The Total Synthesis of Natural Products

VOLUME 3

Edited by

John ApSimon

Department of Chemistry
Carleton University, Ottawa

A WILEY-INTERSCIENCE PUBLICATION

John Wiley & Sons, New York • London • Sydney • Toronto

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Library of Congress Cataloging in Publication Data:

ApSimon, John.
The total synthesis of natural products.
Includes bibliographical references.

1. Chemistry, Organic–Synthesis. I. Title.

QD262.A68 547'.2 72-4075
ISBN 0-471-02392-2 (V. 3)

10 9 8

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Preface

Throughout the history of organic chemistry, we find that the study of natural products frequently has provided the impetus for great advances. This is certainly true in total synthesis, where the desire to construct intricate and complex molecules has led to the demonstration of the organic chemist's utmost ingenuity in the design of routes using established reactions or in the production of new methods in order to achieve a specific transformation.

These volumes draw together the reported total syntheses of various groups of natural products and commentary on the strategy involved with particular emphasis on any stereochemical control. No such compilation exists at present, and we hope that these books will act as a definitive source book of the successful synthetic approaches reported to date. As such, it will find use not only with the synthetic organic chemist but also perhaps with the organic chemist in general and the biochemist in his specific area of interest.

One of the most promising areas for the future development of organic chemistry is synthesis. The lessons learned from the synthetic challenges presented by various natural products can serve as a basis for this ever-developing area. It is hoped that these books will act as an inspiration for future challenges and outline the development of thought and concept in the area of organic synthesis.

The project started modestly with an experiment in literature searching by a group of graduate students about nine years ago. Each student prepared a summary in equation form of the reported total syntheses of various groups of natural products. It was my intention to collate this material and possibly publish it. During a sabbatical leave in Strasbourg in 1968-1969, I attempted to prepare a manuscript, but it soon became apparent that the task would take many years and I wanted to enjoy some of the other benefits of a sabbatical leave. Several colleagues suggested that the value of such a collection would be enhanced by commentary. The only way to encompass the amount of data

collected and the inclusion of some words was to persuade experts in the various areas to contribute.

Volume 1 presented six chapters describing the total synthesis of a wide variety of natural products. The subject matter of Volume 2 was somewhat more related, being a description of some terpenoid and steroid syntheses. The present volume considers the syntheses of several classes of alkaloids. The authors originally provided me with their manucripts three years ago, and the delay in producing this volume is a result of a hope that another planned chapter would also appear in time for inclusion. Unfortunately, the author of that chapter has been unable to produce his contribution.

I have asked the authors of these chapters to provide wherever possible, an updating of their work by the use of supplementary references and addenda. The delay in producing the original work is in no way the fault of the present authors, and I apologize to them for this tardiness. However, I believe that their work is outstanding and well worth publishing. I hope the readers of this volume will find it useful as a reference work on total syntheses preformed in the alkaloid field.

I wish to express my thanks to Ms. Karen Bergenstein for preparing the index and to Karl Diedrich for preparing the illustrations to Chapter 2.

JOHN APSIMON

Ottawa, Canada
January 1977

Contents

The Total Syntheses of Isoquinoline Alkaloids

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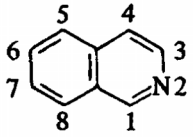
*The author is deeply indebted to Dr. Keiichiro Fukumoto and Dr. Shiroshi Shibuya, Pharmaceutical Institute, Tohoku University, for many help for suggestions, as well as for help in the preparation of this review.

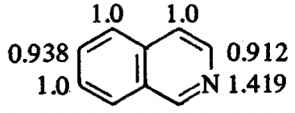
Isoquinoline or benzo[c]pyridine, an isomer of quinoline, was first obtained from coal tar by Hoogewerff and van Dorp in 1885 together with various alkylisoquinolines, and isoquinoline itself was synthesized by Gabriel in the same year. However, the natural occurrence of the isoquinoline ring system was first recognized in the opium alkaloid; papaverine, isolated as needles, m.p. 147°, $C_{20}H_{21}O_4N$, by Goldschmidt,[1] in one of the first structural determinations of alkaloids. Since Goldschmidt's recognition, efforts by chemists have been devoted to the chemistry of the alkaloids and by now about 1000 isoquinoline alkaloids are known.[2]

The numbering of isoquinoline ring system is shown as follow.

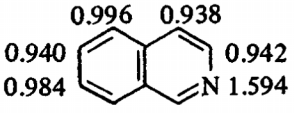


Isoquinoline is obtained as hygroscopic colorless crystals, m.p. 24.6°, $b.p._{760}$ 243.3°, $b.p._{40}$ 142° with *p*Ka 5.14 in water at 20°. The odor of isoquinoline is almost the same as that of quinoline, but the former smells somewhat likes benzaldehyde. The basicity of isoquinoline is stronger than that of quinoline, which has *p*Ka 4.85 in water at 20°. Electronically, the chief difference between naphthalene and isoquinoline is due to the fact that the latter, isoquinoline has the "lone pair" at its nitrogen atom. Furthermore, the nitrogen attracts electron density from the carbon atoms so that these carbon atoms have a deficiency of the electron charge compared with the atoms in naphthalene.[3] Quantitatively, the charge on each atom can be calculated by the valence bond method or by the method of molecular orbitals.[3]

π-Electron Densities for Isoquinoline



V. B. Method



M. O. Method

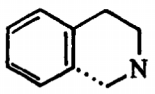
In general, it would be expected that substitution with electrophilic reagents would occur at the carbon having the greatest π-electron density and that substitution with nucleophilic reagents would occur at the position having the smallest π-electron density.

1. GENERAL METHODS

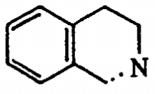
A. Introduction

The methods for the synthesis of isoquinoline ring system can be classified systematically in five ways according to the mode of formation of the pyridine ring (Chart 1-1). The first type involves ring closure between the benzene ring and

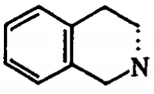
Chart 1-1.



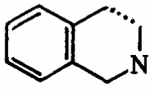
Type 1



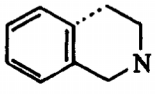
Type 2



Type 3



Type 4

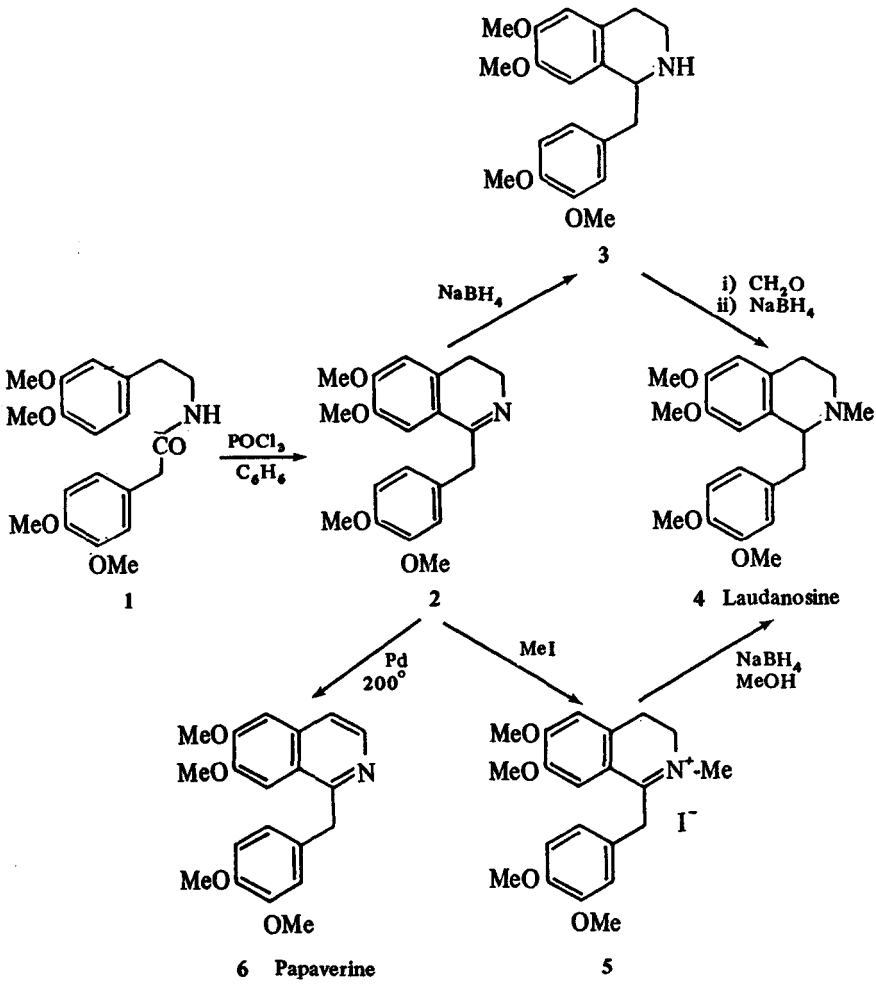


Type 5

the carbon atom, which forms the C_1-position of the resulting isoquinoline ring. The second type uses bond formation between the C_1-position and nitrogen, and the third type uses cyclization by the combination of nitrogen with the C_3-position. The fourth type is due to the formation of isoquinoline ring by ring closure between the C_3- and C_4-position. The fifth type necessitates ring closure between the benzene ring and C_4-position.

In the Chart 1-1, the dotted lines indicate the bond formation by cyclization. Although all the types of these reactions are known, the most popular reactions are the type of 1 and 5, giving usually dihydro- or tetrahydroisoquinoline derivatives and aromatic isoquinolines can be prepared by the dehydrogenation of the corresponding dihydro- or tetrahydroisoquinolines. Among reactions of type 1 and 5, the Bischler-Napieralski, Pictet-Spengler, and Pomeranz-Fritsch reactions are especially important.

Chart 1-2.

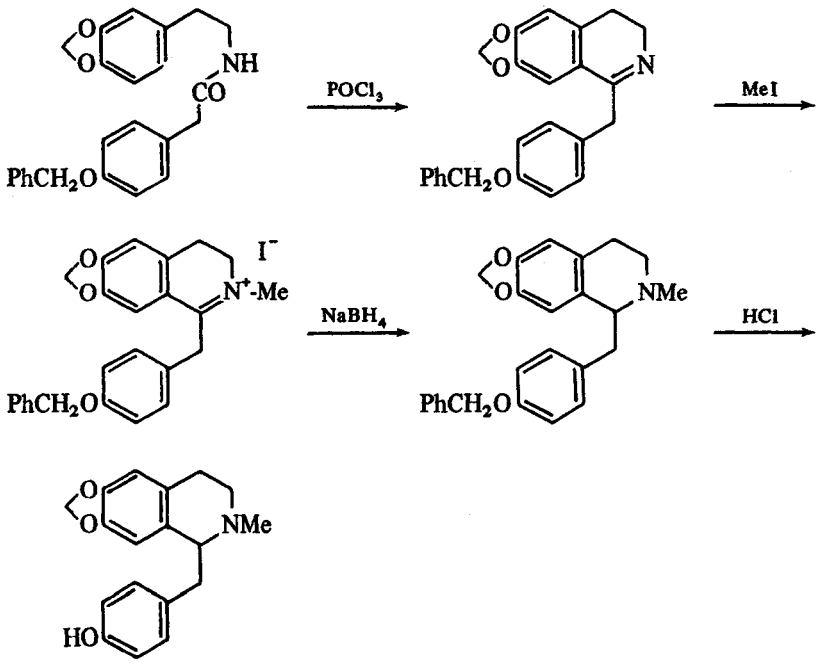


B. Type 1 Synthesis

Bischler-Napieralski Reaction[4] *(Chart 1-2)*

The Bischler-Napieralski route involves the cyclodehydration of an acyl derivative 1 of β-phenethylamine in the presence of a Lewis acid such as phosphoryl chloride or phosphorous pentoxide in an inert solvent to give a 3,4-dihydroisoquinoline 2, which must be reduced to a 1,2,3,4-tetrahydroisoquinoline 3 since the isoquinoline alkaloids[5] exist as the tetrahydro derivatives in most cases. For this purpose, 3,4-dihydroisoquinoline hydrochloride can be directly reduced with sodium borohydride to give the tetrahydroisoquinoline derivative 3.[6] When the *N*-methyl derivative 4 is desired, the Eschweiler-Clarke reaction of 3 with formalin and formic acid or sodium borohydride gives the expected *N*-methyl compound 4.[7] Reduction of the methiodide 5 of a 3,4-dihydroisoquinoline with sodium borohydride to 4 is also recommended.[8] Recently, cinnamolaurine was synthesized by this method as shown Chart 1-3A.[8a] On the other hand, the mild dehydrogenation of a 3,4-dihydroisoquinoline 2 can be

Chart 1-3A.

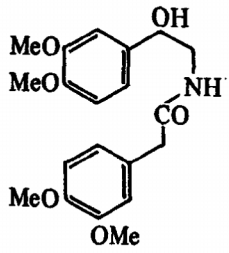


Cinnamolaurine

carried out to obtain the aromatic isoquinoline alkaloids such as papaverine 6.[9]

One of the most important modifications of the Bischler-Napieralski reaction was introduced by Pictet and Gams.[10] This reaction gives the isoquinoline derivative instead of the 3,4-dihydro-compound by cyclization of a β-hydroxy-β-phenethylamide 7 with phosphorous pentoxide. For example, papaverine 6 was obtained directly from 7 (Chart 1-3).

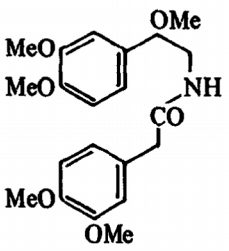
Chart 1-3.



7

Application of the Pictet-Gam's modification to β-methoxy-β-phenethylamide 7a also gives the isoquinoline derivatives 6, directly.[11] Therefore, the choice of the foregoing variation of the Bischler-Napieralski reaction should be made according to the availability of the starting amide (Chart 1-4).

Chart 1-4.

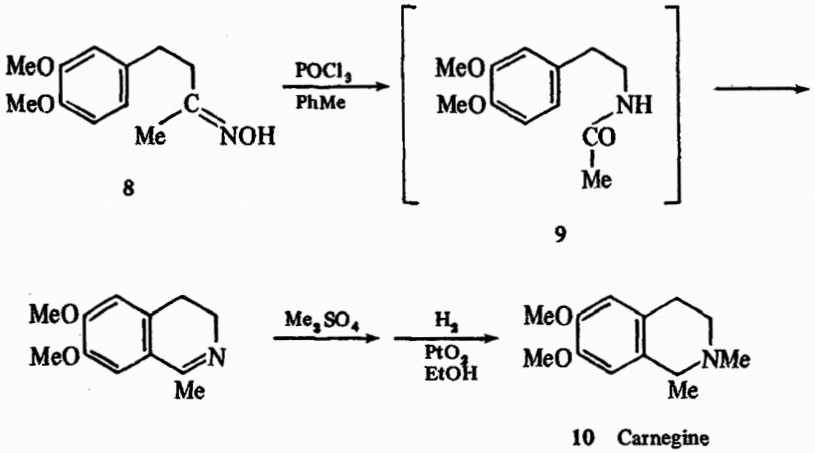


7a

Oximes 8, which could lead to *N*-acyl-β-phenethylamide 9 by Beckmann rearrangement, are also useful as starting materials for the Bischler-Napieralski route, a method applied to the synthesis of carnegine 10[12] (Chart 1-5).

These oximes are converted into the corresponding isoquinolines or 3,4-dihydroisoquinolines without isolation of the amides formed as intermediates.[13]

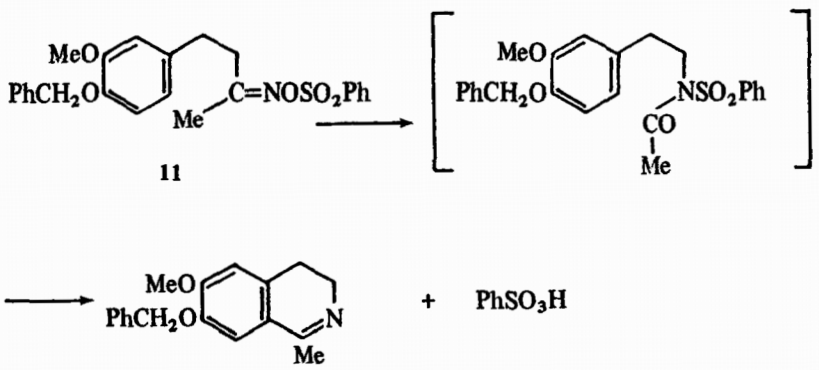
Chart 1-5.



8 9 10 Carnegine

The benzenesulfonyl ester **11** of an oxime undergoes cyclization to give the 3,4-dihydroisoquinoline derivative **12** by heating alone without any other reagent[14] (Chart 1-6). In some cases, the amidine, instead of the amide, is used

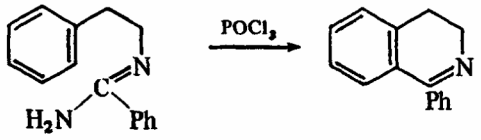
Chart 1-6.



11 12

for cyclization to give the phenanthridine derivatives in good yields.[15] Short and Brodrich[16] synthesized 3,4-dihydro-1-phenylisoquinoline **13** from amidine **14** by treatment with phosphoryl chloride (Chart 1-7).

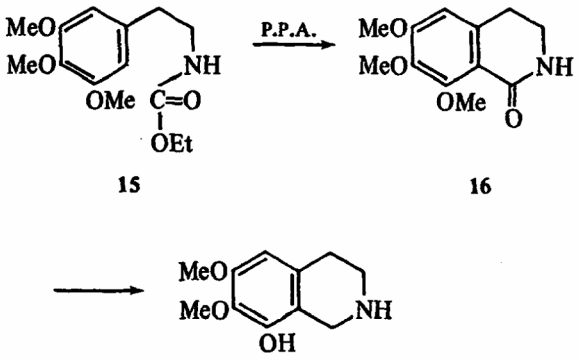
Chart 1-7.



14 13

N-β-Phenylethylurea and urethane derivatives are also useful for the syntheses of 3,4-dihydroisoquinolines having an amino or hydroxyl group at the C_1-position.[17] For example, an urethane **15** yields 3,4-dihydro-1-hydroxy-6,7,8-trimethoxyisoquinoline **16**,[18] which was converted into anhalamine **17** by Brossi[18] (Chart 1-8).

Chart 1-8.



15 16

17 Anhalamine

Similarly, the isocyante was converted into the isocarbostyril, which was transformed into haemanthidine and tazettine[18a] (Chart 1-8A).

Syntheses of β-Arylethylamides

Since the syntheses of *N*-acylarylethylamines are very important as starting materials for Bischler-Napieralski reaction, and representative synthetic methods to the amides are described as follows.[19,20]

Schotten-Baumann Reaction (Chart 1-9). This reaction involves an acylation of amines by treatment with an acyl chloride under ice-cooling in dilute alkaline solution. In the case of substances labile to strong alkali, weaker alkaline reagents such as sodium carbonate, bicarbonate, or triethylamine can be used. In some cases, an excess of amine is used to remove the resulting hydrogen chloride

Chart 1-8A.

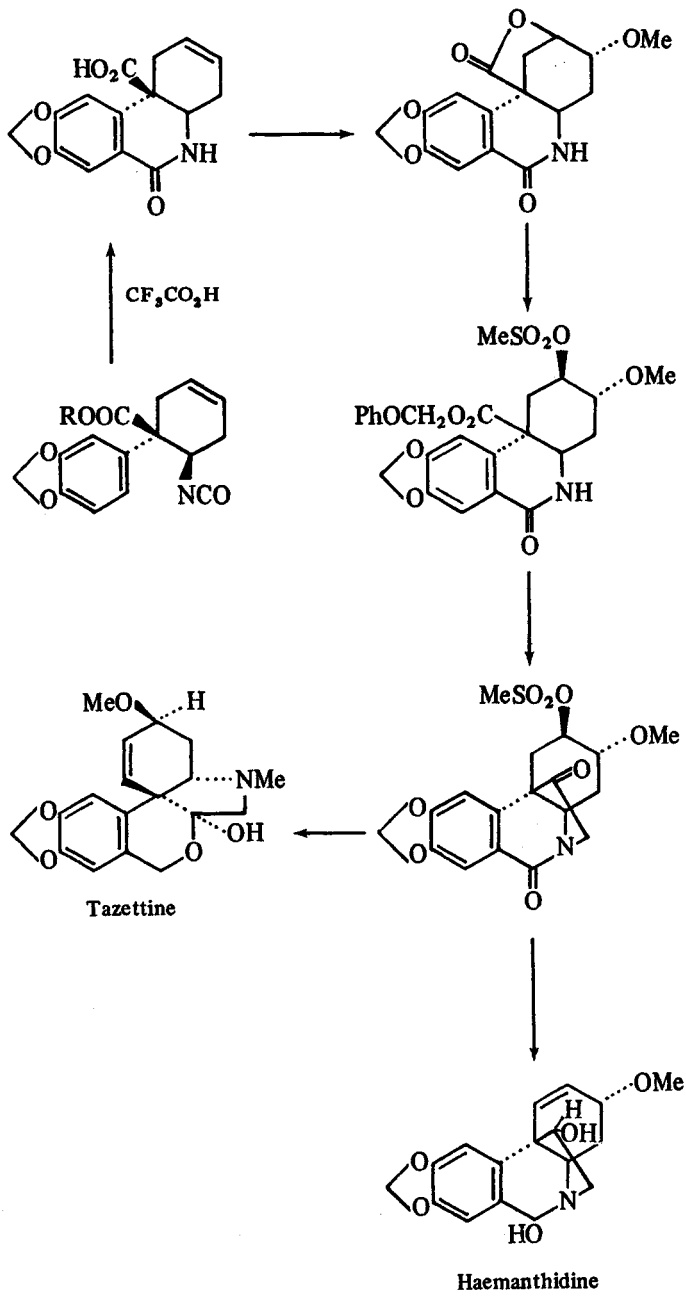
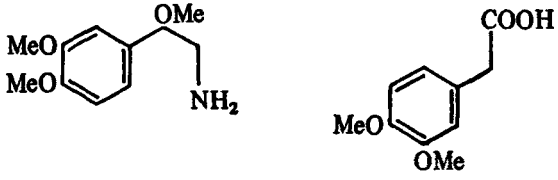

HO2C
NH
O
OMe
CF3CO2H
ROOC
NCO
MeSO2O
PhOCH2O2C
MeO
H
NMe
OH
Tazettine
HO
Haemanthidine

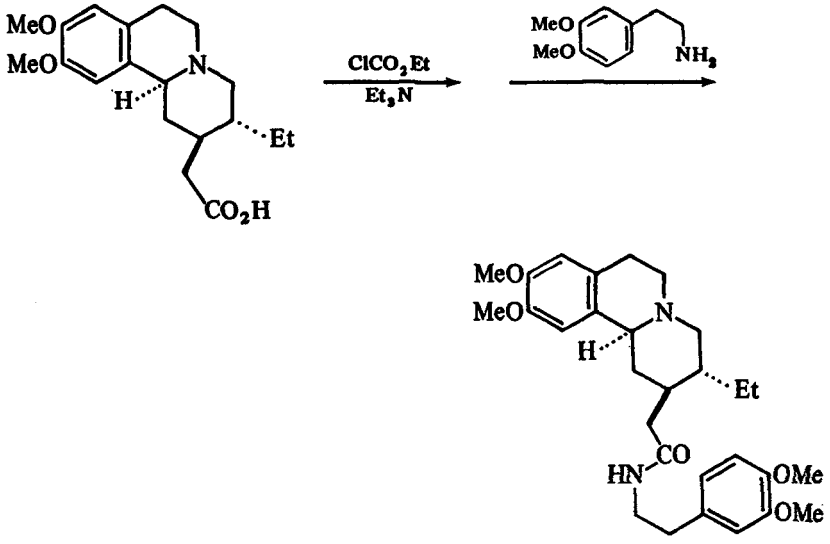
Chart 1-9.



18 19

as its hydrochloride. Acylation with acid chloride in anhydrous pyridine also gives the amide in good yield. Sugasawa directly synthesized papaverine 6 by heating a mixture of the amine 18 and carboxylic acid 19, without the isolation of the corresponding amide, in the presence of phosphoryl chloride.[21] The modification of this method was carried out by Battersby as follows.[21a] The carboxylic acid was treated with ethyl chlorocarbonate in the presence of triethylamine in dimethylformamide at $-5°$, and the resulting mixed anhydride, without isolation, was condensed with the homoveratrylamine at $-5\sim0°$ to afford the amide (Chart 1-10).

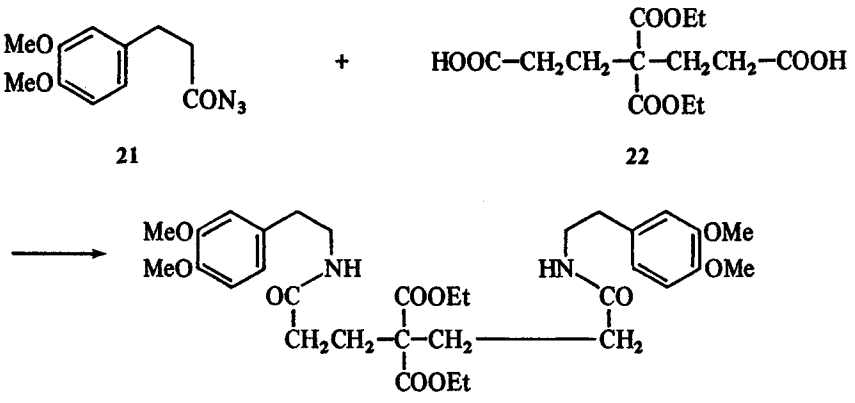
Chart 1-10.



The Condensation of a Carboxylic Acid with an Isocyanate (Chart 1-11). Amides, which are difficult to prepare by the Schotten-Baumann or other reactions, can often be obtained by the condensation of isocyanates with car-

boxylic acids. For instance, Sugasawa and Shigehara[22] prepared the amide 20 by the condensation of 2 moles of 3,4-dimethoxyhydrocinnamic acid azide 21 with γ,γ-ethoxycarbonylpimelic acid 22.

Chart 1-11.

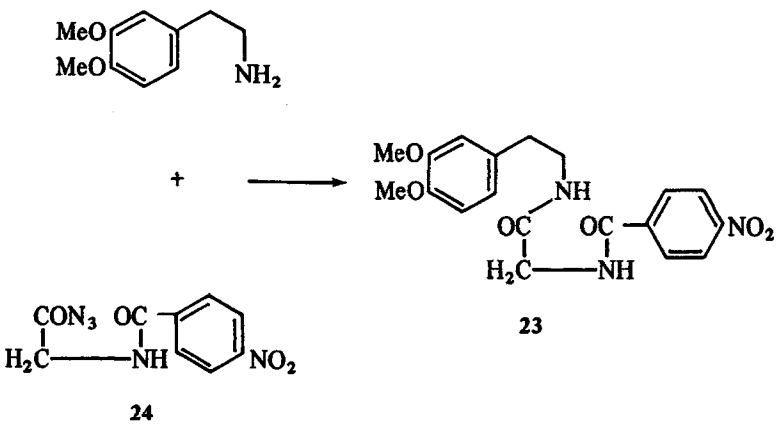


21 22

20

In this reaction, the azide 21 can be converted into the corresponding isocyanate as an intermediate by heating in benzene solution, and the resulting isocyanate can also be used for the condensation, but normally a mixture of the azide 21 and dicarboxylic acid is heated in benzene to give the amide 20 directly. When the materials are not dried completely the urea derivative is formed as a by-product.

Chart 1-12.



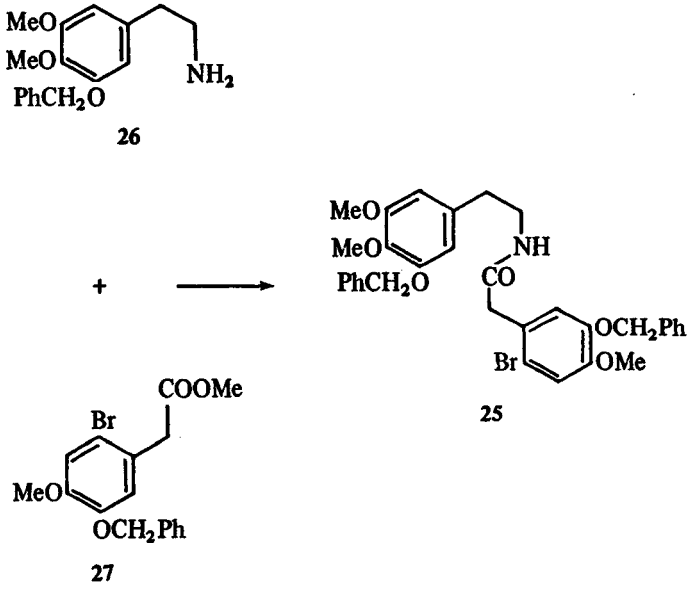
23

24

The Condensation of an Amine with an Azide (Chart 1-12). This procedure uses the acylation of the amine with azide in cold solvent. Since this reaction is quite different from the preceding method, it must be carried out without formation of isocyanate from the azide. For example, 4-nitrohippuro-β-veratrylethylamide 23 was prepared by the condensation between 4-nitrohippuric acid azide 24 and homoveratrylamine.[23]

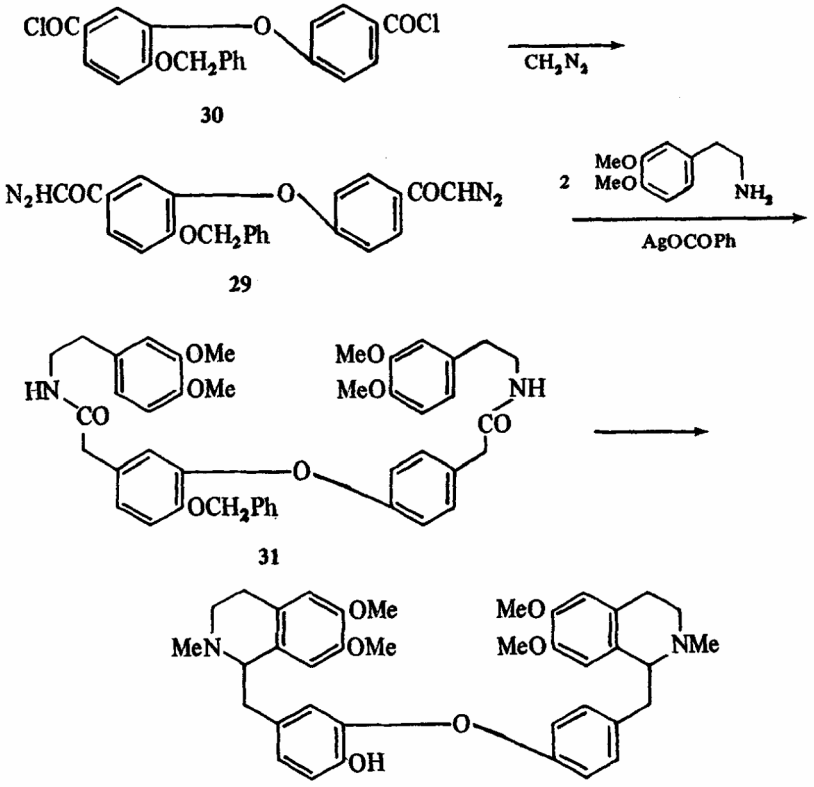
The Condensation Between an Ester and an Amine (Chart 1-12A). By heating or fusion of a mixture of an ester and an amine, the amide can be obtained easily. *N*-(3-Benzyloxy-4,5-dimethoxyphenethyl)-5-benzyloxy-2-bromo-4-methoxyphenylacetamide 25 was prepared from 3-benzyloxy-4,5-dimethoxyphenethylamine 26 with methyl 5-benzyloxy-2-bromo-4-methoxyphenylacetate 27.[24]

Chart 1-12A.



Application of the Arndt-Eistert Reaction (Chart 1-13). This procedure involves the conversion of an acid to the amide via the diazoketone prepared from an acid chloride. In the presence of a suitable catalyst, such as colloidal silver, platinum, or copper, the diazoketone produces a ketene that reacts with an amine, leading to the formation of the corresponding amide. For example, Kametani prepared the amide 31 for the synthesis of dauricine 28. The diazoketone 29 prepared from acid chloride 30 was reacted with homoveratrylamine

Chart 1-13.

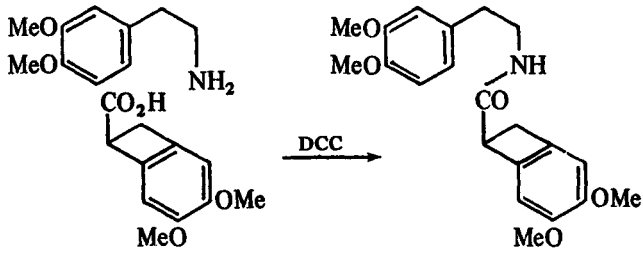


28 Dauricine

to give the corresonding amide 31.[25] This type of a double Bischler-Napieralski reaction is used for a synthesis of *O*-methyldauricine[25a] and cepharanthine.[25b]

Other Amide Syntheses. Beckmann rearrangement of an oxime can also give an amide, and, in many instances, further cyclization to isoquinoline is known to occur during the course of the foregoing reaction.[12] Furthermore, a mixture of arylethylamine and carboxylic acid gives the corresponding amide on heating to 170 to 180°.[26] On the other hand, Ritter and Murphy[27] obtained the 3,4-dihydro-3-methylisoquinoline from the nitrile and an allylbenzene in the presence of concentrated sulfuric acid, but not the amide. When the amine and/or carboxylic acid are susceptible to acid, base, or heat, a mixture of the amine and carboxylic acid is treated with dicyclohexylcarbodiimide as a condensation reagent in methylene dichloride at room temperature in order to obtain the corresponding amide (Chart 1-13A).[27b]

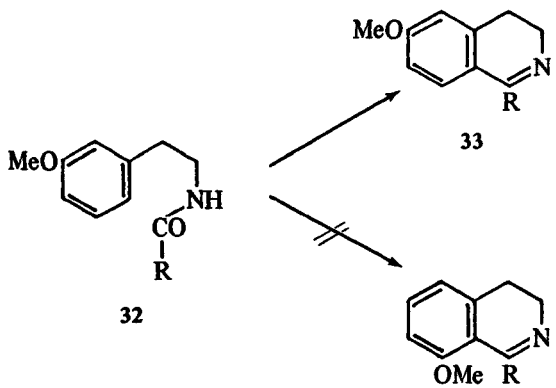
Chart 1-13A.



Direction of Ring Closure (Chart 1-14)

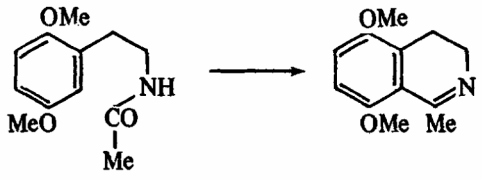
Cyclization of *m*-methoxy-β-phenethylamide 32 would be expected to give either 6-methoxy- or 8-methoxy-3,4-dihydroisoquinoline depending on the direction of ring closure. When the *para* position to the methoxyl group has no substituent, cyclization preferentially occurs at the *para* to give a 6-methoxy-isoquinoline derivative 33. When the *para* position is blocked, cyclization will proceed to the *ortho* position to the methoxyl group. For instance, *N*-acetyl-2,5-dimethoxyphenethylamine 34 was readily converted to 3,4-dihydro-5,8-dimethoxy-1-methylisoquinoline 35[27a] (Chart 1-15).

Chart 1-14.



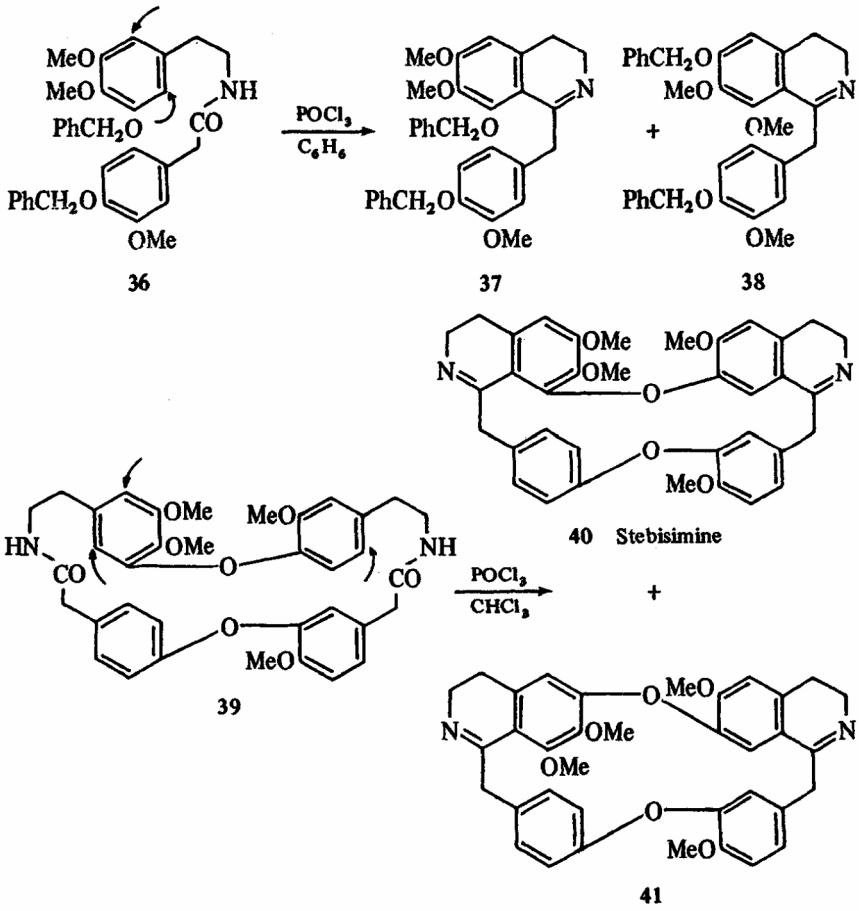
If both available positions are activated to a similar extent, a mixture of both cyclized products is obtained, as in the case of cyclization of *N*-(3-benzyloxy-4,5-dimethoxyphenethyl)-4-benzyloxy-3-methoxyphenylacetamide 36 to the 8-benzyloxy-6,7-dimethoxy- 37 and 6-benzyloxy-7,8-dimethoxy-3,4-dihydroisoquinoline derivative 38.[28] Moreover, the cyclic bisamide 39 also gave stebisimine

Chart 1-15.



34 35

Chart 1-16.



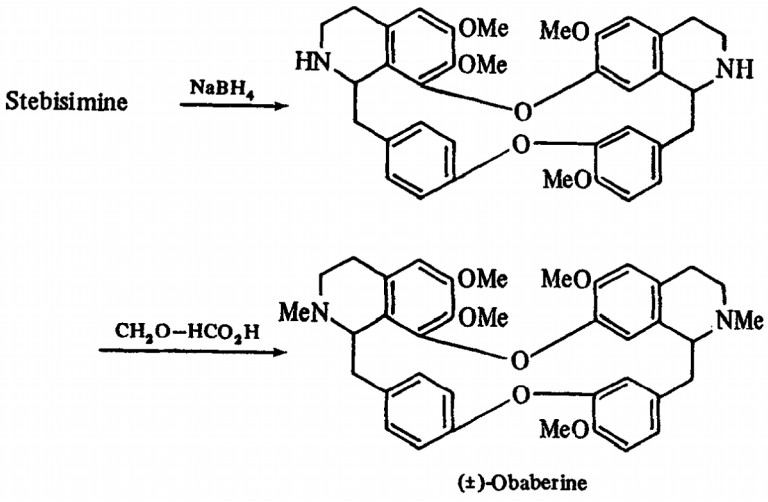
36 37 38

40 Stebisimine

39

41

Chart 1-16A.



(±)-Obaberine

40 and its isomer 41 on cyclization[29] (Chart 1-16). Stebisimine was converted into obaberine by reduction and methylation[29a] (Chart 1-16A).

In an attempt to synthesize a berberine, the formamide 42 was treated with phosphoryl chloride to yield the bromine-free compound 43 rather than the expected bromodihydroberberine 43a. This result is a remarkable instance of the preferred direction of ring closure, a bromine atom being removed to allow cyclization to proceed at the *para* position to the electron-releasing group.[30] However, Kametani has assumed that the replacement of methoxyl by hydroxyl offsets the inactivation of the nucleus caused by the I-effect of the bromine atom, leading to the cyclization at the *ortho* position to the hydroxyl group. Thus N-(2-bromo-5-hydroxy-4-methoxyphenethyl)-4-methoxyphenylacetamide gave the 5-bromo-3,4-dihydro-8-hydroxy-7-methoxyisoquinoline derivative by the action of phosphoryl chloride in chloroform, which was converted into petaline 44 by the standard method. Recently, 8-oxygenated isoquinoline derivatives were obtained in the cyclization of *trans-N*-[2-(3-methoxyphenyl)cyclohexyl]-benzamide, but the main product was 6-methoxyisoquinoline derivative[30a] (Chart 1-17). Moreover, Tani[30b] achieved a cyclization of the formamide to the expected bromodihydroprotoberberine and succeeded in a synthesis of cheilanthifoline. This route provides a useful method for the total synthesis of the 9,10-disubstituted protoberberine alkaloids (Chart 1-17A).

This method is applied to the synthesis of caseadine-type compounds.[30c] Moreover, this problem was circumvented by using an ethoxycarbonylamino-β-phenethylamide in order to activate the *para* position and thus to effect the required

Chart 1-17.

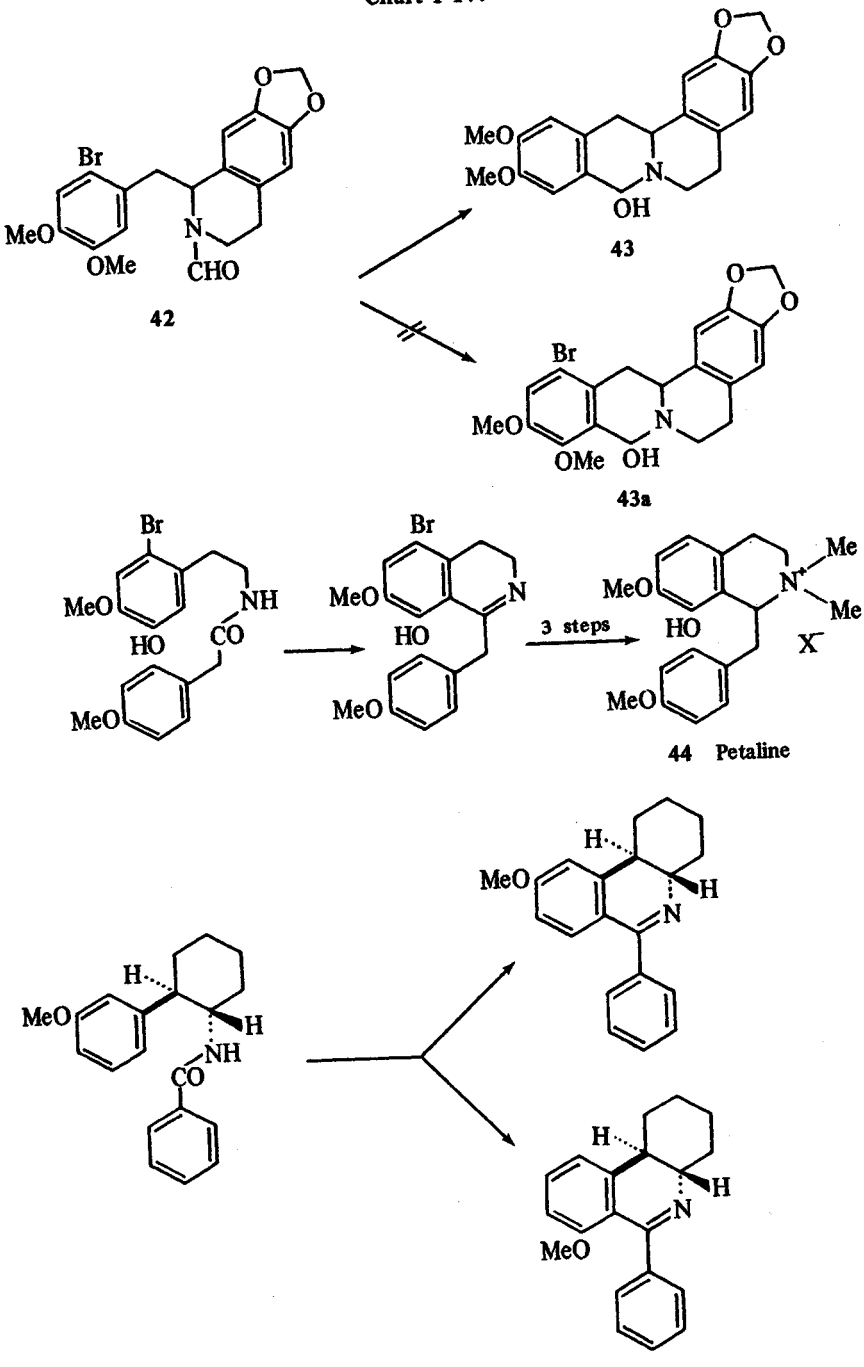
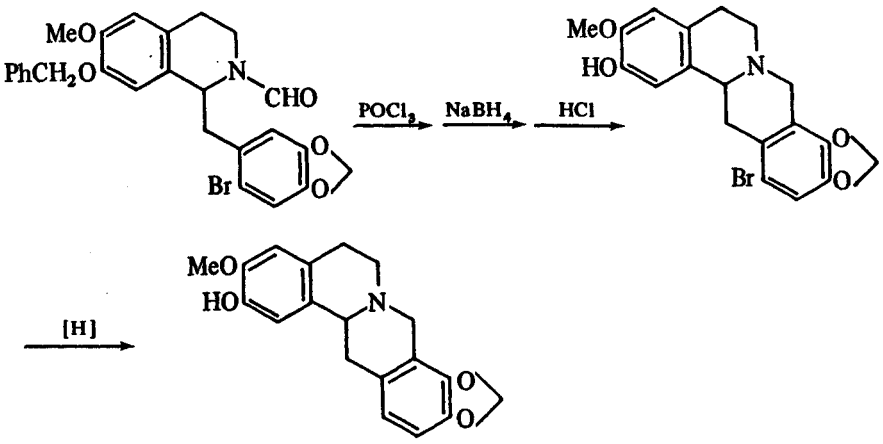

Br
MeO
OMe
N
CHO
42
MeO
MeO
OH
43
Br
MeO
OMe
OH
43a
Br
MeO
NH
HO
CO
MeO
Br
MeO
HO
N
MeO
3 steps
MeO
HO
N+
Me
Me
X-
MeO
44 Petaline
H
MeO
H
N
H
MeO
NH
CO
H
MeO
H
N
H
MeO

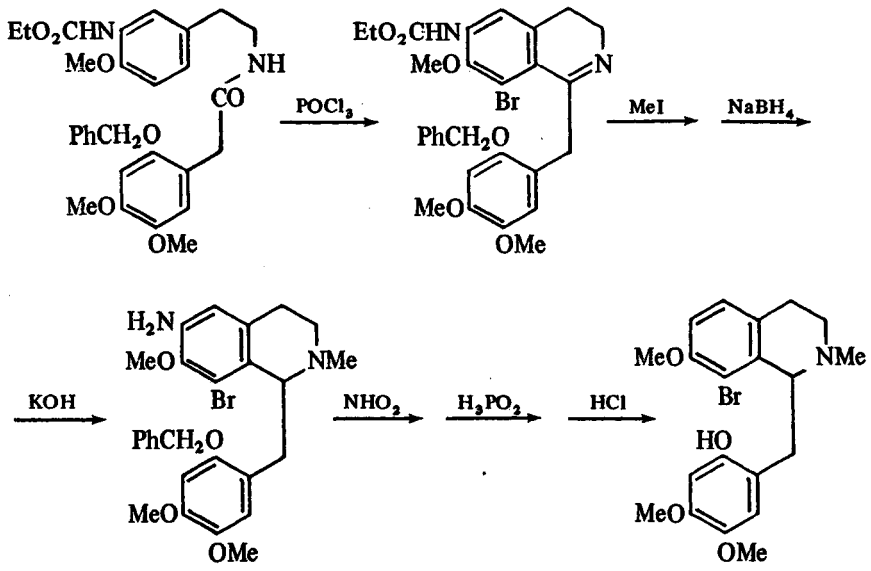
Chart 1-17A.

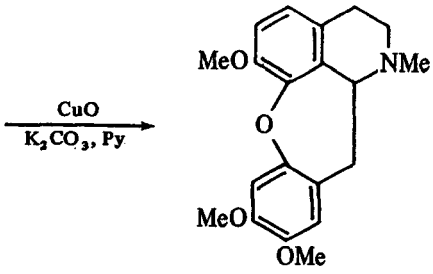


Cheilanthifoline

cyclization reaction. Conventional steps then led to the phenolic isoquinoline, which gave (±)-cularine[30d] under Ullmann reaction (Chart 1-17B).

Chart 1-17B.



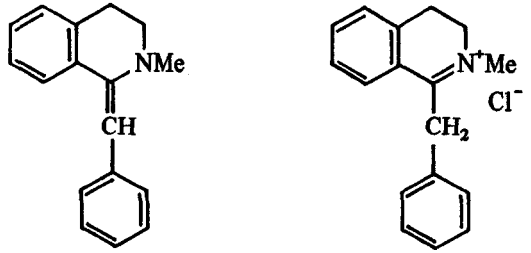


Cularine

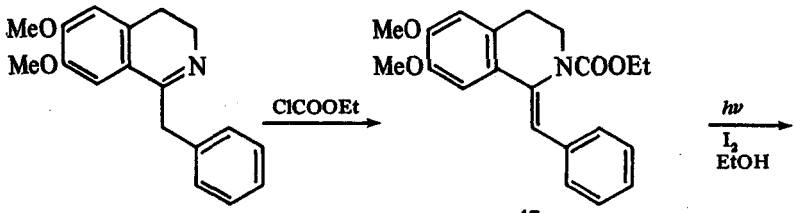
Position of the Double Bond

In most Bischler-Napieralski reactions, 3,4-dihydroisoquinolines are obtained; the double bond is formed between the carbonyl carbon and the nitrogen atom in the cyclodehydration. The presence of an active methylene group at the C_1-position in the compounds analogous to **45b** allows the double bond to become exocyclic in the free base, as in 1-benzal-1,2,3,4-tetrahydro-2-methylisoquinoline **45a**, whose color is yellow because of the extended conjugation. Cava synthesized an aporphine **46** by photooxidation of this type of isoquinoline **47**[31] (Chart 1-18).

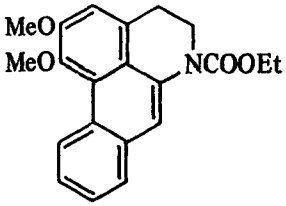
Chart 1-18.



45a **45b**



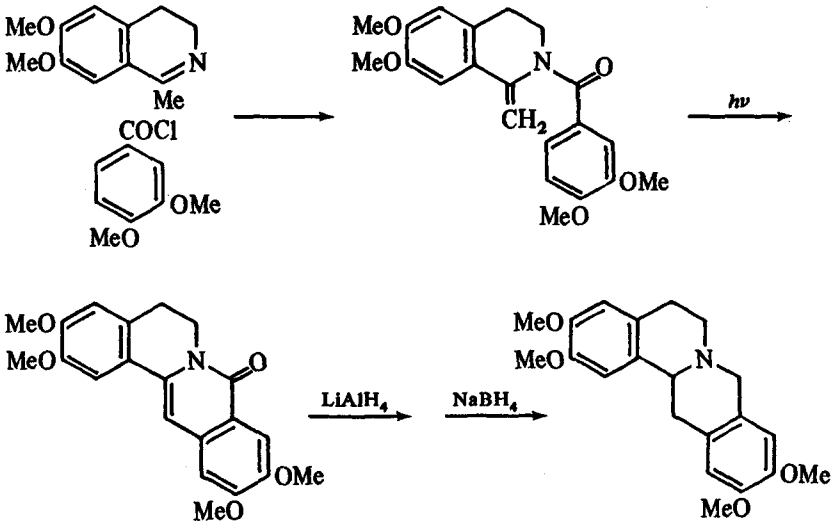
47



46

Ninomiya also synthesized a protoberberine alkaloid, xylopinine, by a photolysis of the exo-methylene compound derived from 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline and veratric acid[31a] (Chart 1-18A).

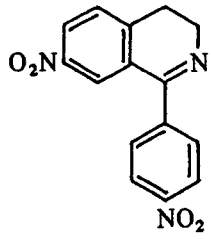
Chart 1-18A.



Peculiarities

The Bischler-Napieralski reaction is an electrophilic attack on the benzenoid ring of the β-phenethylamine, and the reactivity of the aromatic nucleus depends upon electron density increased at the cyclized position. Hence a β-phenethylamine that has alkoxyl group at the *meta* position can be cyclized easily, and it is clear that an electron-attracting group such as nitro group will inhibit this reaction. Nevertheless, the 3,4-dihydroisoquinoline derivative[32] **48** was prepared in 13% of the yield (Chart 1-19).

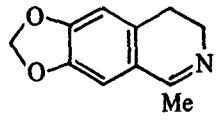
Chart 1-19.



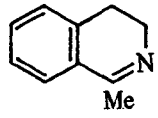
48

On the other hand, it is more obvious that an electron releasing group has an influence on the cyclization in the synthesis of 3,4-dihydroisoquinolines. For example, the yield of 3,4-dihydro-1-methyl-6,7-methylenedioxyisoquinoline[33] **49** is better than that of 3,4-dihydro-1-methylisoquinoline[34] **50** under the same conditions (Chart 1-20).

Chart 1-20.



49

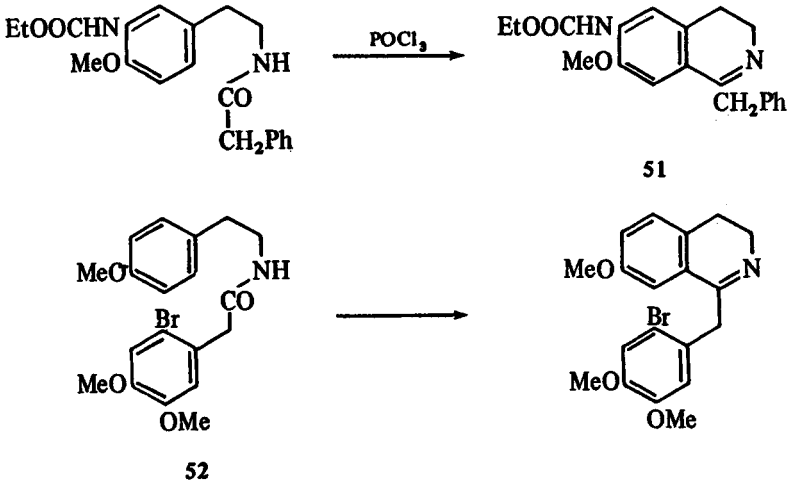


50

The influence of the other groups besides an alkoxyl group was examined in some cases. For example, 1-benzyl-6-ethoxycarbonylamino-3,4-dihydro-7-methoxyisoquinoline **51** has been prepared in good yield,[35] but the cyclization of *N*-(4-methoxyphenethyl)phenylacetamide was very difficult. Under the special condition using phosphorus pentoxide absorbed on Celite, cyclization of **52** gave the 3,4-dihydroisoquinoline in poor yield[35a] (Chart 1-21).

In general, the Bischler-Napieralski reaction is carried out by heating the appropriate amide with a dehydrating reagent in the presence of an inert and anhydrous solvent, such as chloroform, acetonitrile, benzene, toluene, xylene, nitrobenzene, or tetralin according to its boiling point. Cyclization is often carried out in the presence of an excess of phosphoryl chloride without solvent.

Chart 1-21.



Phosphoryl chloride is the most popular dehydrating agent, but phosphorus pentoxide and pentachloride are also important in specific cases. Furthermore, various reagents such as polyphosphoric acid and its ester have been found to be useful.[35b]

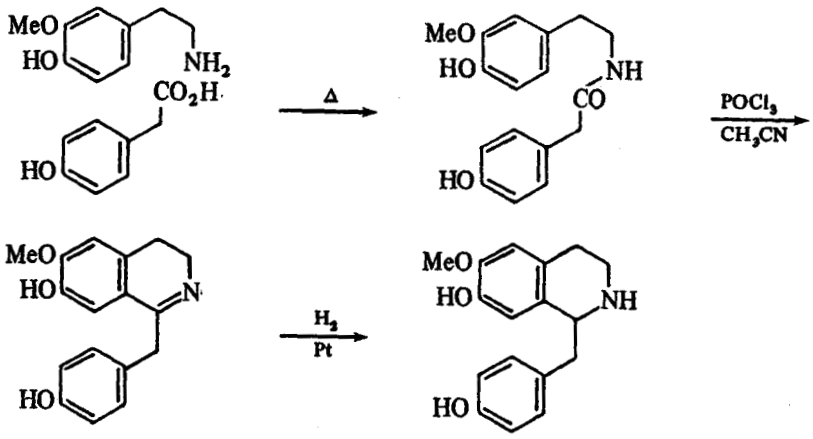
Brossi and Teitel reported an improved synthesis of the phenolic benzylisoquinolines without protection of the hydroxy-group, in which Bischler-Napieralski reaction of the appropriate amide is achieved with phosphoryl chloride in chloroform or acetonitrile. In this fashion, coclaurine is obtained in 61% of the overall yield from the phenolic amine, isococlaurine and reticuline have been prepared in this way[35c] (Chart 1-21A).

Application of Bischler-Napieralski Reaction to the Total Synthesis of the Isoquinoline Alkaloids

Cherylline. Resolution of the β-(*p*-benzyloxyphenyl)homoveratrylamine with (-)-diacetone-5-keto-L-gulonic acid gave the (2R)-(+)- and (2S)-(-)-L-gulonate salts, which were transformed into the diastereomeric hydrobromides. The latter were formylated and subjected to Bischler-Napieralski reaction to give the 3,4-dihydroisoquinolines, which were debenzylated to yield the (4R)-(+)- and (4S)-(-)-dihydroisoquinoline hydrochlorides. The latter was selectively *O*-demethylated by 48% hydrobromic acid, quaternized with methyl iodide, and reduced with sodium borohydride to give (-)-cherylline[35d] (Chart 1-21B).

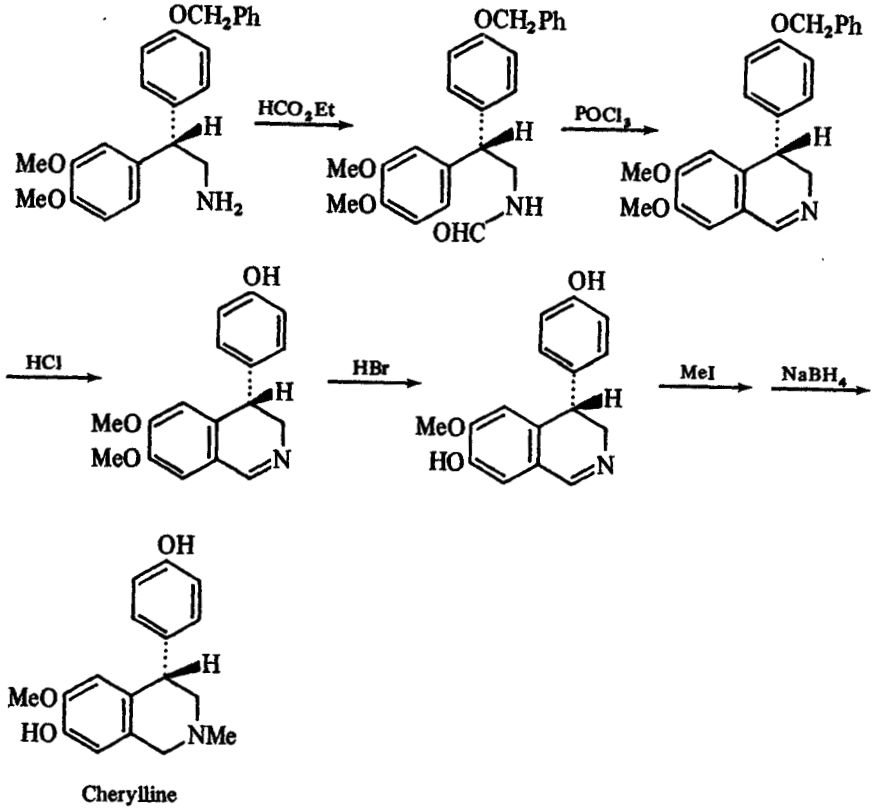
Phenylisoquinoline Alkaloids. (+)-Cryptostyline I, II, and III have been synthesized by the Bischler-Napieralski reaction and sodium borohydride reduction, followed by a resolution using (-)-diacetone-2-keto-L-gulonic acid and reductive *N*-methylation[35e] (Chart 1-21C).

Chart 1-21A.



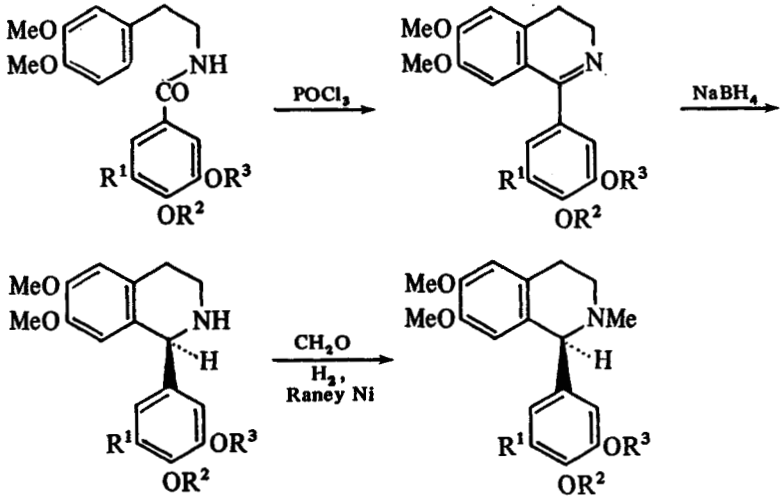
Coclaurine

Chart 1-21B.



Cherylline

Chart 1-21C.

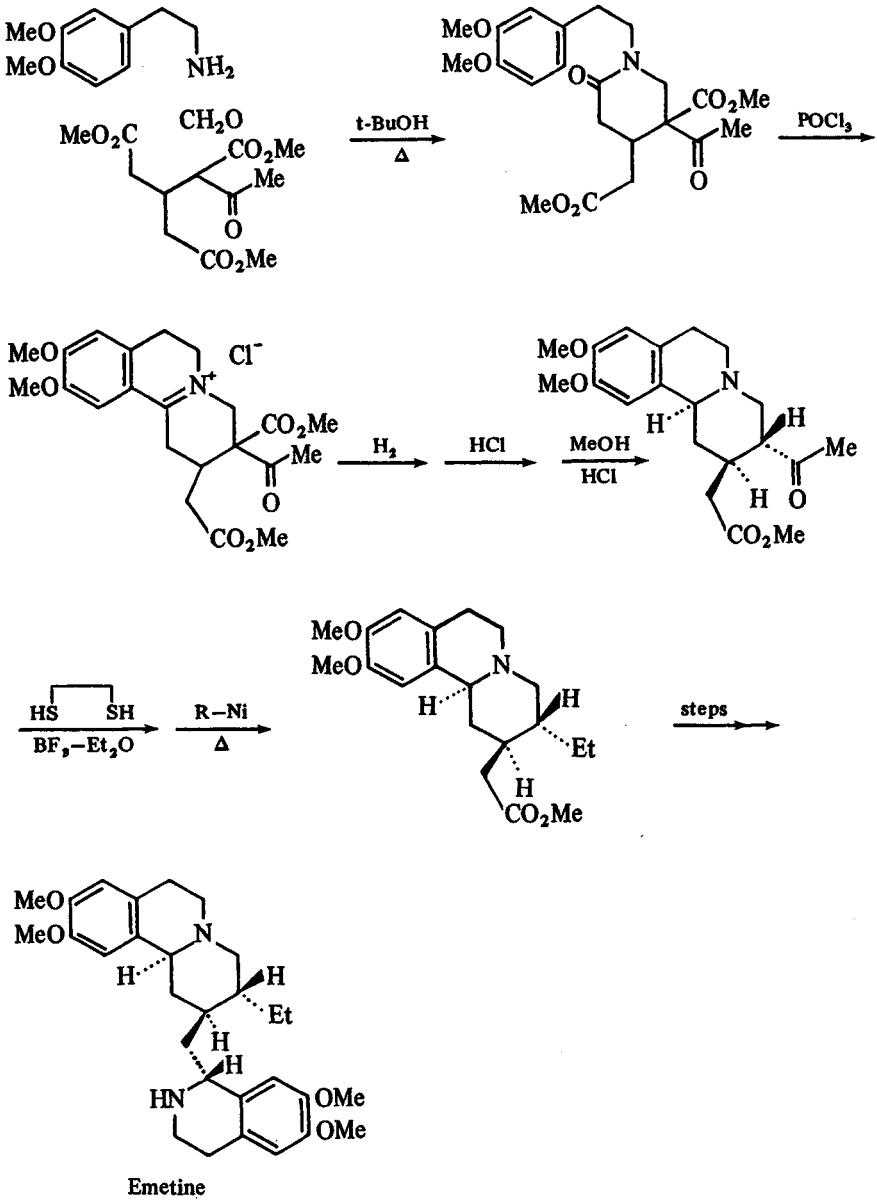


Emetine. The lactone, obtained by a Mannich-type condensation of homoveratrylamine with keto triester and formalin, was subjected to Bischler-Napieralski reaction to give the benzoquinolizidine derivative. The remainder of the synthesis followed the usual way to afford the tricyclic ester, which had been converted into emetine[35f] (Chart 1-21D).

Bisbenzylisoquinoline Alkaloids. In a synthesis of the bisbenzylisoquinoline alkaloids, tetrandrine, isotetrandrine, and phaeanthine, the bases A and B were prepared by successive Ullmann reactions, and the latter was converted into the macrocyclic lactam, which was subjected to a Bischler-Napieralski reaction, *N*-methylation, and reduction[35g] (Chart 1-21E).

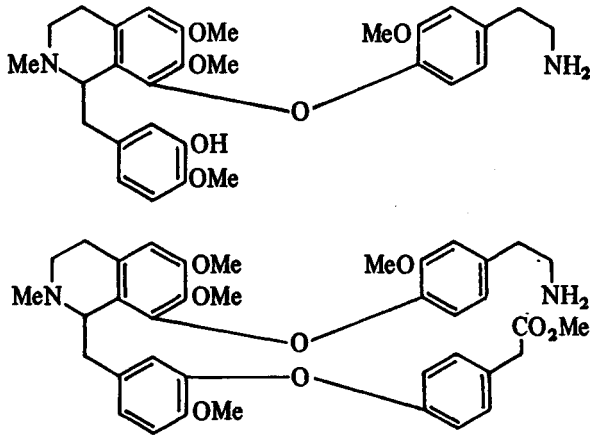
For example, *O*-methylthalicberine was synthesized as follow. The norlaudanidine derivative, prepared via a Bischler-Napieralski condensation, was resolved, and the (S)-(+)-chiral substance was subjected to Ullmann reaction with *N*-butoxycarbonyl-3-hydroxy-4-methoxyphenethylamine to yield a biphenyl ether. Hydrogenolysis, followed by a second Ullmann reaction with methyl *p*-bromophenylacetate, gave the *bis*-diphenyl ether, which was converted into the *p*-nitrophenyl ester, and the latter, after removal of the *t*-butoxycarbonyl group, was cyclized to a macrocyclic lactam. Bischler-Napieralski reaction of this followed by sodium borohydride reduction gave *O*-methyl-*N*-northalicberine as a single product, indicating that the latter reaction had proceeded stereoselectively. *N*-Methylation gave the naturally occurring alkaloid *O*-methylthalicberine[35h] (Chart 1-21F).

Chart 1-21D.



Emetine

Chart 1-21E.



Tubocurarine iodide and its isomers have been prepared by a double Bischler-Napieralski reaction, followed by debenzylation, Ullmann reaction and quaternization[35f] (Chart 1-21G).

The occurrence of the dibenzo-*p*-dioxan unit in (±)-*O*-methyltiliacorine presented problems not encountered in the synthesis of other dimeric benzylisoquinoline alkaloids. Attempts to effect a double Bischler-Napieralski reaction of the bisamide under vigorous conditions were synthetically very inefficient, but milder conditions gave the monocyclized product. Possibly, as a result of less

Chart 1-21G.

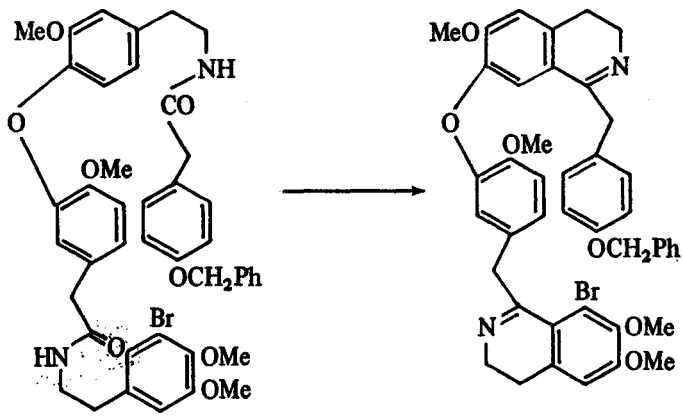
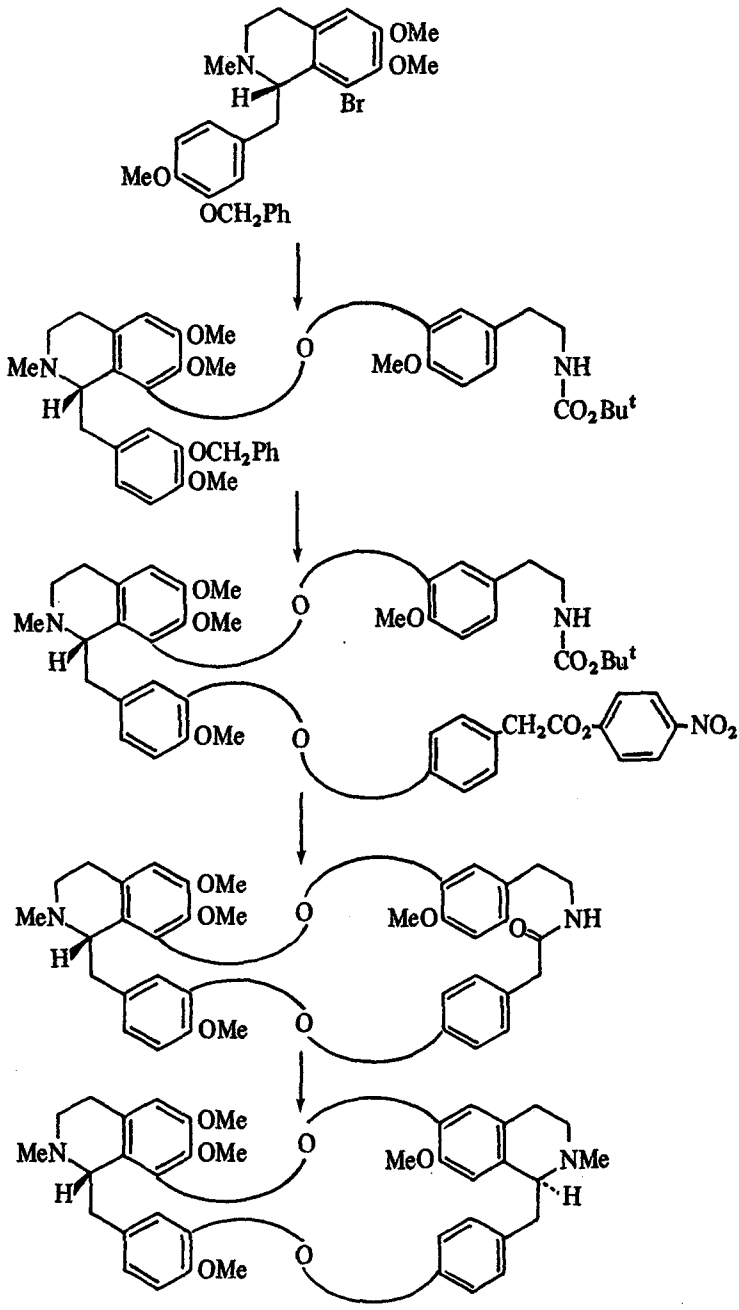


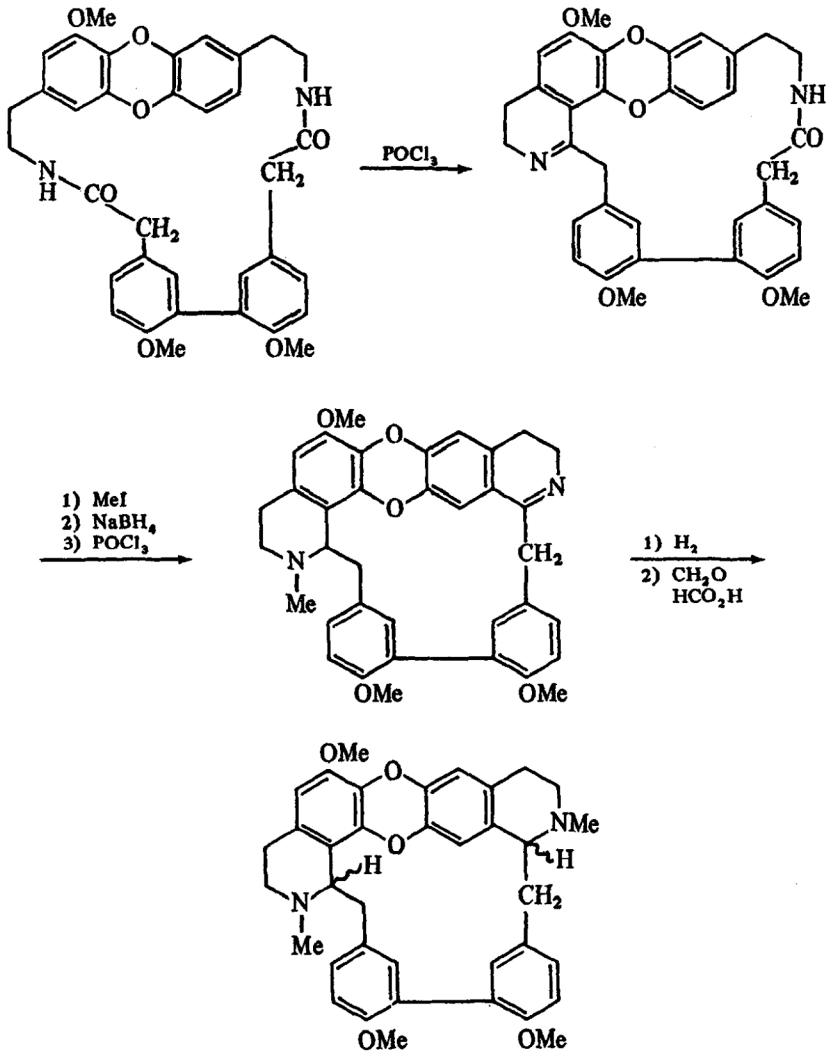
Chart 1-21F.



O-Methylthalicberine

molecular flexibility in the monocyclized compound in comparison to a starting bisamide, the second Bischler-Napieralski cyclization could now be effected under forcing conditions to yield the bicyclized product. Reduction and methylation yielded a diastereoisomeric mixture, from which (±)-*O*-methyltiliacorine could be isolated as the major product, thus completing the synthesis. Other alkaloids

Chart 1-21H.



O-Methyltiliacorine