation of 7-benzyloxy-1-(4-benzyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (16)**

N-(4-Benzyloxy-3-methoxyphenethyl)-4-benzyloxy-3-methoxyphenyl-propionamide (15, 12.0 g, 23 mmole) and phosphorus oxychloride (55.0 g, 360 mmole) were refluxed for 1 hr in dry benzene (200 ml). The solvent was removed under reduced pressure and the residue taken up in chloroform (250 ml). The chloroform solution was then washed with two portions of 10% aqueous ammonia (100 ml), two portions of water (50 ml) and dried over sodium sulfate. Evaporation of the solvent left a tan oil, which was induced to crystallize by the addition of 10:1 hexane-benzene solution to give 16 (11.5 g, 99%) as tan crystals. Compound 16 was found analytically pure as white needles, mp 89.5-90.8°, after four recrystallizations from hexane-benzene. The hydrochloride salt derivative of 16 had a melting point of 195-197°. \( \nu_{\text{max}} \text{(cm}^{-1} \text{)} \) 1640 (C=N), 1575 (C=N); nmr (CHCl\(_3\)-d): \( \tau \) 7.40 (m, 2, CH\(_2\)), 7.10 (s, 4, CH\(_2\)), 6.38 (s, 2, CH\(_2\)), 6.08 (s, 3, OCH\(_3\)), 6.12 (s, 3, OCH\(_3\)), 4.84 (s, 4, OCH\(_2\)), 3.20
(m, 4, ArH), 2.92 (s, 1, ArH), 2.56 (m, 10, ArH); \( \lambda_{\text{max}} \) \text{EtOH} 230 nm (e 12,600).

Anal. calcd. for C\textsubscript{33}H\textsubscript{33}NO\textsubscript{6}: C, 78.08; H, 6.55; N, 2.75.
Found: C, 78.31; H, 6.27; N, 2.70.

Preparation of 7-benzyloxy-1-(4-benzyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline methiodide (17)

4-Benzylxoy-1-(4-benzylxoy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (16, 4.75 g, 9.4 mmole) and methyl iodide (1.35 g, 9.5 mmole) were dissolved in benzene (75 ml) and allowed to stand at room temperature for 24 hr. The yellow salt which separated was collected by filtration, washed with cold benzene (20 ml) and recrystallized from acetone to give 17 (6.1 g, 100%) as pale yellow needles, mp 131-133\(^\circ\). An analytical sample was prepared by three recrystallizations of 17 from dry acetone, mp 131-133\(^\circ\); \( \nu_{\text{Nujo}} \) (cm\(^{-1}\)) 1650 (C=N), 1570 (C=N); nmr (CHCl\textsubscript{3}-d); \( \begin{array}{c} \text{N} \text{H} \\ \text{m} \text{H} \end{array} \) 7.84 (s, 3, NCH\textsubscript{3}), 6.80 (m, 8, CH\textsubscript{2}), 6.15 (s, 3, OCH\textsubscript{3}), 6.05 (s, 3, OCH\textsubscript{3}), 4.89 (s, 2, OCH\textsubscript{2}), 4.83 (s, 2, OCH\textsubscript{2}), 3.30 (m, 5, ArH), 2.60 (m, 10, ArH); \( \lambda_{\text{max}} \) \text{EtOH} 360 nm (e 9,450), 310 nm (e 9,400).

Anal. calcd. for C\textsubscript{33}H\textsubscript{33}NO\textsubscript{6}: C, 62.86; H, 5.58; N, 2.15.
Found: C, 62.87; H, 5.57; N, 2.06.

Preparation of 7-benzyloxy-1,2,3,4-tetrahydro-1-(4-benzyloxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline oxalate (18)

using LiAlH\textsubscript{4}

7-Benzylxoy-1-(4-benzyloxy-3-methoxyphenethyl)-3,4-dihydro-6-
methoxyisoquinoline methiodide (17, 13.5 g, 20 mmole) was added to a stirred solution of lithium aluminum hydride (3.8 g, 0.1 mole) in absolute ether (550 ml) over a period of 2 hr. Stirring was continued at room temperature for 30 min. The reaction mixture was cooled in an ice-salt bath and, under an atmosphere of nitrogen gas, water (5 ml), aqueous sodium hydroxide solution (5 ml, 15%) and water (15 ml) were added respectively. The salts were removed by filtration and the water separated from the ethereal solution. The ethereal solution was dried over K₂CO₃ and filtered. With vigorous stirring, a saturated ethereal solution of oxalic acid was slowly added. Compound 18 separated rapidly as an oil which soon solidified with scratching and cooling. After filtration and recrystallization from methanol-ether, the product 18 (9.6 g, 78%) was obtained as clumps of white crystals, mp 105-109° (effervescence). An analytical sample was prepared by four recrystallizations from methanol-ether, mp 110-112° (effervescence); \( \gamma_{\text{Nujol max}} \) (cm⁻¹) 1700 (C=O); nmr (CDCl₃-d): 7.80-5.40 (m, 9, CH₃), 7.22 (s, 3, NCH₃), 6.16 (s, 6, OCH₃), 4.92 (s, 2, OCH₂), 4.88 (s, 2, OCH₂), 3.30 (m, 5, ArH), 2.62 (s, 10, ArH), -1.18 (s, 1, CO₂H); \( \lambda_{\text{EtOH max}} \) 283 μ (ε 6,700), 230 μ (ε 19,000).

Anal. calcd. for C₃₄H₂₄N₂O₆: C, 70.46; H, 6.41; N, 2.28.
Found: C, 70.36; H, 6.47; N, 2.24.

Preparation of 7-benzylxoy-1,2,3,4-tetrahydro-1-(4-benzyloxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline oxalate (18) using NaBH₄.
A slurry of 7-benzyloxy-1-(4-benzyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline methiodide (17, 8.0 g, 12.3 mmole) and methanol (100 ml) was cooled to 5-10° in an ice-salt bath. Over a period of 1.5 hr, sodium borohydride (3.2 g, 87 mmole) was added in small amounts. Stirring was continued for 45 min at 5-10° and then for 1 hr at room temperature. Aqueous sodium hydroxide solution (25 ml, 10%) was added and the mixture refluxed for 1 hr. After which, the solution was concentrated under reduced pressure and water (100 ml) was added to the resulting residue. This aqueous mixture was then extracted with three portions of ether (100 ml). After drying (K₂CO₃) and filtration, a saturated ethereal solution of oxalic acid was slowly added with rapid stirring. The oxalate salt, which first separated as an oil, soon solidified and was filtered. Recrystallization of this solid from methanol-ether gave 18 (6.1 g, 81%) as colorless clusters of crystals, mp 108-110° (effervescence). Three recrystallizations of this solid from methanol-ether gave analytically pure clusters of crystals, mp 110-112°.\[\text{\textsuperscript{\textnu}}\text{Nujol (cm}^{-1}\text{) 1700 (C=O); nmr (CHCl₃-d)}; \tau 7.80-5.40 (m, 9, \text{CH}, \text{CH})\text{, 7.22 (s, 3, NCH₃), 6.16 (s, 6, OCH₃), 4.92 (s, 2, OCH₂), 4.88 (s, 2, OCH₃), 3.30 (m, 5, ArH), 2.62 (s, 10, ArH), -1.18 (s, 1, CO₂H).} \]\[\lambda_{\text{max}} \text{EtOH 283 mµ (c 6.700), 230 mµ (c 19.000).} \]\[\text{Anal. calcd. for C}_{36}\text{H}_{38}\text{NO₆: C, 70.46; H, 6.41; N, 2.28.}\text{ Found: C, 70.36; H, 6.47; N, 2.24.}\text{Preparation of 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxy-phenethyl)-6-methoxy-2-methylisoquinoline hydrochloride (19)}\]
7-Benzylxoy-1,2,3,4-tetrahydro-1-(4-benzylxoy-3-methoxy-phenethy1)-6-methoxy-2-methylisoquinoline oxalate (18, 9.6 g) was dissolved in 10% aqueous sodium hydroxide solution (100 ml) and extracted with chloroform (200 ml). After drying over potassium carbonate followed by filtration and vacuum evaporation, 7-benzylxoy-1,2,3,4-tetrahydro-1-(4-benzylxoy-3-methoxyphenethy1)-6-methoxy-2-methylisoquinoline (7.4 g, 14.1 mmole) was obtained. This material was then dissolved in methanol (250 ml) containing palladium on powdered charcoal (0.7 g, 10%) and concentrated hydrochloric acid (5 ml). Hydrogenation was carried out at an initial pressure of 40 psi for 18 hr. The mixture was filtered through Celite and the solvent removed in vacuo to leave 19 as a colorless oil. Compound 19 was induced to crystallize by treatment with benzene-methanol-ether solution. This compound recrystallized from benzene-methanol-ether as a solvate of benzene to leave 4.8 g, (90%), of white crystals, mp 108-110° (effervescence). Compound 19 recrystallized from acetonitrile as colorless clusters of needles also as a solvate, mp 103-105° (effervescence). Two separate analytical samples were prepared; one from benzene-methanol-ether and one from acetonitrile. Each sample was recrystallized four times with no change in the melting points reported above. $\gamma^{\text{CHCl}_3}_{\text{max}}$ (cm$^{-1}$) 3400 (O-H); nmr (DMSO-d$_6$); $\gamma$(benzene solvate) 8.00-5.60 (m, 8, CH$_2$), 7.24 (s, 3, NCH$_3$), 6.24 (s, 6, OCH$_3$), 3.20 (m, 5, ArH), 2.60 (s, 2, benzene), 1.20 (s, 1, OH), 0.80 (s, 1, OH); nmr (DMSO-d$_6$); $\gamma$(acetonitrile solvate) 8.00 (s, 2, acetonitrile), 8.00-5.60 (m, 8, CH$_2$), 7.24 (s, 3, NCH$_3$), 6.24 (s, 6, OCH$_3$), 3.20 (m, 5, ArH),
1.20 (s, 1, OH), 0.80 (s, 1, OH); \( \lambda_{\text{max}}^{\text{EtOH}} \) 284 \( \text{mu} \) (c 6,700), 229 \( \text{mu} \) (c 13,100) (for both solvates).

**Anal. calcd. for C_{20}H_{26}ClNO_4 + C_6H_6:** C, 64.38; H, 6.93; N, 3.54. Found: C, 64.24; H, 7.20; N, 3.40.

**Anal. calcd. for C_{20}H_{26}ClNO_4 + C_4H_2CN:** C, 62.88; H, 6.93; N, 5.96. Found: C, 62.98; H, 7.05; N, 5.76.

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**Phenolic oxidation of 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline; preparation of kreyssigone (6a)**

A solution of 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline hydrochloride (19, 4.5 g, 11.8 mmole) in degassed water (200 ml) was added, under nitrogen gas, dropwise to FeCl_3·6H_2O (19.4 g, 720 mmole) dissolved in degassed water (100 ml). Stirring was continued for 3.5 hr and the solution made alkaline with 28% aqueous ammonia. The resulting brown gel was filtered through Celite and washed with chloroform (800 ml). The filtrate was extracted with the chloroform washings and with fresh chloroform (200 ml). The chloroform extracts were combined, dried (Na_2SO_4) and filtered. Vacuum evaporation left a brown oil (2.0 g) which was chromatographed over silica gel (30 g) and eluted with 1% methanol in chloroform. Twelve 50 ml fractions were collected. Fractions 5 through 10 contained the dienone product 6a as observed by thin-layer chromatography and infrared spectroscopy. Recrystallization of the product from hexane containing a small amount of chloroform gave 6a (0.55 g, 12%) as...
colorless crystals, mp 190-192°, Lit.20,21 mp 193-195°. A mixed melting point of these crystals with a sample prepared by the procedure of Kametani and coworkers22 showed no depression and the infrared spectra (CHCl₃) of the two samples were superimposable. 
\[ \chi_{\text{max}} \text{CHCl}_3 (\text{cm}^{-1}) 3505 (\text{O-H}), 1660 (\text{C}=\text{O}), 1640 (\text{C}=\text{C}), 1610 (\text{C}=\text{C}); \]
\[ \lambda_{\text{max}} \text{EtOH} 286 \text{m} \mu (c 13,500), 244 \text{m} \mu (c 6,500). \]

Photolysis of kreyssignone (6a)

Kreyssignone (6a, 150 mg, 0.44 mmole) was dissolved in Mallin-cred thiophene free analytical reagent grade benzene (150 ml) and purified argon was passed through the solution for 2 hr. The solution was then photolyzed for 69 hr using a Rayonet Photochemical reactor with a pyrex filter. Thin-layer chromatography was used to monitor the reaction with methanol in chloroform (1:3) as the developing solvents. After the reaction was essentially complete, the reaction vessel was washed with methanol and the benzene-methanol solution was evaporated under reduced pressure to a dark oil. This oil was then subjected to preparative thin-layer chromatography using three 20 x 20 cm glass plates with a 0.5 mm coating of Silica Gel G and methanol-chloroform (1:3) as the developing solvent. Five spots were shown to exist using iodine vapor. However, only the fraction at R_f 0.7-0.8 contained a significant amount of material. After a second preparative thin-layer chromatography of this fraction, 15 mg of a light yellow oil 22, was obtained which darkened rapidly when exposed to air and light. An analytical sample was obtained by chromatography over 10 g silica gel using 1 % meth-
anol in chloroform as the eluting solvents. $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm$^{-1}$) 1690 (C=O); nmr (CHCl$_3$-$d$): $\gamma$ 7.60 (s, NCH$_3$), 7.00 (m, CH$_2$), 6.37 (s, OCH$_3$), 6.16 (s, OCH$_3$), 3.99 (m, =CH), 3.54 (s, ArH); $\lambda_{\text{max}}^{\text{EtOH}}$ 276 mp (e 1,510); mass spectrum m/e 341 (M$^+$), 340 (M$^+$-1), 324 (M$^+$-17), 313 (M$^+$-28), 312 (M$^+$-29), 298 (M$^+$-43).

Anal. calcd. for C$_{20}$H$_{23}$NO: C, 70.37; H, 6.78; N, 4.10.
Found: C, 71.02; H, 7.09; N, 3.68.

Preparation of 4-benzyloxy-3-methoxy-$\gamma$-phenylpropylamine (27)

4-Benzylxoy-3-methoxyphenylpropionic acid (50 g, 175 mmole), thionyl chloride (50 ml) and dry benzene (300 ml) were refluxed for 1 hr. The solvent was removed under reduced pressure and the residue was dissolved in ether (50 ml). This solution was added to a vigorously stirred ice cold solution of aqueous ammonia (200 ml, 28%). The resulting precipitate was collected by filtration, washed with water and dried to give 42 g of 4-benzyloxy-3-methoxy-phenylpropionamide. This amide (42 g, 147 mmole) was then added to an ethereal solution (1000 ml) of lithium aluminum hydride (15 g, 395 mmole) over a period of 2 hr. Refluxing was continued for 6 hr after which the solution was cooled in an ice-salt bath and water (15 ml), aqueous sodium hydroxide solution (15 ml, 15%) and water (45 ml) were added successively. The mixture was filtered, dried over potassium carbonate and the ether removed in vacuo to leave the product 27 (23.0 g, 58%) as a tan oil which was characterized as its hydrochloride salt, mp 155-156° (ethanol-ether).

$\nu_{\text{max}}^{\text{Neat}}$ (cm$^{-1}$) 3350 (NH$_2$); nmr (DMSO-$d_6$): $\gamma$ 8.10 (m, 2, CH$_2$), 7.40
Preparation of N-(4-benzyloxy-3-methoxyphenylpropyl)-4-benzyloxy-3-methoxyphenylpropionamide (28)

4-Benzylxoy-3-methoxy-\(\gamma\)-phenylpropylamine (27, 23.0 g, 85 mmole) and 4-benzyloxy-3-methoxyphenylpropionic acid (14, 24.3 g, 85 mmole) were dissolved in methylene chloride and cooled to 0°. To this stirred solution was added N,N-dicyclohexylcarbodiimide (20.0 g, 97 mmole) in methylene chloride (200 ml) over a period of 30 min. After stirring at 0° for 20 hr the solution was filtered and the solvent evaporated under reduced pressure. After recrystallization from 95% ethanol (norit), 28 (37.3 g, 82%) was obtained as colorless crystals, mp 128-131°. An analytical sample, mp 129-130°, was prepared by three recrystallizations from 95% ethanol. \(\lambda_{\text{max}}^{\text{EtOH}}\) (cm\(^{-1}\)) 3310 (N-H), 1640 (C=O); nmr (CDCl\(_3\)-d): \(\tau\) 8.60-6.60 (m, 10, CH\(_2\)), 6.20 (s, 6, OCH\(_3\)), 5.00 (s, 4, OCH\(_2\)), 4.30 (s, 1, NH), 3.30 (m, 6, ArH), 2.60 (m, 10, ArH); \(\lambda_{\text{max}}^{\text{EtOH}}\) 281 mp (c 6,500), 229 mp (c 21,000).

Anal. calcd. for C\(_{17}\)H\(_{23}\)ClNO\(_2\): C, 75.67; H, 6.91; N, 2.60.
Found: C, 75.71; H, 7.10; N, 2.43.

Attempted cyclodehydration of N-(4-benzyloxy-3-methoxyphenylpropyl)-4-benzyloxy-3-methoxyphenylpropionamide
Procedure A

N-(4-Benzylxyo-3-methoxyphenylpropyl)-4-benzylxyo-3-methoxy-phenylpropionamide (28, 1.0 g, 1.86 mmole) was heated to 120° for 1 hr in PPE (4.0 g, 9.3 mmole). The reaction mixture was cooled and poured into ice water (50 ml). The solution was made strongly alkaline with aqueous sodium hydroxide solution and extracted with chloroform (200 ml). The chloroform layer was dried (Na₂SO₄), filtered and vacuum evaporated to leave a brown gum which was shown to be starting material and other unidentified products by infrared and tlc. No alkaline material was ever detected in the reaction mixture.

Procedure B

Several experiments were performed as in Procedure A except that chloroform (100 ml) was used as a solvent and the reaction time was varied from 2 hr to 3 days as well as the reaction temperature (25-64°). As before, workup afforded no alkaline material and only tars and starting material were obtained.

Procedure C

Phosphorus oxychloride (10 g, 65 mmole) and 28 (1.0 g, 1.86 mmole) were refluxed in dry benzene (100 ml) for 2 hr. Vacuum evaporation of the solvent left a residue which was dissolved in chloroform (200 ml) and washed successively with aqueous ammonia (50 ml, 28%) and water (110 ml). After drying (Na₂SO₄), filtration and vacuum evaporation, starting material and tars were obtained. Prolonged reaction time (3 days) and increased
temperatures (110°) only increased the amount of tars.
CONCLUSIONS

The total synthesis of kreysiginone (6a) was successfully completed with each product in the reaction sequence being carefully characterized by the use of ir, uv, nmr, and elemental analysis. This synthesis utilized vanillin (9) as the starting material for both phenolic moieties of 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (19). In turn, 19 was converted to kreysiginone by phenolic oxidative coupling using aqueous ferric chloride. During this route, the hydroxyl groups were protected by preparing the benzyl ether and subsequent selective reductions were chosen so that this group could be removed at the proper time; the isoquinoline nucleus was formed by use of the Bischler-Napieralski reaction.

Photolysis of kreysiginone in the absence of a proton source gave a rearrangement product which was shown not to be of the homoaporphine type. A structure for this product, which was supported by nmr, ir, uv, mass spectra, and elemental analysis, was proposed. A mechanism for the formation of this compound was also postulated.

As a possible route to a "bishomoaporphine", the cyclization of N-(4-benzyloxy-3-methoxyphenylpropyl)-4-benzyloxy-3-methoxyphenylpropionamide (27) was attempted. However, all cyclodehydration experiments directed toward this end were unsuccessful.
PART II

THE SYNTHESSES AND ANTIBACTERIAL ACTIVITY OF 1-VINYL-3,4-DIHYDROISOQUINOLINE METHIODIDES
HISTORICAL

1-Styryl-3,4-dihydroisoquinolines as a class of compounds are rarely encountered in the literature. However, their chemistry and pharmacology is of substantial interest. Until 1950, the conventional methods for the synthesis of 1-styrylisoquinolines (eq 31) or its derivatives (eq 32) centered around two main approaches, the cyclization of the Schiff bases derived from cinnamaldehyde (eq 32) (XVIII) or the condensation of 1-methylisoquinoline (34) with aromatic aldehydes (XIX).

\[
\begin{align*}
&\text{HC} & \text{I} \\
&\text{CH=CH-Ar} & \text{H} \\
&\text{f-H-H} (XVIII) \\
&\text{AxCHO} & \text{CH=CH-Ar} \\
&\text{(XIX)}
\end{align*}
\]

Since the late 1950's, several research groups have taken an active interest in developing new synthetic routes to these compounds. For instance, Brossi and coworkers condensed 2-acetyl-N-acetyl-phenethylamines 35 with aromatic aldehydes to give 36, which were converted directly to 1-styryl-3,4-dihydroisoquinolines 37 by heating in dilute acid (XX).

The most convenient approach to this series was described by Tomimatsu who used substituted cinnamamides (38). These compounds
were allowed to undergo cyclodehydration according to the Bischler-Napieralski procedure to give the 1-styrylsubstituted 3,4-dihydroisoquinoline (37). This reaction is shown in XXI.

\[
\begin{align*}
\text{C}=\text{O} & \quad \text{NH-} \text{C}=\text{CH}_3 + \text{ArCHO} \quad \rightarrow \quad \text{C}=\text{O} & \quad \text{NH-} \text{C}=\text{CH}_3 \\
& \quad \text{CH}=\text{CH}-\text{Ar} \\
\end{align*}
\]

Recently, Brossi, et al.\textsuperscript{36} stated that synthetic isoquinoline derivatives of the 1-styrylisoquinoline type are of great interest because of their biological activity. Of particular interest, were those 1-aralkylisoquinolines and their partially or fully hydrogenated derivatives. Many of these compounds showed significant analgetic activity. Structure versus activity studies showed that the following substituents were essential for activity; N-methyl, 6,7-dimethoxy and nitro groups or halogen substituents on the phenyl group. Several of the partially or fully unsaturated derivatives, however, were devoid of analgetic effectiveness.
EXPERIMENTAL

Analytical Procedure. Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. The nmr spectra were obtained with a Varian A-60 spectrometer. A Beckman IR-8 spectrophotometer was used to determine the ir spectra. Ultraviolet spectra were obtained with a Cary 14 recording spectrophotometer. The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Chemicals. β-Methylcinnamic acid (42f) was prepared according to the procedure of Lipkin and Stewart\textsuperscript{37} and was obtained in 40% yield, mp 97-98°, Lit.\textsuperscript{37} mp 98°. β,β-Dimethyl acrylic acid (42h), α-methylcinnamic acid (42g) and other starting materials were purchased as reagent grade chemicals.

Biological Activity Data. The zones of growth inhibition were measured by Dr. L.J. Hanka, Research Laboratories, The Upjohn Company, Kalamazoo, Michigan and supported by Contract PH43-68-1023 with Chemotherapy, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Preparation of Disubstituted Acryl Chlorides

Procedure A

The general procedure is exemplified by the synthesis of β,β-diphenylacryl chloride (41a). The synthesis of 1,1-diphenylethylene (39a), as well as 1,1-diarylethylenes (39c-39e), were prepared according to the procedure of Allen and Converse\textsuperscript{38}.
Scheme IV
Preparation of Disubstituted Acryl Chlorides

Procedure A

$$R_1X + Mg \rightarrow R_1MgX \quad 1/2 \text{CH}_3\text{CO}_2\text{Et} \rightarrow R_1\text{CO}-\text{CH}_3$$

$$R_1\text{C}=\text{CH}-\text{Cl}$$

$$(R_1=R_2) \ 41$$

Procedure B

$$R_1X + Mg \rightarrow R_1MgX \quad \text{CH}_3\text{CH}-\text{O} \rightarrow R_1\text{OH} \quad 20\% \text{H}_2\text{SO}_4$$

$$R_1\text{C}=\text{CH}-\text{Cl}$$

$$(R_2=\emptyset) \ 41$$

Procedure C

$$R_1\text{C}=\text{CH}-\text{C}-\text{OH} \quad \text{SOCl}_2 \rightarrow R_1\text{C}=\text{CH}-\text{C}-\text{Cl}$$

$$42 \ 41$$

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Using this method 1,1-diphenylethylene (39a) was obtained in 52% yield as a colorless liquid bp 100-103°C/1 mm, Lit.38 bp 113°C/2 mm.

β,β-Diphenylacryl chloride (41a) was prepared by refluxing 1,1-diphenylethylene (39a, 13.0 g, 72 mmole) in oxalyl chloride (40, 28.0 g, 0.22 mole) for 2 hr. Evaporation of the solution left an oil which was dissolved in ether (50 ml) and stored under nitrogen gas.

Procedure B

This experimental procedure was identical to Procedure A except that 1-phenyl-1-(p-tolyl)-ethylene (39b) was prepared from acetophenone and p-tolylmagnesium bromide. The corresponding acryl chloride (41b) was then prepared by refluxing the olefin (39b, 10.0 g, 51 mmole) in oxalyl chloride (19.0 g, 0.15 mole) for 20 hr. As before, the solution was evaporated and the resulting oil dissolved in ether (50 ml) and stored under nitrogen gas.

Procedure C

This general procedure is exemplified by the synthesis of β,β-dimethylacryl chloride (41h). β,β-Dimethylacrylic acid (42h, 10.0 g, 0.1 mole) and thionyl chloride (25 ml) were refluxed for 1 hr. The solution was then concentrated under reduced pressure and excess thionyl chloride was removed by addition of benzene (25 ml) and vacuum evaporation. Repetition of this process left an oil which was distilled under reduced pressure to leave β,β-dimethylacryl chloride (41h) as a colorless liquid, bp 35-40°C/1 mm, Lit.39 bp 145-150°C (yield 91%).
Preparation of 1-Vinylsubstituted 3,4-dihydroisoquinoline Methiodide Salts (46)

The following preparation of 1-vinyl-(β,β-diphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline methiodide (46a) serves to illustrate this general method. β,β-Diphenylacryl chloride (41a), as prepared in Procedure A Scheme IV, was added dropwise to a stirred mixture of β-(3,4-dimethoxyphenyl)-ethylamine (42, 10.9 g, 60 mmole), ether (75 ml) and 10% aqueous sodium hydroxide solution (50 ml) at 0°. The reaction mixture was stirred at 5° until the precipitation of the acrylamide (44a) had been completed. Filtration followed by recrystallization of the solid from ethanol-water gave white crystals of N-(3,4-dimethoxyphenethyl)-β,β-diphenylacrylamide (44a, 10.5 g, 39%) (yield based on 1,1-diphenylethylene), mp 101-102°; νmax Nujol (cm⁻¹) 3300 (N-H), 1650 (C=O); nmr (CHCl₃-d); δ 7.49 (t, 2, J=7.0 cps, CH₂), 6.65 (m, 2, CH₂), 6.14 (s, 6, OCH₃), 4.60 (s, 1, NH), 3.62 (s, 1, HCO =), 3.33 (m, 3, ArH), 2.72 (s, 5, ArH).

Acrylamide (44a) (7.3 g, 19 mmole) and phosphorus oxychloride (20 ml) were refluxed in dry benzene (125 ml) for 1 hr. Vacuum evaporation of the solvent left a yellow oil which was dissolved in chloroform (200 ml). This chloroform solution was washed successively with ammonia (100 ml, 10%) and water (100 ml). The organic layer was dried (Na₂SO₄), filtered and vacuum evaporated. The resulting oil (45a) was dissolved in benzene (100 ml) and warmed on a steam-bath. Methyl iodide (15 ml) was added to this warm solution in one portion. The yellow benzene solution instantly turned red and, after 24 hr at room temperature, yellow crystals
Scheme V

Preparation of 1-Vinylsubstituted 3,4-dihydroisoquinolines

41

\[
\begin{align*}
\text{CH}_3\text{O} & \text{CH}_3\text{O} \\
R_1 & \text{C} = \text{C} = \text{O} \\
R_2 & \text{Cl} \\
R_3 &
\end{align*}
\]

+ \quad \text{CH}_3\text{O} \text{CH}_3\text{O} \text{NH}_2

\[
\text{FOCl}_3
\]

\[
\begin{align*}
\text{CH}_3\text{O} & \text{CH}_3\text{O} \\
R_1 & \text{C} = \text{C} = \text{R}_2 \\
R_3 &
\end{align*}
\]

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

\[
\begin{align*}
\text{CH}_3\text{O} & \text{CH}_3\text{O} \\
+ & \quad \text{N} = \text{C} = \text{N} \\
R_3 & \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
46
\end{align*}
\]

\[
\begin{align*}
a & R_1 = R_2 = \text{Ph}, \ R_3 = \text{H} \\
b & R_1 = \text{Ph}, \ R_2 = \text{CH}_3, \ R_3 = \text{H} \\
c & R_1 = R_2 = \text{Ph}, \ R_3 = \text{H} \\
d & R_1 = R_2 = \text{CH}_3, \ R_3 = \text{H} \\
e & R_1 = R_2 = \text{Ph}, \ R_3 = \text{H} \\
f & R_1 = \text{CH}_3, \ R_2 = \text{Ph}, \ R_3 = \text{H} \\
g & R_1 = \text{H}, \ R_2 = \text{Ph}, \ R_3 = \text{CH}_3 \\
h & R_1 = R_2 = \text{CH}_3, \ R_3 = \text{H}
\end{align*}
\]
(46a, 7.5 g, 78%) which had separated were filtered, washed with benzene (25 ml) and recrystallized from methanol-ether, mp 165-167° (dec.). An analytical sample was prepared by four recrystallizations from methanol-ether, mp 168-170° (dec.); $\nu^\text{KBr}_{\text{max}}$ (cm$^{-1}$) 1605, 1550, 1520 (C=O), 780, 700 (aromatic); nmr (CHCl$_3$-d); $\tau$ 7.00-5.50 (m, 4, CH$_2$), 6.60 (s, 3, NCH$_3$), 6.12 (s, 3, OCH$_3$), 6.08 (s, 3, OCH$_3$), 3.10 (s, 1, H$_3$), 3.00-2.30 (m, 12, ArH); $\lambda^\text{EtOH}_{\text{max}}$ 365 m$\mu$ (c 12,000), 323 m$\mu$ (c 11,300), 249 m$\mu$ (c 17,500).

Anal. calcd. for C$_{30}$H$_{30}$INO$_2$: C, 61.07; H, 5.13; N, 2.74.

Preparation of N-(3,4-dimethoxyphenethyl)-cinnamamide (48)

A solution of cinnamoyl chloride (47, 14.0 g, 80 mmole) in ether (100 ml) at 0° was added dropwise and with stirring to an ethereal (250 ml) mixture containing β-(3,4-dimethoxyphenyl)-ethylamine (43, 14.5 g, 80 mmole) in aqueous sodium hydroxide solution (250 ml, 5%) at 0°. The reaction mixture was stirred at 5° until the precipitation of the amide (48) was complete. N-(3,4-Dimethoxyphenethyl)-cinnamamide (48) was collected by filtration and recrystallized from ethanol-water to give colorless crystals (14.5 g, 57%), mp 120-122°. An analytical sample was obtained by three recrystallizations of 48 from ethanol-water, mp 122-123°; $\nu^\text{Nujol}_{\text{max}}$ (cm$^{-1}$) 3340 (N-H), 1660 (C=O), 1625 (C=O); nmr (CHCl$_3$-d); $\tau$ 7.18 (t, 2, J=8.0 cps, CH$_3$), 6.42 (t, 2, J=8.0 cps, CH$_3$), 6.22 (s, 6, OCH$_3$), 3.56 (d, 1, H$_3$), 3.24 (s, 3, ArH), 2.70 (s, 5, ArH), 2.38 (d, 1, J=8.0 cps, H$_3$); $\lambda^\text{EtOH}_{\text{max}}$ 277 m$\mu$ (c 29,000),
Preparation of 8,9-dimethoxy-6-phenyl-3-benzazocin-4-one (49)

N-(3,4-Dimethoxyphenethyl)-cinnamsunide (48, 2.0 g, 6.4 mmole) and polyphosphoric acid (PPA) (40.0 g) were heated to 120-130° for 15 min. The reaction mixture was cooled and poured over crushed ice (100 ml). The yellow mass, thus obtained, was recrystallized from ethanol-water and finally twice from benzene to yield 8,9-dimethoxy-6-phenyl-3-benzazocin-4-one (49, 0.5 g, 25%) as colorless needles, mp 190-191°. An analytical sample of 49 was obtained by two recrystallizations from benzene, mp 191-192°;

\[ \gamma_{\text{Nujol}}^{\text{max}} (\text{cm}^{-1}) 3245 (\text{N-H}), 1665 (\text{C}=\text{O}); \text{nmr (CHCl}_3-d): \tau 6.98 (d, 1, J=10.0 \text{ cps, CH}_2), 6.68 (m, 4, \text{CH}_2), 6.30 (s, 3, O\text{CH}_3), 6.20 (s, 3, O\text{CH}_3), 5.38 (t, 1, J=10.0 \text{ cps, CH}) , 3.80 (m, 1, \text{NH}), 3.38 (s, 2, ArH), 2.80 (m, 5, ArH); \lambda_{\text{EtOH}}^{\text{max}} 284 \text{ mu} (\varepsilon 3,600). \]

Anal. calcd. for C_{19}H_{21}NO_3: C, 73.29; H, 6.80; N, 4.50.

Found: C, 73.52; H, 7.06; N, 4.46.

Attempted cyclodehydration of N-(3,4-dimethoxyphenethyl)-cinnamamide (48) using phosphorus oxychloride

N-(3,4-Dimethoxyphenethyl)-cinnamamide (48, 5.0 g, 16 mmole) and phosphorus oxychloride (25 ml) were refluxed in dry toluene (80 ml) for 2 hr. After 30 min, the amide dissolved and a yellow solid began to separate. The mixture was evaporated under reduced pressure to leave a yellow semi-solid which was recrystallized.
from dilute hydrochloric acid as yellow needles, mp >165° (dec.).

\[ \gamma_{\text{Nujol}} (\text{cm}^{-1}) 1600, 1550 (\text{C=C}), 752, 735, 708, 689 \text{ (aromatic)}; \]

\[ \nu (\text{DMSO-d}_6); \tau 7.60-6.00 \text{ (m, 11, CH}_2); 5.00 \text{ (s, 6, OCH}_3); 3.00-1.40 \text{ (m, ArH, } \text{HC}=) \]

Anal. Found: C, 64.71; H, 6.20; N, 3.86.

The yellow solid was dissolved in water (100 ml) and heated for 30 min at 55°. The solution was made alkaline with aqueous sodium hydroxide solution and extracted with chloroform (200 ml). Drying of the chloroform extract (Na\textsubscript{2}SO\textsubscript{4}), filtration and vacuum evaporation left a brown uncharacterizable oil which failed to react with methyl iodide.

Procedures for preparing acryl chlorides (41a-41h), melting points for acrylamides (44a-44h) and infrared data for acrylamides (44a-44h) are presented in Table I. Analytical data for 1-vinyl-substituted 3,4-dihydroisoquinoline methiodide salts (46a-46h) are summarized in Table II. Nuclear magnetic resonance and ultraviolet spectra data are tabulated in Table III for 1-vinylsubstituted 3,4-dihydroisoquinoline methiodide salts (46a-46h).
Table I

Procedures for Preparing Acryl Chlorides (41a-41h); Infrared and Melting Point Data for Acrylamides (44a-44h)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Procedure for Preparing Acryl Chlorides (41)</th>
<th>Mp(°C) Acrylamides (44)</th>
<th>Infrared (cm⁻¹ Nujol) of Acrylamides (44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>A</td>
<td>101-102</td>
<td>N-H 3300</td>
</tr>
<tr>
<td>b</td>
<td>B</td>
<td>108-110</td>
<td>C=O 1650</td>
</tr>
<tr>
<td>c</td>
<td>A</td>
<td>135-137</td>
<td>N-H 3290</td>
</tr>
<tr>
<td>d</td>
<td>A</td>
<td>116-118</td>
<td>C=O 1650</td>
</tr>
<tr>
<td>e</td>
<td>A</td>
<td>186-188</td>
<td>N-H 3290</td>
</tr>
<tr>
<td>f</td>
<td>C</td>
<td>85-87</td>
<td>C=O 1630</td>
</tr>
<tr>
<td>g</td>
<td>C</td>
<td>115-117</td>
<td>C=O 1645</td>
</tr>
<tr>
<td>h</td>
<td>C</td>
<td>45-50</td>
<td>C=O 1650</td>
</tr>
</tbody>
</table>
Table II

Analytical Data for 1-Vinylsubstituted 3,4-Dihydroisoquinoline Methiodide Salts (46a-46h)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mp, °C</th>
<th>Yield, %</th>
<th>Empirical Formulae</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Found, %</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>46a</td>
<td>168-170</td>
<td>78</td>
<td>C_{26}H_{27}INO_{2}</td>
<td>61.07</td>
<td>5.13</td>
<td>2.74</td>
<td>61.31</td>
<td>5.19</td>
<td>2.78</td>
<td></td>
</tr>
<tr>
<td>46b</td>
<td>202-204</td>
<td>92</td>
<td>C_{27}H_{29}INO_{2}</td>
<td>61.72</td>
<td>5.37</td>
<td>2.69</td>
<td>61.54</td>
<td>5.31</td>
<td>2.57</td>
<td></td>
</tr>
<tr>
<td>46c</td>
<td>236-238</td>
<td>97</td>
<td>C_{28}H_{31}INO_{2}</td>
<td>62.94</td>
<td>5.61</td>
<td>2.60</td>
<td>62.12</td>
<td>5.63</td>
<td>2.59</td>
<td></td>
</tr>
<tr>
<td>46d</td>
<td>194-197</td>
<td>86</td>
<td>C_{30}H_{33}INO_{2}</td>
<td>63.49</td>
<td>6.04</td>
<td>2.47</td>
<td>63.72</td>
<td>6.22</td>
<td>2.56</td>
<td></td>
</tr>
<tr>
<td>46e</td>
<td>232-235</td>
<td>54</td>
<td>C_{28}H_{33}ClINO_{2}</td>
<td>53.82</td>
<td>4.17</td>
<td>2.41</td>
<td>54.05</td>
<td>4.22</td>
<td>2.80</td>
<td></td>
</tr>
<tr>
<td>46f</td>
<td>195-198</td>
<td>43</td>
<td>C_{24}H_{25}INO_{2}</td>
<td>56.13</td>
<td>5.38</td>
<td>3.12</td>
<td>56.03</td>
<td>5.33</td>
<td>3.02</td>
<td></td>
</tr>
<tr>
<td>46g</td>
<td>205-208</td>
<td>58</td>
<td>C_{24}H_{25}INO_{2}</td>
<td>56.13</td>
<td>5.38</td>
<td>3.12</td>
<td>55.95</td>
<td>5.24</td>
<td>3.07</td>
<td></td>
</tr>
<tr>
<td>46h</td>
<td>205-207</td>
<td>58</td>
<td>C_{25}H_{27}INO_{2}</td>
<td>59.62</td>
<td>5.73</td>
<td>3.62</td>
<td>59.84</td>
<td>5.73</td>
<td>3.60</td>
<td></td>
</tr>
</tbody>
</table>

1 All the compounds melted with decomposition.

2 Yields are based on the starting amides.
Table III

Nuclear Magnetic Resonance and Ultraviolet Spectra of 1-Vinylsubstituted 3,4-Dihydroisoquinoline Methiodide Salts (46a-46h)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Nmr (T)</th>
<th>Uv EtOH λmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>46a</td>
<td>7.00-5.50 (m, CH₂), 6.25 (s, NCH₃), 6.12 (s, OCH₃), 6.08 (s, OCH₃), 3.10-2.30 (m, HC=, ArH)</td>
<td>365 μ (ε 12,000)</td>
</tr>
<tr>
<td>46b</td>
<td>7.67 (s, CH₃), 7.53 (s, CH₃), 7.00-5.50 (m, CH₂), 6.20 (s, NCH₃), 6.10 (s, OCH₃), 5.98 (s, OCH₃), 3.10-2.30 (m, HC=, ArH)</td>
<td>372 μ (ε 13,000)</td>
</tr>
<tr>
<td>46c</td>
<td>7.90-6.60 (m, CH₃, CH₂), 6.34 (s, NCH₃), 6.26 (s, OCH₃), 6.16 (s, OCH₃), 3.00-2.50 (m, HC=, ArH)</td>
<td>375 μ (ε 15,000)</td>
</tr>
<tr>
<td>46d</td>
<td>9.10-5.80 (m, CH₃, CH₂), 6.30 (s, NCH₃), 6.20 (s, OCH₃), 6.10 (s, OCH₃), 3.30-2.40 (m, HC=, ArH)</td>
<td>379 μ (ε 14,500)</td>
</tr>
<tr>
<td>46e</td>
<td>7.00-5.50 (m, CH₂), 6.27 (s, NCH₃), 6.04 (s, OCH₃), 3.17-2.40 (m, HC=, ArH)</td>
<td>362 μ (ε 12,000)</td>
</tr>
</tbody>
</table>

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Table III  
(continued)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Nmr (γ)*</th>
<th>Uv EtOH λmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>46f</td>
<td>7.89 (s, CH₃), 6.70-5.50 (m, CH₃), 6.00 (s, OCH₃), 5.89 (s, OCH₃), 3.00-2.00 (m, HC=, ArH)</td>
<td>368 μ (ε 10,900)</td>
</tr>
<tr>
<td></td>
<td>309 μ (ε 12,300)</td>
<td></td>
</tr>
<tr>
<td>46g</td>
<td>7.59 (s, CH₃), 6.70-5.50 (m, CH₃), 6.18 (s, OCH₃), 5.88 (s, NCH₃), 3.00-2.40 (m, HC=, ArH)</td>
<td>370 μ (ε 11,800)</td>
</tr>
<tr>
<td></td>
<td>313 μ (ε 10,200)</td>
<td></td>
</tr>
<tr>
<td>46h</td>
<td>8.33 (s, CH₃), 7.83 (s, CH₃), 7.00-5.50 (m, CH₃), 6.14 (s, OCH₃), 6.00 (s, NCH₃), 3.56 (s, HC=, ArH)</td>
<td>367 μ (ε 10,000)</td>
</tr>
<tr>
<td></td>
<td>312 μ (ε 9,500)</td>
<td></td>
</tr>
</tbody>
</table>

* Nmr spectra were obtained using deuterio-chloroform (CHCl₃-d) as the solvent.

* The infrared spectra for compounds 46a-46h were consistent with the proposed structures.
DISCUSSION

The preparation of a number of 1-vinylsubstituted 3,4-dihydroisoquinoline methiodide salts was carried out. The procedure for the syntheses of these compounds made use of disubstituted acryl chlorides (41) which were available through several methods. The most novel method made use of β,β-diarylacryl chlorides (41a-41e) prepared by the reaction of 1,1-diarylethlenes (39) and oxalyl chloride*(40) (Procedure A & B of Scheme IV). Other disubstituted acid chlorides (41f-41h) were prepared by treating the corresponding acid (42) with thionyl chloride (Procedure C of Scheme IV). Treatment of 41 with β-(3,4-dimethoxyphenyl)-ethylamine (43), in the presence of 5% aqueous sodium hydroxide and ether, afforded the amides (44). The cyclodehydration of 44 to the corresponding disubstituted 1-vinyl-3,4-dihydroisoquinolines (45) was achieved by using phosphorus oxychloride. The reaction of 45 with methyl iodide gave crystalline methiodide salts (46) which were isolated in 43-97% yield for the final two steps.

The methiodide salts (46a-46h) were subjected to in vitro screening for antimetabolites by a new method developed by Hanka**. In this method, the detection system utilizes the gram-positive Bacillus subtilis and gram-negative Escherichia coli. Both organisms were grown in two types of agar: nutrient agar and a completely synthetic medium with glucose as the only source of carbon. These eight compounds were tested at concentrations of...
1 mg/ml and the results are presented in Table IV.

**Table IV**

Inhibition of B. subtilis Grown in Two Different Media*

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Nutrient</th>
<th>Synthetic</th>
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<tbody>
<tr>
<td>46a</td>
<td>Ph</td>
<td>Ph</td>
<td>H</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>46b</td>
<td>Ph</td>
<td>p-methylphenyl</td>
<td>H</td>
<td>25</td>
<td>36</td>
</tr>
<tr>
<td>46c</td>
<td>p-methylphenyl</td>
<td>p-methylphenyl</td>
<td>H</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>46d</td>
<td>p-ethylphenyl</td>
<td>p-ethylphenyl</td>
<td>H</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>46e</td>
<td>p-chlorophenyl</td>
<td>p-chlorophenyl</td>
<td>H</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>46f</td>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>46g</td>
<td>H</td>
<td>Ph</td>
<td>Me</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>46h</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*The numbers in the body of the table are zones of growth inhibition in mm beyond a 13 mm paper disc.*

The inhibition of the test organisms by compounds 46a-46h was stronger on synthetic agar than on nutrient agar, however, the difference was not large enough to suggest an antimetabolite-like mode of action*. None of the compounds significantly inhibited the growth of E. coli. These results indicate that substituted 1-vinyl-3,4-dihydroisoquinoline methiodides possess significant bacterial activity.

Although more extensive testing will be required before any definite structure-activity correlations can be drawn, several points of interest should be raised. All compounds which contained substituted phenyl groups, compounds 46a-46e, showed definite
antibacterial activity against *B. subtilis* and this activity was essentially the same regardless of the substituents on the phenyl groups. However, replacement of a phenyl by an alkyl group (46f, 46h) greatly reduced the activity. Moreover, the replacement of R₃=H by R₃=CH₃ seems to suggest that this proton is of importance in determining biological activity since 46f showed definite activity while its structural isomer 46g showed only a trace of antibacterial activity against *B. subtilis*.

During the course of this study, the reaction of cinnamoyl chloride (47) with 43 afforded the amide 48 which failed to give the expected methiodide salt *via* cyclodehydration using phosphorus oxychloride. However, when 48 was heated in polyphosphoric acid, it gave an anomalous compound, which was subsequently characterized as 8,9-dimethoxy-6-phenyl-3-benzazocin-4-one (49). This is illustrated in Scheme VI.

```
Scheme VI

\[
\begin{align*}
\text{CH}═\text{CH}─\text{C}═\text{Cl} \quad + \quad \begin{array}{c}
\text{CH}_3\text{O} \\
\text{CH}_3\text{O} \\
\text{NH}_2 \\
\end{array} \\
\downarrow \\
\begin{array}{c}
\text{CH}═\text{CH}─\text{O} \quad \text{O} \\
\text{CH}_3\text{O} \\
\text{CH}_3\text{O} \\
\end{array}
\end{align*}
\]

No Characterizable Product

\[
\begin{align*}
\text{POCl}_3 \quad \rightarrow \quad \begin{array}{c}
\text{CH}_3\text{O} \\
\text{CH}_3\text{O} \\
\text{O}═\text{C} \quad \text{N}═\text{H} \\
\text{CH}═\text{CH}─\text{O} \\
\end{array} \\
\rightarrow \quad \begin{array}{c}
\text{CH}_3\text{O} \\
\text{CH}_3\text{O} \\
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{PPA} \quad \rightarrow \quad \begin{array}{c}
\text{CH}_3\text{O} \\
\text{CH}_3\text{O} \\
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{PPA} \quad \rightarrow \quad \begin{array}{c}
\text{CH}_3\text{O} \\
\text{CH}_3\text{O} \\
\end{array}
\end{align*}
\]
```

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The characterization of 49 was based on elemental analysis, spectroscopic data (ir, nmr, uv) and analogy with the reported cyclization of N-phenylcinnamides to 3,4-dihydro-4-phenylcarbostyril (50) with polyphosphoric acid\(^\text{a}\). Table V shows a comparison of the spectroscopic data.

Table V

Spectroscopic Data of Compounds 49 and 50

<table>
<thead>
<tr>
<th></th>
<th>49</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nmr ((\tau))</td>
<td>CHCl(_3-d)</td>
<td>DMSO-d(_6)</td>
</tr>
<tr>
<td>6.98</td>
<td>(d, 2, J=10 cps, (H_b))</td>
<td>7.26 (d, 2, J=6 cps, (H_{b1}))</td>
</tr>
<tr>
<td>6.68</td>
<td>(m, 4, (CH_2))</td>
<td>5.74 (t, 1, J=6 cps, (H_{a1}))</td>
</tr>
<tr>
<td>6.30</td>
<td>(s, 3, (OCH_3))</td>
<td>3.00 (m, 9, (ArH))</td>
</tr>
<tr>
<td>5.38</td>
<td>(t, 1, J=10 cps, (H_a))</td>
<td>-0.18 (s, 1, (NH))</td>
</tr>
<tr>
<td>3.80</td>
<td>(m, (1, NH))</td>
<td></td>
</tr>
<tr>
<td>3.38</td>
<td>(s, 2, (ArH))</td>
<td></td>
</tr>
<tr>
<td>2.80</td>
<td>(m, 5, (ArH))</td>
<td></td>
</tr>
</tbody>
</table>

\(\nu_{\text{max}}\) (N-H) 3245 cm\(^{-1}\) 3190 cm\(^{-1}\)
\(\nu_{\text{max}}\) (C=O) 1665 cm\(^{-1}\) 1660 cm\(^{-1}\)

\(\lambda_{\text{max}}\) (EtOH) 284 \(\mu\) (\(\epsilon\) 3,600) 254 \(\mu\) (\(\epsilon\) 10,400)
A proposed mechanism for the formation of 8,9-dimethoxy-6-phenyl-3-benzazocin-4-one from 48 is shown in Scheme VII. The first step involves the protonation of the carbonyl oxygen of 48 to give 51. Its resonance reference structure 52 can now undergo an intramolecular electrophilic attack on the benzene ring, which with proton rearrangement, yields 49.

Scheme VII

\[ \text{CH}_3\text{O} \quad \text{OH} \quad \text{N}\text{-H} \quad \text{C} \quad \text{H} \quad \text{O} \quad \text{CH}=\text{CH}-\phi \]

\[ \text{CH}_3\text{O} \quad \text{OH} \quad \text{N}\text{-H} \quad \text{C} \quad \text{H} \quad \text{O} \quad \text{CH}=\text{CH}-\phi \]

48

51

\[ \text{CH}_3\text{O} \quad \text{OH} \quad \text{N}\text{-H} \quad \text{C} \quad \text{H} \quad \text{O} \quad \text{CH}=\text{CH}-\phi \]

\[ \text{CH}_3\text{O} \quad \text{OH} \quad \text{N}\text{-H} \quad \text{C} \quad \text{H} \quad \text{O} \quad \text{CH}=\text{CH}-\phi \]

49

52

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CONCLUSIONS

In this investigation, the syntheses of a number of highly substituted 1-vinyl-3,4-dihydroisoquinolines have been successfully accomplished. The method of choice utilized disubstituted acrylamides derived from β-(3,4-dimethoxyphenyl)-ethylamine. Most of these amides smoothly underwent a cyclodehydration in the presence of phosphorus oxychloride to yield the corresponding 3,4-dihydroisoquinolines which were isolated and characterized as their methiodide salts.

Preliminary in vitro screening showed that these salts possess significant antibacterial activity provided the 1-vinyl moiety carries a phenyl or substituted phenyl group on the β-position. These compounds thus add to the known pharmacology of the simple 1-styrylisooquinolines whose saturated derivatives showed analgetic activity.

During the course of this study, N-(3,4-dimethoxyphenethyl)-cinnamamide failed to give the expected methiodide salt after treatment with phosphorus oxychloride and methyl iodide. When this compound was treated with hot polyphosphoric acid, the reaction product was shown to be 8,9-dimethoxy-6-phenyl-3-benzazocin-4-one.
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VITA

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The author received his primary and secondary education at Marcellus Community Schools. After four years, he graduated with a degree of Bachelor of Science in Chemistry with a Secondary Teachers Certificate from Western Michigan University in April 1966. On September 1966 he was admitted to the Ph.D. program in Organic Chemistry where he was awarded a National Defense Education Act Title IV fellowship for his continuing graduate studies. During his course of study he worked under the direct supervision of Dr. Robert E. Harmon.