THE TOTAL SYNTHESIS OF (±)-OCHROBIRINE
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By

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SCOPE AND CONTENTS:

The spirobenzylisoquinoline alkaloids form a group of twelve bases incorporating a ring system which has only recently been recognized. The total synthesis of several of them has been realized. A new route to the spirobenzylisoquinolines is described here and differs from those previously reported. The readily available 2-phenyl-1,3-indandiones were used as starting materials and the synthesis of the spiro system was completed by construction of ring B through a modified Pomeranz-Fritsch reaction. The introduction of the nitrogen and the two carbons required to complete the carbon framework was achieved through bromination followed by displacement of bromine by aminoacetaldehyde diethyl acetal. Acid cyclisation after protection of the nitrogen completed the synthesis of the spiro system. The scheme was tested using 2-(3,4-dimethoxyphenyl) -1,3-indandione to give an analogue of ochrobirine. (±)-Ochrobirine, a member of the spirobenzylisoquinoline alkaloids, was then synthesized according to the scheme outlined.
During the course of this work, two rearrangements of the spiro-
benzylisoquinoline system were observed. The first offers a route to the
phthalide isoquinoline alkaloids while the second provides a route to the
protoberberine alkaloids. A possible mechanism for the two rearrangements
is offered. In the light of the results obtained from this work and of
those from the work of others, a model for the biogenesis of the spiro-
benzylisoquinoline is proposed.
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GENERAL INTRODUCTION

Alkaloids are nitrogenous bases of plant origin that nearly always contain their nitrogen as part of a heterocyclic system and often have interesting pharmacological properties. Several thousand alkaloids have been isolated and characterized. The most abundant of the various classes of alkaloids are those belonging to the isoquinoline family. This thesis is concerned with the synthesis of an isoquinoline alkaloid that has a spirobenzylisoquinoline ring system. Alkaloids with this ring system have only recently been recognized.

The spirobenzylisoquinoline alkaloids were first isolated some thirty years ago but it was not until 1964 that a structure was assigned to ochotensimine, an alkaloid of this group. Since then structures have been proposed for other related alkaloids and the total synthesis of several of them has been realized. The alkaloids of this family vary in the nature of the substituents present on aromatic ring A and on the type
and number of substituents on the spiro ring. The main structural variants are exemplified in ochotensimine, fumaricine, and ochobriline shown above.

The synthesis of alkaloids related to ochotensimine and fumaricine has been realized by a route in which the key step is a Pictet-Spengler condensation of the appropriately substituted 1,2-indandione with an appropriately substituted phenylethylamine as shown in Figure 1.

![Figure 1](image_url)

By using ninhydrin instead of an indandione in the Pictet-Spengler condensation compounds in which two oxygens were incorporated into the spiro ring have been synthesised. Recently the total synthesis of (±)-ochobriline by this method has been reported. Other routes to the spiro system have also been developed. In one a phenylpyruvic acid is substituted for the indandione in the Pictet-Spengler reaction and the spiro ring completed by a cyclisation of the acid function. In another a protoberberine system is rearranged to the spiro system.
This thesis will deal with a new synthesis of spirobenzylisoquinolines by a route different from those previously reported. The readily available 2-phenyl-1,3-indandiones are used as starting compounds and the synthesis of the spiro system is completed by construction of ring B through a modified Pomeranz-Fritsch synthesis as shown in Figure 2.

\[ \text{Figure 2} \]

\((\pm)-\text{Ochrobirine}\) has been synthesised by this method. The introduction of the nitrogen and the two carbons required to complete the carbon framework was brought about by bromination followed by displacement of bromine by aminoacetaldehyde diethyl acetal. The completion of the synthesis to the spiro system was achieved through acid cyclisation after the nitrogen was protected. This scheme was tested using 2-(3,4-dimethoxyphenyl)-1,3-indandione before proceeding to the synthesis of \((\pm)-\text{ochrobirine}\).

During the course of this work, two rearrangements of the spirobenzylisoquinoline system were observed, the first offers a route to the phthalide isoquinoline skeleton and the second provides a route to the protoberberine skeleton. A mechanism for these transformations is discussed.
HISTORICAL INTRODUCTION

This thesis deals with the synthesis of an isoquinoline alkaloid. It is appropriate therefore to begin this chapter with a brief review of the most common methods of synthesis of isoquinolines. A section follows on the biogenesis of the isoquinoline alkaloids that serves to introduce the common ring systems found in the isoquinoline family of alkaloids in terms of their biogenetic relationship to one another. The synthesis of some representative isoquinoline alkaloids is then discussed in general terms and the chapter is concluded with a detailed review of the spirobenzylisoquinoline alkaloids, the group of alkaloids on which this thesis is focused.

SYNTHESIS OF ISOQUINOLINES

Only three reactions (1) have been widely used in isoquinoline alkaloid synthesis. They are the first three illustrated in Figure 3 and each one is discussed separately below.

The Bischler - Napieralski Reaction (2)

This reaction consists of the cyclodehydration of acyl derivatives of substituted β-phenylethlamines 1. It is usually effected by heating with a dehydrating agent in an inert high boiling solvent, resulting in the formation of a 3,4-dihydroisoquinoline 2. An important modification of this reaction is that developed by Pictet and Gams (3) where the β-phenylethlamide is replaced by an α-hydroxy-β-phenylethlamide 3 which
Synthesis of Isoquinolines

Bischler–Napieralski Reaction

\[
\text{RO} \begin{array}{c} \text{R} \end{array} \begin{array}{c} \text{NH} \end{array} \begin{array}{c} \text{K} \end{array} \xrightarrow{\text{POCl}_3} \begin{array}{c} \text{RO} \end{array} \begin{array}{c} \text{R} \end{array} \begin{array}{c} \text{N} \end{array}
\]

Pictet–Spengler Reaction

\[
\text{RO} \begin{array}{c} \text{R} \end{array} \begin{array}{c} \text{NH}_2 \end{array} \xrightarrow{\text{H}^+} \begin{array}{c} \text{RO} \end{array} \begin{array}{c} \text{R} \end{array} \begin{array}{c} \text{N} \end{array}
\]

Pictet–Gams Reaction

\[
\text{RO} \begin{array}{c} \text{R} \end{array} \begin{array}{c} \text{OH} \end{array} \xrightarrow{\text{H}^+} \begin{array}{c} \text{RO} \end{array} \begin{array}{c} \text{R} \end{array} \begin{array}{c} \text{N} \end{array}
\]

Pomeranz–Fritsch Reaction

\[
\text{RO} \begin{array}{c} \text{R} \end{array} \begin{array}{c} \text{CHO} \end{array} + \text{NHC}H\text{CH(OEt)}_2 \xrightarrow{\text{H}^+} \begin{array}{c} \text{RO} \end{array} \begin{array}{c} \text{R} \end{array} \begin{array}{c} \text{N} \end{array}
\]

Figure 3
on heating with a dehydrating agent undergoes simultaneous ring closure and dehydration to an isoquinoline system 4.

**The Pictet-Spengler Reaction (4)**

In this reaction a β-arylethylamine 5 is condensed with a carbonyl compound under acidic conditions to give a tetrahydroisoquinoline system 6.

**The Pomeranz-Fritsch Reaction (5) (6)**

This reaction involves the condensation of an aromatic aldehyde 7 with aminoacetaldehyde diethyl acetal to yield a Schiff base 8 which, on treatment with a suitable acidic catalyst, cyclises to the fully aromatic isoquinoline system 9. This reaction complements the other two in the sense that it offers the possibility of preparing isoquinolines with substituents at the C-7 and C-8 positions and leads to a fully aromatic system.

Other reactions listed below have been developed which have proved useful in isolated syntheses of alkaloids.

**Iso carbostyrils from Isocoumarins**

The reaction of 3-phenylisocoumarins 10 with alcoholic or aqueous ammonia or with primary amines gives 3-phenylisocarbostyril derivatives 11 (7). This reaction has been used by Kametani and coworkers (8) in the synthesis of cularimine and by Bailey and coworkers (9) in the synthesis of the benzophenanthridine alkaloids.

**Homophthalimide Synthesis**

Heating homophthalic acid diammonium salts 12 or homophthalamic acid 13 gives homophthalimides 14 in excellent yield (10) (11).
Isocarbostyrils from Isocoumarins

\[ \text{Ph} \quad \text{O} \quad \text{Ph} \quad \xrightarrow{\text{RNH}_2 \quad 100^\circ} \quad \text{Ph} \quad \text{N}_R \quad \text{O} \]

10

11

Homophthalimide Synthesis

\[ \text{CO}_2\text{NH}_4 \quad \text{CH}_2\text{CO}_2\text{NH}_4 \quad \xrightarrow{} \quad \text{Ph} \quad \text{O} \quad \text{NH} \quad \text{O} \]

12

13

14

Phthalimidoacetic Ester and the 2-aminoindandione Rearrangement

\[ \text{O} \quad \text{N} \quad \text{CH} \quad \text{CO}_2\text{C}_2\text{H}_5 \quad \xrightarrow{-\text{OCH}_3} \quad \text{OH} \quad \text{N} \quad \text{Ph} \quad \text{O} \]

15

16

17

Figure 3 (cont'd)
reaction was advantageously used in the total synthesis of morphine (12). Phthalimidoacetic Ester and the 2-aminooindandione Rearrangement

Gabriel and Colman (13) in 1900 reported the base-catalysed rearrangement of phthalimidoacetic ester 15 to 4-hydroisocarbostyryl 16 and in 1938 Wanag and Wolbe (14) found that 2-aminooindandiones 17 follow a similar base-catalysed rearrangement to isocarbostyryl derivatives. Although these two reactions offer potential routes to isoquinoline systems they have received little attention. Numerous other synthetic routes to isoquinoline systems have been developed but have found little use in alkaloid synthesis.

In the work described in this thesis the Pomeranz-Fritsch reaction was used in construction of the isoquinoline moiety.

BIogenesis of the Isoquinoline Alkaloids

The origin and mode of synthesis of alkaloids in plants had been a subject of speculation until the advent of radioactive isotopes in the 1950's when the subject became amenable to direct experimental investigation. Although knowledge of the biosynthesis of alkaloids is only of recent standing, the theoretical consideration of this problem has occupied chemical thought for over sixty years. Among the various biogenetic schemes put forward, the ones advanced by Winterstein and Trier (15) Robinson (16,17,18) and Barton (19,20,21) were able to interpret the formation of the great majority of known alkaloids. These hypotheses were based on chemical analogy and were without direct experimental support. They have stood the test of time in the sense that they have been largely substantiated by recent radioactive tracer work.
According to Robinson the aromatic amino acids, phenylalanine and/or tyrosine, serve as precursors of the isoquinoline alkaloids. It was postulated that phenylalanine 18 was first converted to tyrosine 19 and then further to dihydroxyphenylalanine (DOPA) 20 by hydroxylation (Figure 4). Decarboxylation of DOPA would give dopamine 21 whereas deamination of DOPA would give 3,4-dihydroxyphenylpyruvic acid 22. The aldehyde 23 could be obtained by decarboxylation of 22. A Mannich type condensation between 21 and 23 would give norlaudanosoline 24.

Robinson has placed norlaudanosoline as the common intermediate for the biogenesis of the morphine, aporphine, erythrina, protopine, protoberberine, phthalideisoquinoline and benzophenanthridine alkaloids. Methylation gives laudanosine 25 (or phenolic or methylenedioxy variants). Oxidative coupling of two phenolic rings in the laudanosine-type precursor can proceed in several ways, namely:

(a) Carbon-carbon bond formation between position 8 and 2' in 24 gives the aporphine skeleton 26.
(b) Rotation of the isoquinoline ring around the 1 - 9 axis and oxidative coupling of carbon 10 and 6' in 24 accounts for the skeleton of morphine 27.
(c) Oxidative coupling between 2 molecules leads to the bisbenzylisoquinoline alkaloids exemplified in dauricine 28.

A molecule of the laudanosine type may be further oxidised by aromatization of ring B to papaverine 29 or by activation of the N-methyl for Mannich type cyclisation to the protoberberine skeleton 30, which can undergo further oxidation at each of the three carbons (α, β and γ).
Biogenesis of some Isoquinoline Alkaloids

Figure 4
Figure 4 (cont'd)
linked to the nitrogen. α-Oxidation may lead to aromatization to give berberine \(^{31}\) or to ring cleavage to give the phthalideisoquinoline skeleton \(^{32}\). β-Oxidation results in ring cleavage to give the protopine type \(^{33}\). γ-Oxidation leads to another series of compounds. Rotation of the top ring in the intermediate \(^{34}\) about bond \(d\) yields an equivalent structure \(^{35}\), which may cyclize to give the benzophenanthridine family \(^{36}\). Thus, the hypothesis predicts that two \(C_6-C_2\) units, derived from tyrosine or from 3,4-dihydroxyphenylalanine would supply the entire carbon skeleton, of the 1-benzylisoquinoline, aporphine, and morphine alkaloids. The same 2 units would supply all but one of the carbon atoms in the nucleus of the protoberberine, the phthalideisoquinoline and the benzophenanthridine alkaloids. The Winterstein-Robinson hypothesis has recently been substantiated by tracer work.

Radioactive samples of papaverine \((22,23)\), morphine \((24,25)\), narcotine \((26)\), hydastine \((27,28)\), thebaine \((29)\), berberine \((28,30)\), and chelidonine \((31)\) isolated from various species of plants to which α-\(^{14}\)C-\(±\)-tyrosine had been fed, showed, after degradation, that in each case radioactivity was confined entirely to the positions predicted by the classical hypothesis.

Based on known chemical examples of oxidation of phenols by one-electron transfer processes, Barton and Cohen \((19,20,21)\) postulated the biogenesis of a large number of alkaloids. Figure 5 summarizes the postulated mechanism for the biogenesis of a few alkaloids derived by phenol-coupling processes. Tracer work here again has recently substantiated the validity of the hypothesis \((32,33)\).
Figure 5
The erythrina alkaloids can also be shown to be biogenetically derived from norlaudanosoline by phenolic coupling and intramolecular rearrangements (34). Recently it has been shown that phenylalanine (35) and tyrosine (36) are incorporated into colchicine, a fact that classifies colchicine as an isoquinoline alkaloid.

SYNTHESIS OF SOME ISOQUINOLINE ALKALOIDS

The total synthesis of isoquinoline alkaloids has attracted the attention of chemists since the beginning of this century. The description to follow is by no means a complete survey of the synthetic methods available for the synthesis of isoquinoline alkaloids. These methods have been exhaustively surveyed (37). The treatment here is confined to the synthesis of a few isoquinoline alkaloids where the benzylisoquinoline system has been used as a common intermediate.

The general method of synthesis of the benzylisoquinoline alkaloids involves the condensation of a properly substituted phenylacetyl chloride 37 and a substituted phenylethylamine 38 to give an amide which can then undergo a Bischler-Napieralski ring closure to yield an imine 39 which may either be dehydrogenated to a molecule of type 40 or hydrogenated to a molecule of type 41 (Figure 6).

Reduction of papaverine 40 with tin and hydrochloric acid (38) gives, besides the major product, (±)-tetrahydropapaverine 41a, a new tetracyclic skeleton 42 which was later shown to exist in nature in the pavine alkaloids.

A cularine-like molecule 44 has been synthesised by Kametani and coworkers (39) through an acid catalysed rearrangement of a diene of
The Synthesis of some Isoquinoline Alkaloids

\[
\begin{align*}
R_1 & R_2 & R_3 & R_4 & R_5 & R_6 & R_7 \\
a: \text{CH}_3 & \text{CH}_3 & \text{CH}_3 & \text{CH}_3 & \text{H} & \text{H} & \text{H} \\
b: \text{CH}_3 & \text{CH}_3 & \text{H} & \text{CH}_3 & \text{OH} & \text{H} \\
c: \text{CH}_3 & \text{H} & \text{H} & \text{CH}_3 & \text{CH}_3 & \text{H} & \text{H} \\
d: \text{CH}_3 & \text{CH}_3 & \text{CH}_3 & \text{CH}_3 & \text{CH}_3 & \text{H} & \text{NO}_2 \\
e: \text{CH}_3 & \text{CH}_3 & \text{CH}_3 & \text{CH}_3 & \text{H} & \text{H} & \text{H} \\
f: \text{CH}_3 & \text{CH}_2 - \text{CH}_2 & \text{H} & \text{H} & \text{Cl}
\end{align*}
\]

\[
\begin{align*}
41 & \\
40 & \\
\text{H}^+ & \\
43 & \\
42 & \\
44 & \\
45 & \\
46 & \\
47 & \\
\end{align*}
\]

Figure 6
type 43 which was prepared by the phenolic oxidative coupling of a
diphenolic benzyltetrahydroisoquinoline 41b.

Battersby and coworkers (40) have synthesised the proaporphine
skeleton via an intramolecular phenolic oxidative coupling of orientaline
41c using aqueous ferricyanide to give orientalinone 45. Reduction of
45 with sodium borohydride and subsequent treatment with acid resulted in
a dienol-benzene rearrangement to (±)-isothebaine 46. This series of
reactions in vitro parallels the biosynthesis in living plants.

The tetrahydrobenzylisoquinoline system of type 41d has been used
in the synthesis of the aporphine alkaloids. Pschorr cyclisation gives
the desired tetracyclic skeleton (41).

The most common method of synthesis of the tetrahydropseudoberberines
involves the condensation of a substituted benzylisoquinoline of type
41e with formaldehyde and hydrochloric acid. In the past decade several
new approaches to the synthesis of the protoberberines have been developed
(42,43,44).

Kametani and coworkers (45) have treated the tetrahydroisoquinoline
41f with sodamide in liquid ammonia to give the dibenzindolizine
derivative 47.

Recently Shamma and coworkers (46,47,48) have been able to convert
a protoberberinimum salt into a spirobenzylisoquinoline system. This
rearrangement will be discussed later.
THE SPIROBENZYLISOQUINOLINE ALKALOIDS

Structure of the Alkaloids

In 1940, Manske (49) reported the isolation of the alkaloids, ochotensine and ochotensimine, from Corydalis ochotensis Turcz. He showed that ochotensimine was the 0-methyl ether of the phenolic base ochotensine. Degradative methods for determining structure gave no useful results. Twenty-four years later, McLean and Mei-Sie Lin (50,51), on spectroscopic grounds, proposed structures \(48a\) and \(48b\) for ochotensimine and ochotensine, respectively.

\[
\begin{align*}
\text{RO} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{H}_2\text{C} = \\
\text{N} & \quad \text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2 & \quad \text{6} \\
\text{5} & \quad \text{N} \\
\text{4} & \quad \text{RO} \\
\text{OCH}_3 & \quad \text{1} \\
\text{14} & \quad \text{10} \\
\text{11} & \quad \text{12} \\
\end{align*}
\]

\[
\begin{align*}
\text{48a} & : R = \text{CH}_3 \\
\text{48b} & : R = \text{H}
\end{align*}
\]

Two years later their proposals were confirmed by an x-ray crystallographic study of ochotensine methiodide (52). The absolute configurations of ochotensimine, ochotensine, ochrobin and fumarilone have recently been established by Shamma and coworkers (52a) and conform to those shown in \(48a\), \(48b\), and in Figure 7. The absolute configuration of the other alkaloids shown in Figure 7 is not known.
The Spirobenezylisoquinoline Alkaloids

Fumaricine

Fumariline

Ochrobirine

Fumarophycine

Corydaine

Fumaritine

Sibiricine

Parfumine

Fumarofine

Corpaine

Figure 7
These alkaloids were of considerable interest since they belonged to a new structural class in which the basic benzylisoquinoline framework had been modified to incorporate a spiro union. Since then a number of alkaloids of the same skeleton have been characterized (53-58). A list of them is shown in Figure 7. The numbering system adopted for the spirobenzylisoquinoline alkaloids follows that shown in 48a.

Synthesis of the Alkaloids

(i) General methods

Once the structures of the spirobenzylisoquinoline alkaloids were established, the next logical step in their study was their total syntheses. These alkaloids are found in three different structural ramifications, 49, 50, and 51. Structure 50 can be converted into a positional isomer of 49 through a Wittig reaction. Thus the methods used to synthesize 50 may be applied to a synthesis of 49. The discussion here will be confined to structure 50. There are three general approaches by which the spiro system can be synthesized as illustrated in Figure 8. The first one involves the Pictet-Spengler condensation of an appropriately substituted phenylethylamine with an appropriately substituted 1,2-indandione to give the spiro system 52. This approach forms the basis for the synthesis of ochotensimine and ochotensine by McLean and coworkers (59,60), Kelly and Beckett (61,62), and Irie and coworkers (63).

A similar Pictet-Spengler condensation between ninhydrin and a substituted phenylethylamine will provide the spiro framework 53 incorporating two oxygen atoms in the five membered ring. This scheme materialized in the work of Kametani and coworkers (64) and Manske and Ahmed (65).
Figure 8
A second possible approach to the synthesis of the spirobenzyl-isoquinoline skeleton involves a Pictet-Spengler condensation between an appropriately substituted phenylethylamine and an appropriately substituted phenylpyruvic acid to give a tetrahydrobenzylisoquinoline which upon treatment with acid would be expected to cyclise to the spiro system.

A third possible approach to the spirobenzylisoquinoline system would start with the readily available 2-phenyl-1,3-indandiones and complete the synthesis of the spiro system by construction of ring B through a modified Pomeranz-Fritsch synthesis. The work described in this thesis is based on this approach.

The modes of execution of each individual synthesis will now be discussed. The first total synthesis of (±)-ochotensimine was reported by McLean and Mei-Sie Lin (59,60) in 1966. Since then Uyeo and coworkers (63) and Kelly and Beckett (61,62) have achieved the total synthesis of (±)-ochotensine. Though these three syntheses closely follow the same lines, yet they differ in execution.

(ii) McLean's Synthesis of (±)-ochotensimine

The Pictet-Spengler condensation between a substituted phenylethylamine and a ketone has been reported in only two cases. In one case derivatives of pyruvic acid (66) were used and in the other a cyclic ketone was employed (67). Both classes of ketones offer potential routes to the spirobenzylisoquinoline skeleton. This prompted McLean and Mei-Sie Lin to approach the synthesis of ochotensimine from the direction shown in Figure 9.
They first established that when 3,4-dimethoxyphenylethylamine 54a and 2-indanone 55a were heated with 85% phosphoric acid to 90° under nitrogen for 21 hours, a 16% yield of the desired spiro product 56a was obtained. Next they showed that 1,2-indandione 55b reacted with 54a to form the ketone 56b in 30% yield. No product resulting from reaction at position 1 was isolated. The ketone 56b was N-methylated to 56c which underwent a Wittig reaction to give (±)-des-(methylenedioxy)-ochotensimine 56d in 44% yield.

With the synthesis of the model compound achieved the next logical step was to synthesize 4,5-methylenedioxy-1,2-indandione, the required precursor. This synthesis was achieved through a surprisingly large number of steps starting with o-vanillin. The Pictet-Spengler condensation between 3,4-dimethoxyphenylethylamine 54a and 4,5-methylenedioxy-1,2-indandione 55c gave no recognizable product and it was suspected that the methylenedioxy group might not have survived the strongly acidic conditions. It was then found that 4,5-methylenedioxy-1,2-indandione 55c reacted with 3-hydroxy-4-methoxyphenylethylamine 54b in the presence of 2.5% HCl at 50° to give the desired product 56e in 80% yield. Treatment of 56e with diazomethane gave a quantitative yield of the O-methyl derivative (56f) and N-methylation carried out under Eschweiler-Clarke conditions gave 56g. Finally a Wittig reaction on 56g gave (±)-ochotensimine 56h. The identity of the synthetic and natural compounds was established by comparison of their spectra and their behaviour on T.L.C.
McLean  Synthesis of (±)-Ochotensimine

54  a : \( R = \text{CH}_3 \)

54  b : \( R = \text{H} \)

55  a : \( X = \text{H}_2 \); \( R_1 = R_2 = \text{H} \)

55  b : \( X = \text{O} \); \( R_1 = R_2 = \text{H} \)

55  c : \( X = \text{O} \); \( R_1 + R_2 = \text{OCH}_2\text{O} \)

56  a : \( X = \text{H}_2 \); \( R_1 = R_2 = R_3 = \text{H} \); \( R_4 = \text{CH}_3 \)

b : \( X = \text{O} \); \( R_1 = R_2 = R_3 = \text{H} \); \( R_4 = \text{CH}_3 \)

c : \( X = \text{O} \); \( R_1 = R_2 = \text{H} \); \( R_3 = R_4 = \text{CH}_3 \)

d : \( X = \text{CH}_2 \); \( R_1 = R_2 = \text{H} \); \( R_3 = R_4 = \text{CH}_3 \)

e : \( X = \text{O} \); \( R_1 + R_2 = \text{OCH}_2\text{O} \); \( R_3 = R_4 = \text{H} \)

f : \( X = \text{O} \); \( R_1 + R_2 = \text{OCH}_2\text{O} \); \( R_3 = \text{H} \); \( R_4 = \text{CH}_3 \)

g : \( X = \text{O} \); \( R_1 + R_2 = \text{OCH}_2\text{O} \); \( R_3 = R_4 = \text{CH}_3 \)

h : \( X = \text{CH}_2 \); \( R_1 + R_2 = \text{OCH}_2\text{O} \); \( R_3 = R_4 = \text{CH}_3 \)

Figure 9
(iii) Uyeo's Synthesis of (±)-ochotensimine and (±)-ochotensine

The total synthesis of (±)-ochotensine achieved by Uyeo and coworkers (63) followed the same line as that described by McLean and Mei-Sie Lin. A Pictet-Spengler condensation of 5,6-methyleneedioxy-1,2-indandione with 3,4-dihydroxyphenylethylamine hydrobromide in refluxing absolute ethanol gave a 60% yield of the spirobenzylisoquinoline 57a (Figure 10). A similar reaction using 4,5-methyleneedioxy-1,2-indandione gave 57b which on treatment with diazomethane did not give the expected product, but instead a neutral compound. It was later found (69) that the neutral compound was formed by the action of methyl isocyanate generated as a contaminant in the diazomethane preparation from nitrosomethylurea.

A Pictet-Spengler condensation between 3,4-dimethoxyphenylethylamine hydrochloride and 4,5-methyleneedioxy-1,2-indandione gave, however, a low yield of the spiro compound 57c which was subjected to a Wittig reaction followed by N-methylation to (±)-ochotensimine.

The synthesis of ochotensine, which has a phenolic group in the 3 position, calls for the protection of this group before a Wittig reaction is carried out. The protective group should be stable to alkali and easily removed later. Among the various protective groups tried, the methoxymethyl proved to be the most stable under basic condition.

The model compound 57d was prepared by condensing 3-hydroxy-4-methoxyphenylethylamine hydrochloride with 5,6-methyleneedioxy-1,2-indandione. Compound 57d was then N-methylated to 57e. Methoxymethylation of the hydroxy - keto base 57e was carried out by treatment of its dry
Uyee Synthesis of (±)-Ochotensimine and Related Alkaloids

57a: $R_1 = R_2 = R_3 = R_6 = H; R_4 + R_5 = OCH_2O$

57b: $R_1 = R_2 = R_3 = R_4 = H; R_5 + R_6 = OCH_2O$

57c: $R_1 = R_2 = CH_3; R_3 = R_4 = H; R_5 + R_6 = OCH_2O$

57d: $R_1 = R_3 = R_6 = H; R_2 = CH_3; R_4 + R_5 = OCH_2O$

57e: $R_1 = R_6 = H; R_2 = R_3 = CH_3; R_4 + R_5 = OCH_2O$

57f: $R_1 = CH_2OCH_3; R_2 = R_3 = CH_3; R_4 + R_5 = OCH_2O; R_6 = H$

58

59a: $R = R = H$

59b: $R = R = CH_3$

60a

60b
sodium salt with chloromethylmethyl ether. The resulting methoxymethyl
derivative 57f was subjected to a Wittig reaction followed by hydrolysis
with dilute HCl to an isomer of ochotensine. The synthesis of ochotensine
was carried out in a similar way using 4,5-methylenedioxy-1,2-indandione.

The total synthesis of (±)-ochotensine by Kelly and Becket (61, 62) was achieved along parallel lines except that the phenolic group was
protected as the tetrahydropyranyl derivative which was removed by acid
hydrolysis after the Wittig reaction had been carried out.

(iv) Synthesis of Fumaricine

Fumaricine, fumaritine and fumarilene form a group of three
spirobenzylisoquinoline alkaloids in which the five membered ring is
oxygenated. The first synthesis of this type of alkaloid was reported by
Kishimoto and Uyeo (68) who condensed the diketone 58 and 3-hydroxy-4-
methoxyphenylethylamine hydrochloride to the spiro isoquinoline (59a)
which was then O-methylated with diazomethane and N-methylated with formic
acid and formaldehyde to 59b. Reduction of the carbonyl group with
lithium aluminum hydride gave a mixture of the epimeric alcohols, 60a, 
and 60b, which were separated by fractional crystallisation. Alcohol
60a was identical with fumaricine.

(v) Synthesis of spirobenzylisoquinolines via the tetrahydro-
benzylisoquinoline approach

Uyeo and coworkers (63) in their first attempt to work out a
general synthesis for the spirobenzylisoquinoline system attacked the
problem in the direction shown in route 2 (Figure 8). The Pictet-Spengler
condensation of 2,3-dimethoxyphenylpyruvic acid with 3,4-dihydroxyphenyl-
ethylamine hydrochloride at 25° and at pH 4.5 for 12 days yielded the amino acid 61 in 49% yield (Figure 11). The amino acid 61 on treatment with diazomethane gave a mixture of the O-methylated 62a and O,N-dimethylated compounds 62b which were separated by column chromatography. Attempts to cyclise the O,N-dimethylated product 62b by a Friedel-Crafts reaction using various Lewis acids failed; starting material was obtained. Heating 62 with polyphosphoric acid at 145° resulted in extensive hydrolysis of the methoxyl groups followed by lactonisation to give a compound which has been assigned the partial structure 63. Since a methylenedioxy group is required on the phenylpyruvic moiety in the synthesis of ochotensimine and is less stable to acid than methoxyl groups, it was thought that the method was not worth pursuing.

Similarly, Shamma and Jones (70) failed to cyclise compounds 64a or 64b or derivatives of 64b to the spiroketone 65 under a variety of Friedel-Crafts conditions.

Kametani and coworkers (71) following a similar line were more successful in the synthesis of a positional isomer of ochotensine. Phenolic cyclisation of 3-hydroxy-4-methoxy-phenylethylamine with 3,4-methylenedioxyphenylpyruvic acid gave 66 (Figure 12). Ethoxycarbonylation of 66 followed by cyclisation with polyphosphoric acid ester gave the spiro compound 67. The rest of the synthesis to iso-ochotensine followed the pattern outlined earlier, namely, a Wittig reaction to give a mixture of compounds 68a and 68b. Compound 68a was reduced with lithium aluminum hydride to 69 which was also obtained by the reaction of 68b with formalin and sodium borohydride.
Figure 11
Synthesis of simple analogues of ochrobirine
(vi) Synthesis of Analogues of Ochrobirine

The isolation and characterization of spiropentylisoquinoline alkaloids with two oxygen atoms in the five membered ring prompted Kametani and coworkers (64) to attempt their synthesis. In 1968 they reported the condensation of 3-hydroxy-4-methoxyphenylethylamine with ninhydrin to form a compound which they claimed to be 3-hydroxy-2-methoxy-ochotensinan-8,13-dione 70a. However, in this laboratory (72) when the amine hydrochloride was used in the condensation with ninhydrin, a different product was obtained. After treatment with diazomethane the 60 MHz p.m.r. spectrum of the methylated compound showed two methoxyl signals at 3.28 δ and 3.73 δ, one singlet of area 2 at 6.68 δ corresponding to two aromatic protons in ring A, and a multiplet of area 4 in the region of 7.7 - 8.1 δ arising from protons in ring D. A 220 MHz p.m.r. spectrum showed that the aromatic signal at 6.86 δ was split into a well defined AB quartet with a coupling constant of 8 Hz. This pointed out that during the condensation of ninhydrin and 3-hydroxy-4-methoxyphenylethylamine hydrochloride cyclisation had occurred at the carbon ortho rather than para to the phenolic hydroxyl as claimed by Kametani and coworkers who did not elaborate on the p.m.r. spectrum of their condensation product.

In any case this condensation provides a one step synthesis to the spiropentylisoquinoline structure incorporating 2 oxygen atoms in the five membered ring. If cyclisation occurs ortho to the phenolic group then the 1,2-disubstituted spiropentylisoquinoline system is obtained which will not provide a route to the natural alkaloids since all of them are 2,3-disubstituted. Whether or not the use of the amine salt instead of
the free base affected the mode of cyclisation remains to be tested.

Manske and Ahmed (65) independently carried out the Pictet-Spengler condensation between 3,4-methylenedioxyphenylethylamine and ninhydrin in absolute ethanol at low temperature to give the spiro compound 70b in 86% yield.

(vii) **Rearrangement of a Protoberberine to a Spirobenzylisoquinoline**

The presence of protopine and protoberberine alkaloids in *Corydalis ochotensis* Turcz, the source of ochotensine and ochotensimine, led Shamma and Jones (46,47) to advance a biogenetic hypothesis for the spirobenzylisoquinoline alkaloids. They speculated that the protoberberine system is the most likely precursor of the spirobenzylisoquinolines. Carrying the analogy further the protoberberine precursor should have its oxygen substituents present at positions 2, 3, 9, and 10, should have methyl groups at N-7 and C-13, and unsaturation in an endocyclic C-13-C-14 double bond in the protoberberine precursor. Thus, a likely precursor is the dihydroprotoberberine salt, 71.
They considered that the two phenolic groups at C-9 and C-10 coupled with the quaternary nitrogen at position 7 would provide the functionality through which 71 might rearrange to the spirobenzylisoquinoline. In order to test this hypothesis the protoberberine 72 was synthesised and subjected to base treatment for 12 hours (Figure 13). On work up the quinone methide 73 was obtained which most probably derived its stability from intramolecular hydrogen bonding. The quinone methide 73 enolizes quantitatively in DMSO to the diphenolic spirobenzylisoquinoline 74 demonstrating that a protoberberine can rearrange into a spirobenzylisoquinoline in vitro.

A dihydroprotoberberine salt of type 75 could equally well act as a precursor by the route indicated. This hypothesis was also tested (48). Compound 75 was synthesised and subjected to prolonged refluxing (4 days). On work up, 77 was obtained. The quinone methide 76 could not be isolated because apparently it lacks the stability imparted by the internal hydrogen bonding present in 73.

Thus, protoberberine salts of types 72 and 75 can generate a spirobenzylisoquinoline skeleton on base treatment. Whether or not this same rearrangement takes place in the plant can only be answered by in vivo experiments with labelled precursors.
A Model for the Biogenesis of the Spirobenzylisoquinoline Alkaloids.

Figure 13
DISCUSSION OF RESULTS

THE SYNTHESIS OF THE SPIROBENZYLISOQUINOLINES

The various approaches to the synthesis of the spirobenzylisoquinoline alkaloids have been described. The Pictet-Spengler condensation was invariably used in building up the spiro skeleton in which the five membered ring carried a carbonyl function. The carbonyl was converted through a Wittig reaction to an exocyclic double bond as in ochotensine or, reduced to an alcohol as in fumaricine. Kametani and Manske extended the Pictet-Spengler reaction with ninhydrin and a substituted phenylethylamine to give a spirobenzylisoquinoline skeleton incorporating two carbonyl groups in the five-membered ring.

When this study was begun a synthesis of a spirobenzylisoquinoline skeleton with two oxygen functions in the five-membered ring had not been reported. Our interest was centered around the total synthesis of ochrobirine which is the first example of an alkaloid possessing a spirostructure in the naturally occurring benzylisoquinoline alkaloids having two hydroxyl groups in the five membered ring. The approach described here differs completely from those already discussed. A modified Pomeranz-Fritsch reaction was used in the final ring closure as shown in Figure 8, route 3.

The key intermediates in this synthetic approach are substituted 2-phenyl-1,3-indandiones which are readily obtained in almost quantitative
yield by the base-catalysed rearrangement of substituted 3-benzylidene-phthalides 78 (73). The mechanism of the rearrangement presumably involves attack of methoxide at the lactone carbonyl followed by ring opening to the enolate anion 79 as shown in Figure 14. Attack of the enolate on the ester results in ring closure to the 2-phenyl-1,3-indandione, 80. Shapiro and coworkers (74) have developed an alternative method whereby 2-arylindandiones are obtained in excellent yields through the condensation of phthalides 84 and aromatic aldehydes 85 in the presence of base. This reaction has now been recognized to proceed through the 3-(α-hydroxybenzyl)phthalide 81 via elimination of water to give the benzylidene phthalide 78 which in the presence of base rearranges to the 2-phenylindandione. Shapiro and coworkers (75) have improved the yield of the reaction by carrying out the condensation in the presence of an ester which serves as a scavenger for the water formed, thereby driving the reaction to completion. Substituted 3-benzylidenephthalides 78, the precursors of 2-phenyl-1,3-indandiones, may be prepared by a modified Perkin reaction between substituted phthalic anhydrides 82 and substituted phenylacetic acids 83 in the presence of fused sodium acetate. The mechanism proposed is shown in Figure 14. Thus, two excellent methods are available by which substituted 2-phenylindandiones may be obtained in high yield.

The next problem was to find a method of introducing a nitrogen atom at C-2 of the indandione. A search of the literature showed that nitrogen had been introduced at C-2 via the displacement of bromine. The bromination of substituted 2-phenylindandiones has been extensively studied
Mechanism for the formation of 2-phenyl-13-indandione
by Arens and coworkers (76) who have also reported the displacement of the bromine with a series of amines (77). This approach was tested therefore in the synthesis of 2-(2,2-diethoxyethylamino)-2-phenyl-1,3-indandione. Though 3-benzylidene phthalide 78a is available commercially it was synthesised by the method of Weiss (78). Rearrangement of the phthalide in the presence of sodium methoxide afforded an almost quantitative yield of 2-phenylindandione 80a which on treatment with bromine in chloroform at 0° gave a 92% yield of the 2-bromo-2-phenyl-indandione 86a (Figure 15). Treatment of 86a with aminoacetaldehyde-diethylaceta! gave a good yield of the amine 87a. The oily amine, 87a, was identified as its crystalline acetamide derivative which had the correct elemental analysis and spectroscopic properties in keeping with the proposed structure.

Once a route to the synthesis of the 2-(2,2-diethoxyethylamino)-2-phenyl-1,3-indandione was established, the next objective was to synthesize 87b which, with its activated benzene ring, should cyclise under acidic conditions to the spiro skeleton. 3-(3,4-dimethoxybenzylidene)-phthalide 78b was prepared in 78% yield and rearranged in 95% yield to the substituted indandione 80b. Alternatively 80b was prepared by a condensation between phthalide 84a and 3,4-dimethoxybenzaldehyde (85b) in 95% yield.

Difficulties were encountered at the bromination stage. Bromination of the dione 80b in chloroform at 0° gave a mixture of variable amounts of the desired bromide, a dimer of the starting dione, and a dibromide as revealed in the mass spectrum of the reaction product. The
Figure 15
Figure 15 (cont'd)
Figure 15 (cont'd)
use of degassed chloroform improved the yield of the monobromide with respect to the undesired by-products. Finally it was found that bromination could be carried out in glacial acetic acid at room temperature to give an almost quantitative yield of the desired bromide 80b, but the bromo compound 86b was very unstable to air, heat, and light. The handling of compounds of this type proved difficult and no attempts were made to purify them. Instead they were taken up in anhydrous ether after the acetic acid had been removed under high vacuum and treated with two equivalents of the appropriate amine at room temperature for 15 hours. A 73% yield of 2-(2,2-diethoxyethylamino-2-(3,4-dimethoxyphenyl)-1,3-indandione 87b was obtained when 86b was treated with aminoacetaldehyde diethyl acetal.

Bobbit and coworkers (79,80) have studied the cyclisation of substituted N-benzylaminoacetaldehyde diethyl acetals under acidic conditions to give substituted 1,2,3,4-tetrahydroisoquinolines. Following Bobbit's procedure of cyclisation, 87b was stirred in a 6M ethanolic HCl solution at room temperature for 18 hours in the hope of cyclising it to the desired spiro skeleton. On work up of the reaction a crystalline product was obtained in high yield which proved to be 2-(3,4-dimethoxyphenyl)-1,3-indandione. Obviously cyclisation had failed to take place; instead cleavage of the C-N bond had occurred. This may be explained by the mechanism outlined in Figure 16. Under the acidic conditions the nitrogen atom is protonated, the N-C-2 bond broken and the hydrogen on the carbon adjacent to nitrogen transferred to the carbonyl in a six-membered transition state. The positive charge on the nitrogen atom
Figure 16
provides the driving force for the cleavage of the C-N bond resulting in the formation of the enol form of the indandione and the imine salt which, under acid conditions, suffers hydrolysis to glyoxal, ammonia, and ethanol. Glyoxal was isolated from the reaction mixture and characterized as its 2,4 DNP derivative. If indeed the C-N bond cleavage proceeds according to the mechanism proposed, then it appears necessary to reduce the basicity of the nitrogen atom to enable cyclisation to occur. Therefore, the amine was converted to a neutral amide entailing a lengthening of the synthesis as the amide must be hydrolysed at a later stage. Two amide derivatives were prepared, namely, \textbf{88} and \textbf{89a}. A protecting group which might have served a dual purpose in our case is the carboethoxy group which at a later stage could have been reduced to the N-methyl derivative with lithium and aluminum hydride. It was not used because of the uncertainty of its behaviour under acidic conditions.

Treatment of \textbf{87b} with acetic anhydride and pyridine at room temperature for 48 hours gave in 84\% yield the N-acetyl derivative \textbf{89a}. A quantitative yield of the carbobenzyoxy derivative \textbf{88} was obtained by treating the amine \textbf{87b} with carbobenzyoxy chloride in 2M NaOH for 30 minutes. The amide \textbf{88} was then stirred in a 6M-ethanolic hydrochloric acid at room temperature for 16 hours resulting in cyclisation to the spiro compound \textbf{90}. Hydrogenolysis of \textbf{90} with palladium on charcoal gave a mixture of compounds which proved difficult to separate. It was anticipated that hydrogenolysis would result in the generation of the free base and removal of the benzylic OH to give \textbf{93a}. Since separation of the reaction mixture presented a problem, this method was not pursued
further. However, treatment of the N-acetyl derivative 89a with 6M-ethanolic-hydrochloric solution for 18 hours at room temperature gave a 57% yield of the cyclised product 91a. Attempts to reduce the double bond in 91a with Pd/C under various pressures failed. Finally it was found that reduction proceeds smoothly with hydrogen over platinum in a short time leaving the two benzylic carbonyls unaffected. Now that the desired spiro skeleton 92a was obtained, the rest of the synthesis of the model compound was achieved without difficulty. Thus the N-acetyl group of 92a was removed by hydrolysis in refluxing 6M HCl-ethanol solution for one hour to yield 93a.

While this work was in progress Manske and Ahmed (65) had developed an excellent method of synthesizing compounds of type 93 in a one step synthesis. Following their approach, we carried out the Pictet-Spengler condensation between 3,4-dimethoxyphenylethylamine and ninhydrin at 0°C. In the presence of dry hydrogen chloride gas. A high yield of a yellow crystalline product was obtained on work-up. Comparison of the physical properties of this product with those of 93a showed that they were identical confirming that the synthesis had proceeded in the expected manner.

N-methylation of 93a to 94a by the Eschweiler-Clarke procedure proceeded in very low yield which was surprising since this reaction had already been applied successfully to similar systems (65, 81). However the reduction of 93a to the corresponding diol had already been reported (81) and it was found that the diol was N-methylated with formaldehyde and sodium borohydride to 95a. The configuration of the diol was not
established in this study. With the successful completion of the model synthesis attention was turned to the synthesis of (±)-ochrobirine.

To proceed to the synthesis of ochrobirine it was necessary to find a practical synthesis of either 6,7-methylenedioxyphthalide or its phthalic anhydride analogue. Although both are simple molecules their synthesis requires a large number of steps. The problem lies in the position of the methylenedioxy group. The most readily available starting material incorporating a methylenedioxy group is 3,4-methylenedioxybenzaldehyde commonly known as piperonal. Any reaction on piperonal aiming at the introduction of a one carbon unit will result in substitution para to the oxygen atom of the methylenedioxy group thereby giving the 4,5-methylenedioxy derivative. Bromination of piperonal would introduce a bromine atom at the 6-position, thus blocking that position. Debromination could be later carried out by reduction but this would involve lengthening the synthetic sequence thereby reducing the overall yield.

The other alternative is to start with a derivative of catechol already incorporating a carbon unit at the 3-position. Here the most readily available material is 2-hydroxy-3-methoxy benzaldehyde commonly known as o-vanillin. Various methods are available to convert o-vanillin to 3,4-methylenedioxyphthalic anhydride. McLean and coworkers (60) have converted o-vanillin to 4,5-methylenedioxyindandione in a five-step synthesis. Oxidation would give the desired skeletal unit. Here again the method is lengthy and good yields could not be expected.
A few new synthetic pathways were explored in the hope of developing a shorter serviceable route to the synthesis of 3,4-methylene-dioxyphthalic anhydride but none was successful and attention is directed to the one synthesis that has proved practical (Figure 17). Perkin and coworkers (82) have shown that chloromethylation of veratic acid with formaldehyde and concentrated hydrochloric acid gave a 50% yield of m-meconine. This reaction was duplicated in our laboratory. Therefore the synthesis of 2,3-methylenedioxybenzoic starting with o-vanillin was undertaken using a recently published procedure (83) in which o-vanillin is subjected to a Cannizzaro reaction giving 2,3-dihydroxybenzoic in 70% yield. Methylenation was carried out in DMSO/NaOH with dibromomethane to give 2,3-methylenedioxybenzoic acid in 60% yield and this was then subjected to chloromethylation affording a 23% yield of 4,5-methylenedioxyphthalide (84).

A condensation between the phthalide 84b and 3,4-methylenedioxybenzaldehyde gave the expected substituted dione 80c in a yield of less than five per cent. Attempts to improve the yield by using a variety of bases such as potassium t-butoxide in t-butyl alcohol or in xylene and sodium hydride in benzene failed.

The 4,5-methylenedioxyphthalide was then oxidised to 3,4-methylenedioxyphthalic acid and converted to the anhydride by treatment with acetic anhydride. The condensation between 3,4-methylenedioxyphenylacetic acid and 3,4-methylenedioxyphthalic anhydride in the presence of fused sodium acetate afforded the substituted benzylidene phthalide 78c in a yield of less than 10%. In a modification of the reaction, the condensation of
The Synthesis of 3,4-methylenedioxyphthalic anhydride

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{CHO} \\
& \quad \xrightarrow{\text{NaOH/KOH} \atop 250^\circ} \\
& \quad \text{HO} \quad \text{COOH} \\
& \quad \xrightarrow{\text{CH}_2\text{Br}_2/\text{NaOH}} \\
& \quad \text{HCHO/HCl} \\
& \quad \text{COOH} \\
& \quad \xrightarrow{\text{KMnO}_4} \\
& \quad \text{COOH} \\
& \quad \xrightarrow{\text{Ac}_2\text{O}}
\end{align*}
\]

Figure 17
dimethyl 3,4-methylenedioxyphthalate with methyl 3,4-methylenedioxy phenyl acetate in the presence of sodium methoxide was attempted but the yield of the dione 80c was not improved. It was found, however, that condensation between 3,4-dimethoxyphthalic anhydride and 3,4-dimethoxy-phenylacetic acid gave a 57% yield of the substituted 3-benzylidene-phthalide 78d so that the low yields in the other reactions could not be attributed to a steric effect. The very marked difference in behaviour of compounds 82b and 84b from their analogues 82a and 84a in the model series indicated that the reaction of both the phthalide and the phthalic anhydride is markedly influenced by the presence of the methylenedioxy group. Alternatively, it may be that the methylenedioxy group does not survive the basic conditions of the reaction. Surprisingly no starting material was isolated from the reaction mixture; instead, a polymeric compound which could not be purified by column chromatography was obtained and remains uncharacterized.

Finally, a 60-65% yield of the substituted 3-benzylidene phthalide 78c was realized through the condensation of 4,5-methylenedioxy-phthalic anhydride and 3,4-methylenedioxyphenylacetic anhydride. With 78c available we turned our attention to completing the synthesis of ochrobririne by the route established in the synthesis of the model compound. The phthalide 78c was rearranged in an almost quantitative yield to the dione 80c by refluxing in a solution of sodium methoxide. Bromination of the dione 80c with bromine in acetic acid afforded a quantitative yield of 86c which was not isolated but immediately treated with two equivalents of aminoacetaldehyde diethylacetal in ether to give
an 82% yield of the amine 87c. The amine 87c on treatment with acetic anhydride and pyridine for 48 hours at room temperature gave an 85% yield of the amide 89b which, on treatment with 6M ethanolic hydrochloric acid solution at room temperature for 15 hours, cyclised to the spiro compound 91b in a 63% yield. Reduction of 91b with Adams' catalyst afforded a quantitative yield of the dihydro compound 92b which on refluxing with 6M ethanolic hydrochloric acid solution suffered hydrolysis to the free base 93b. At the time of writing Kametani and coworkers (85) reported the stereospecific total synthesis of (±)-ochrobirine through a different synthetic route. One of the intermediates in their synthesis was compound 93b which they described as pale brown prisms (from ether-hexane) m.p. 167-171°. In this case compound 93b crystallised from ether-hexane and melted at 198-199°. N-methylation of 93b with a mixture of 95% formic acid and 37% formaldehyde solution afforded the N-methyl compound 94b as bright yellow crystals (from ether-hexane) m.p. 195-196°. Here again there is a discrepancy in melting points. Kametani and coworkers reported a melting point range 118-122° for the N-methyl compound 94b. On the other hand compounds 93b and 94b reported here have melting points identical with those found by Manske and coworkers who have recently completed the total synthesis of (±)-ochrobirine (86).

The diketone 94b was reduced with sodium borohydride in absolute ethanol at room temperature for 15 hours. Examination of the reaction product by TLC showed the presence of two components, one of which (the major one) had the same Rf value as natural ochrobirine. Crystallization from benzene-hexane and recrystallization from methanol gave a crystalline
product. Its i.r. spectrum in chloroform, the p.m.r. spectrum in CDCl₃, and its mass spectrum were identical with those of natural ochrobirine. Attempts to isolate the second component by preparative TLC were unsuccessful.

Kametani and coworkers (85) claimed that the sodium borohydride reduction of the diketone 94b took place stereospecifically to give (±)-ochrobirine exclusively. The melting point of their product was 25°C lower than that of my synthetic compound. On the other hand, Manske and coworkers (86) obtained a mixture similar to mine in the final sodium borohydride reduction of 94b and successfully isolated (±)-ochrobirine from the mixture by preparative TLC. Their sample of (±)-ochrobirine has a melting point identical with mine. The second component was not isolated.

Since the second component was not isolated and its nature not determined it cannot be claimed that the sodium borohydride reduction of the diketone 94b took place stereospecifically. Previous experience with similar systems (68,65) has shown that sodium borohydride reduction results in a mixture of isomeric diols. Manske and Ahmed in the synthesis of an analogue of ochrobirine carried out the reduction of 98 with sodium borohydride and obtained a mixture of isomeric diols 99 and 100 in the ratio of 1:2.

Kametani and coworkers (87) obtained a similar result in the sodium borohydride reduction of compound 98b obtaining a mixture of isomeric diols 99b and 100b in the ratio of 1:2. Examination of models of the diketones 98a, 98b, and 94b shows that the carbonyl groups are more
sterically hindered by the isoquinoline moiety on one side of the molecule than on the other. Kametani and coworkers (87) suggest that sodium borohydride reduction of 94b proceeds stereospecifically because the substituents at C-10 and C-11 are hindering attack at the C-9 carbonyl. They consider that initial attack of sodium borohydride on the diketone 94b occurs at the C-14 carbonyl from the less hindered side and that the trans-orientation of the two hydroxyl groups results from intramolecular migration of hydride ion to the C-9 carbonyl from the alkoxyborohydride anion rather than by the attack of a second sodium borohydride molecule at the C-9 carbonyl. It is accepted now (88) that the attack of borohydride ion on ketones is rate-determining and slower than the subsequent transfer of hydride from the alkoxyborohydride. It would be of interest to test this mechanism by using a metal hydride in which three of the hydrogen atoms have been replaced by alkoxy groups, for example, a reagent of the type NaBH(OR)₃. Reduction of compound 94b with such a reagent should give a C-9 keto-C-14-alcohol with attack from the less hindered side.

The Kametani mechanism will explain the preferential formation of the isomers 100a and 100b in the reduction of 98a and 98b. It is conceivable that attack by sodium borohydride on the diketones 98a and 98b occurs at C-14 from the less hindered side with subsequent hydride transfer from the alkoxyborohydride anion at the C-9 carbonyl rather than by attack of a second sodium borohydride from the more hindered side.
The formation of the isomers 99a and 99b cannot be explained in terms of this mechanism as the cis compound is obtained. Furthermore, to account for the formation of 99a and 99b sodium borohydride must attack at both centres from the more hindered side of the molecule contradicting the argument put forward above. It is, therefore, apparent that more than one mechanism is operating in the reduction of the diketones of type 98a and 94b.
THE CONVERSION OF A SPIROBENZYLISOQUINOLINE TO A PROTOBERBERINE

Wanag and Walbe (14) have shown that 2-amino-2-phenyl indandione undergoes rearrangement in base to 3-phenylisocarbostyril (Figure 3). It was anticipated that an extension of this rearrangement on compounds of type 93 would result in the protoberberine skeleton. Compound 93a on treatment with sodium methoxide in absolute methanol underwent a spontaneous rearrangement to a bright yellow salt which precipitated from the mixture. Work-up of the reaction mixture gave an amorphous compound in excellent yield which was tentatively assigned structure 96a. Very few spectroscopic data were obtained because the compound was insoluble in most common organic solvents. However, its 0-methyl ether 97, prepared by refluxing it in dimethyl sulphate and NaOH solution, was crystalline and soluble in chloroform. The elemental analysis and the spectroscopic data support the assigned structure. Thus it has been shown that a spiro compound of type 93 may undergo rearrangement in base to the protoberberine skeleton.

The mechanism of this rearrangement presumably takes the course outlined in Figure 18. Attack of base at one of the carbonyl sites followed by ring opening of the indandione system gives the intermediate enolate salt 101. Ring closure to the lactam completes the protoberberine system 96a. Initial base attack at either carbonyl on a system such as 93a where ring D does not carry any substituent leads to the same product. In the case of a system such as 93b where ring D carries substituents at position 10 and 11, two possible rearranged products, 96b and 96c, are possible, depending on which of the two carbonyl sites,
\[ 93a: R_1 = R_2 = H \]
\[ b: R_1 = R_2 = OR \]

\[ 96c: R_1 = R_2 = OR \]

\[ 96a: R_1 = R_2 = H \]
\[ 96b: R_1 = R_2 = OR \]

\[ 103 \]

\[ \text{Figure 18} \]
which are now non-equivalent, undergoes attack. The site of base attack will depend on both the electronic effects and the steric effect of the C-10 C-11 substituents. Attack of base at the C-9 carbonyl will afford a protoberberine skeleton of type 96b which corresponds to the naturally occurring alkaloids while on the other hand base attack at the C-14 carbonyl will result in a structure of type 96c which is not found in nature.

This rearrangement of the spirobenzylisoquinoline to the protoberberine system presents another route for the synthesis of the newly discovered alkaloids of type 102 (89,90) which carry oxygenated substituents in the 1,2 positions. Classical syntheses of protoberberine alkaloids involve the Bischler-Napieralski ring closure of a properly substituted acyl derivative of a β-phenylethylamine. Cyclisation invariably occurs para to an electron releasing group in which case the 6,7 oxygen-substituted-1-benzyl 3-4 dihydroisoquinoline is obtained. After reduction and treatment with formaldehyde and hydrochloric acid, the substituted protoberberine is obtained. On the other hand if a 2,3 oxygenated phenylacetic acid is used in our scheme the end product, after rearrangement of the spiro compound 103, will be the 1,2-substituted protoberberine skeleton.

THE CONVERSION OF A SPIROBENZYLISOQUINOLINE TO A PHTHALIDEISOQUINOLINE

An interesting rearrangement was observed during the course of this work. As mentioned earlier various attempts aimed at the reduction of the C=C bond in 91a with Pd/C failed. It was feared at first that
reduction with platinum might affect the benzylic carbonyls (later this proved not to be the case). It was therefore decided to hydrolyse the N-acetyl group and then attempt a reduction of the enamine thus formed.

Treatment of 91a in 6M HCl in refluxing ethanol for 4 hours produced on work-up a single crystalline product whose IR showed, as expected, the disappearance of the amide group. Surprisingly the characteristic absorptions of the indandione at 1710 and 1740 cm⁻¹ were absent and there appeared a strong carbonyl absorption at 1772 cm⁻¹, presumably that of a lactone. The mass spectrum of the product showed a molecular ion at m/e 321. These data indicated a phthalide isoquinoline system. This assumption was confirmed by a 60 MHz p.m.r. spectrum of the compound. The two methoxyl groups appeared as two singlets of area 3 at 3.77 δ and 4.03 δ respectively. A singlet of area 1 at 7.07 δ was attributed to the benzylic proton adjacent to the lactone. The aromatic region consisted of a multiplet pattern of area 8 attributed to the isoquinoline protons and the aromatic protons in ring D.

A mechanism for this transformation is outlined in Figure 19. Presumably 91a first suffers hydrolysis to the amine salt 104. Attack by water at one of the carbonyl sites followed by ring opening of the indandione system gives the intermediate 105 which in the presence of acid lactonizes to the phthalide 106. Isomerization then gives the phthalide isoquinoline system 107a. This rearrangement provides a new route to the phthalide isoquinoline alkaloids. Here again two possible rearranged products are possible when the spiro compound 91 carries substituents at the 10,11 positions. The product(s) of the rearrangement
Figure 19
will depend on the site of initial attack on the two carbonyl groups. The electronic and steric effects of the oxygenated substituents at the 10,11 positions on the two carbonyl sites will determine the mode of rearrangement. Attack at the C-9 carbonyl will afford a phthalideisoquinoline system of type 107b which will have the substitution pattern of the naturally occurring bases, whereas attack at the C-14 carbonyl will result in a structure of type 108 which will have a substitution pattern not found in nature.

OTHER ROUTES TO THE SPIROBENZYLISOQUINOLINE ALKALOIDS AND A MODEL FOR THEIR BIOGENESIS

Other routes to the spirobenzylisoquinoline system with two oxygen atoms in the five-membered ring may be envisaged through a base-catalysed rearrangement of a phthalideisoquinoline of type 109, Figure 20. The phthalide 109 may be synthesised according to the method of Robinson and coworkers (91). The condensation of the acid chloride of 6,7-methylenedioxyphthalide - carboxylic acid with 3,4-dimethoxyphenyl-ethylamine would give the amide 110 which could undergo a Bischler-Napieralski reaction to the desired compound 109. Alternatively, an extension of the Perkin reaction between a substituted isoquinoline-1-carboxylic acid and a substituted phthalic anhydride might give the phthalide 109.

By base-catalysed rearrangement the phthalide 109 should rearrange to a protoberberine system. Attack of base at the carbonyl followed by ring opening of the lactone would give the intermediate enolate salt 111 and on lactamization the protoberberine system 112.
Figure 20
would result. Lactamization might be prevented, however, if the nitrogen atom were protected as an amide. In this case attack of the enolate anion on the carbomethoxy group should lead to the spirobenzylisoquinoline system 113.

At this point it is of interest to point out that this transformation provides another model for the biogenesis of the spirobenzylisoquinoline alkaloids. Shamma and coworkers (46,47,48) have converted a protoberberinium salt into a spirobenzylisoquinoline system (Figure 10) and by implication have placed ochotensimine and ochotensine as the precursors of the other spirobenzylisoquinoline alkaloids which carry oxygenated substituents on the five-membered ring. On the other hand, a phthalide isoquinoline system of type 109 may serve as the precursor of the spirobenzylisoquinoline alkaloids as shown in Figure 20. In this event the alkaloids oxygenated in the five-membered ring serve as the precursors of the ochotensimine alkaloids.

Recently Irie and coworkers (92) have converted the spiroisoquinoline base 114 to rhoeadine through a series of reactions. Thus it has been demonstrated that in vitro a protoberberine can be rearranged to a spiroisoquinoline skeleton which in turn can be converted to rhoeadine. It is also conceivable that phthalideisoquinolines may serve as precursors of the same ring systems. Whether or not these transformations occur in the plant can only be answered by experiments with labelled precursors.
CONCLUSION

Ochrobirine, one of the spirobenzylisoquinoline alkaloids, whose structure was elucidated solely on spectroscopic grounds, has been synthesised through an unambiguous route. Comparison of the synthetic product with that derived from natural sources has provided ultimate proof of the assigned structure. The synthetic scheme used was based on reactions which have already been successfully applied to other similar systems. The scheme provides a new route to the spirobenzylisoquinoline system incorporating two oxygen atoms in the five membered ring, and is applicable to other alkaloids of this type. The various steps involved were straightforward and good yields were obtained in most steps. One shortcoming of the synthetic sequence lies in the laborious synthesis of 3,4-methylenedioxyphthalide anhydride. A shorter and more practical synthesis of this anhydride should be explored.

The condensation between 6,7-methylenedioxyphthalide and the substituted benzaldehyde gave a low yield of the substituted 2-phenyl-1,3-indandione and the reason for this behaviour should be investigated. If the yield were to be improved, the synthetic sequence would be shortened by three steps. The ring closure to the spiro dione 91b was achieved through acid treatment after protection of the nitrogen atom. New ways of cyclisation to the spiro dione should be explored. For example, in a photochemical ring closure the nitrogen might not need to be protected. Improvements along these lines would make this scheme an even more attractive route to the spirobenzylisoquinoline system.
The high degree of stereospecificity in the final sodium borohydride reduction of the spiro dione 94b to (±)-ochrobirine was unexpected and the reason for this behaviour remains to be explored.

An important consequence of this work has been the discovery of the rearrangement of the spirobenzylisoquinoline system firstly to the phthalideisoquinoline skeleton and secondly to the protoberberine system. These two rearrangements should be further investigated in the hope that they may offer synthetic routes to the naturally occurring alkaloids.
EXPERIMENTAL

Apparatus, Methods and Materials

Melting points were recorded on a Kofler micro hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann IR5 or a Perkin Elmer 337 spectrophotometer in chloroform solution unless otherwise stated. The p.m.r. spectra were recorded on a Varian A60 or a T60 spectrophotometer in solution in CDCl₃ using tetramethylsilane as an internal standard. Chemical shifts are reported in p.p.m. (δ) from T.M.S. The symbols s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet are used in reporting spectra. Mass spectra were routinely run on all samples to check their molecular weights either on a Hitachi RMU 6A mass spectrometer or on a C.E.C. 21-110B double focusing instrument. High resolution mass spectrometry was used to confirm the composition of several compounds and mass measurements were made by procedures described elsewhere (81).

The microanalyses were performed by Gygli Microanalytical Laboratory, Toronto, Ontario.

3-(3,4-Dimethoxybenzylidene)-phthalide, (78b)

A mixture of 3,4-dimethoxyphenylacetic acid (0.025 mole) phthalic anhydride (0.021 mole), and freshly fused sodium acetate (150 mg) was rapidly heated in an oil bath to 240-245° and the temperature maintained there until the reaction was complete (1-2 h). The reaction mixture was
cooled, dissolved in the minimum amount of hot methanol, and the solution filtered. Upon cooling yellow crystals of the phthalide were deposited melting at 133-134°. Yield: 78%. Anal. Calc. for \( \text{C}_{17}\text{H}_{14}\text{O}_4 \): C, 72.35; H, 4.97%. Found: C, 72.13; H, 4.98%. i.r.: \( \nu_{\text{max}} \) 1775 cm\(^{-1}\); p.m.r.: 3.80 (3H, s, OCH\(_3\)), 3.85 (3H, s, OCH\(_3\)), 6.24 (1H, s, benzylic H), and 6.74 - 6.90 (7H, m, aromatic H's).

3-(3,4-Methylenedioxybenzylidene)-6,7-methylenedioxyphthalide (78c)

The method described above for the preparation of the 3-(3,4-dimethoxybenzylidene)-phthalide gave very low yields when applied to the preparation of the methylenedioxy compound. It was found, however, that the following procedure was satisfactory. A mixture of 3,4-methylenedioxy phenyl acetic acid (0.025 mole) and freshly distilled acetic anhydride (0.05 mole) was heated on a steam bath for 15 m. 3,4-methylenedioxyphthalic anhydride (0.021 mole) and freshly fused sodium acetate (200 mg) were added and the mixture was heated rapidly to 170-180° until the distillation of acetic acid and other volatile components was complete (45-60 m). The solid was dissolved in hot methanol, the solution filtered, and cooled. The bright yellow crystals which separated melted at 259-261°. Yield: 60-62%. Anal. Calc. for \( \text{C}_{17}\text{H}_{10}\text{O}_5 \): C, 65.80; H, 3.23%. Found: C, 65.70; H, 3.33%. i.r.: \( \nu_{\text{max}} \) 1772 cm\(^{-1}\).

3-Benzylidene-phthalide (78a)

Compound 78a was prepared by the method of Weiss (78). Yield: 73%. m.p. 145-147°. Lit. m.p. 145°.
2-[(3,4-Dimethoxyphenyl)-1,3-indandione, (80b) from 3-(3,4-dimethoxybenzyldene)-phthalide (Method A)

The benzylidene phthalide (0.025 mole) in boiling absolute methanol (200 ml) was treated with a solution of sodium methoxide freshly prepared from sodium (750 mg) and absolute methanol (25 ml). The bright red solution so obtained was heated under reflux for one hour, cooled, and the solvent removed under vacuum. The red residue was dissolved in water and extracted with ether. The aqueous layer was separated, acidified to pH 4 with 10% sulfuric acid and extracted several times with chloroform. The extract was washed several times with water, dried over anhydrous sodium sulfate and evaporated to dryness. The white solid residue was recrystallized from benzene and melted at 196-197°. Yield: 92-95%.

Anal. Calc. for C_{17}H_{14}O_4: C, 72.35; H, 4.97%. Found: C, 72.51; H, 4.83%. i.r.: v\text{max} 1710, 1745 cm^{-1}; p.m.r.: 3.79 (6H, s, 2 x OCH_3), 4.17 (1H, s, benzylic H), 6.69 (3H, m, aromatic H), 7.73 - 8.10 (4H, m, aromatic H).

2-[(3,4-Dimethoxyphenyl)-1,3-indandione, (80b) from 3,4-dimethoxybenzaldehyde and phthalide (Method B)

A boiling mixture of phthalide (0.025 mole), aldehyde (0.025 mole) and freshly distilled methyl formate (12 ml) was treated with a solution of sodium methoxide in methanol prepared from sodium (1.95 g) in anhydrous methanol (24 ml). The solution, which became red immediately upon addition of the methoxide, was boiled for one hour under reflux and then worked up as in the procedure above. Compound 80b was obtained in 95% yield.
2-(3,4-Methylenedioxyphenyl)-4,5-methylenedioxy-1,3-indandione, (80c)

This compound was prepared from the phthalide (78c) by the procedure outlined previously (Method A) for the rearrangement of 3-(3,4-dimethoxybenzyldiene)-phthalide. Like its analogue this compound was recrystallized from benzene and then melted at 209-210°. Yield: 93%. When its preparation from piperonal and 6,7-methylenedioxyphthalide (Method B above) was attempted only 5-10% of the desired product was obtained. Anal. Calc. for C_{17}H_{10}O_{6}: C, 65.81; H, 3.23%. Found: C, 65.66; H, 3.11%. i.r. \( \nu_{\text{max}} \) 1708, 1740 cm\(^{-1}\); p.m.r.: 4.17 (1H, s, benzylic H), 5.88 (2H, s, OCH\(_2\)O), 6.16 (2H, s, OCH\(_2\)O), 6.89, 7.46 (2H, AB quartet, J = 8 Hz, C\(_6\)H and C\(_7\)H), 6.70 - 7.42 (3H, m. aromatic H).

2-Phenyl-1,3-indandione, (80a)

This compound was prepared from the phthalide 78a by the procedures outlined for the preparation of 80b. m.p. 104-106° (Lit. (73) m.p. 104-106°).

2-Bromo-2-(3,4-dimethoxyphenyl)-1,3-indandione, (86b)

A stirred solution of dione 80b (0.005 mole) in glacial acetic acid (100 ml) under an atmosphere of oxygen-free nitrogen at room temperature was treated rapidly with a solution of bromine (0.005 mole) in glacial acetic acid (15 ml). The absorption of bromine was instantaneous but the reaction was stirred for five minutes before removing the glacial acetic acid under vacuum. It was necessary to keep the temperature below 20° at this stage to avoid decomposition of the bromo compound. The residue was a yellow crystalline material melting at 133-34°. In most
cases it was used directly in the next step because attempts to recrystal-
ize it resulted in its decomposition. i.r.: \( \nu_{\text{max}} \) 1710, 1745 cm\(^{-1}\).
p.m.r.: 3.78 (3H, s, OCH\(_3\)), 3.83 (3H, s, OCH\(_3\)), 6.70 - 8.3 (7H, m,
aronomic H).

2-Bromo-2-(3,4-methylenedioxyphenyl)-4,5-methylenedioxy-1,3-indandione,
(86c)

Compound 80c was brominated by a procedure identical with that
used for the preparation of 80b. The crude product melted at 176-178\(^{\circ}\).
i.r.: \( \nu_{\text{max}} \) 1708, 1745 cm\(^{-1}\). p.m.r.: 5.90 (2H, s, OCH\(_2\)O), 6.16 (2H, s,
OCH\(_2\)O), 7.03, 7.57 (AB quartet, J = 8 Hz, C\(_6\)H and C\(_7\)H), 6.6 - 7.3 (3H,
m, aromatic H).

2-Bromo-2-phenyl-1,3-indandione, (86a)

Compound 86a was brominated by a procedure identical with that
used for the preparation of 86b except that chloroform was used as
solvent. m.p. 104-106\(^{\circ}\) (Lit. (73) m.p. 105\(^{\circ}\)). Yield: 89-91%.

2-(2,2-Diethoxyethylamino)-2-(3,4-dimethoxyphenyl)-1,3-indandione, (87b)

A stirred solution of compound 86b (0.01 mole) in anhydrous ether
(75 ml) was cooled in an ice bath and to it was added dropwise a solution
of freshly distilled aminoacetal (0.02 mole) in anhydrous ether (15 ml).
The resulting solution was stirred for a total of 15 h under an atmos-
phere of dry nitrogen. The reaction mixture, containing suspended solids,
was washed twice with water, the ether layer separated, dried over anhy-
drous sodium sulfate and evaporated to dryness. The yellow gum that
resulted was used directly in the next step. Yield: 74%. i.r. $\nu_{\text{max}}$
1715, 1750 cm$^{-1}$; p.m.r.: 1.08 (6H, t, $J = 7$ Hz, 2 x OCH$_2$CH$_3$), 2.68 (2H, 
d, $J = 5$ Hz, >N-CH$_2$-CH), 3.24 - 3.74 (4H, m, 2 x OCH$_2$CH$_3$), 3.72 (3H, s, 
-OCH$_3$), 3.76 (3H, s, -OCH$_3$), 4.54 (1H, t, $J = 5$ Hz, N-CH$_2$-CH), 6.7 - 8.2 
(7H aromatic).

2-(2,2-Diethoxyethylamino)-2-(3,4-methylenedioxyphenyl)-4,5-methylene-
dioxy-1,3-indandione, (87c)

Compound 87c was prepared from 87b in a manner identical with the preparation of 87b from 86b above. Yield: 71-73%. i.r.: $\nu_{\text{max}}$ 1710,
1748 cm$^{-1}$; p.m.r.: 1.14 (6H, t, $J = 7$ Hz, 2 x OCH$_2$CH$_3$), 2.64 (2H, d, 
$J = 5$ Hz, N-CH$_2$CH<), 2.30 (1H, broad s, NH), 3.27 - 3.74 (4H, complex m, 
2 x 0-CH$_2$-CH$_3$), 4.57 (1H, t, $J = 5$ Hz, N-CH$_2$-CH), 5.87 (2H, s, OCH$_2$O), 
6.15 (2H, s, -OCH$_2$O), 6.87, 7.44 (AB quartet, $J = 8$ Hz, C$_6$H and C$_7$H), and 
6.70 - 7.00 (3H, m, aromatic).

2-(2,2-Diethoxyethylamino)-2-phenyl-1,3-indandione, (87a)

Compound 87a was prepared from 86a in a manner identical with the preparation of 87b from 86b. It was obtained as a yellow oil in a 74% 
yield. i.r.: $\nu_{\text{max}}$ 1712, 1748 cm$^{-1}$ (CO). p.m.r.: 1.08 (6H, t, $J = 7$ Hz, 
2 x OCH$_2$CH$_3$), 2.66 (2H, d, $J = 5$ Hz, NCH$_2$CH), 3.24 - 3.74 (4H, m, 2 x 
OCH$_2$CH$_3$), 4.54 (1H, t, $J = 5$ Hz, N-CH$_2$-CH), 6.82 (5H, broad s, aromatic 
H), 7.80 - 8.20 (4H, m, aromatic H).
Treatment of 87b with 6M aqueous ethanolic hydrochloric acid

A solution of 0.005 mole of 87b in 75 ml of 6M aqueous ethanolic hydrochloric acid was stirred for 16 hours at room temperature. The resulting mixture contained a white precipitate. The solvent was removed under vacuum and the white residue so obtained was washed with water and filtered. Recrystallisation from benzene afforded 1.35 g of needle-like crystals m.p. 194-196°. A mixture melting point of the product and compound 80b showed no depression. The i.r. spectrum in CHCl₃ and the p.m.r. spectrum in CDCl₃ were superimposable on those of compound 80b.

The filtrate was concentrated to about 10 ml and was treated with a solution of 2,4-dinitrophenylhydrazine in ethanol and allowed to stand at room temperature for 15 minutes. The reddish precipitate that formed was filtered, washed with water, and air dried. Recrystallisation from aqueous ethanol gave orange crystals which melted at 328-330°. Authentic glyoxal bis-2,4-dinitrophenylhydrazone is reported to melt at 328° (93).

N-Acetyl-2-(2,2-diethoxyethylamino)-2-(3,4-dimethoxyphenyl)-1,3-indandione, (89a)

A mixture of amine 87b (0.001 mole) in anhydrous pyridine (1 ml) and freshly distilled acetic anhydride (3 ml) was stirred at room temperature for 48 h. The solution was added to water and the mixture extracted several times with chloroform. The chloroform extract was washed several times with cold aqueous hydrochloric acid and with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was adsorbed on basic alumina and the column eluted with chloroform. After
removal of chloroform from the eluant a crystalline residue was obtained
which, after recrystallization from ethanol, melted at 132-133°.

Yield: 83%. Anal. Calc. for C_{25}H_{29}NO_{7}: C, 65.94; H, 6.37; N, 3.08%.
Found: C, 66.02; H, 6.63; N, 3.12%. i.r.: \nu_{\text{max}} 1635 (amide), 1712,
1748 cm^{-1}; p.m.r.: 0.97 (6H, t, J = 7 Hz, 2 x OCH_2CH_3), 2.09 (3H, s,
COCH_3), 3.04 - 3.60 (6H, m, 2 x OCH_2-CH_3 + \geq N-CH_2-CH\geq), 3.61 (3H, s,
OCH_3), 3.67 (3H, s, OCH_3), 4.37 (1H, t, J = 5 Hz, N-CH_2-CH\geq), 6.6 - 7.9
(7H, m, aromatic).

N-Acetyl-2-(2,2-diethoxyethylamino)-2-(3,4-methylenedioxy phenyl)-
4,5-methylenedioxy-1,3-indandione, (89b)

Compound 89b was prepared from 87c in a manner analogous to the
preparation of 89a above. After recrystallization from ethanol it melted
at 172-174°. Yield: 80%. Anal. Calc. for C_{25}H_{25}NO_{8}: C, 62.12; H, 5.18;
N, 2.90%. Found: C, 62.37; H, 5.30; N, 3.08%. i.r.: \nu_{\text{max}} 1640, 1710,
1740 cm^{-1}. p.m.r.: 1.13 (6H, t, J = 7 Hz, 2 x OCH_2CH_3), 2.24 (3H, s,
COCH_3), 3.27, 3.74 (6H, complex m, 2 x OCH_2CH_3 + \geq N-CH_2-CH\geq), 4.47 (1H, t,
J = 5 Hz, N-CH_2-CH\geq), 5.90 (2H, s, OCH_2O), 6.17 (2H, s, -OCH_2O), 6.87,
7.44 (2H, AB quartet, J = 8 Hz, C_8H and C_7H), and 6.97 - 7.10 (3H, m,
aromatic).

N-Acetyl-2-(2,2-diethoxyethylamino)-2-phenyl-1,3-indandione, (89c)

Compound 89c was prepared from 87a in the same way that 89a was
prepared from 87b. Crystallization from ethanol gave colourless crystals
melting at 170-172°. Yield: 83%. i.r.: \nu_{\text{max}} 1712, 1748 cm^{-1} (CO),
1638 cm^{-1} (N-CO-CH_3). Anal. Calc. for C_{23}H_{25}NO_{5}: C, 69.87; H, 6.33;
N, 3.55%. Found: C, 69.87; H, 6.37; N, 3.60%.

**N-Carbobenzoxy-2-(2,2-diethoxyethylamino)-2-(3',4'-dimethoxyphenyl)-1,3-indandione, (88)**

To a stirred suspension of the amine **87b** (0.003 mole) in 15 ml of 2M NaOH cooled in ice, there was added dropwise carbobenzoxy chloride (0.003 mole). The mixture was stirred at 0°C for 4 hr and during this period a yellow oil separated. The mixture was diluted with 20 ml of water and extracted twice with ether. The ether was separated, combined, washed with water and brine and dried over anhydrous sodium sulphate. The ether was evaporated under reduced pressure giving a brown gum which was taken up in chloroform and filtered through a short column of neutral alumina (Brockman activity 1). The pale yellow oil (1.48 g) obtained after evaporation failed to crystallise from ethanol or ether. i.r. ν\text{max} 1710, 1745 (C=O), 1700 (N-C\text{\alpha}_OR) cm\text{^{-1}}.

p.m.r.: 1.04 (6H, t, J = 7 Hz, 2 x OCH\text{\beta}CH\text{\beta}), 3.25 - 3.81 (6H, m, 2 x OCH\text{\beta}CH\text{\beta} + N-CH\text{\textsubscript{2}}-CH), 3.82 (3H, s, OCH\text{\alpha}), 3.90 (3H, s, OCH\text{\alpha}), 4.43 (1H, t, J = 5 Hz, N-CH\text{\textsubscript{2}}-CH), 5.00 (2H, s, O-CH\text{\textsubscript{2}}-C\text{\textsubscript{6}}H\text{\textsubscript{5}}), 6.6 - 7.6 (12H, m, aromatic H's). The mass spectrum showed a molecular ion at m/e 547 corresponding to C\textsubscript{31}H\textsubscript{33}NO\textsubscript{8}.

**2-Carbobenzoxy-4-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'- (1',3'-indandione), (90)**

A solution of **88** (0.0015 mole) in 6M aqueous ethanolic hydrochloric acid (65 ml) was stirred at room temperature for 16 hr. The ethanol was then removed under vacuum, the aqueous acid solution neutralized with ammonia, and the solution extracted twice with chloroform.
The chloroform extract was washed with water, then dried over anhydrous sodium sulfate. Evaporation of the chloroform gave a yellow amorphous solid which was further purified by chromatography over a short column of basic alumina using chloroform as eluant. Evaporation of the chloroform gave a pale yellow solid (308 mg) which failed to crystallise from ethanol. The powder melted at 162-173°C. I.r.: \( \nu_{\text{max}} \) 3400 (OH), 1712, 1748 (C=O) (N-C\( \text{OR} \)) cm\(^{-1}\). p.m.r.: 3.45 (2H, m, C\(_3\)H's), 3.82 (3H, s, OCH\(_3\)), 3.93 (3H, s, OCH\(_3\)), 4.60 (1H, broad s, OH, disappeared on shaking with D\(_2\)O), 4.95 (1H, broad s, C\(_4\)H), 5.21 (2H, s, O-CH\(_2\)-C\(_6\)H\(_5\)), 6.80 (1H, s, C\(_9\)H), 7.12 (1H, s, C\(_5\)H), 7.26 (5H, s, O-CH\(_2\)-C\(_6\)H\(_5\)), 7.60 - 8.10 (4H, m, aromatic H's). The mass spectrum had a molecular ion at m/e 473 corresponding to C\(_{27}\)H\(_{23}\)NO\(_7\).

**Hydrogenolysis of 90**

Compound 90 (0.001 mole) dissolved in ethanol (30 ml) was shaken with hydrogen at 35 psig, in the presence of palladium on charcoal (120 mg) for 5 hours. The catalyst was removed by filtration and the ethanol evaporated under vacuum giving a brown tarry material. Thin layer chromatography on silica gel (chloroform) revealed the presence of six components of equal proportions and of very close Rf values. Attempts to effect separations on column and preparative thin layer chromatography failed.
2-Acetyl-6,7-dimethoxy-1,2-dihydroisoquinoline-1-spiro-2'-{(1',3'-indandione), (91a).

A mixture of 89a (0.003 mole) in 6M aqueous ethanolic hydrochloric acid (50 ml) was stirred at room temperature for 18 h. The ethanol was removed under vacuum, the aqueous acid solution neutralized with ammonia, and the solution extracted twice with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and then evaporated to give a reddish brown residue which was purified by chromatography over basic alumina using chloroform as eluant. Evaporation of the chloroform gave an orange solid which crystallized readily from hot ethanol, m.p. 263-264°. Yield: 47-52%. Anal. Calc. for C_{21}H_{17}NO_{5}: C, 69.42; H, 4.68; N, 3.86%. Found: C, 69.39; H, 5.02; N, 3.96%. i.r.: ν_{max} 1642 (N-COCH_{3}), 1668 (>=<), 1715, 1750 cm^{-1}. p.m.r.: 2.26 (3H, s, COCH_{3}), 3.37 (3H, s, OCH_{3}), 3.81 (3H, s, OCH_{3}), 5.64, 6.77 (2H, AB quartet, J = 8 Hz, C_{3}H and C_{4}H), 5.90 (1H, s, C_{8}H)”, 6.60 (1H, s, C_{5}H), 7.80 - 8.15 (4H, m, aromatic).

2-Acetyl-6,7-methylenedioxy-1,2-dihydroisoquinoline-1-spiro-2'-(4',5'-methylenedioxy-1',3'-indandione), (91b)

This compound was prepared from 89b in a manner analogous to the preparation described above of 91a from 89a. After recrystallization from hot ethanol the compound melted at 305-308°. Yield: 57-61%. Anal. Calc. for C_{21}H_{13}NO_{7}: C, 64.44; H, 3.33; N, 3.58%. Found: C, 64.33; H, 3.30; N, 3.49%. i.r.: ν_{max} 1640 (N-COCH_{3}), 1675 (>=<), 1715 and 1745 cm^{-1}. p.m.r.: 2.17 (3H, s, N-COCH_{3}), 5.54, 6.71 (2H, AB quartet, J = 8 Hz, C_{3}H.
and C₄H), 5.81 (2H, s, OCH₂O), 6.24 (2H, s, OCH₂O), 6.05 (1H, s, C₆H), 6.54 (1H, s, C₅H), 7.21, 7.61 (2H, AB quartet, J = 8 Hz, C₆H and C₇H).

2-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'(1',3'-indandione), (92a)

Compound 91a (0.001 mole) dissolved in acetic acid (20 ml) was shaken with hydrogen at 35 psig, in the presence of Adams catalyst (25 mg) for one hour. The catalyst was removed by filtration and the acetic acid evaporated under vacuum. The pale yellow residue was recrystallized from ethanol and melted at 238-240°. Yield: 95%. Anal. Calc. for C₂₂H₁₉NO₅: C, 69.23; H, 5.22; N, 3.85%. Found: C, 69.40; H, 5.37; N, 3.85%.

i.r.: νmax 1640 (N-COCH₃), 1718 and 1750 cm⁻¹. p.m.r.: 2.35 (3H, s, COCH₃), 3.15, 3.94 (4H, A₂B₂m, C₃ and C₄ H's); 3.55 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 6.01 (1H, s, C₈H), 6.85 (1H, s, C₅H), 7.85 - 8.1 (4H, m, aromatic H's).

2-Acetyl-6,7-methyleneoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'(4', 5'-methyleneoxy-1',3'-indandione), (92b)

This compound was prepared from 91b in the same way that 92a was prepared from 91a. Recrystallization from ethanol gave yellow crystals melting at 300-301°. Yield: 91%. Anal. Calc. for C₂₂H₁₅NO₇: C, 64.27; H, 3.87; N, 3.56%. Found: C, 64.33; H, 3.76; N, 3.56%. i.r.: νmax 1640 (N-COCH₃), 1715 and 1740 cm⁻¹. p.m.r.: 2.13 (3H, s, N-COCH₃), 3.01, 3.85 (4H, A₂B₂m, C₃ and C₄ H's), 5.82 (2H, s, OCH₂O), 6.20 (2H, s, OCH₂O), 6.18 (1H, s, C₈H), 6.67 (1H, s, C₅H), 7.16, 7.55 (2H, AB quartet, J = 8 Hz, C₆H and C₇H).
6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'- (1',3'-indandione), (93a)

The amide 92a (0.5 mmole) was boiled under reflux with 6M ethanolic aqueous HCl (25 ml) for 2 h. The mixture was taken to dryness, water added, the solution basified, and extracted with chloroform. The extract was washed, dried, and evaporated to a residue which crystallized from ether-hexane and melted at 180-182°C. Yield: 80%. Anal. Calc. for C_{19}H_{17}NO_4: C, 70.60; H, 5.26; N, 4.64%. Found: C, 70.52; H, 5.30; N, 4.50%. i.r.: v_{max} 1715 and 1750 cm^{-1}. p.m.r.: 2.79, 3.48 (4H, A_2B_2m, C_3 and C_4 H's), 3.50 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.92 (1H, s, C_8H), 6.71 (1H, s, C_5H), 7.8 - 8.2 (4H, m, aromatic H's).

6,7-Methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'- (4',5'-methylenedioxy-1',3'-indandione), (93b)

The amide 92b was hydrolysed in the same way that 92a was converted to 93a. The resulting amine was recrystallized from ether-hexane and melted at 198-199°C. Yield: 82-84%. Anal. Calc. for C_{19}H_{13}NO_6: C, 64.95; H, 3.70; N, 3.99%. Found C, 64.91; H, 3.91; N, 4.04%. i.r.: v_{max} 1715 and 1748 cm^{-1}. p.m.r.: 2.74, 3.37 (4H, A_2B_2m, C_3 and C_4 H's), 5.78 (2H, s, OCH_2O), 6.28 (2H, s, OCH_2O), 5.99 (1H, s, C_8H), 6.60 (1H, s, C_5H), 7.20, 7.64 (2H, AB quartet, J = 8 Hz, C_6 and C_7 H). The sample was analysed by high resolution mass spectrometry. Calc. for C_{19}H_{13}NO_6: 351.074; Found: 351.071.
2-Methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'-
(4',5'-methylenedioxy-1',3'-indandione), (94b)

Amine 93b (100 mg), 92% formic acid (2 ml), and formaldehyde
(2 ml) were heated on a steam bath for 10 hours. Water was added to the
mixture which was then basified with sodium bicarbonate solution and
extracted twice with chloroform. The chloroform extract was washed with
water, dried over sodium sulfate, and evaporated to dryness. The yellow
residue after recrystallization from ether-hexane melted at 195-196°C.
Yield: 79%. Anal. Calc. for C20H15NO6: C, 65.75; H, 4.10; N, 3.84%.
Found: C, 65.52; H, 4.03; N, 3.88%. i.r.: νmax 1705 and 1737.
p.m.r.: 2.41 (3H, s, N-CH₃), 2.97 - 3.47 (4H, complex m, C₃ and C₄ H's),
5.81 (2H, s, OCH₂O), 6.31 (2H, s, OCH₂O), 5.96 (1H, s, C₆H), 6.62 (1H,
s, C₅H), 7.24, 7.64 (2H, AB quartet, J = 8 Hz, C₆ and C₇ H). The sample
was analysed by high resolution mass spectrometry. Calc. for C20H15NO6:
365.090; Found: 365.089.

2-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'-(1',3'-
indandiol), (95a)

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'-(1',3'-
indandiol) (410 mg) obtained by reduction of 93a with sodium borohydride
(81) was treated without purification with 2.5 ml of formalin (37%) at
reflux for 2 h. The mixture was taken to dryness under vacuum, the
residue so obtained was dissolved in methanol (5 ml), the solution cooled
in ice, and then treated with 200 mg of NaBH₄. The mixture was stirred
for 30 minutes, the solvent removed under reduced pressure, water added
and the resulting mixture extracted with methylene chloride. The dry methylene chloride solution was evaporated to dryness and crystallized from benzene yielding 139 mg of product. Recrystallization from benzene-petroleum ether gave an analytical sample melting at 161-2°C.

Anal. Calc. for C_{20}H_{23}NO_4: C, 70.20; H, 6.73; N, 4.10. Found: C, 70.57; H, 6.81; N, 3.99. p.m.r.: 2.04 (2H, broad s, 2 x OH); 2.65 (3H, s, N-CH_3), 2.78 (2H, t, N-CH_2), 3.48 (2H, t, Ar-CH_2), 3.27 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.35 (2H, broad s, 2 x CH-OH), 5.92 (1H, s, C_6H), 6.67 (1H, s, C_5H), 7.4 (4H, m, ArH's). The two proton singlet at 2.04δ disappeared in the presence of D_2O.

(±)-Ochrobinine (95b)

Compound 94b (32 mg) in absolute ethanol (35 ml) was treated with sodium borohydride (90 mg) and the mixture was stirred at room temperature for 15 h. The solvent was then removed under reduced pressure, the residue taken up in H_2O, and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and evaporated to dryness giving 26 mg of white residue. Examination by TLC showed the presence of two components, one of which (the major one) had the same Rf value as natural ochrobinine. Crystallization from benzene-hexane gave 21 mg of crystalline product melting at 210-12°C which on TLC showed only traces of the minor component noted above. Recrystallization from methanol removed the traces of impurity without altering the melting point. The i.r. spectrum in chloroform, the p.m.r. spectrum in CDCl_3, and the mass spectrum of the synthetic sample were identical with those of natural ochrobinine. The
sample was analysed by high resolution mass spectrometry. Calc. for C_{20}H_{19}NO_5: 369.121; Found: 369.120.

2,3-Dihydroxybenzoic acid

A mixture of sodium hydroxide (56 g), potassium hydroxide (222 g), and water (34 ml) was heated to 160° in a 1-litre porcelain crucible. 2-hydroxy-3-methoxybenzaldehyde (100 g) was added with stirring. After the initial exothermic reaction had subsided, the temperature was raised to 250° and maintained there until the reaction was complete (no further evolution of gas). The mixture was cooled with stirring and water (660 ml) added. The reddish brown solution was neutralized with 6M hydrochloric acid to pH2. The aqueous solution was extracted several times with ether, the ether layers combined, dried over anhydrous sodium sulphate and evaporated in vacuo. A brown crystalline compound was obtained which was then purified through sublimation (130°, 0.01 mm) giving 75 g of product. m.p. 207-209°. (Lit. (83), 200-202°).

2,3-Methylenedioxybenzoic acid

2,3-dihydroxybenzoic acid (77 g) was added to freshly distilled dimethyl sulfoxide (250 ml) in a 1-litre three-necked flask equipped with a mechanical stirrer, condenser, and nitrogen inlet. Pulverized sodium hydroxide (70 g) was added to the solution and the mixture heated on an oil bath to 100°. After three minutes, dibromomethane (90 g) was added and the mixture refluxed at 130-135° for two hours with the assembly protected against moisture. Additional dibromomethane (45 g) was added and the reflux continued for another hour. The reaction mixture was then
cooled, the dark brown cake which was formed was dissolved in hot water (500 ml), the solution was made alkaline and then filtered through celite. The resulting clear brown filtrate was cooled in ice and acidified with concentrated hydrochloric acid. The yellow precipitate was filtered, washed with water, and dried. Recrystallization from ethanol afforded 45 g of colourless crystals (prisms). m.p. 227-229°. Lit. (84) m.p. 229°.

6,7-Methylenedioxyphthalide

A mixture of concentrated hydrochloric acid (120 ml) and 40% formaldehyde (45 g) was added to 2,3-methylenedioxybenzoic (30 g) dissolved in hot glacial acetic acid (150 ml). The reaction mixture was then boiled until the solution became clear (40 minutes). The solution was diluted with water (200 ml) and neutralized with sodium bicarbonate. The precipitate thus obtained was filtered, dried, and recrystallized from hot acetic acid giving 8 g of colourless prisms. m.p. 233-234°. (Lit. (84) m.p. 226°).

3,4-Methylenedioxyphthalic acid

3,4-methylenedioxyphthalide (8 g) was dissolved in 3% sodium hydroxide solution (800 ml). To this solution cooled in ice water, a 1% aqueous solution of potassium permanganate (1500 ml) cooled in ice was added slowly with stirring, keeping the temperature below 10°. The resulting green mixture was stirred for 5 hours at room temperature, then filtered, cooled and acidified with concentrated hydrochloric acid. The solution was then evaporated to dryness in vacuo, and the resulting white
residue was taken up in hot acetone. The solution was filtered and evaporated giving 6 g of pale yellow plates m.p. 170-172°C. This material was converted to the anhydride derivative without further purification.

3,4-Methylenedioxyphthalic anhydride

3,4-methylenedioxyphthalic acid (10 g) and freshly distilled acetic anhydride (8 ml) were heated for a half hour on a steam bath. The brown solution that resulted was evaporated to dryness in vacuo giving a brown solid. The solid was sublimed (150°C, 0.01 mm) whereupon colourless prisms (7.8 g) were obtained. m.p. 168-170°C (Lit. (94) m.p. 169-170°C).

6,7-Dimethoxy-1-(3'-phthalide)isoquinoline, (107a)

The amide 91a (0.5 mmole) was boiled under reflux with 6M ethanolic aqueous HCl (25 ml) for 12 hours. The mixture was taken to dryness, water added, the solution basified with ammonia solution, and extracted with chloroform. The extract was washed, dried, and evaporated to a residue which crystallized from ether and melted at 175-177°C.

Yield: 83%. Anal. Calc. for C_{19}H_{15}NO_{4}: C, 71.03; H, 4.67; N, 4.36%. Found: C, 70.84; H, 4.58; N, 4.44%. i.r.: ν_{max} 1772 cm^{-1} (lactone). p.m.r.: 3.77 (3H, s, OCH₃), 4.03 (3H, s, OCH₃), 7.07 (1H, s, benzylic H), 7.32 - 8.27 (8H, aromatic H's).

Conversion of 93a to a protoberberine

To a refluxing solution of the amine 93a (435 mg) in absolute methanol (50 ml) there was added with constant stirring a solution of
sodium methoxide (100 mg in 10 ml). Reflux was maintained for another hour. The solvent was then removed in vacuo, the bright yellow salt was taken up in water, and a saturated ammonium chloride solution added. The white precipitate so obtained was filtered and dried. (422 mg). The precipitate was then dissolved in sodium hydroxide solution and refluxed for four hours with 4 ml of dimethylsulphate. The resulting solution was extracted with chloroform and the extract dried and evaporated to give a yellow residue which crystallized from ethanol. m.p. 185-186°. Yield: 387 mg. Anal. Calc. for C₁₉H₁₇NO₄: C, 71.22; H, 5.64; N, 4.16%. Found: C, 71.23; H, 5.75; N, 4.27%. i.r.: \(\nu_{\text{max}}\) 1638, 1600 cm\(^{-1}\). p.m.r.: 2.70 (2H, t, J = 5 Hz, N-\(\text{CH}_2\)), 3.50 (3H, s, O\(\text{CH}_3\)), 3.86 (6H, s, 2 \(\times\) O\(\text{CH}_3\)), 4.16 (2H, t, J = 5 Hz, Ar-\(\text{CH}_2\)), 6.71 (1H, s, C\(_6\)H), 8.20 (1H, s, C\(_1\)H), 7.41 - 8.58 (4H, m, aromatic H's).
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