A TOTAL SYNTHESIS OF PROTOBERBERINE ALKALOIDS

by

© ROBERT HARRY FICHTNER, B.Sc.

A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfilment of the Requirements

for the Degree

Master of Science

McMaster University

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A TOTAL SYNTHESIS OF PROTOBERBERINE ALKALOIDS

To my mother, who is simply the nicest person I've ever known; and to my late grandmother, who would have been so proud to see this in print.

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ABSTRACT

The synthesis of protoberberines developed in this laboratory by Kiparissides has been studied in greater detail. The key intermediate in this synthesis is formed by the condensation of 3,4-dihydro-6,7-dimethoxy-N-(2,3-dimethoxybenzyl)-isoquinolinium chloride with the anion of methyl methylthiomethylsulfoxide. Careful chromatography of the product has established that it is a complex mixture of diastereomers. The separated fractions were individually cyclized to dihydropalmatine chloride, which was isolated in crystalline form directly from the reaction mixture. This quarternary salt was reduced directly to tetrahydropalmatine, and also used in the synthesis of corydaline.

This work has also shown that isoquinolines may be substituted for 3,4-dihydroisoquinolines as starting materials in the synthetic sequence.

ACKNOWLEDGEMENTS

I have always said that five minutes with Professor MacLean were worth as many days in the library. His scholarship in science must only be compared to his warm hospitality and knowledge of good wines and restaurants.

I remain indebted to the following international group of colleagues who taught me the art of organic synthesis, and allowed me to sample their culture and friendship: Drs. Janusz Popławski (Poland), Luis Contreras (Venezuela), Louise Hellwig (U.S.A.), Peter Buist (Canada), Andrzej Leniewski (Poland), and Jean-Pierre Ruder (Switzerland).

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I am very grateful to my sister Linda for doing such a super job of the typing of this thesis, and her help with the diagrams.

My love and appreciation go to my Mother, who knew no chemistry, but always listened.

I thank the Department of Chemistry, McMaster University, for generous financial support.

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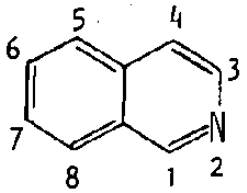
CHAPTER 1

INTRODUCTION

1.1 Historical Background

Alkaloids are naturally occurring nitrogenous bases, widely distributed in plants. These compounds are usually heterocyclic, and can display a variety of structural features.

Of interest in this thesis are specific members of the protoberberine group of alkaloids. These compounds belong to the isoquinoline family of alkaloids, and contain within their structures an isoquinoline 1 or hydroisoquinoline ring system. For the purpose of nomenclature, they are considered derivatives of the dibenzo [a, g] quinolizidine system 2.



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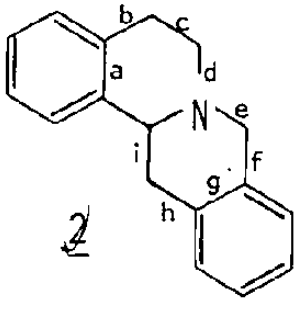

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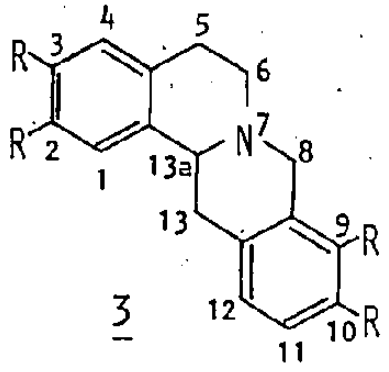
In nature, most protoberberine alkaloids exist either as tetrahydroprotoberberines 3, or as quarternary berberinium salts 4.



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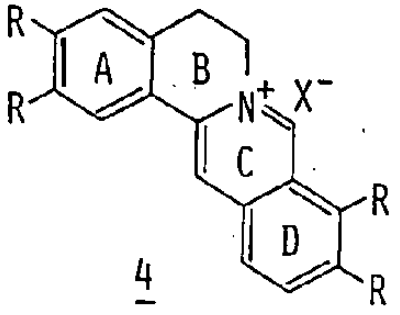


4

R = -OH, -OCH_3, -O-CH_2-O-

Substituents are usually present at C-2 and C-3 on aromatic ring A, and either at C-9 and C-10 or at C-10 and C-11 of aromatic ring D, the former being more common. Also known are compounds where a hydroxyl or methoxyl substituent is present at C-1, and an alcoholic hydroxyl may be found at C-13 or at C-5. In some protoberberines, a methyl group is present at C-8 or C-13, and more recently, quarternary N-methyltetrahydroprotoberberine salts, as well as N-oxides have been reported (1, 2).

The final step in the structural elucidation of natural products was traditionally the total synthesis. Although modern instrumental

techniques can now be used to determine unambiguously both the structure and stereochemistry of natural products, synthetic studies still present a challenge to the organic chemist. In the context of this thesis, they are useful for the development of new synthetic reactions and intermediates, and in the synthesis of non-naturally occurring isomers.

In assembling the protoberberine skeleton, three classical synthetic reactions are commonly used, as well as numerous comtemporary methods, one of which has been developed in our laboratories in recent years. The three traditional synthetic routes to protoberberines will now be examined, followed by a brief summary of some of the more contemporary methods.

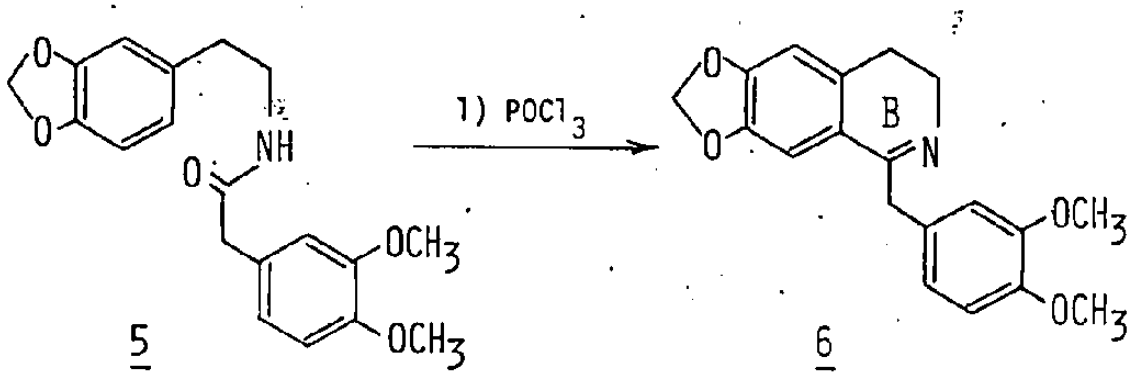
1.2 Traditional Synthetic Routes to the Protoberberines

The three synthetic reactions which are of interest here are the Bischler-Napieralski reaction (3), the Pomeranz-Fritsch cyclization (4, 5) and the Pictet-Spengler synthesis which is now recognized as a specific example of the Mannich reaction (6).

1.2.1 The Bischler-Napieralski Reaction

This reaction consists of a dehydrative cyclization which can be used (a) to form ring B from an amide 5 and yield a benzylisoquinoline intermediate 6, or (b) to form ring B from a lactam 7 in the final step of construction of the protoberberine skeleton.

(a)



5 6

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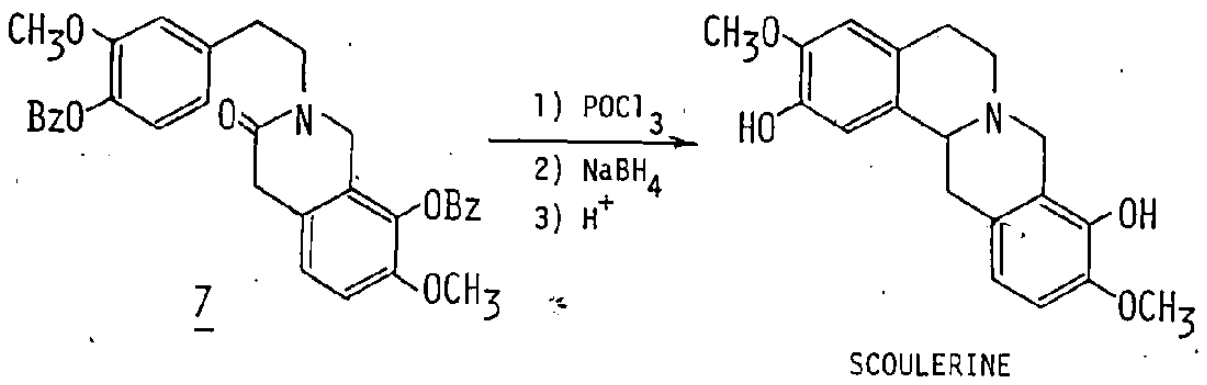
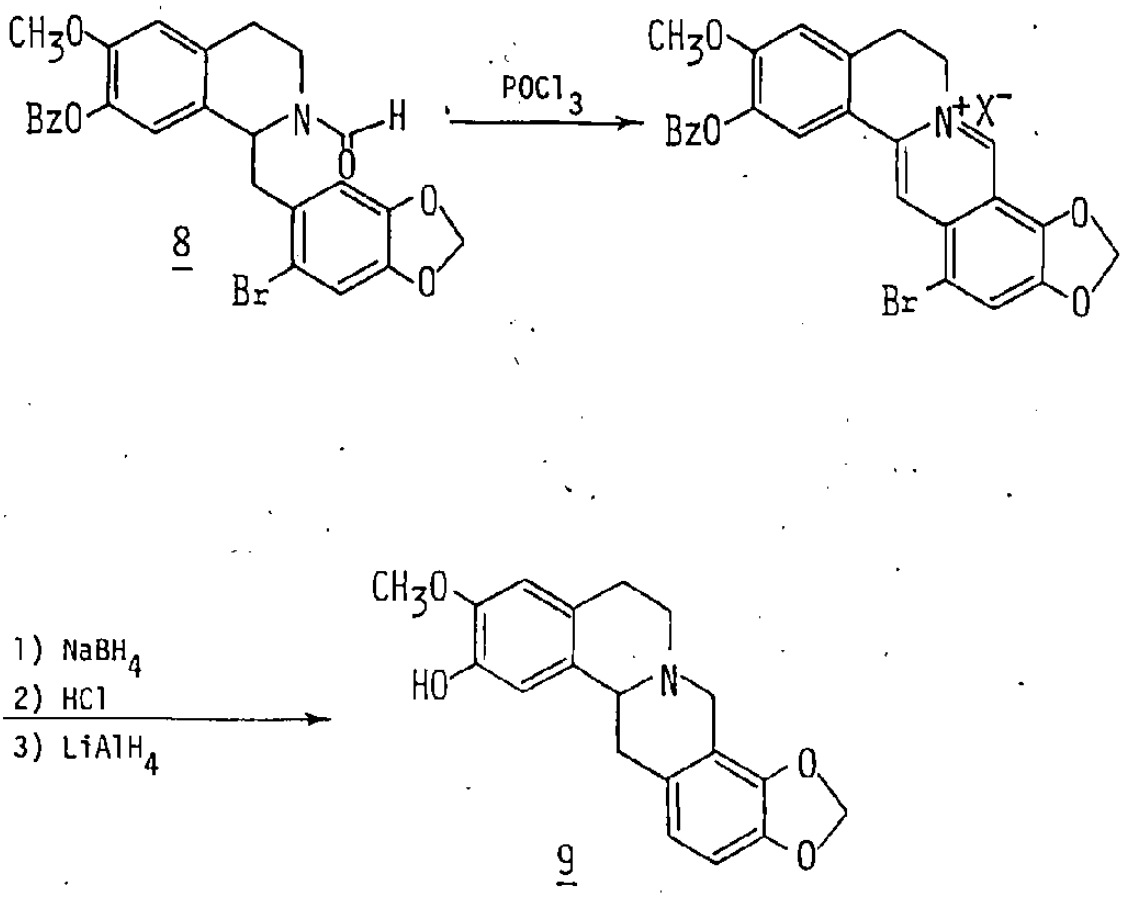


7

SCOULERINE

Tani and co-workers (7) in a more recent application of the Bischler-Napieralski reaction, have used the brominated tetrahydrobenzylisoquinoline formamide 8 to ring-close regiospecifically to yield the desired 2,3,9,10-substitution pattern required in the total synthesis

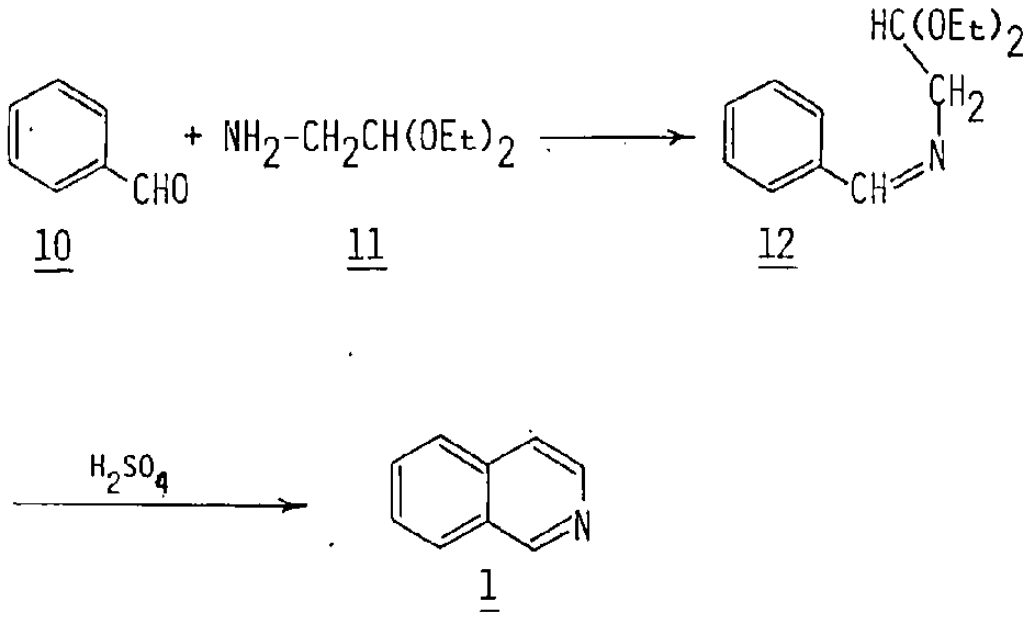
of cheilanthifoline 9 (Scheme 1).



SCHEME 1

1.2.2 The Pomeranz-Fritsch Cyclization

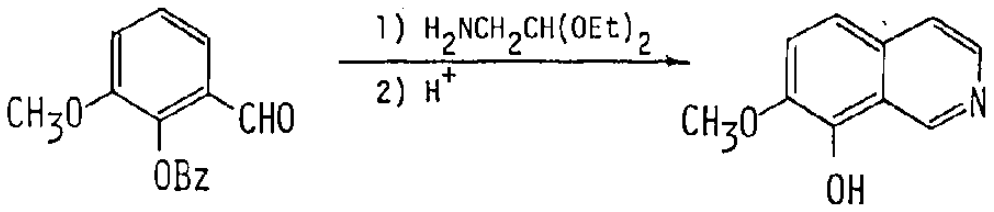
This reaction, as proposed independently by Pomeranz (4) and Fritsch (5), was a two-step synthesis to isoquinoline 1. In the first step, a Schiff base 12 is formed by the reaction of benzaldehyde 10 with aminoacetaldehyde diethyl acetal 11. Cyclization of the benzylaminoacetal was effected with sulfuric acid (Scheme 2).



10 11 12 1

SCHEME 2

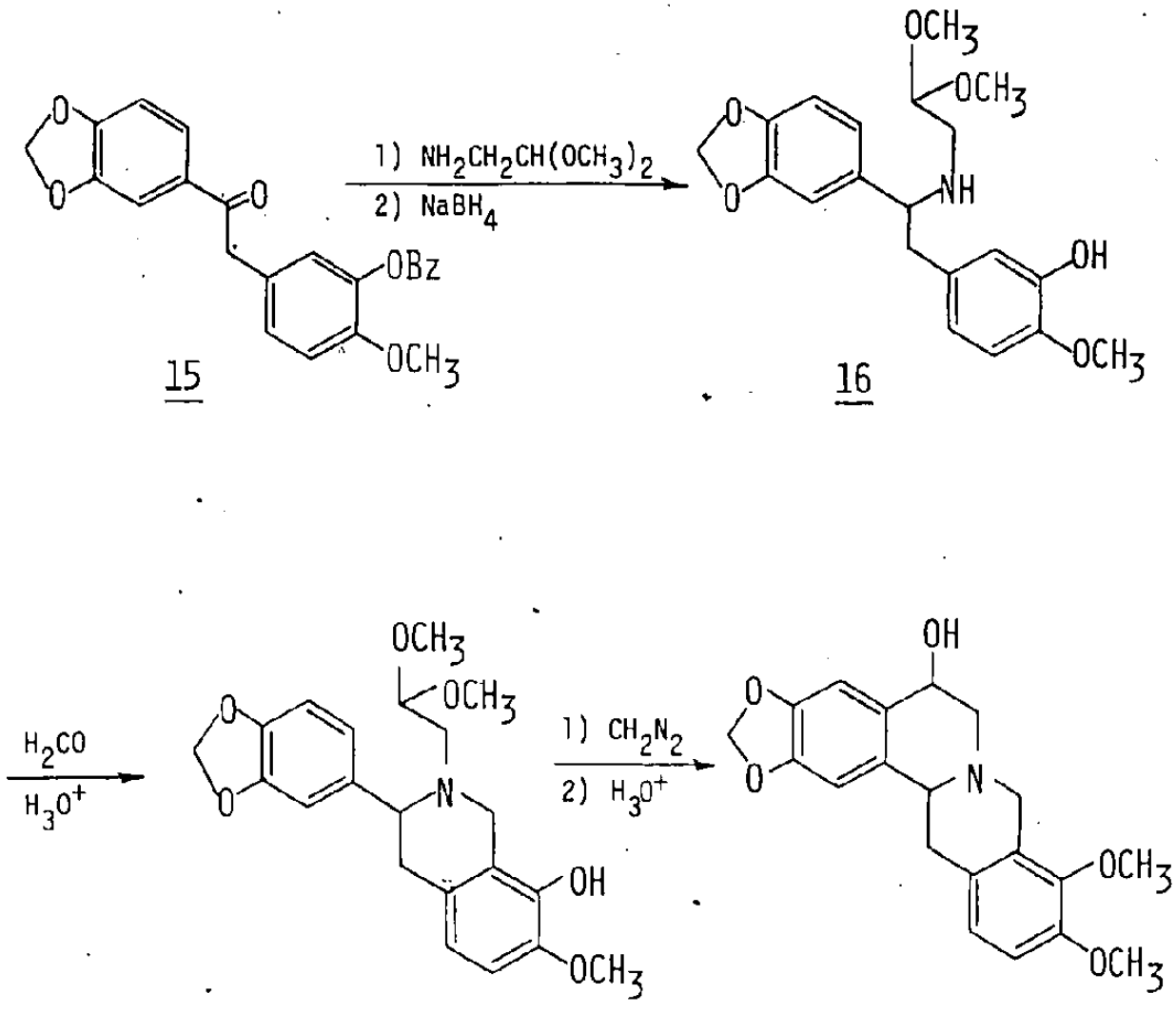
Although the yields of the synthesis are usually below 50%, the Pomeranz-Fritsch cyclization is of importance in the context of this thesis, as it offers the possibility of preparing isoquinolines with substitution patterns difficult to obtain by the Bischler-Napieralski or Mannich syntheses. For example, the Pomeranz-Fritsch cyclization should allow for the preparation of the isoquinoline 14 in two steps from the 2,3-disubstituted benzaldehyde 13.



13 14

In 1965, Bobbitt and co-workers (8) realized that yields in the Pomeranz-Fritsch reaction could be greatly improved if the Schiff base 12 was first reduced before acid-catalyzed cyclization. In 1975, Dyke and Tiley (9) used the Bobbitt modification of the Pomeranz-Fritsch cyclization in the total synthesis of tetrahydroberberastine. In their synthesis, the deoxybenzoin 15 was condensed with aminoacetaldehyde dimethyl acetal, and the resulting Schiff base reduced with sodium borohydride to give the amine 16. A Mannich reaction *vide infra* using formaldehyde was then carried out to form ring C. This was followed by an acid-catalyzed Pomeranz-Fritsch cyclization, which completed the

synthesis of the protoberberine skeleton (Scheme 3).

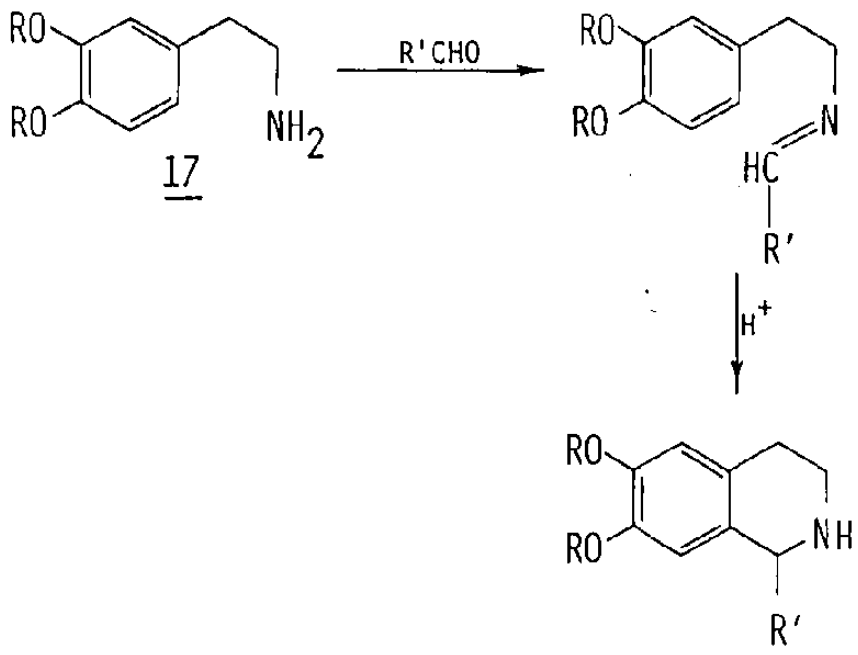


SCHEME 3

1.2.3 The Intramolecular Mannich Reaction

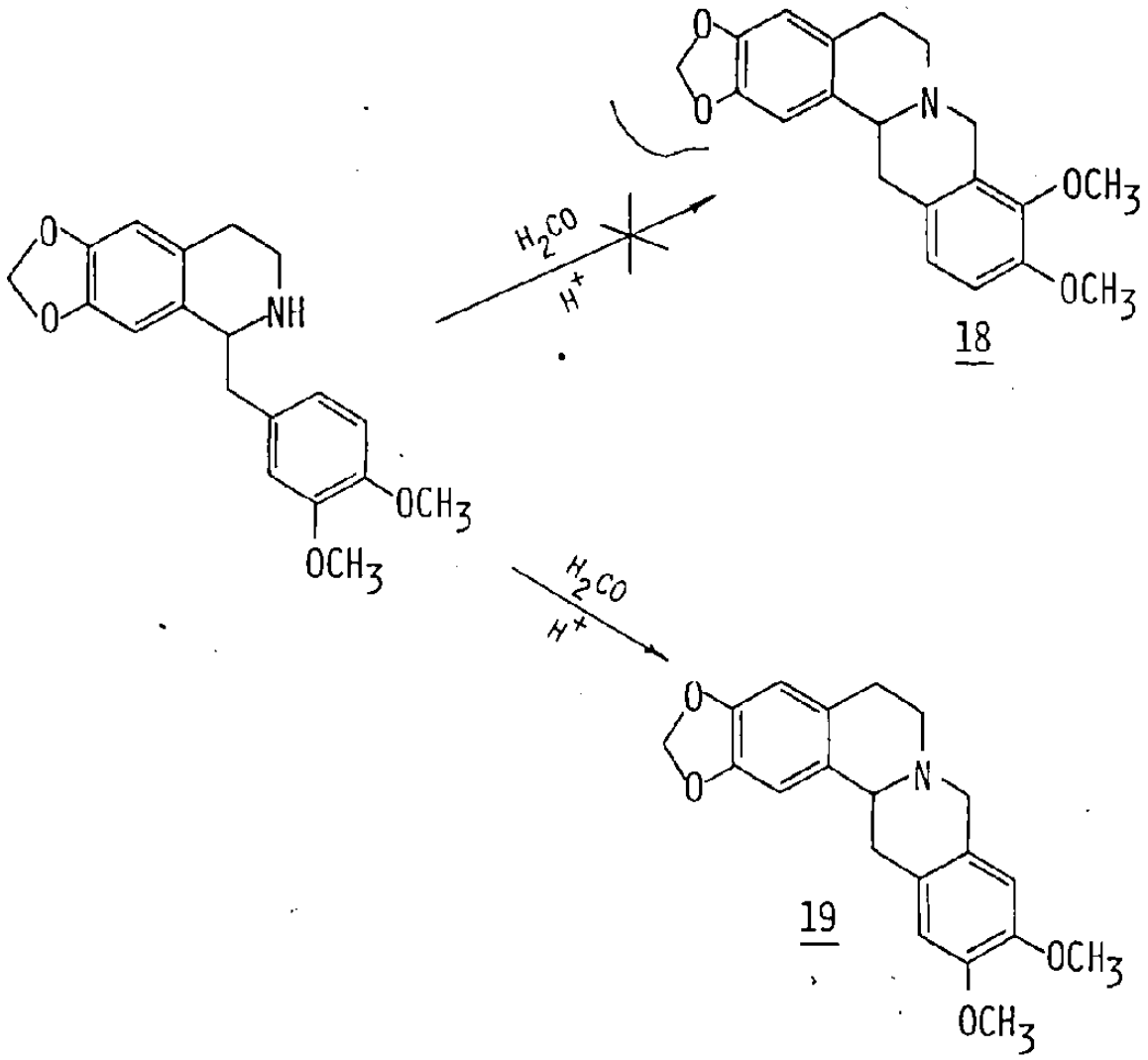
As early as 1911, Pictet and Spengler (10) had developed an ingenious reaction which would, later in history, be recognized as a special example of the Mannich reaction (6). Today, this intramolecular Mannich condensation is known to be the most general method for producing a wide variety of tetrahydroprotoberberine alkaloids.

In its earliest form, the Pictet-Spengler reaction involved the condensation of β-phenylethylamine with formaldehyde in concentrated HCl to form 1,2,3,4,-tetrahydroisoquinoline. The reaction was extended by Decker (11) who used substituted phenylethylamines 17 and various aldehydes in a two-step synthesis, shown in Scheme 4.



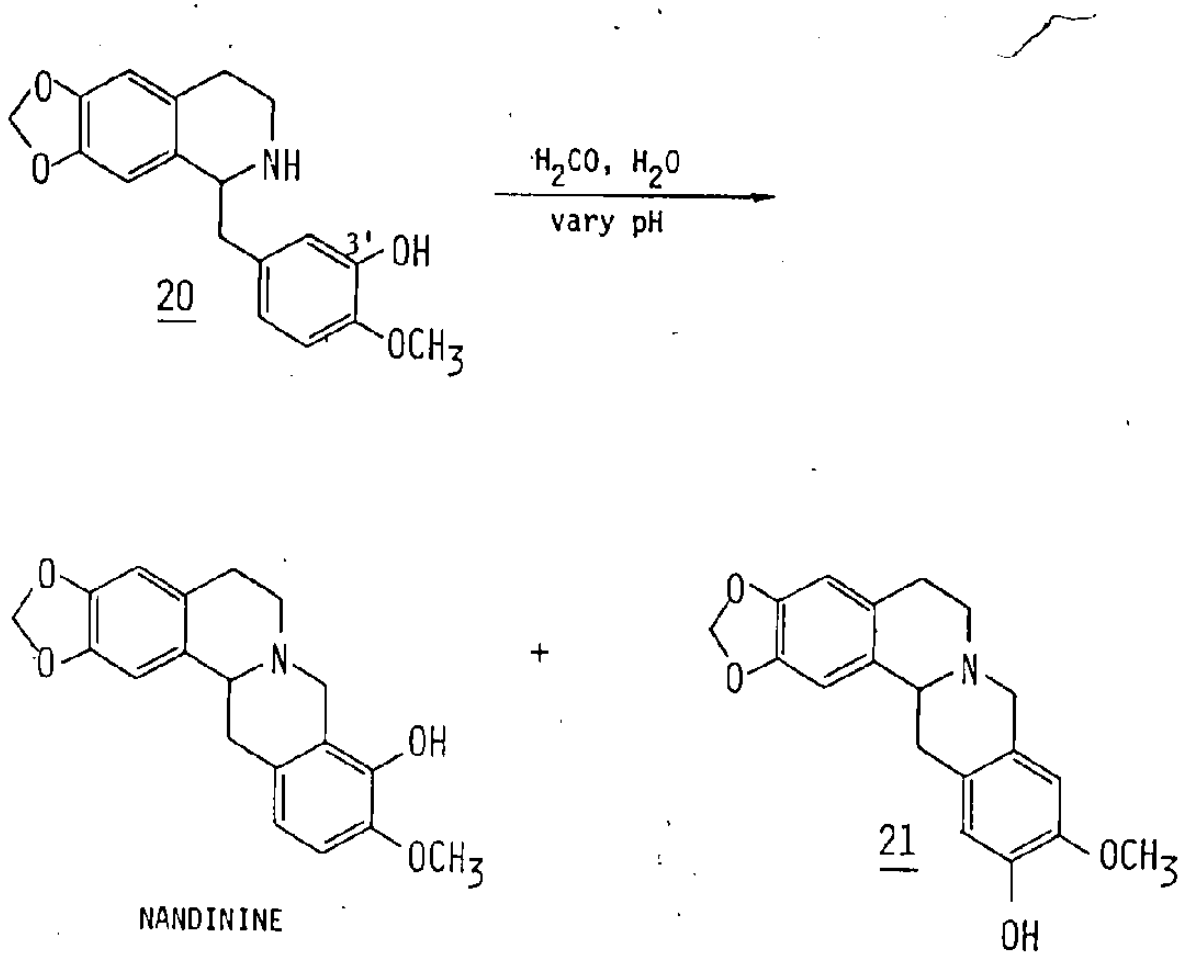
SCHEME 4

The application of the Pictet-Spengler reaction to the synthesis of protoberberines occurred as early as 1911 when Pictet and Gams (12) claimed to have synthesized tetrahydroberberine 18. Later work by Haworth and co-workers (13) showed that tetrahydro-ψ-berberine 19 was the product of their reaction, as would be expected (Scheme 5).



SCHEME 5

In more recent synthetic work, the Mannich condensation of the benzylisoquinoline 20 with formaldehyde was seen to yield products with both 2,3,9,10- and 2,3,10,11-oxygenation patterns (14) (Scheme 6).



SCHEME 6

In other studies done on this system (15), it was observed that as the pH of the reaction mixture increases from 1.2 to 7.8, the ratio of nandinine to 21 changes from 1:1 to 1:3.8. Furthermore, when the activating hydroxyl at the C-3' position of the benzylisoquinoline unit is not present, only products having the 2,3,10,11-oxygenation pattern are obtained.

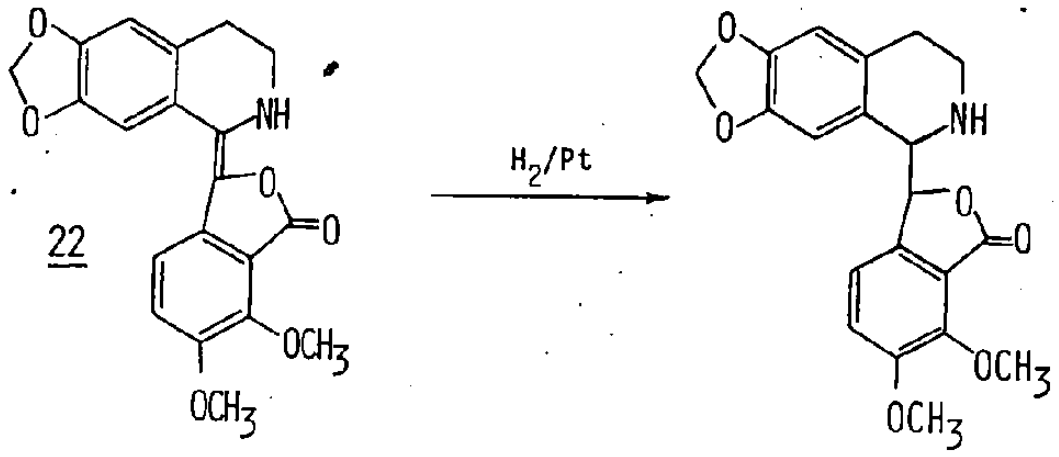
For more complete reviews on the traditional synthetic reactions used in protoberberine chemistry, the reader is referred to the following references (16, 17, 18, 19, 20, 21, 22).

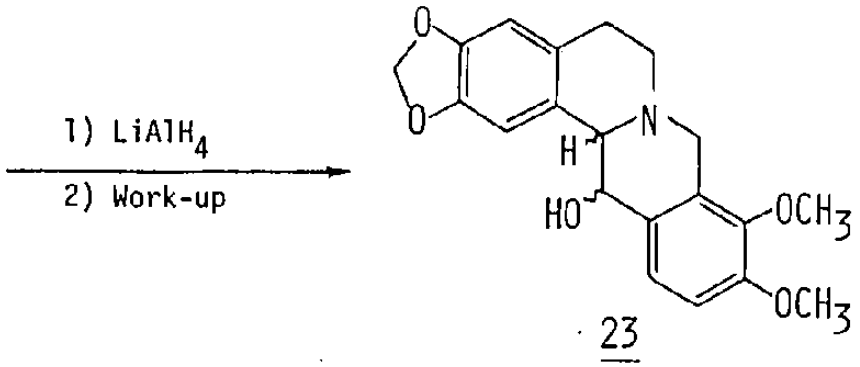
1.3 Modern Synthetic Routes to the Protoberberines

Innovations in the synthesis of protoberberine alkaloids are far too numerous to be mentioned here, and the reader is referred to the leading reviews for a more complete treatment (22, 23, 24, 25, 35). What is of interest at present is the examination of novel chemical (as opposed to photo or thermochemical) routes that have been developed recently for the construction of the protoberberine skeleton.

1.3.1 The Synthesis of Protoberberines Through Phthalideisoquinolines

As early as 1925 it was shown that protoberberine alkaloids could be synthesized through phthalideisoquinolines (26). In a more recent synthesis, the mixture of diastereomers 23 was synthesized through the phthalideisoquinoline 22, as shown in Scheme 7 (27).



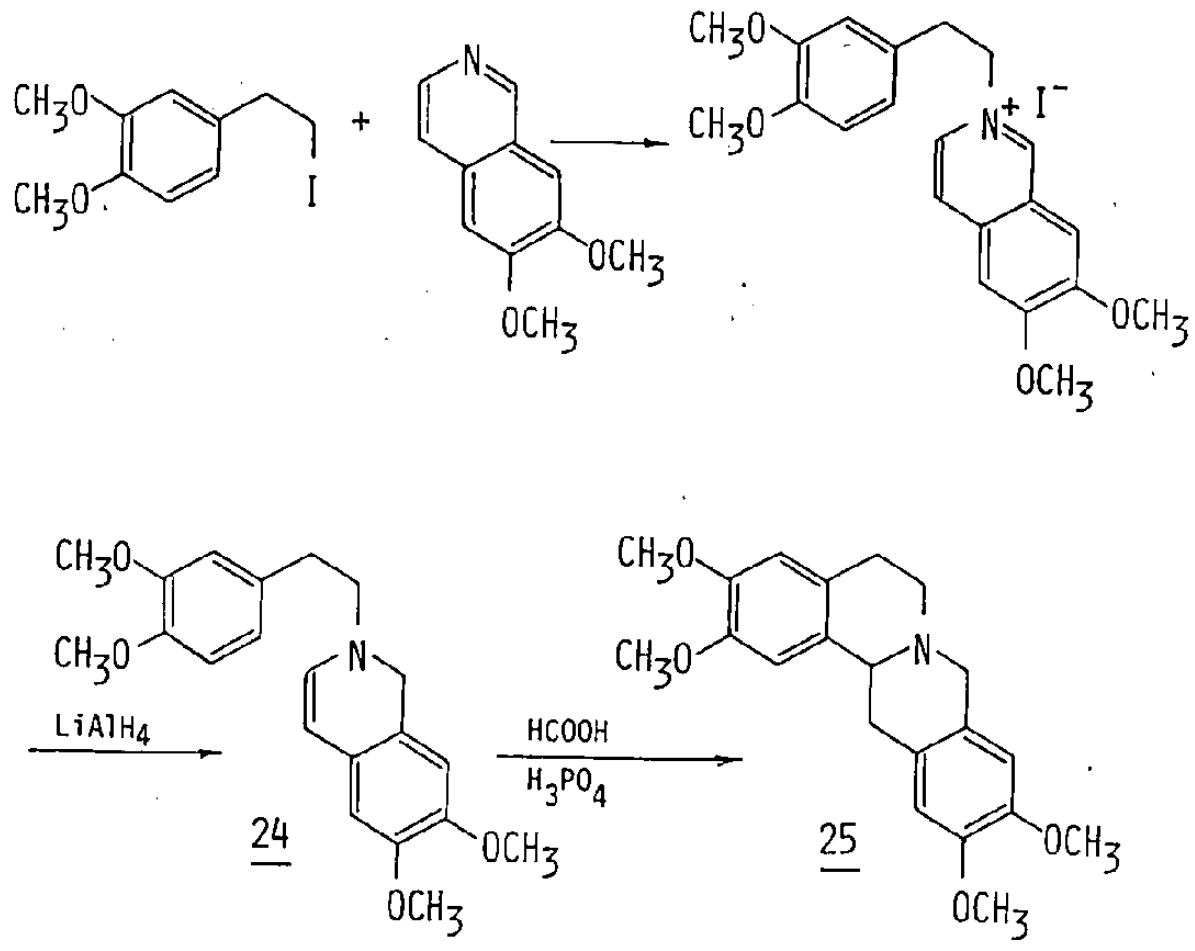


OPHIOCARPINE
and EPIOPHIOCARPINE

SCHEME 7

1.3.2 Synthesis Using a Dihydroisoquinoline Intermediate

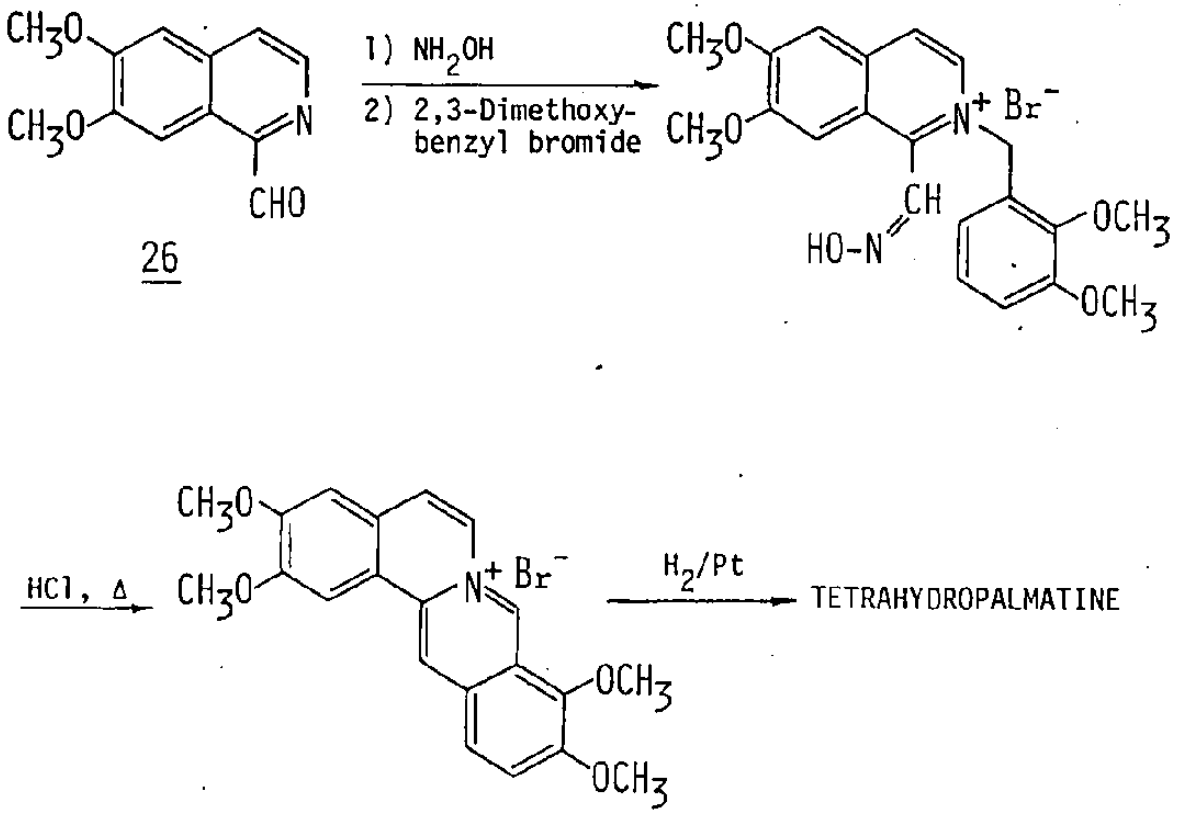
Several workers have shown that tetrahydroprotoberberines such as xylopinine 25 can be obtained from the acid catalyzed ring closure of dihydroisoquinolines like 24 (Scheme 8) (28, 29, 30).



SCHEME 8

1.3.3 The Use of Isoquinoline-1-Carboxaldehydes as Intermediates

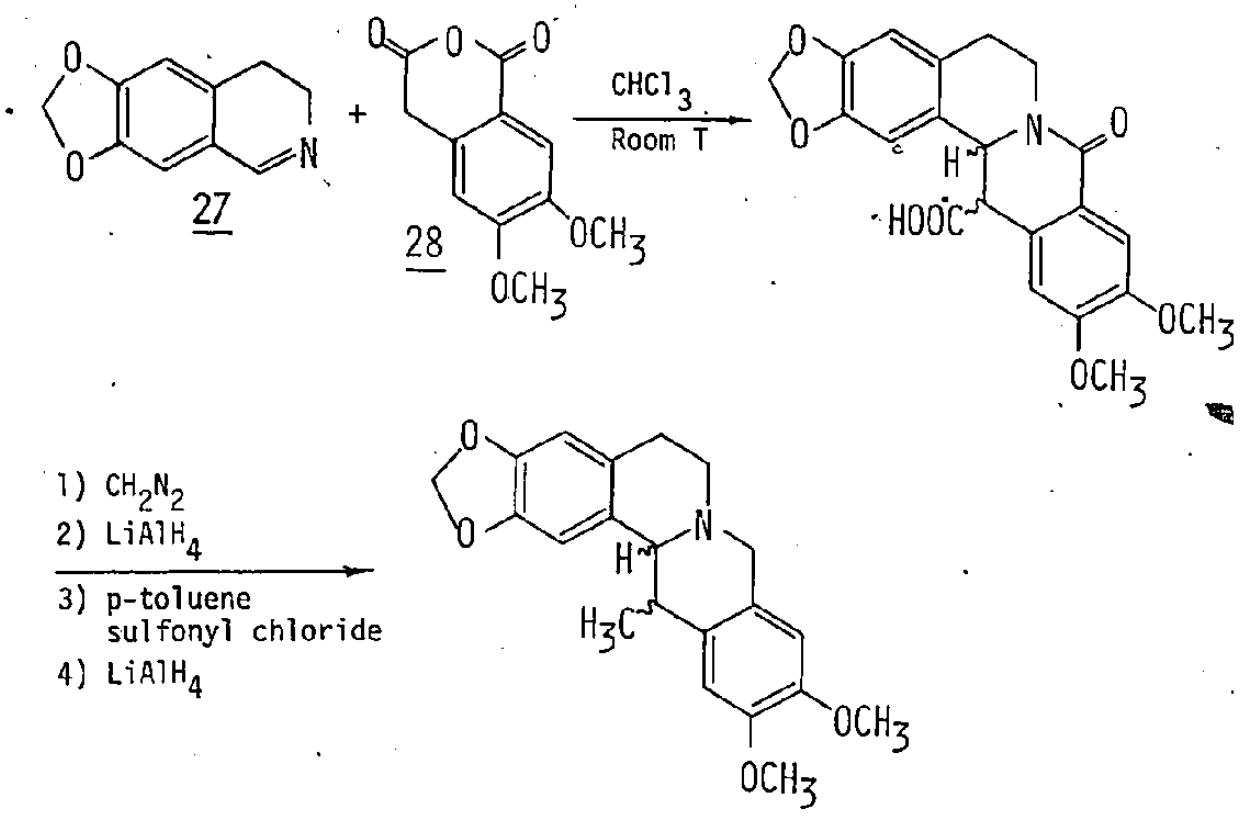
Bradsher and Dutta have described the synthesis of the isoquinoline-1-carboxaldehyde 26 which they used in the synthesis of tetrahydropalmatine, as shown in Scheme 9 (31).



SCHEME 9

1.3.4 Synthesis from Homophthalic Anhydrides

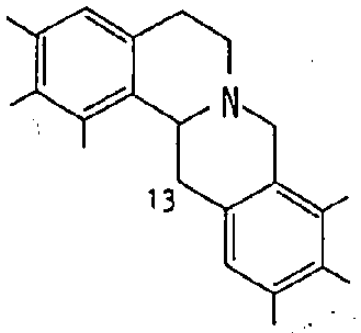
An interesting synthetic route to 13-methyl-tetrahydroprotoberberines has been developed by several workers (32, 33) and is shown in Scheme 10. The synthesis is based on the condensation of norhydrastinine 27 with 4,5-dimethoxyhomophthalic anhydride 28.



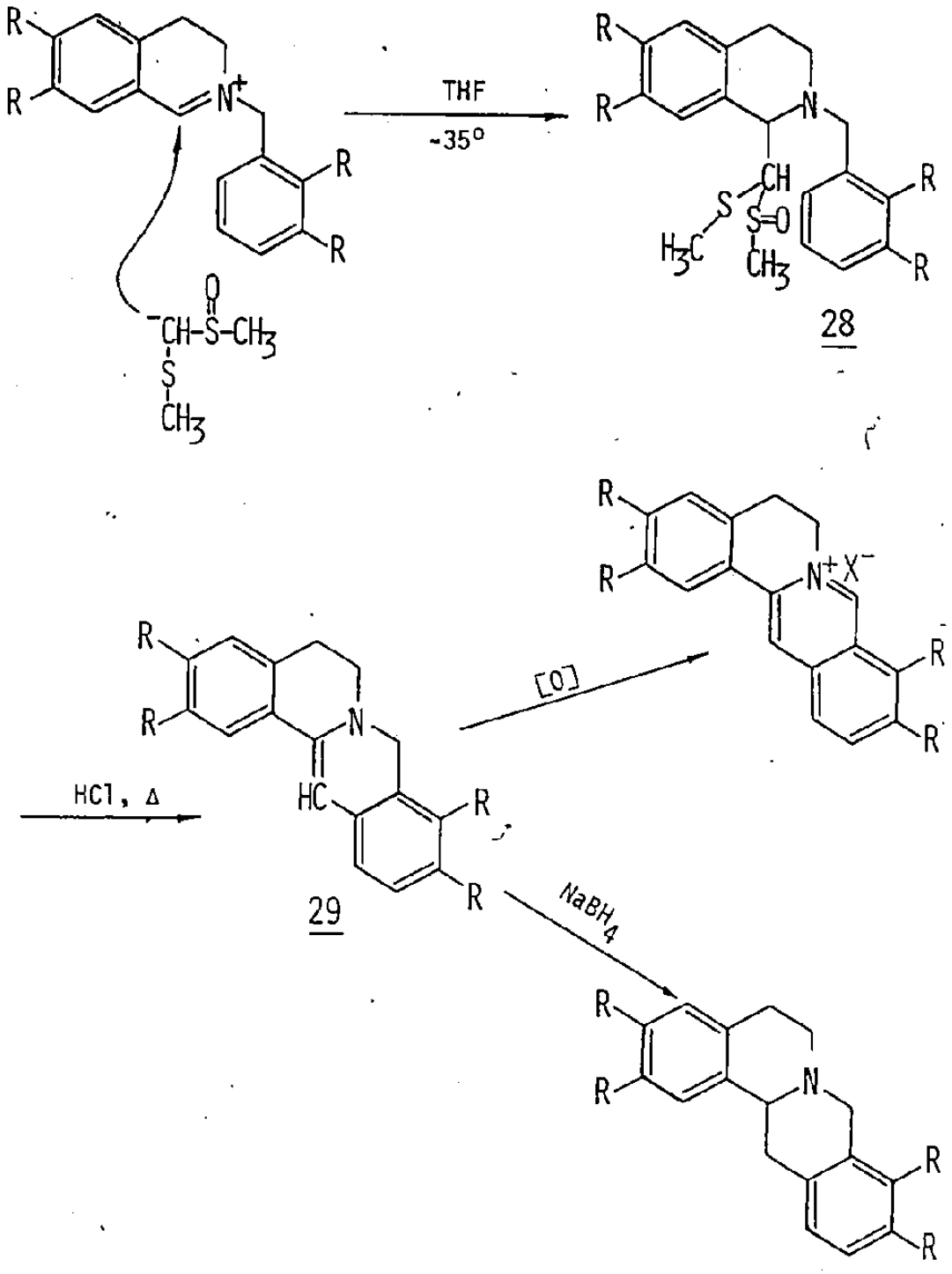
SCHEME 10

1.3.5 Synthesis Using a Substituted Mercaptal Intermediate

One of the objectives of the protoberberine research in our laboratories has been to develop a synthesis which would allow for the introduction of a labelled carbon atom at position 13 in the protoberberine skeleton.



In such a synthesis, the C-13 fragment must be efficiently introduced into the molecule at a late stage in the synthetic route. Since there was no precedent for such a synthesis by either classical or modern routes, the reactions shown in Scheme 11 were developed in our laboratories (34).

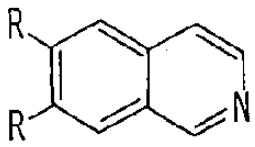


SCHEME 11

In this synthetic route, the key intermediate, 28, is generated by condensing the anion of methyl methylthiomethyl sulfoxide (MMTS) with a 3,4-dihydro-N-benzyl-isoquinolinium salt as shown. The substituted mercaptal 28 was shown to undergo cyclization rapidly to the dihydroprotoberberine 29 in hot, concentrated HCl (34).

It was the purpose of the present work to expand upon this synthetic route, with the following objectives in mind:

1. To apply the synthesis to other 2,3,9,10-substituted protoberberines than those produced previously in our laboratories.
2. To analyze the complex mixture of products produced in the reaction of the MMTS anion with the 3,4-dihydro-N-benzyl-isoquinolinium salt.
3. To investigate the applicability of isoquinoline derivatives 30 as starting materials in our synthetic route.



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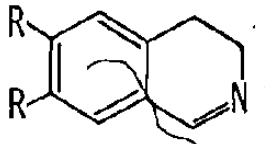
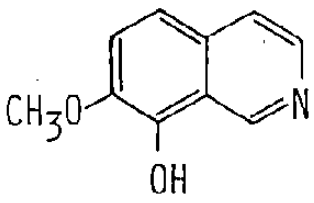
Before the present work was performed, the synthetic intermediates used were 3,4-dihydroisoquinolines 31, generated by the Bischler-Napieralski reaction.



31

This reaction lends itself readily to the synthesis of intermediates with substituents at C-6 and C-7 of the isoquinoline system. Other substitution patterns, particularly 7,8 are difficult to obtain by the Bischler-Napieralski route. By starting with the substituents already in place, many substitution patterns become possible. For example, the number of protoberberines which might be synthesized would be greatly increased if the Pomeranz-Fritsch reaction were used to create intermediates such as 14.



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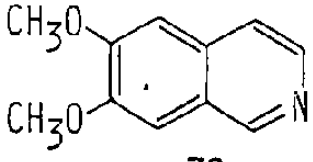
It was of interest, therefore, to investigate the use of isoquinoline 1 and 6,7-dimethoxyisoquinoline 33 as starting materials in our total synthesis of protoberberine alkaloids.



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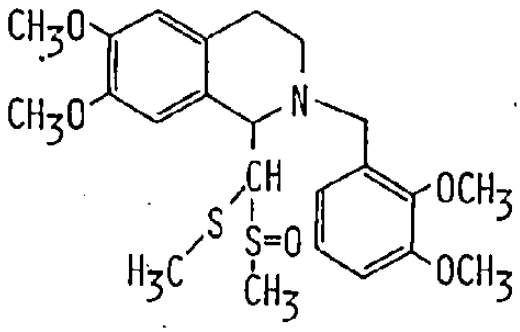
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Introduction

In pursuit of the objectives outlined in Chapter 1, the synthetic route developed by Kiparissides (34) was investigated in greater detail. The substituted mercaptal 33 was subjected to careful chromatographic studies, and was found to be a mixture of four diastereomers, although it was not possible to completely separate them. Each of the fractions that were isolated were cyclized to dihydropalmatine chloride 34, which could be isolated in crystalline form directly from the reaction mixture. This method of isolation was found preferable to that used previously. This dihydro compound underwent reduction readily to tetrahydropalmatine 35 and was also converted to corydaline 36.

The use of isoquinolines as starting materials in the Kiparissides synthesis was also investigated. Procedures were developed to convert isoquinoline 1 and 6,7-dimethoxyisoquinoline 32 into the protoberberine 37 and tetrahydropalmatine 35, respectively.



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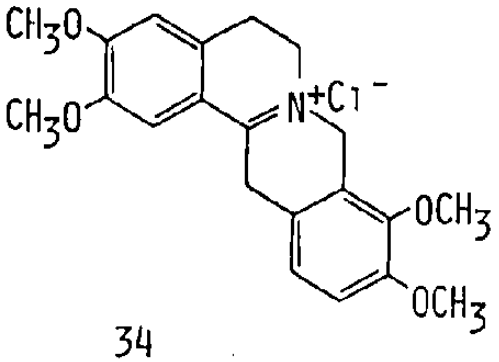

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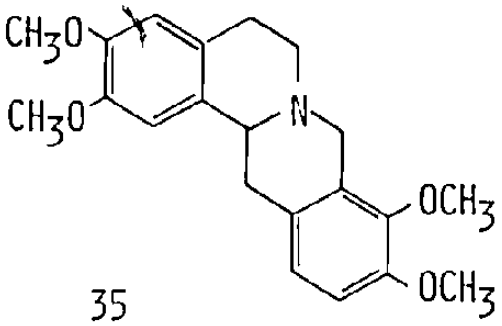

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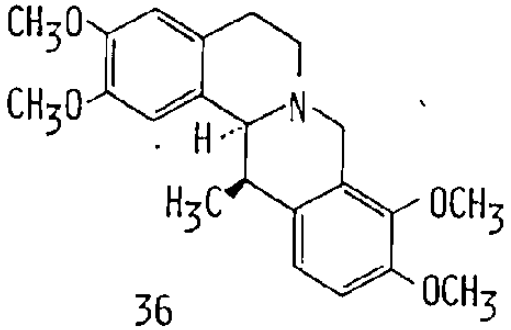

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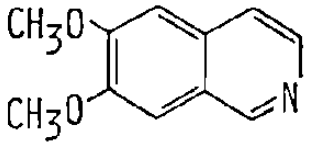

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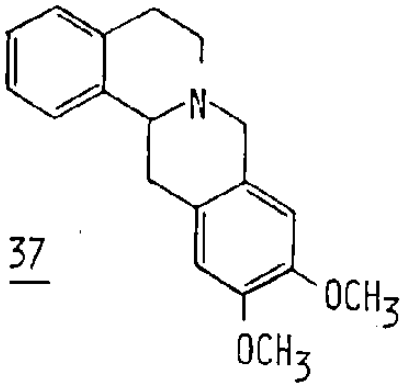

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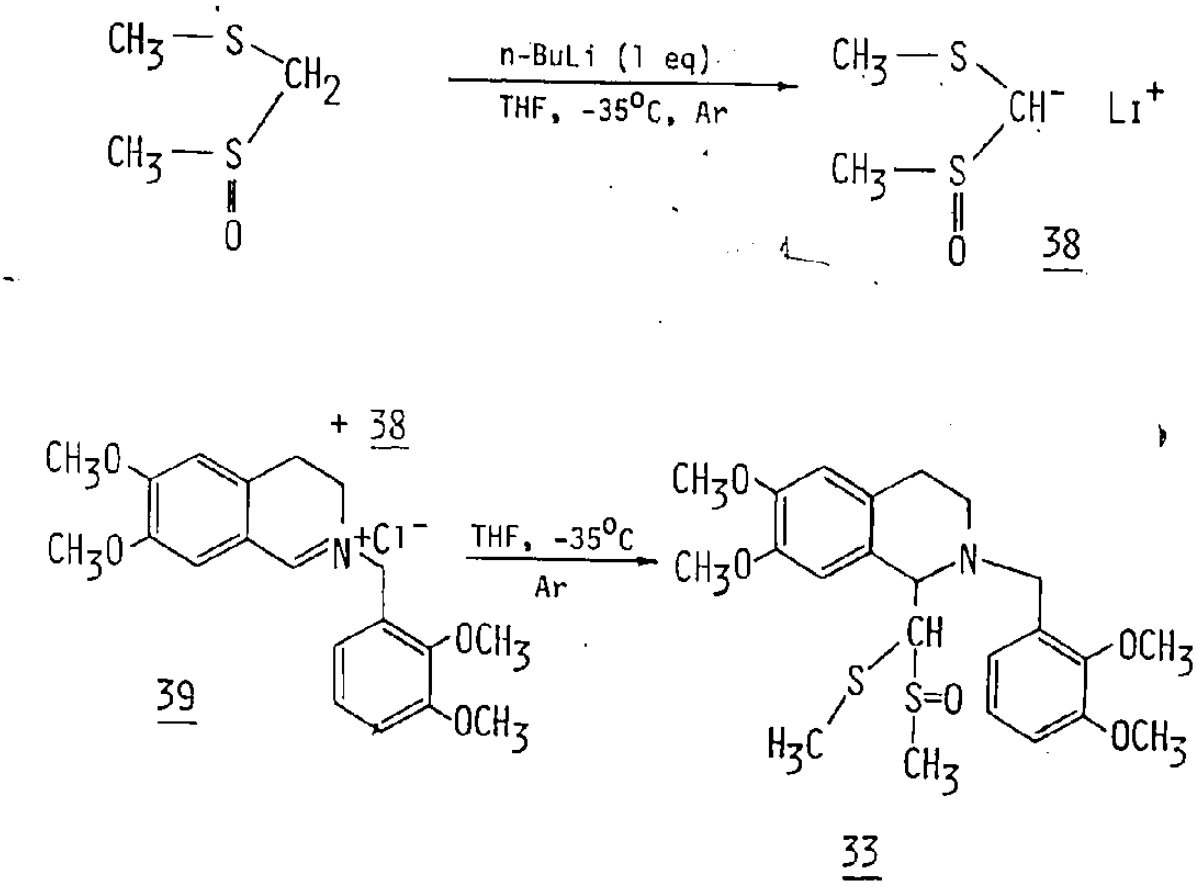
2.2 The Synthesis of (±)-Tetrahydropalmatine by the Kiparissides Route

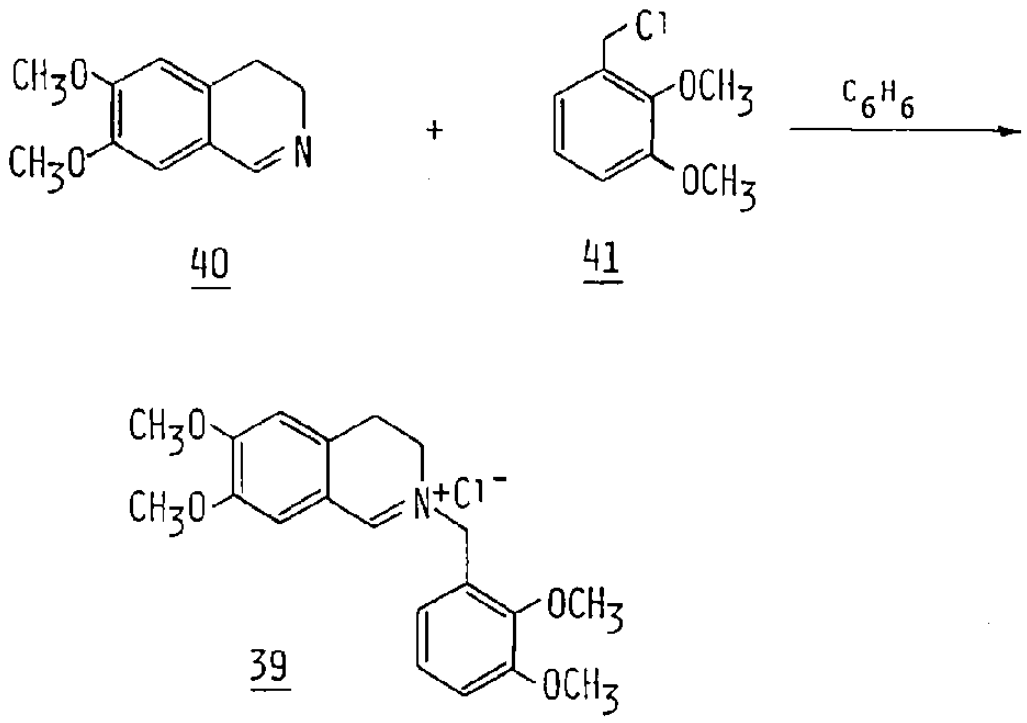
The key intermediate in the Kiparissides synthesis is the substituted mercaptal 33. This compound was prepared by the condensation of the anion of methyl methylthiomethyl sulfoxide (MMTS) 38, with the N-benzylisoquinolinium salt 39 (Scheme 12), using her procedure.



SCHEME 12

Although Kiparissides was the first to use sulfur stabilized carbanions in the synthesis of protoberberines, their use as aldehyde equivalents is well documented (37, 38, 39, 40, 41) as is their addition to iminium salts (42).

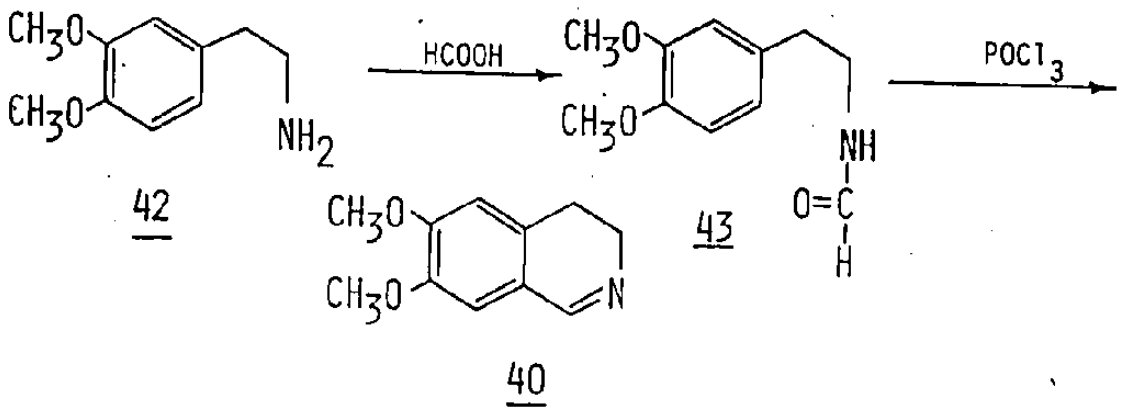
The quarternary salt 39 was prepared by the reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline 40 with the benzylchloride 41, as shown in Scheme 13.



40 41 39

SCHEME 13

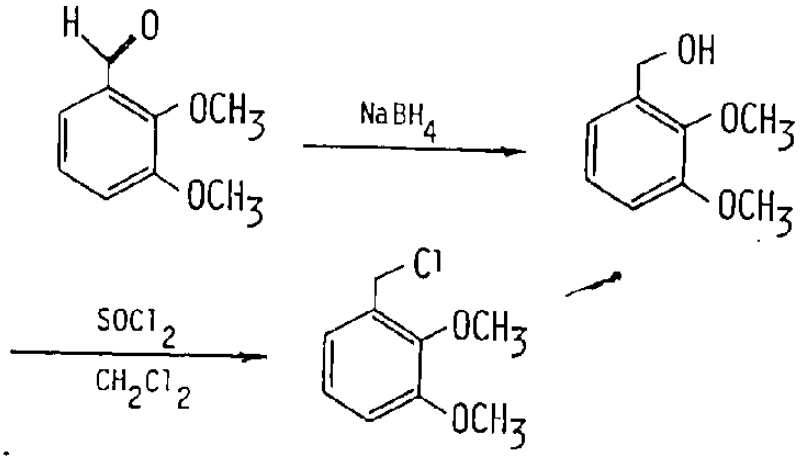
The isoquinoline 40 was prepared by a Bischler-Napieralski cyclization of formamide 43 with $POCl_3$ (Scheme 14).



42 43 40

SCHEME 14

The benzyl chloride 41 was obtained in two steps from 2,3-dimethoxybenzaldehyde, as shown in Scheme 15.



41

SCHEME 15

The mercaptal 33 produced by Kiparissides was shown by her to exhibit one major component, and two minor components on TLC (Alumina, chloroform : ethyl acetate = 8:2). Chromatography on alumina yielded one component in 98% yield, that had four, rather than two, S-CH_3 resonances in its ^1H NMR spectrum. It was proposed that the product isolated from the alumina column contained a mixture of rotamers or diastereomers (34).

In the present work, an attempt was made to determine the nature of this mixture. Thin layer chromatography (Silica, ether : ethanol (absolute) = 8:1) gave the first indication that the system was more complex than previously imagined. Three distinct components were visible at R_f 0.16, 0.20 and 0.33. Column chromatography by the "flash" method (36) was chosen because of its great speed, which is so desirable in the chromatography of large amounts of material. From one gram of crude product, three fractions were isolated, and subjected to ^1H NMR spectroscopy. The results of this work are given in Table 1.

TABLE 1: Chromatography Data of the Substituted Mercaptal 33 (Eluant; Ether : Ethanol = 8:1)

Component (R_f on TLC)	Amount Isolated (mg)	^1H NMR Chemical Shifts of S-CH_3 Protons ($CDCl_3$)
0.33	360	2.16, 2.22, 2.36, 2.62
0.20	120	2.22, 2.64
0.16	280	2.02, 2.30, 2.68, 2.70

Since two of the fractions isolated still appeared to be mixtures, they were subjected to variable temperature ^1H NMR. It was expected that if these fractions contained mixtures of rotamers as opposed to diastereomers, that the four S-CH_3 signals of these spectra would coalesce into two. Samples of the mercaptals R_f = 0.33 and 0.16 were dissolved in DMSO-d_6 and their spectra run at room temperature, 40°, 60° and 90°. For the mercaptal R_f = 0.16, there was no evidence of peak coalescence at 90°. The spectra of the mercaptal R_f = 0.33 showed that the 2.16 ppm and 2.36 ppm signals* were moving to lower field with increasing temperature, measured relative to the DMSO multiplet (Figure 1).

* These chemical shifts refer to $CDCl_3$ solution, as no internal reference was used in the DMSO experiments.

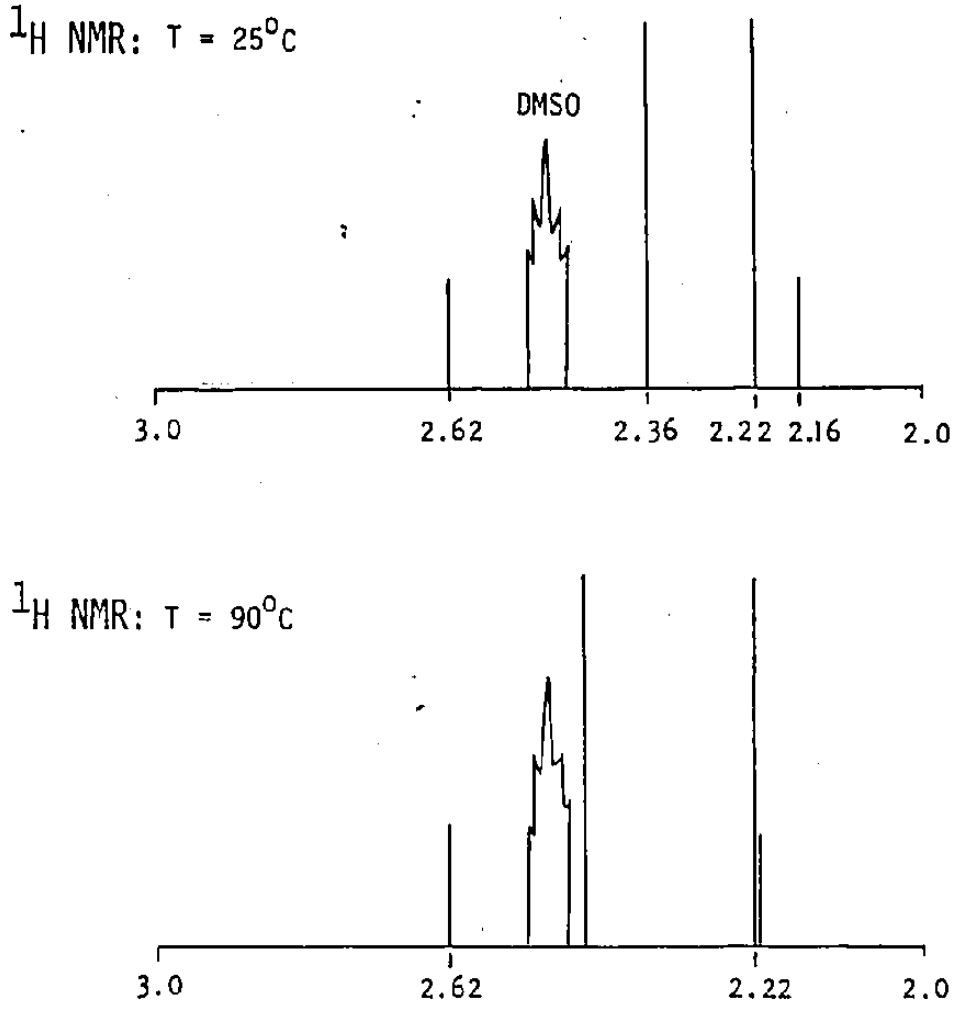


FIGURE 1: ^{1}H NMR of Mercaptal R_f = 0.33 at 25° and 90°

It is clear from Figure 1 that the 2.62 and 2.16 ppm signals arise from one component of the mixture, as do the 2.36 and 2.22 ppm signals. If true coalescence was occurring, each pair of signals would converge to yield a singlet at a chemical shift which was an average of those of the parent signals. Since the 2.62 and 2.22 ppm

peaks did not shift relative to DMSO, it was concluded that the 2.16 and 2.36 ppm signals were merely drifting to lower field with increasing temperature, and that the mercaptal R_f = 0.33 contained a mixture of diastereomers as opposed to rotamers.

Several attempts were made to resolve these mixtures of diastereomers into their component parts. In preliminary studies, the crude reaction product, showing three components by TLC (ether : ethanol = 8:1) was used. Chromatography of this material was attempted on a prepacked Merck silica gel 60, size B column, using a U.V. detector (254 nm) and a fraction collector. The ether based solvent system which worked so well in flash chromatography proved unsuitable, because of the formation of gas pockets in the tubing of the chromatograph, which interfered with the detection system. Other solvent systems including 1% EtOH in THF and Hexane : EtOH : THF = 7:2:1 were used but did not afford any separation. Extensive investigation of TLC solvent systems was undertaken, but no others were found that were capable of separating the mercaptal mixture. Chromatography on the Merck column was therefore abandoned.

The final attempt made to separate the mixture of diastereomers was by High Pressure Liquid Chromatography (HPLC). A preliminary flash chromatography (silica, ether : ethanol = 8:1) was used to obtain aliquots of each mercaptal component in "pure" form. Solutions of concentration 1 mg/ml in CH_2Cl_2 were injected onto a reverse phase column. Under these conditions, no further separation was achieved.

During the course of these studies, several interesting

observations were made. Close examination of the ^1H NMR spectrum of the R_f = 0.16 component showed that two of the four S-CH_3 peaks belonged to unreacted MMTS. This result should have been considered earlier, since the R_f of MMTS on TLC in the same solvent system is ~0.2. Furthermore, a more complex solvent system was found to resolve the R_f = 0.33 component into two spots on TLC (Figure 2).

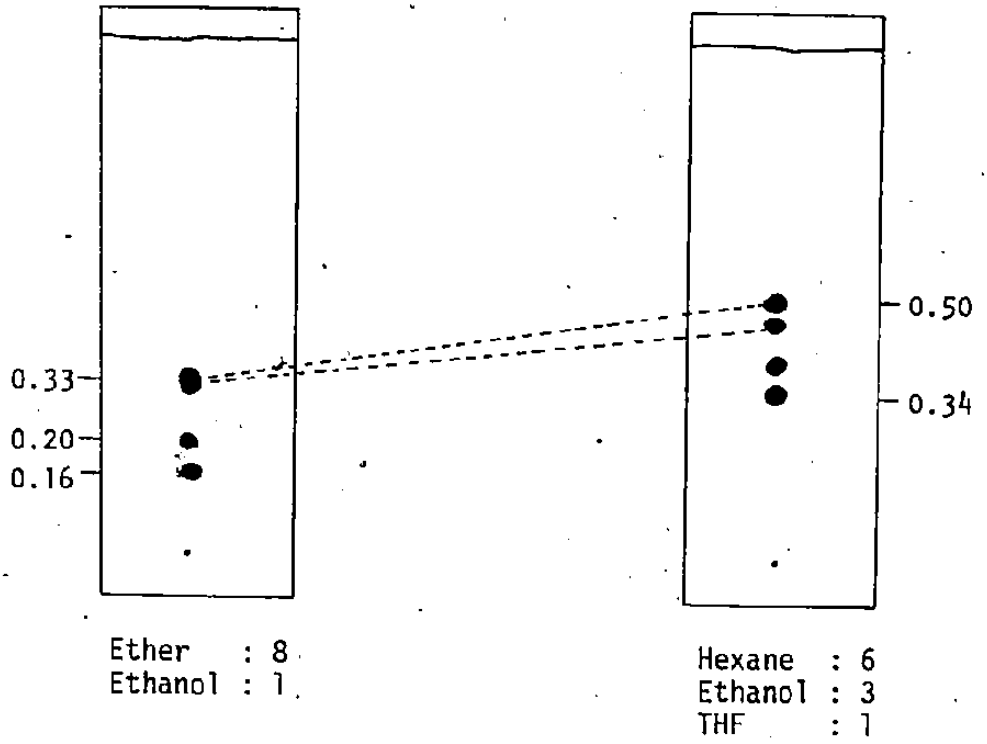
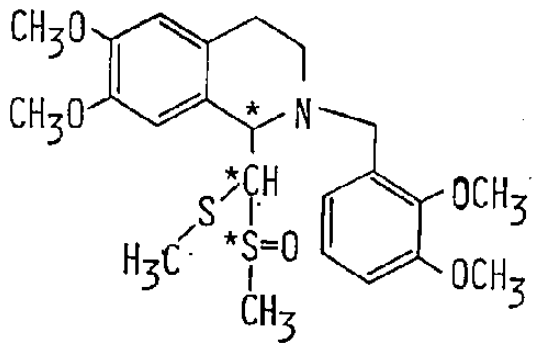


FIGURE 2: TLC of Substituted Mercaptal 33

These observations can be summarized as follows: on TLC in Ether : Ethanol = 8:1, the mercaptal appeared as a mixture of three components. The R_f = 0.33 spot would seem to contain two diastereomers; the R_f = 0.20 component is one diastereomer; the R_f = 0.16 spot is a mixture of one diastereomer and unreacted MMTS. It is not unreasonable that the crude reaction product should contain four diastereomers, as the substituted mercaptal 33 possesses two asymmetric carbon centers, as well as a chiral sulfoxide.** A molecule containing three asymmetric centers is expected to give rise to $2^3 = 8$ stereoisomers or four pairs of enantiomers.



33 * Denotes an asymmetric center

** Sulfoxides are stable to pyramidal inversion below 190°. (See D. R. Rayner *et al.* J. Am. Soc., 90, 4854 (1968)).

In the absence of a more powerful chromatography system, it was important to confirm that the fractions were structurally related. Accordingly, several grams of the crude mercaptal were chromatographed on a flash column (ether : ethanol = 8:1) and the three fractions isolated were analyzed by mass spectrometry. The three components gave a similar, complex fragmentation pattern, given in Table 2 and rationalized in Figure 3.

TABLE 2 : Mass Spectrometry Data of the Mercaptal R_f = 0.33

m/e	I (Percent Base Peak)
447	10
432	20
401	80
386	40
370	40
354	100
342	40
340	15
338	10
325	40
324	100
323	50
322	60
308	15
250	15

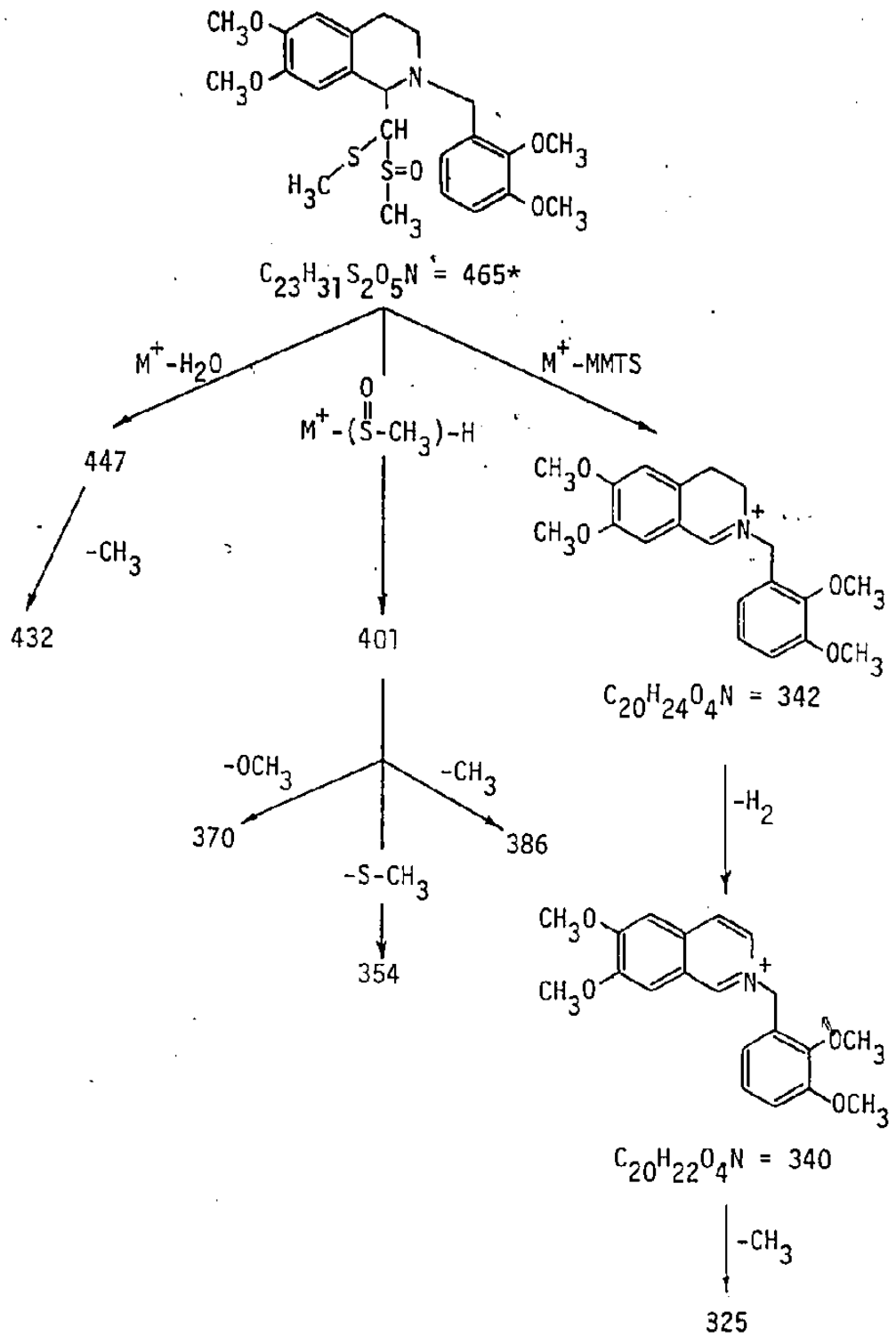
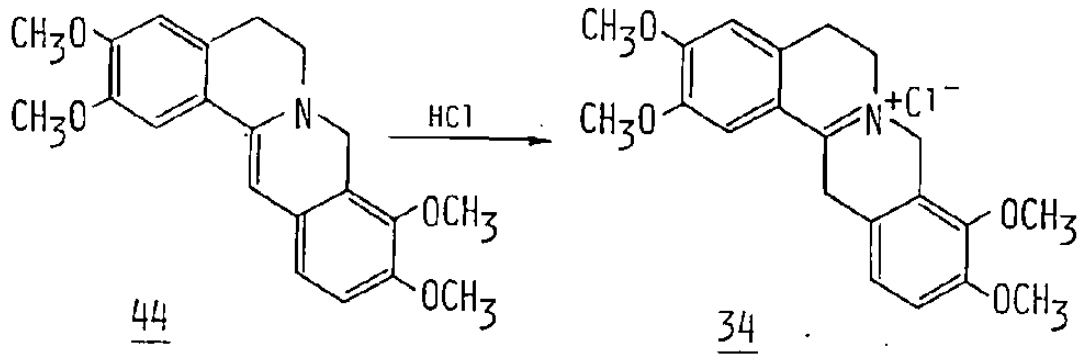


FIGURE 3: M.S. Fragmentation of Substituted Mercaptal 33

* m/e values

It was confirmed that the mercaptal fractions were structurally related by their behaviour in the next step of the total synthesis. Each fraction was treated with conc. HCl according to the procedure of Kiparissides (34). She described the isolation of the unstable enamine 44 by basification of the acidic reaction mixture, followed by extraction with ether. In the present work, fine yellow needles crystallized from the reaction mixture of each cyclization, to which the quarternary salt structure 34 is assigned. This iminium salt is formed from the enamine in the strongly acidic medium.



44 34

The mass spectra of the three cyclized products showed similar fragmentation patterns with varying peak intensitites. Difficulties in obtaining good mass spectra of iminium salts are expected, because their low volatility requires high probe temperatures which are poorly reproducible. The spectra show no parent peak, but give a base peak at m/e = 353 corresponding to the loss of H· from the original iminium ion m/e = 354. Major peaks are also present at m/e = 190, 164 and 149 (Table 4, Chapter 3) which are characteristic fragment ions of tetrahydropalmatine and its salts (*vide infra*).

Good ^{1}H NMR spectra of these salts were not obtained as it was difficult to free them from water of hydration. Drying the crystals over P_2O_5 at 80°C and 0.05 mm Hg for 24 h appeared to remove the water, but under these conditions, the brilliant yellow needles turned deep orange in colour. The NMR spectra of the products were poorly resolved, but showed aliphatic, methoxyl and aromatic signals expected for the iminium salt 34 (p.60, Chapter 3). It is unfortunate that good elemental analyses of the cyclized products could not be obtained, probably owing to the presence of H_2O and HCl remaining in the crystal lattice.

Finally, each of the chloride salts was reduced with $NaBH_4$ to give a white crystalline compound in 70% yield from the mercaptal. The melting point and NMR of the products were identical with those of natural (±)-tetrahydropalmatine 35, and the mass spectra showed a molecular ion at m/e = 355 corresponding to $C_{21}H_{25}O_4N$ and peaks at m/e = 192 and 164, characteristic of the fragmentation of the protoberberine 35. (Figure 4).

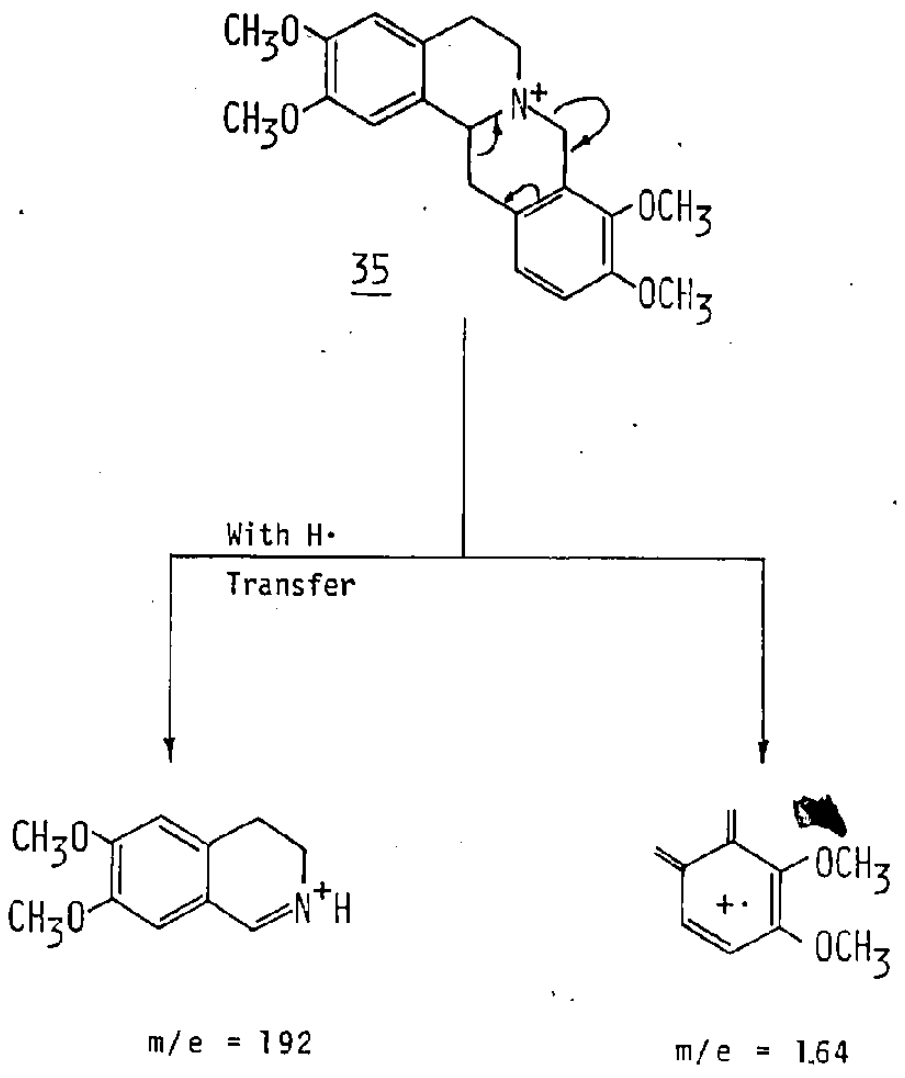
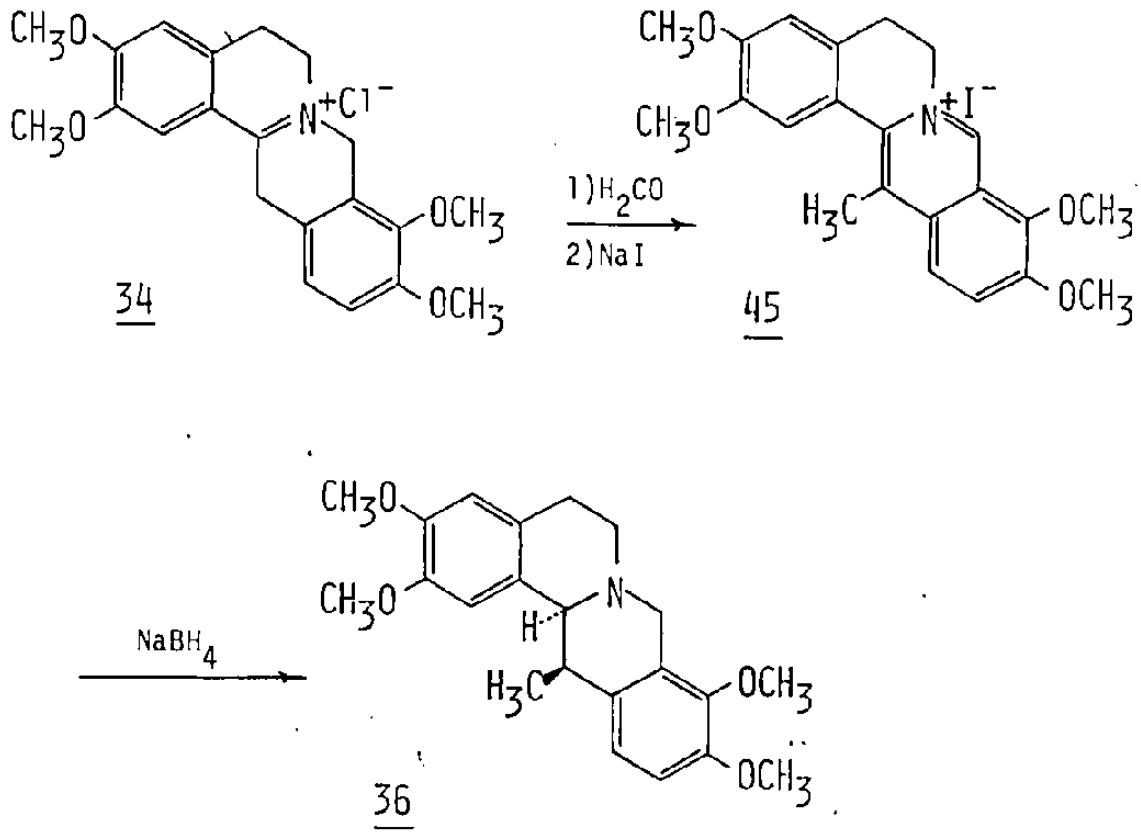


FIGURE 4: Major Fragments of Tetrahydropalmatine 35

2.3 The Synthesis of Corydaline 36

Bersch has described the reaction of formaldehyde with dihydroberberine, yielding a C-13 methylated iminium salt (43). It was a logical extension of the present work to synthesize the 13-methyl protoberberine, corydaline 36 from the dihydro salt 34 using the method of Bersch. The reactions, which are outlined in Scheme 16, yielded a crystalline product in 42% yield, which was shown spectroscopically to be identical with natural corydaline.



SCHEME 16

Kondo has shown that the salt 45 on reaction with $NaBH_4$ yields exclusively corydaline, and none of its diastereomer, mesocorydaline (44).

The total synthesis of corydaline as described here is of interest because it involves fewer steps than previous synthetic routes. The recent synthesis by Cushman* (48) for example, used 3,4-dimethoxy-homophthalic anhidride as the key intermediate in a synthetic route which was at least four steps longer than the present one.

2.4 The Synthesis of 10,11-Dimethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine (10,11-Dimethoxyberbine) 37**

One of the objectives of this work was to determine the applicability of isoquinolines as starting materials in the Kiparissides synthesis of protoberberines. If successful, a wider range of substited protoberberine alkaloids could be synthesized. In particular, the Pomeranz-Fritsch cyclization could be used to prepare starting materials with substituents at positions 7 and 8 of the isoquinoline ring.

The key reaction in the prospective synthesis was the condensation of the salt 46 with the MMTS anion 38 to form the enamine 47 (Scheme 17).

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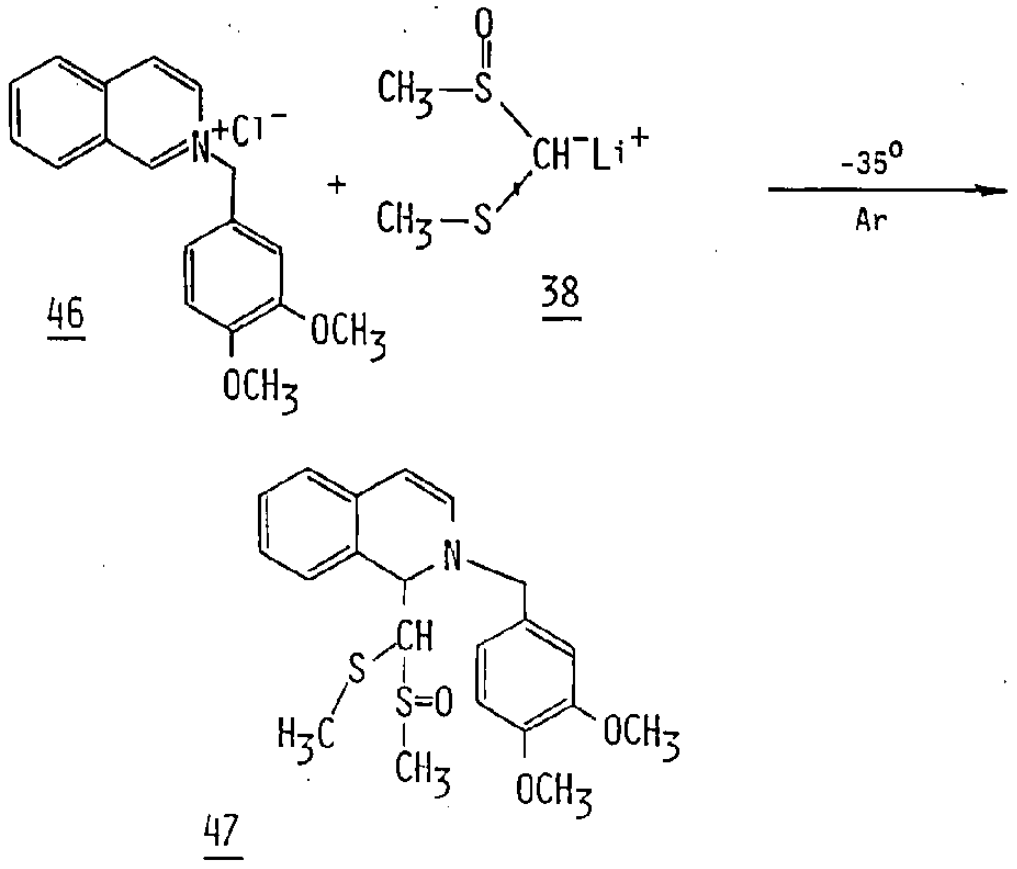
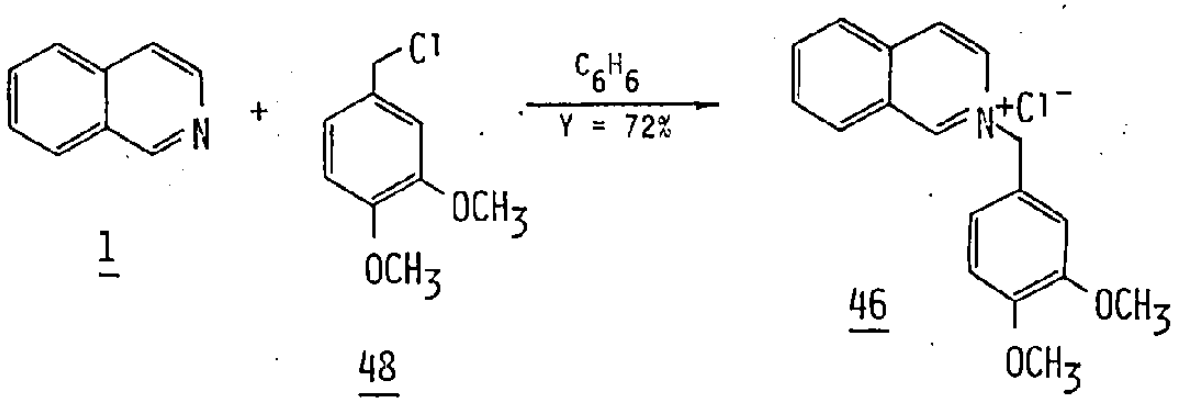
* A typical Synthesis by Cushman is given in Scheme 10, Chapter 1

** This compound has been previously reported (49, 50)



SCHEME 17

The synthetic work began with the reaction of isoquinoline 1 with the benzyl chloride 48 to yield the quarternary salt 46 (Scheme 18). Compound 48 was obtained by treating the benzyl alcohol with $SOCl_2$ in $CHCl_3$.

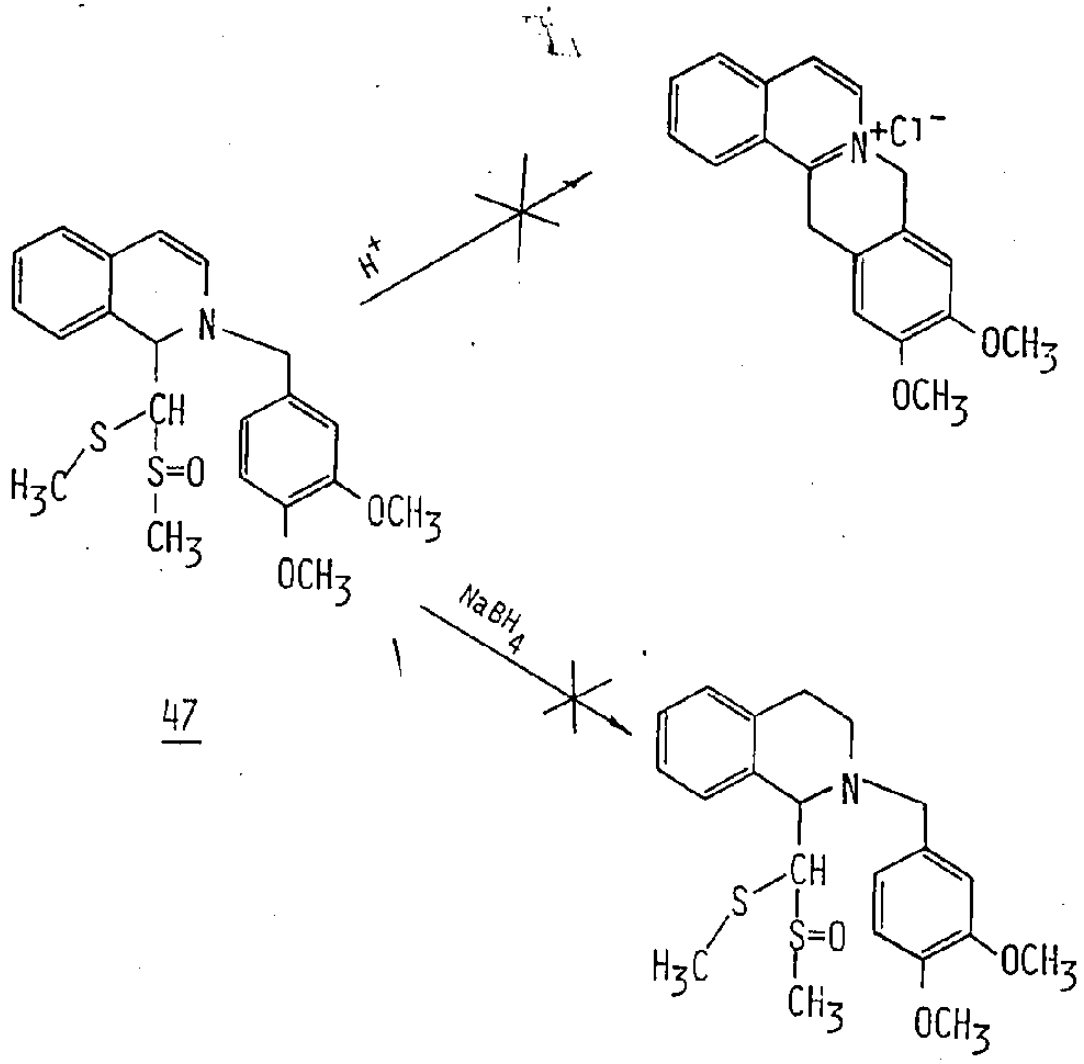


1 48 46

SCHEME 18

In agreement with expectation, compound 46 when reacted with the MMTS anion 38 under the same conditions used in the tetrahydropalmatine synthesis, yielded 47, as shown in Scheme 17. The brown oil isolated clearly showed four components present in roughly equal proportion by TLC (THF : Hexane = 6:4). The product gave a complex NMR spectrum, showing a multiplicity of peaks in the S-CH_3 region. Unfortunately, the material was unstable, and chromatography on silica gel simply resulted in decomposition of the material.

Accordingly, without further purification of the crude reaction product, attempts were made to reduce the enamine functionality with $NaBH_4$, and also to cyclize the material directly. Both of these experiments, outlined in Scheme 19, failed to produce the expected products.



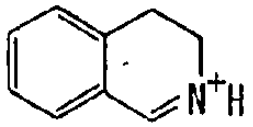
47

49

SCHEME 19

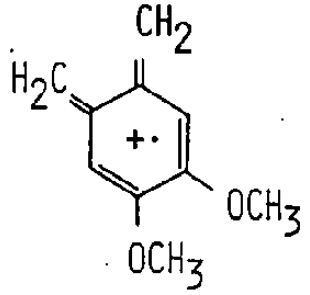
The enamine reduction of Borch and co-workers (45) was attempted next. Using this procedure, the enamine was dissolved in methanolic acetic acid, and $NaBH_3CN$ added in excess. Within two minutes the colour of the solution had changed dramatically from deep purple to clear yellow. Although the TLC of the reaction mixture was not conclusive, that done after workup showed three components present (R_f = 0.12 to 0.24, THF : Hexane = 6:4) whereas the starting material showed four components (R_f = 0.14-0.29) in the same solvent system. The NMR of the product was much simpler than that of the starting material, but still showed four signals in the S-CH_3 region. Two poorly-resolved triplets (J = 3 Hz) present at δ = 3.56 and 3.72 are evidence of the Ar-CH_2-CH_2-N system resulting from the enamine reduction. The yield in the two steps from the N-benzylisoquinolimium chloride 46 was 60%.

Without further purification, the clear yellow oil 49 isolated from the reduction was treated with concentrated HCl and heated for 10 minutes on a steam bath. A yellow solid crystallized from the reaction mixture in 62% yield. The NMR spectrum of the product showed two triplets (J = 7.5 Hz) corresponding to the two methylene groups in ring B, as well as the aliphatic, methoxyl and aromatic signals expected for the iminium salt 52. The mass spectrum showed a peak corresponding to the iminium cation at m/e = 294 and peaks at m/e = 132 and 164 (base peak) corresponding to the fragments 50 and 51 as expected. The enamine reduction and the cyclization reaction are summarized in Scheme 20.



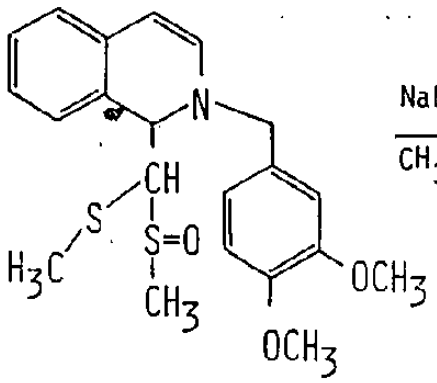
m/e = 132

50



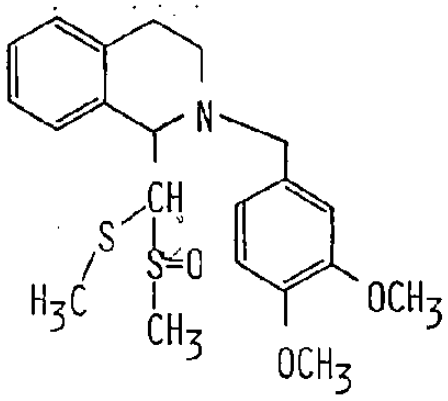
m/e = 164

51



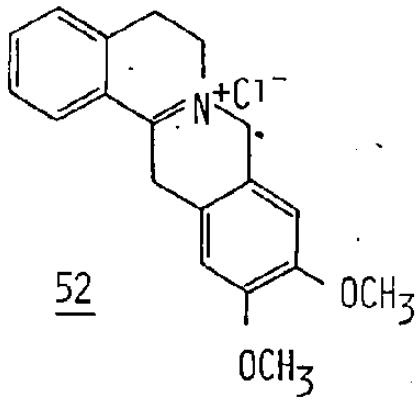
47

$NaBH_3CN$, MeOH, CH_3COOH



49

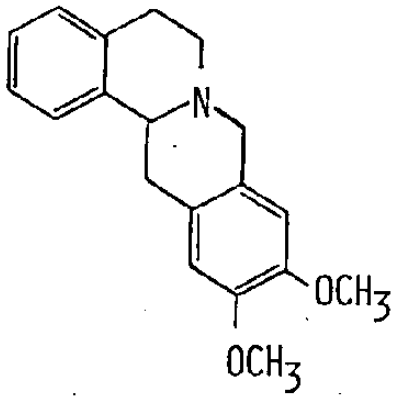
HCl, Δ



52

SCHEME 20

In the final step of the synthesis, the salt 52 was reduced with $NaBH_4$ in ethanol. A white crystalline compound was isolated after workup in 82% yield which crystallized from $EtOH/CHCl_3$, m.p. 124-125°C. The mass spectrum showed a parent peak at m/e = 295 (I = 90%) and a base peak at m/e = 164 corresponding to the cation 51. The NMR was consistent with structure 37, and was characterized by a methoxyl singlet integrating to six protons, and two aromatic singlets arising from the two protons on ring D.

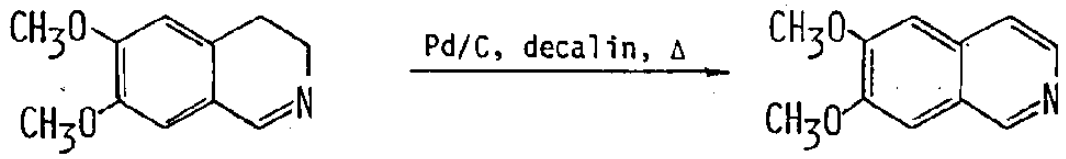


37

2.5 The Synthesis of Tetrahydropalmatine via an Isoquinoline Intermediate

This project was undertaken to confirm the utility of a substituted isoquinoline as an alternative starting material in the Kiparissides synthesis of protoberberines.

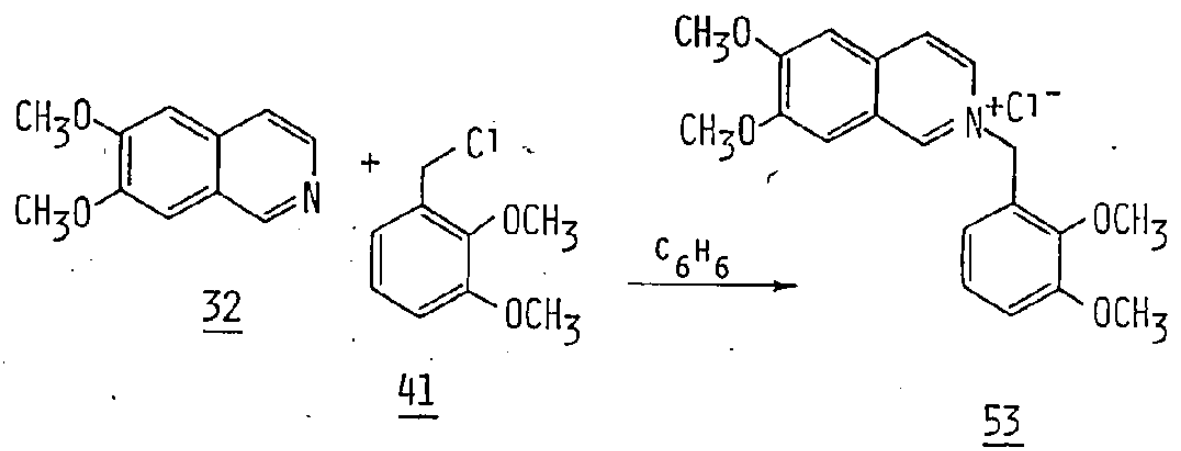
The desired isoquinoline 32 was prepared by dehydrogenation of the dihydro compound 40 over Pd/C in refluxing decalin. The reaction, as adapted from the literature (46), gave the product in 79% yield (Scheme 22).



40 32

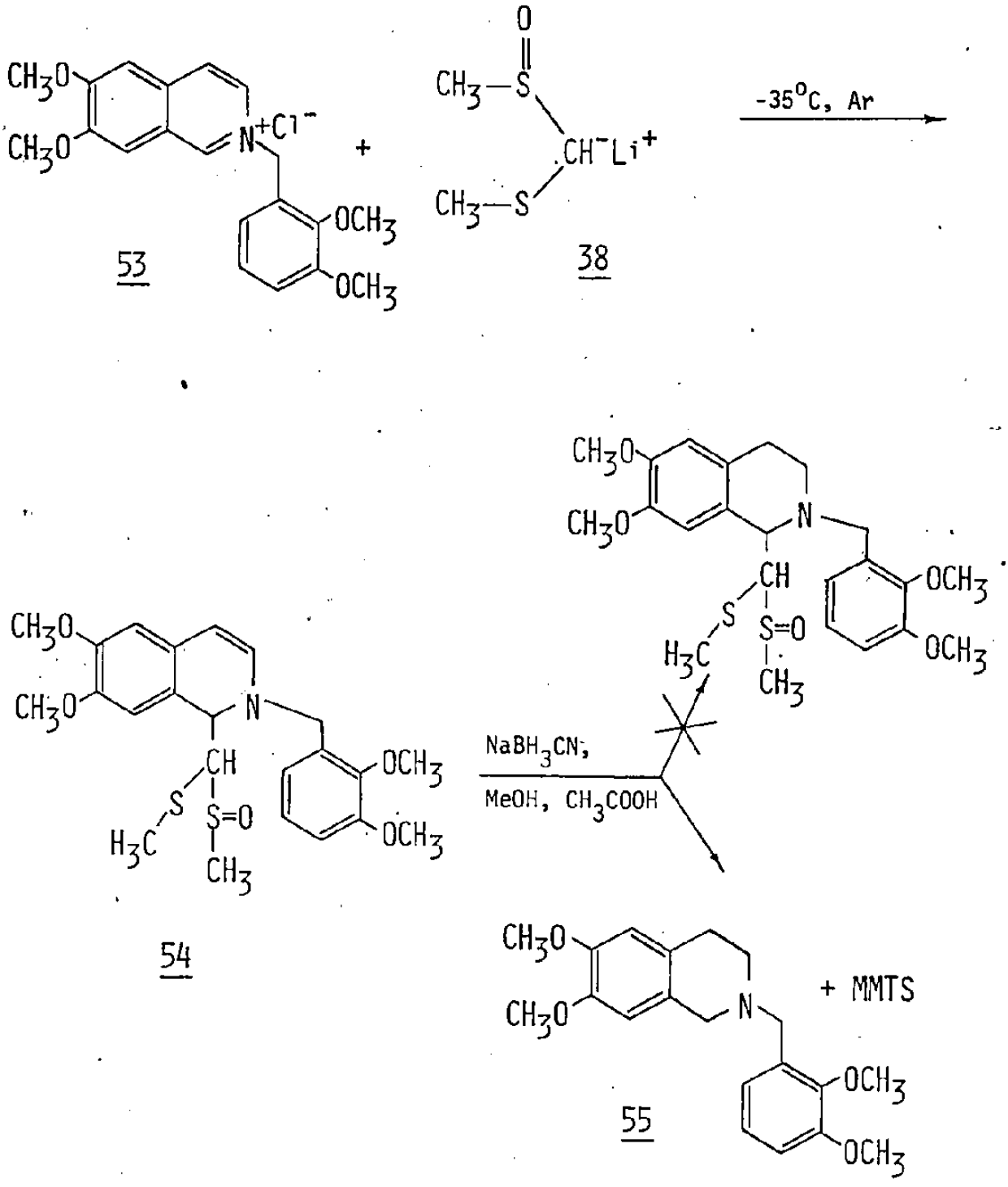
SCHEME 22

The isoquinoline 32 was purified by flash chromatography (silica, acetone, 94% recovery) and then reacted with the benzyl chloride 41 to yield pale white crystals identified by NMR as the quarternary salt 53. The reaction, shown in Scheme 23, went in 87% yield.



SCHEME 23

The reaction of the salt 53 with the MMTS anion 38 produced a brown oil which showed four components by TLC (silica; ether : ethanol = 8:1) and a complex S-CH_3 region in its NMR. As the product was unstable, it was treated directly with $NaBH_3CN$ in methanolic acetic acid as before. Under these conditions, the material decomposed to the N-benzylisoquinoline 55 and MMTS. These reactions are shown in Scheme 24.


CH3O
CH3O
N+Cl−
+
OCH3
OCH3
53
O
CH3—S
CH−Li+
CH3—S
38
-35°C, Ar
CH3O
CH3O
N
CH
S
S=O
H3C
CH3
OCH3
OCH3
NaBH3CN;
MeOH, CH3COOH
54
+ MMTS
55

SCHEME 24

The enamine reduction was attempted again, using THF rather than methanol as the reaction solvent. The course of the reaction was easily followed by dramatic colour changes from deep purple, to red to clear yellow. Thin layer chromatography indicated the reaction had gone to completion (Figure 7 , Chapter 3). The yellow oil isolated in this reduction represented a 43% yield in the two steps from the quarternary salt 53. Purification by flash chromatography (silica, ether : ethanol = 8:1, 70% recovery) produced a clear yellow oil containing a mixture of the three mercaptal components at R_f = 0.33, 0.20, 0.16. This material was immediately cyclized in concentrated HCl as previously described, and the characteristic yellow needles precipitated from the reaction mixture in 60% yield. Reduction with $NaBH_4$ in ethanol produced a white crystalline compound in 60% yield, which had melting point, NMR and mass spectra identical with natural (±)-tetrahydropalmatine 35.

2.6 Proposed Mechanisms of Mercaptal Cyclization

The cyclization of the substituted mercaptal intermediates is the key step in the Kiparissides synthesis of protoberberines. She proposed* that the reaction proceeds through an acidic hydrolysis to an aldehyde intermediate, in accordance with the ideas of Kuhn and co-workers (47), which then cyclized to complete the protoberberine skeleton. The cyclized product that she isolated was the enamine 44, which would be expected to yield the iminium salt 34 in a strongly acidic solution (Scheme 25).

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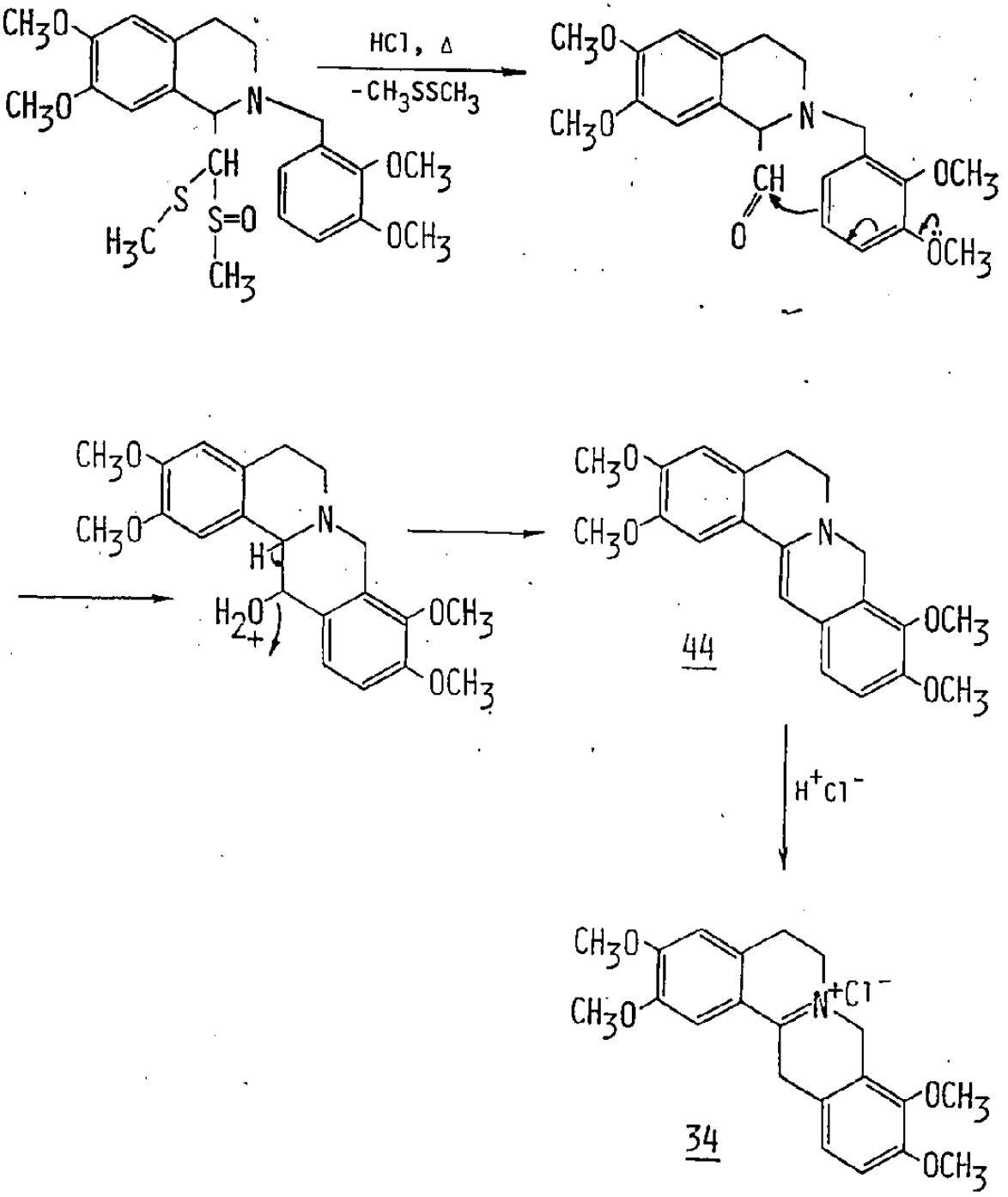
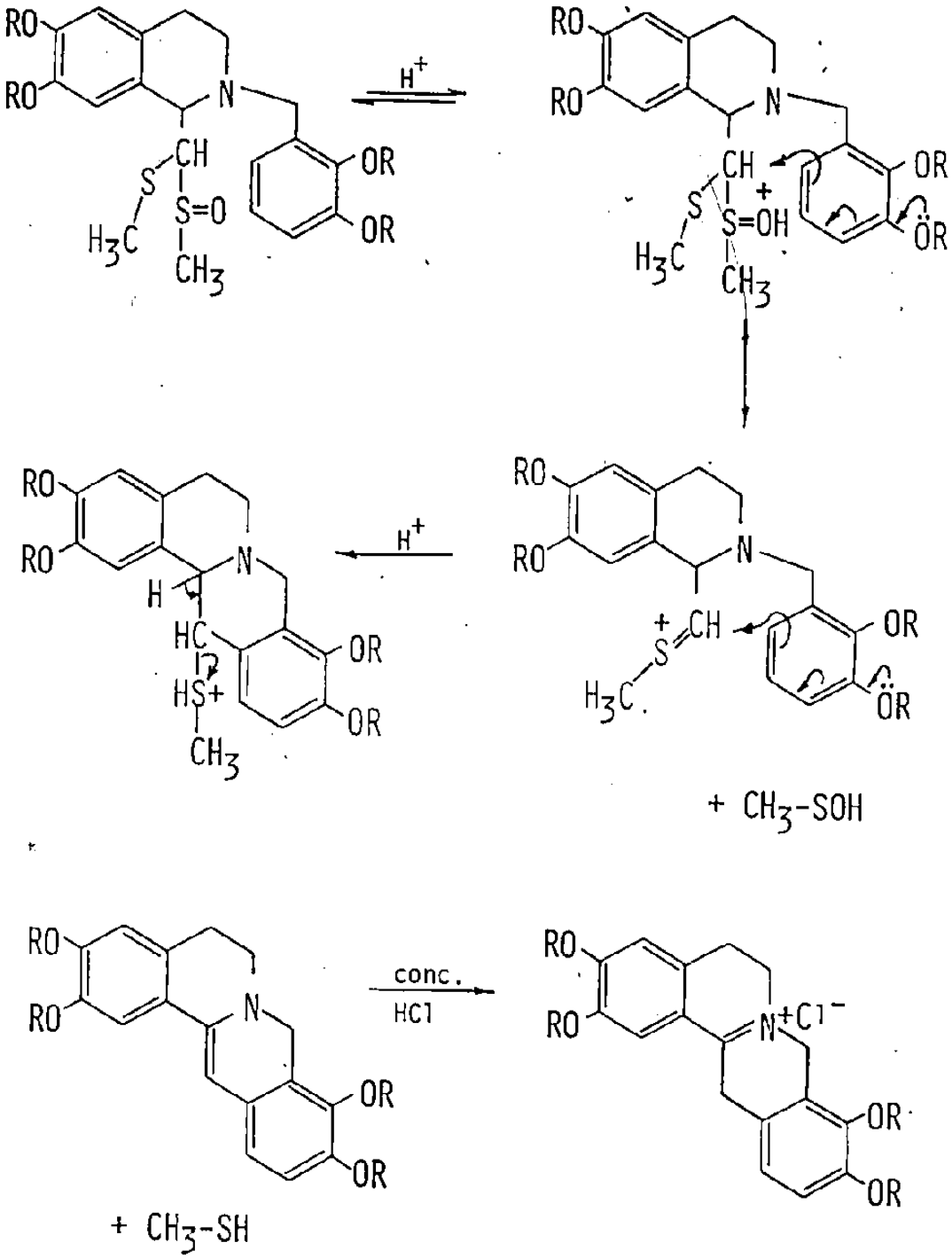
* Reference 34, p. 37.



SCHEME 25

An unsuccessful attempt was made to generate the aldehyde intermediate in chloroform for investigation by infrared methods. Intercepting the aldehyde as the 2,4-dinitrophenylhydrazone was also tried, but this too proved unsuccessful.

An alternate mechanism, not involving the formation of a carbonyl intermediate is also possible, although the fate of sulfur in the reaction is yet unknown. (Scheme 26).


RO
RO
N
CH
S
S=O
H3C
CH3
OR
OR
H+
S=OH
+ CH3-SOH
H
HC
HS+
conc.
HCl
N+Cl−
+ CH3-SH

SCHEME 26

2.7 Conclusion

The adduct of the MMTS anion and the iminium salt 39, which is the most important and unique compound of the synthetic route to (±)-tetrahydropalmatine, has been shown to be a mixture of four diastereomers, as would be expected for a system containing three chiral centers. The diastereomers have been shown to lead to the same product, the dihydroprotoberberinium chloride 34. This iminium salt, which was shown to yield (±)-tetrahydropalmatine on reduction with $NaBH_4$, was used in a new total synthesis of corydaline. This synthetic route, based on a reaction developed by Bersch (43), is much shorter than methods currently available in the literature (48).

Furthermore, the present studies show that isoquinolines may be substituted for 3,4-dihydroisoquinolines as starting materials in the Kiparissides synthesis. With this finding, it should be possible to synthesize tetrahydroprotoberberines with substitution patterns different from those available from the 3,4-dihydro compounds.

CHAPTER 3

EXPERIMENTAL

Apparatus, Materials and Methods

The continuous wave ^1H NMR spectra were run on a Varian EM 390 spectrometer. The Fourier transform spectra were run on either a Bruker WP 80 or WH 90 spectrometer. Unless otherwise specified, the samples were dissolved in chloroform-d using tetramethylsilane (TMS) as the internal standard. Chemical shifts, quoted as δ values, were measured in relation to TMS. The symbols s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet are used in reporting spectra.

Mass spectra were recorded on either a Consolidated Electrodynamics Corporation Model #21-110B mass spectrometer or a V.G. Micromass 7070 F mass spectrometer, at 70 eV.

Infrared spectra were recorded on a Perkin Elmer 283 spectrometer in chloroform solution. Melting points were determined on a Kofler micro hot stage and are uncorrected. The microanalyses were performed by the Guelph Chemical Laboratories Limited, Guelph, Ontario.

Column and thin layer chromatography (TLC) were performed using silica gel 60 as the adsorbent. Gravity columns were run on Baker 60-200 mesh silica, and "flash" columns prepared as described in the literature (36). Lobar columns were run using a prepacked

Merck silica gel 60, size B column. High pressure liquid chromatography (HPLC) was performed on a Spectra-Physics SP-8000 Liquid Chromatograph, using a reverse phase 250 x 4.6 mm ID Spectra-Physics column packed with 10 μm Lichrosorb RP-8. The chromatography was performed at room temperature and the mobile phase was a linear MeOH/H_2O gradient from 6:4 v/v to 9:1 v/v. Detection was by U.V., λ = 254 nm.

Tetrahydrofuran (THF) was dried by distillation from sodium in a nitrogen atmosphere, just prior to use.

Synthesis of (±)-Tetrahydropalmatine 35

3,4-Dihydro-6,7-dimethoxyisoquinoline 40

(a) N-3,4-dimethoxyphenylethylformamide 43: β-3,4-dimethoxyphenylethylamine (38 g, 0.21 moles) and 90% formic acid (14 g) were heated under reflux for 21 hours. Excess formic acid was removed on the rotary evaporator and the clear yellow product vacuum distilled (185°/0.2 mmHg) to yield a clear yellow oil (40.1 g, 90%).

^{1}H NMR: 2.76 (2H, t, $-CH_2-CH_2-N$, J = 7.5 Hz), 3.52 (2H, m, $-CH_2-CH_2-N$), 3.85 (6H, s, 2 x OCH_3), 6.29 (1H, s(broad), -NH), 6.68-6.88 (3H, m, arom.), 8.15 (1H, s, COH).

(b) To a stirred, refluxing solution of the formamide (12 g, 57 mmoles) in 50 ml of acetonitrile was added $POCl_3$ (10.5 ml, 114 mmoles) dropwise over a period of 25 minutes. After the reaction mixture had stirred for 2 h, it was cooled to 0°, and shaken with petroleum ether (20 ml, b.p. 30-60°) and the top layer discarded. Hydrochloric acid

(10%) was then added, followed by basification to pH = 10 with conc. NH_4OH. The resulting mixture was filtered, and the filtrate extracted with benzene (4 x 40 ml). The combined extracts were dried over Na_2SO_4 and the solvent removed on the rotary evaporator. The brown, viscous residue was distilled under vacuum (111^{o} / 0.25 mm Hg) yielding a clear yellow oil (5.0 g, 46%).

^1H NMR: 2.67 (2H, t, $-\underline{CH_2}-CH_2-N$, J = 6 Hz), 3.72 (2H, m, $-CH_2-\underline{CH_2}-N$), 3.88 (3H, s, $-OCH_3$), 3.90 (3H, s, $-OCH_3$), 6.68 (1H, s, arom.), 6.80 (1H, s, arom.), 8.22 (1H, s(broad), HC = N).

2,3-Dimethoxybenzyl Chloride 41

(a) 2,3-Dimethoxybenzyl alcohol: To a cold (0^{o}) solution of 2,3-dimethoxybenzaldehyde (7.62 g, 46 mmoles) in absolute ethanol (25 ml) was added $NaBH_4$ in excess. The mixture was stirred mechanically under nitrogen for 1.5 h after which time reaction appeared complete by TLC (ether). Solvent was removed under vacuum, H_2O added (30 ml) and excess $NaBH_4$ destroyed by the careful addition of 6M HCl. This mixture was extracted with ether (3 x 40 ml), and the organic extracts were dried over Na_2SO_4 and concentrated under vacuum to yield a clear, colourless oil (7.27 g, 43 mmoles, 93%).

^1H NMR: 2.38 (1H, s(broad), -OH), 3.85 (6H, s, 2 x OCH_3), 4.64 (2H, d, $-CH_2-Ar$, J = 3Hz), 6.95 (3H, m, arom.).

(b) To the benzyl alcohol (7.27 g, 43 mmoles) dissolved in CH_2Cl_2 (30 ml, freshly distilled from P_2O_5) was added $SOCl_2$ (4.9 ml, 67 mmoles,

freshly distilled from quinoline then linseed oil) dropwise with mechanical stirring and cooling in ice. The mixture was stirred for 24 h at room T, after which solvent and unreacted $SOCl_2$ were removed on the rotary evaporator. The residue was vacuum distilled (102^{o}/ 0.04 mm Hg) to yield a clear, pale yellow liquid (6.71 g, 36 mmoles, 84%).

^{1}H NMR: 3.72 (3H, s, $-OCH_3$), 3.86 (3H, s, $-OCH_3$), 4.58 (2H, s, $-CH_2$-Ar), 6.90 (3H, m, arom.).

3,4-Dihydro-6,7-dimethoxy-N-(2,3-dimethoxybenzyl)-isoquinolinium chloride 39

To a stirring solution of the isoquinoline 40 (2.0 g, 10.5 mmoles) in benzene (50 ml) was added the benzyl chloride 41 (2.0 g, 10.7 mmoles) dropwise. The solvent was removed under vacuum after 24 h, and the oily residue crystallized from benzene : ethanol = 20:1 to yield yellow prisms (3.87 g, 10.2 mmoles, 97%) m.p. 187-189^{o}C.

^{1}H NMR: 3.16 (2H, t, $-CH_2-CH_2-N^+$, J = 7.5 Hz), 3.81-4.0 (2H, m, $-CH_2-N^+$), 3.88 (3H, s, $-OCH_3$), 3.94 (3H, s, $-OCH_3$), 3.96 (3H, s, $-OCH_3$), 4.00 (3H, s, $-OCH_3$), 5.44 (2H, s, N^+-CH_2-Ar), 6.94-7.34 (4H, m, arom.), 7.74 (1H, s, arom.), 10.46 (1H, s, $-CH=N^+$).

Preparation of the Substituted Mercaptal 33

(a) Anion Generation: To a stirred solution of MMTS (methyl methylthiomethyl sulfoxide, 1.80 g) in freshly-distilled THF (75 mls)

was added n-butyl lithium (2.6 M in n-Hexane, 5.4 ml, ~1 eq.) under an atmosphere of dry argon. The solution was stirred mechanically and its temperature maintained at -35°C during the addition and for 30 minutes afterwards.

(b) Condensation: The cold solution above was added dropwise to a stirred suspension of the iminium chloride 39 (3.0 g, 7.9 mmoles) in anhydrous THF (125 ml). The temperature was maintained at -30° during the addition and for three hours further, during which time the solid entered solution. Methylene chloride was added (200 ml), followed by H_2O (60 ml) to hydrolyze excess LiMMTS. This mixture was shaken, and the organic phase separated, dried over Na_2SO_4 and concentrated under vacuum. The yellow oily residue isolated (4.24 g, > 100%) showed a mixture of components by TLC. Using Et_2O : EtOH (abs) = 8:1 three components were visible at R_f = 0.16, 0.20, 0.33. Later studies using Baker "hexanes" : EtOH (abs) : THF = 6:3:1 showed four components present (R_f 0.3 to 0.5). (See Figure 2, Chapter 2).

Chromatography: 1.0 g of the crude oil was chromatographed on silica gel using Et_2O : EtOH = 8:1 as the eluant, and the "flash" method of chromatography as described by Still (36). Three fractions were isolated and submitted for ^1H NMR spectroscopy. (Table 3). (Figures 8, 9, 10).

TABLE 3: ^1H HNMR Data from Chromatography of Substituted Mercaptal 33

Component (R_f on silica gel, $\frac{Et_2O}{EtOH} = \frac{8}{1}$)	Wt. Recovered from Column (mg)	^1H NMR CHEMICAL SHIFTS		
		$S-CH_3$	$-OCH_3$	Aromatic
0.33	360	2.16(s), 2.22(s) 2.36(s), 2.62(s)	3.78(3H,s), 3.88(3H,s), 3.89(3H,s), 3.91(3H,s).	6.60-7.16 (5H,m)
0.20	120	2.22(s), 2.64(s)	3.87(9H,s), 3.78(3H,s).	6.61-7.06 (5H,m)
0.16	280	2.02(s), 2.30(s) 2.68(s), 2.70(s)	3.78(3H,s), 3.85(6H,s), 3.88(3H,s).	6.62-7.24 (5H,m)

M.S.: All three mercaptal components gave a characteristic fragmentation pattern, similar to that given in Table 2. (Chapter 2).

Cyclization of the Three Mercaptals to Dihydropalmatine Chloride 34

Each of the three residues isolated from the column was subjected to cyclization by the following procedure: 75 mg of the yellow oil were dissolved in concentrated HCl (3.5 ml) and heated in a flask equipped with a reflux condenser, on a steam bath in an atmosphere of N_2. The flask was allowed to cool to room temperature and was then placed in an ice-salt bath. Bright yellow crystals were obtained in 70 to 90% yield, which were recrystallized from conc. HCl and washed with cold acetone and ether. The melting points observed for the cyclized materials were 152-157°(d), 153-162°(d) and 157-165°(d) which were reaction products of the R_f = 0.33, 0.20 and 0.16 mercaptals, respectively. The differences in the melting points of the three products are no doubt due to varying degrees of solvation of the crystals.

M.S.: The three products of cyclization gave similar fragmentation patterns, including a base peak at m/e = 353, corresponding to the loss of H· from the iminium cation. The intensities of the peaks in the three spectra varied, however. This effect is due to differences in probe temperature, which was high in order to volatilize the chloride salts. Table 4 contains the fragmentation data from the cyclization product of the mercaptal R_f = 0.33. Only peaks greater than 20% of the base peak were recorded.

TABLE 4: M.S. Fragmentation of Cyclization Product from R_f = 0.33 Mercaptal

m/e	I (Percent Base Peak)
355	35
354	35
353	100
352	45
338	35
190	25
164	50
149	35

^{1}H NMR (TFA): The cyclized product from the mercaptal R_f = 0.33 showed the following signals:

3.40 (2H, m, C(5)H_2), 4.04 (3H, s, -OCH_3), 4.15 (9H, s, 3 x OCH_3), 4.1-4.35 (2H, m, C(6)H_2), 4.64 (2H, s(broad), C(13)H_2), 5.30 (2H, s(broad), C(8)H_2), 6.94-7.78 (4H, m, arom.).

(±)-Tetrahydropalmatine 35

Each of the cyclized products was subjected to borohydride reduction by a method similar to the following:

To a solution of the chloride (14 mg, 0.04 mmole) in absolute EtOH (10 ml) was added sodium borohydride in excess. The mixture was stirred mechanically under N_2 for 45 minutes, at which time the reaction appeared complete by TLC (ether). Solvent was removed under vacuum, H_2O added (15 ml) and glacial acetic acid added dropwise with cooling to remove unreacted $NaBH_4$. Basification with a saturated solution of NaOH to pH > 10 was followed by extraction with ether (4 x 15 ml). The organic phase was shaken with 10% HCl (3 x 10 ml) after which the aqueous layer was basified to pH > 10 with NaOH (saturated solution). Extraction of the basic solution with ether (3 x 15 ml) followed by drying over Na_2SO_4 and concentration under vacuum yielded a pale white crystalline product (11.7 mg, 90%) m.p. 146-148° (lit. m.p. 148° (21)).

^{1}H NMR: 2.62-4.35 (9H, m, C(5)H_2, C(6)H_2, C(8)H_2, C(13)H_2, C(13a)H), 3.85 (6H, s, 2 x OCH_3), 3.87 (3H, s, -OCH_3), 3.89 (3H, s, -OCH_3), 6.62 (1H, s, arom.), 6.73 (1H, s, arom.), 6.82 (1H, s, arom.), 6.85 (1H, s, arom.).

Similar data were obtained for all three reduction products, and were found to be identical with that for natural (±)-tetrahydropalmatine.

Synthesis of Corydaline 36

Dehydrocorydaline Iodide 45

Dihydropalmatine chloride 34 (288 mg, 0.74 mmole) was treated with 10% acetic acid (10 ml), 30% formaldehyde (1 ml) and sodium acetate (124 mg). The mixture was heated on a steam bath for 15 minutes under N_2, after which 2.5 ml of a saturated solution of NaI was added. The flask was cooled to room temperature, then placed in the refrigerator. The fine yellow needles which formed (247 mg, 68%) were recrystallized from 47-51% HI to yield bright yellow square prisms, m.p. 139-143°(d).

^{1}H NMR: 3.00 (3H, s, $-CH_3$), 3.30 (2H, m, $-\underline{CH_2}-CH_2-N^+$), 3.96 (3H, s, $-OCH_3$), 4.02 (3H, s, $-OCH_3$), 4.08 (3H, s, $-OCH_3$), 4.32 (3H, s, $-OCH_3$), 5.12 (2H, m, $-CH\ -\underline{CH_2}-N^+$), 7.00 (1H, s, arom.), 7.25 (1H, s, arom.), 8.02 (2H, s, arom.), 10.24 (1H, s, arom.).

(±)-Corydaline 36

To a solution of the iodide (65 mg, 0.13 mmole) in 95% EtOH (10 ml) was added $NaBH_4$ (10 mg, 0.26 mmole). The mixture was stirred mechanically under N_2 for 1 hour, at which time the reaction mixture was still deep orange in colour. A further 10 mg of borohydride were then added along with one drop of glacial acetic acid. The colour of the reaction mixture changed immediately to pale yellow, and TLC (Ether : Petroleum ether = 9:1) showed one major component present at R_f = 0.4. Solvent was removed under vacuum, H_2O added (15 ml) and

excess $NaBH_4$ destroyed by the careful addition of glacial acetic acid. Basification to pH > 10 with a saturated solution of NaOH was followed by extraction with ether (3 x 20 ml). This extract was shaken with 10% HCl (2 x 25 ml) and the aqueous layer basified to pH > 10 as before. This alkaline solution was extracted with ether (3 x 25 ml), and the organic extract dried over Na_2SO_4 and concentrated under vacuum to yield a yellow solid (29 mg, 60%). Recrystallization from absolute EtOH yielded deep yellow prisms, m.p. 135-136° (lit. m.p. 135° (21)).

^1H NMR: Was identical with that of natural corydaline.
0.90 (3H, d, $-CH_3$, J = 6Hz), 2.40-4.45 (8H, m, $C(5)H_2$, $C(6)H_2$, $C(8)H_2$, C(13)H, C(13a)H), 3.88 (12H, s, 4 x OCH_3), 6.59 (1H, s, arom.), 6.68 (1H, s, arom.), 6.82 (1H, s, arom.), 6.86 (1H, s, arom.). (Figures 11 and 12).

M.S.: The mass spectrum showed a parent peak at m/e = 369 (Intensity = 30%) and a base peak at m/e = 178 corresponding to $C_{11}H_{14}O_2$.

Synthesis of 10,11-Dimethoxy-5,6,13,13a-tetrahydro-8H-dibenzo [a,g] quinolizine (10,11-Dimethoxyberbine) 37

3,4-Dimethoxybenzyl Chloride 48

(a) 3,4-Dimethoxybenzyl Alcohol: To a cold (0°) solution of freshly distilled veratraldehyde (10 g, 60 mmoles) in 95% EtOH (25 ml) was added excess $NaBH_4$. The mixture was stirred mechanically under N_2 and allowed to warm up to room T. The reaction appeared complete by TLC (ether) after it had been stirred for 1 h at room T. The

solvent was removed under vacuum, H_2O added (10 ml), the mixture cooled in ice and excess $NaBH_4$ destroyed by careful addition of 10% HCl. The solution was extracted with ether (3 x 35 ml) and the extract dried over Na_2SO_4. Concentration under vacuum yielded 10.0 g (59 mmoles, 98%) of clear, almost colourless oil, showing one component by TLC (ether) at R_f = 0.24.

^1H NMR: 2.55 (1H, s, -OH) (Disappears on addition of D_2O), 3.90 (6H, s, 2 x OCH_3), 4.62 (2H, s, $-CH_2-Ar$), 6.90-7.05 (3H, m, arom.).

(b) The benzyl alcohol (2 g, 11.9 mmoles) was dissolved in CH_2Cl_2 (15 ml) freshly distilled from P_2O_5. To this was added $SOCl_2$ (1.4 ml, 19.3 mmoles, distilled from quinoline then linseed oil) dropwise with mechanical stirring. The mixture was allowed to stir for 48 h under a $CaCl_2$ drying tube. At this time, solvent and unreacted $SOCl_2$ were removed on a rotary evaporator and the deep brown oily residue vacuum distilled (75^o/0.03 mm Hg) to yield 1.85 g (9.9 mmoles, 83%) clear colourless oil.

^1H NMR: 3.80 (6H, s, 2 x OCH_3), 4.58 (2H, s, $-CH_2-Ar$), 6.85-7.10 (3H, m, arom.).

M.S.: Base peak at m/e = 151 = M^+ - Cl and parent peaks at m/e = 186 (30%) and 188 (10%).

Quarternary Salt 46

Isoquinoline (3.22 g, 25 mmoles, freshly distilled from zinc dust (224^o / 760 mm Hg)) was dissolved in benzene (30 ml). The benzyl

chloride 48 (4.41 g, 23.6 mmoles) was added slowly, and the mixture refluxed gently for 24 h. At this time, the yellow crystals which had formed were filtered off and washed. The solid was dried on filter paper to yield 3.92 g (12.4 mmoles, 50%) of product. The mother liquor was heated under reflux for a further three hours producing 0.309 g of yellow crystals (total yield 54%).

^{1}H NMR: (CD_3OD): 3.81 (3H, s, $-OCH_3$), 3.85 (3H, s, $-OCH_3$), 5.95 (2H, s, $N-CH_2-Ar$), 6.98-7.30 (3H, m, arom.), 7.96-8.30 (4H, m, arom.), 8.48-8.82 (2H, m, -CH=CH-N), 10.20 (1H, s, HC=N).

Anal. Calc. for $C_{18}H_{18}O_2NCl$: C, 68.52; H, 5.75, N, 4.44; Cl, 11.24%.

Found: C, 68.53; H, 5.69; N, 4.14; Cl, 11.15%.

Condensation of the MMTS Anion with the Quarternary Salt 46

(a) Anion Generation: To 1.10 g of freshly distilled MMTS was added THF (50 ml), and the solution was stirred mechanically under dry argon and cooled to -35°. To this cold solution was added 4.2 ml of n-BuLi (2.14 M in hexane, 1 eq.) dropwise via a syringe. The solution was stirred under dry argon for 45 min. at -35°.

(b) Condensation: The cold solution from (a) was added dropwise via a two-ended needle to a cold (-35°) stirred suspension of iminium chloride 46 (1.57 g, 5.0 mmoles) in THF (75 ml). The suspension was stirred mechanically under argon and its temperature maintained at -35° for a further 3.5 h, during which time the solution became red in colour. At this time, 150 ml of CH_2Cl_2 were added, followed by

40 ml H_2O to hydrolyze excess LiMMTS. The organic layer was drained off, and the aqueous fraction washed with CH_2Cl_2 (20 ml). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to yield 2.66 g (6.6 mmoles, > 100%) of brown oil which showed four components present by TLC (THF : Hexane = 6:1). The ^1H NMR of the crude material was very complex, showing at least six S-CH_3 peaks. Attempts to chromatograph the mixture on silica gel resulted in rapid decomposition to very polar material.

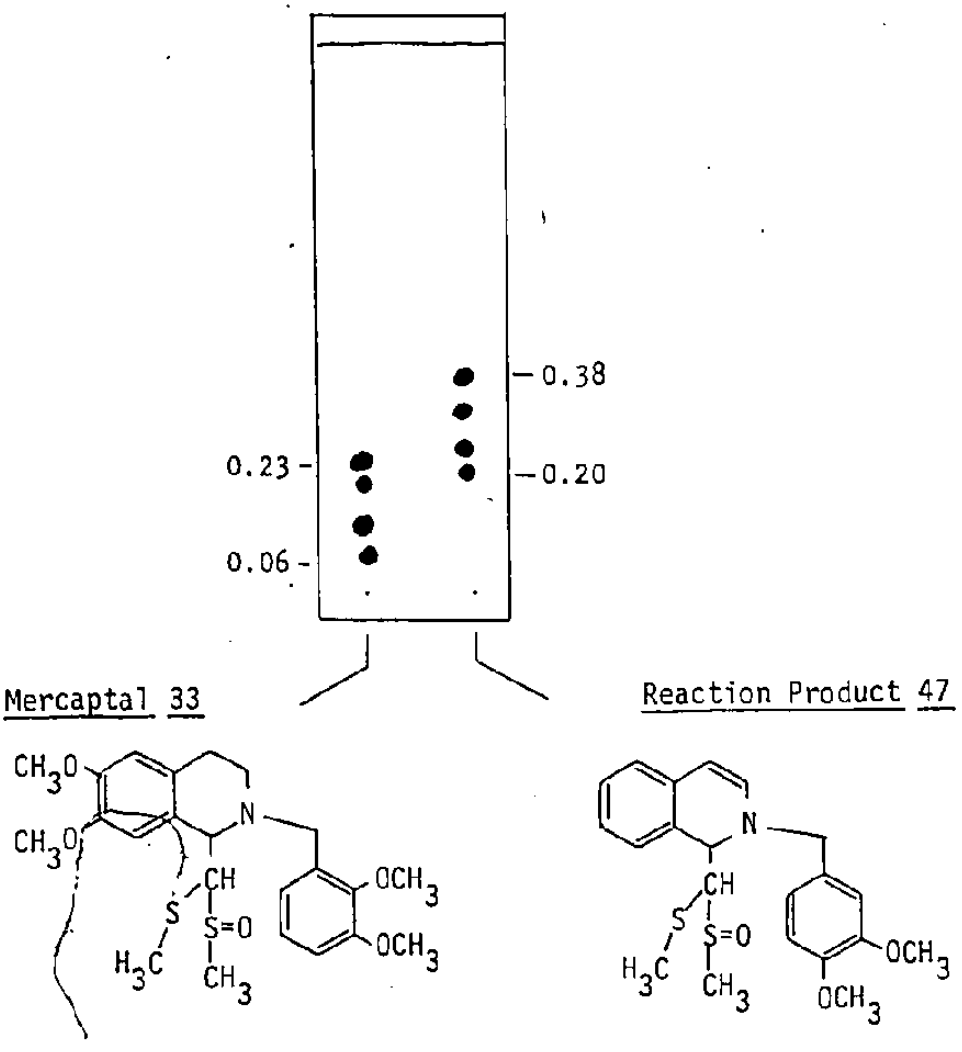


FIGURE 5: TLC of Substituted Mercaptals (THF : Hexane = 6:1)

Reduction of Enamine 47

To a stirred solution of the enamine (2.62 g, 6.5 mmoles as pure compound) in methanol (20 ml) was added glacial acetic acid (50 ml, solution pH = 3) followed by the addition of $NaBH_3CN$ (419 mg, 6.67 mmoles). Within two minutes of the addition of the cyanoborohydride, the deep purple solution turned clear yellow. Since the TLC of the solution (THF : Hexane = 6:4) was not conclusive, and no further changes were noted in the reaction flask, the solvent was removed under vacuum, 0.1 N NaOH added (30 ml) and the solution extracted with ether (3 x 40 ml). During the course of the extraction, 2 M NaOH was added to maintain pH > 10. The etheral layers were combined and shaken with 10% HCl (4 x 20 ml) to take the basic material into the aqueous phase. Basification of the aqueous extract to pH > 10 with saturated NaOH solution was followed by extraction with ether (3 x 50 ml). The extract was dried over Na_2SO_4 and concentrated under vacuum to yield a yellow oil (1.23 g, 3.04 mmole, 60% based on quarternary salt 46 used in the MMTS condensation). The TLC of the oil (THF : Hexane = 6:4) showed three components present at R_f = 0.12, 0.21 and 0.24, whereas the starting material showed four spots from R_f 0.14 to 0.29.

^1H NMR: 1.94 (3H, s, S-CH_3), 2.18 (3H, s, S-CH_3), 2.50 (3H, s, S-CH_3), 2.76 (3H, s, S-CH_3), 2.62-4.75 (4H, m, N-CH_2-Ar and N-CH-CH-S), 3.56 (2H, t, -CH_2-CH_2-N, J = 4.5 Hz), 3.72 (2H, t, -CH_2-CH_2-N, J = 4.5 Hz), 6.72-7.34 (7H, m, arom.).

Cyclization of the Substituted Mercaptal 49 to the Iminium Salt 52

The reduction product above (1.23 g, 3.04 mmoles as pure compound) was dissolved in conc. HCl (15 ml) and heated in a steam bath in a flask equipped with a reflux condenser, under N_2 for 10 minutes. During this time, there was much bubbling and evolution of foul smelling gases. The solution was cooled to room T, and then placed in a refrigerator. No crystal growth was observed after three days, but when the flask was scratched with a stirring rod, crystal formation occurred within two hours. The flask was placed in the refrigerator overnight, after which the crystals were filtered off, washed, and dried on the vacuum line over P_2O_5. The yield of yellow crystals was 617 mg (1.87 mmoles, 62% in this step, 37% relative to the N-benzyl isoquinolinium salt 46).

^{1}H NMR (TFA): 3.40 (2H, t, C(5), J = 7.5 Hz), 4.04 (6H, s, 2 x OCH_3), 4.30 (2H, t, C(6), J = 7.5 Hz), 4.65 (2H, s(broad), C(13)), 5.20 (2H, s(broad), C(8)), 6.98 (1H, s, arom.), 7.08 (1H, s, arom.), 7.50-8.20 (4H, m, arom.).

M.S.: The mass spectrum showed a peak corresponding to the ion M^+-Cl and the expected peaks at m/e = 132 and 164 (base peak).

10,11-Dimethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine 37

To an ice cold solution of the iminium salt 52 (100 mg, 0.30 mmole) in 95% EtOH (10 ml) was added excess $NaBH_4$. The mixture was allowed to warm up to room T, and was stirred under N_2 for 1 h. At

this time the reaction appeared complete by TLC (ether) so the solvent was removed under vacuum, H_2O added (10 ml) and unreacted $NaBH_4$ destroyed by adding glacial acetic acid with cooling in ice. Basification to pH > 10 with a saturated solution of NaOH was followed by extraction with ether (4 x 20 ml). The etheral extract was shaken with HCl (3 x 25 ml) and the aqueous extract basified to pH > 10 as above. Extraction with ether (4 x 25 ml) followed by drying over Na_2SO_4 and concentration under vacuum yielded white crystals (75 mg, 0.25 mmole, 83%) which were recrystallized from EtOH (abs.)/$CHCl_3$. m.p. 124-125°C. Anal. Calc. for $C_{19}H_{21}O_2N$: C, 77.29; H, 7.12; N, 4.74%. Found: C, 77.60; H, 7.55; N, 4.73%.

^1H NMR: 2.62-3.85 (9H, m, $C(5)H_2$, $C(6)H_2$, $C(8)H_2$, $C(13)H_2$, C(13a)H), 3.85 (6H, s, 2 x OCH_3), 6.55 (1H, s, arom.), 6.60 (1H, s, arom), 7.10-7.20 (4H, m, arom.). (Figure 14).

I.R.: (Figure 15)

M.S.: The mass spectrum showed a molecular ion at m/e = 295 (Intensity = 90%) corresponding to $C_{19}H_{21}O_2N$ and a base peak at 164 corresponding to $C_{10}H_{12}O_2$.

The Synthesis of Tetrahydropalmatine Via an Isoquinoline Intermediate

Preparation of 6,7-Dimethoxyisoquinoline 32

(a) 3,4-Dihydro-6,7-dimethoxyisoquinoline was prepared by a Bischler-Napieralski cyclization of 3,4-dimethoxyphenylethylformamide as previously described.

(b) To the dihydroisoquinoline (2 g, 10.5 mmoles) dissolved in decalin (20 ml) was added 10% Pd/C catalyst (0.41 g). The mixture was stirred mechanically under reflux and a stream of N_2 used to sweep away the hydrogen evolved. After the reaction had proceeded for four hours, TLC (acetone) showed traces of starting material were present, so 0.26 g of fresh catalyst were added, and the mixture refluxed for a further 1 h. At this time, the flask was cooled to room temperature, and 50 ml $CHCl_3$ were added. The resulting mixture was filtered on paper, and the filtrate shaken with 6M HCl (3 x 50 ml) to take only the basic material into the aqueous phase. The aqueous solution was basified to pH > 10 with a saturated solution of NaOH, and extracted with $CHCl_3$ (4 x 75 ml). The organic extract was dried over Na_2SO_4 and concentrated under vacuum. The product was a dark brown oil (1.59 g, 0.84 mmoles, 80%) which crystallized into rosettes on standing. Thin layer chromatography (acetone) showed one spot at R_f = 0.34 and some polar, baseline material. The product was therefore chromatographed on a flash column (acetone) producing a clean, clear yellow oil in 94% recovery, which crystallized into rosettes on standing.

^{1}H NMR: 3.98 (6H, s, 2 x OCH_3), 7.00 (1H, s, arom.), 7.12 (1H, s, arom.), 7.45 (1H, d, -CH=CH-N, J = 6 Hz), 8.35 (1H, d, -CH=CH-N, J = 6 Hz), 9.00 (1H, s, -CH=N).

6,7-Dimethoxy-N-(2,3-dimethoxybenzyl)-isoquinolinium chloride 53

To a solution of the isoquinoline 32 (1.5 g, 7.9 mmoles) in

benzene (30 ml, freshly distilled from $CaCl_2$) was added 2,3-dimethoxybenzyl chloride 41 (1.5 g, 8.0 mmoles) dropwise with mechanical stirring. The mixture was gently refluxed under a $CaCl_2$ drying tube for 24 hours. At this time the fine white needles which had formed were filtered off, washed with fresh benzene and dried. Since the yield of crystals was only 1.37 g (3.6 mmoles, 46%), the mother liquor was stirred under reflux for a further 48 h. A further 1.22 g of crystals were obtained (3.2 mmoles, total yield 86%). The solid was recrystallized from benzene/chloroform producing white rods m.p. 109-112°C.

^{1}H NMR: 3.82 (3H, s, $-OCH_3$), 3.94 (3H, s, $-OCH_3$), 4.08 (3H, s, $-OCH_3$), 4.15 (3H, s, $-OCH_3$), 6.10 (2H, s, N^+-CH_2-Ar), 6.92-7.58 (4H, m, arom.), 7.98 (1H, s, arom.), 8.14, 8.48 (2H, AB quartet, $-N^+-CH=CH-$, $J_{3,4}$ = 7.5 Hz), 10.72 (1H, s, $HC=N^+$).

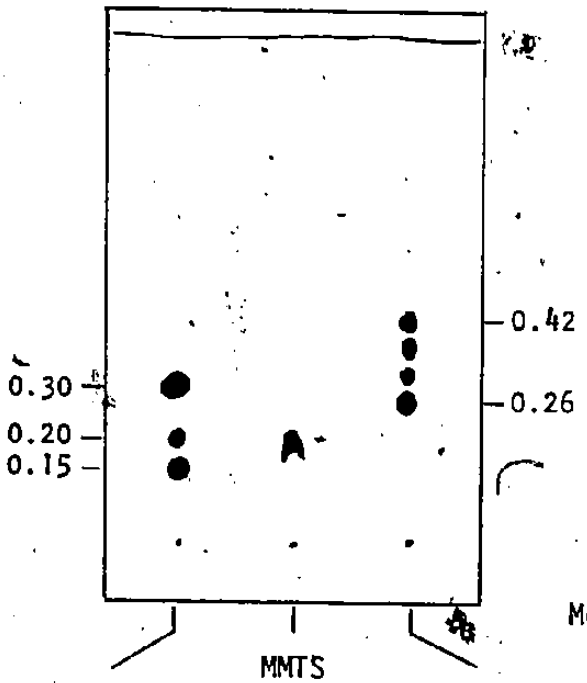
Preparation of Mercaptal Enamine 54

(a) Generation of MMTS anion: To 455 mg of freshly distilled MMTS (62°/0.01 mm Hg) was added 20 ml freshly distilled THF. The solution was stirred mechanically under dry argon and cooled to -35°. To this solution was added 2.4 ml n-BuLi (1.5 M in n-hexane, 1 eq.) dropwise via a syringe. The solution was stirred mechanically under argon at -35° for 30 minutes, during which time the clear, colourless solution turned clear yellow.

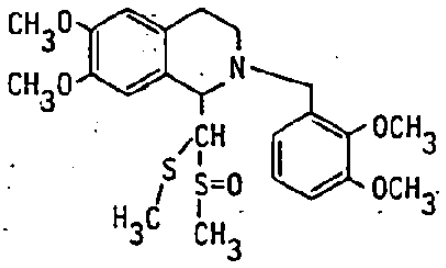
(b) Condensation: The cold solution above was added dropwise to a stirring suspension of the iminium chloride 53 (735 mg, 1.96 mmoles, dried overnight over P_2O_5, 0.01 mm Hg at 82°C) in 30 ml freshly

distilled THF. The suspension was stirred mechanically under argon at -35° for three hours.

To the flask was then added 80 ml CH_2Cl_2, followed by 20 ml H_2O to hydrolyze excess LiMMTS. The organic layer was drained off, and the aqueous layer washed with 10 ml CH_2Cl_2 which was then combined with the organic extract. This organic solution was dried over Na_2SO_4 and concentrated under vacuum to yield 1.09 g (2.4 mmoles, > 100%) of brown oil.



Mercaptal 33



Mercaptal 54

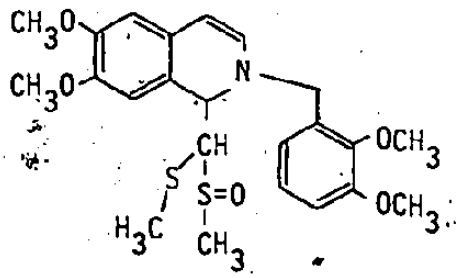
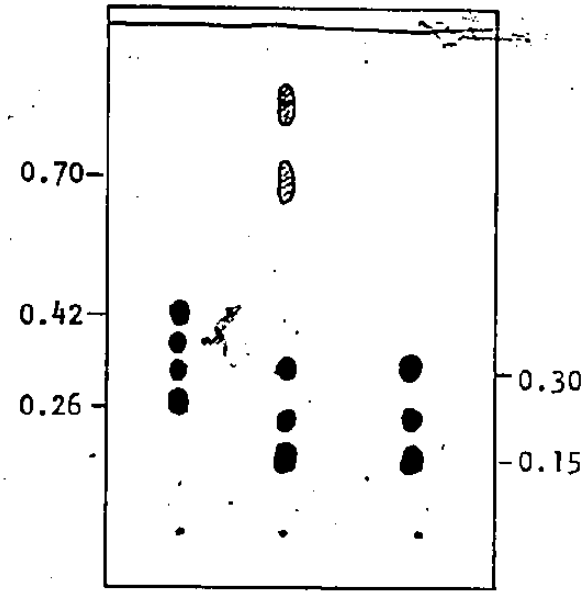
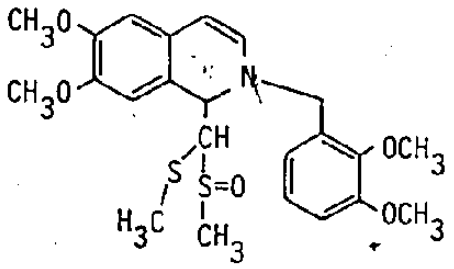


FIGURE 6: TLC of Mercaptals (Ether : EtOH = 8:1)

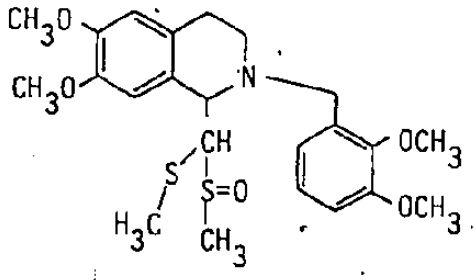
Enamine Reduction

To 1.06 g of the enamine (2.3 mmoles as pure material) was added 15 ml THF and 25 ml glacial acetic acid. The deep purple mixture was stirred mechanically under N_2. To this solution was added $NaBH_3CN$ (239 mg, 3.8 mmoles) and within 15 minutes, the following colour changes were noted: deep purple to deep red, to red, to orange, to clear golden yellow. At this time, TLC (Ether : EtOH = 8:1) showed that the reaction was complete. The solvent was removed under vacuum, 20 ml H_2O added, then 20 ml 2M NaOH to make the solution strongly alkaline. This solution was extracted with ether, and the organic extracts filtered on paper to remove an oily precipitate. The etheral solution was shaken with 10% HCl (3 x 30 ml) and the ether layer was discarded. The aqueous solution was rendered strongly alkaline with a saturated NaOH solution. Extraction with ether (3 x 30 ml) followed again by filtration of the organic layer on paper yielded a clear yellow etheral solution which was dried over Na_2SO_4 and concentrated under vacuum. The product was a yellow-green oil (383 mg, 0.824 mmoles, 43% relative to quarternary salt 53).





STARTING MATERIAL 54



COMPOUND 33

FIGURE 7 : TLC of Mercaptals (Ether : EtOH = 8:1)

To remove both the polar and fast-moving contaminants, 200 mg of the crude oil were chromatographed on a flash column (Ether : EtOH = 8:1) which yielded 140 mg (70% recovery) of clear yellow oil. TLC in this solvent system showed only the characteristic three components to be present at R_f 0.15, 0.26, 0.30.

^{1}H NMR: Was identical with the mercaptal 33 (containing the mixture of components) synthesized as per the procedure on page 56. The characteristic peaks of the spectrum are given as follows:

2.02-2.70 (6H, m, 2 x SCH_3), 3.88 (6H, s, 2 x OCH_3), 3.89 (6H, s, 2 x OCH_3), 6.60-7.19 (5H, m, arom.).

Tetrahydropalmatine 35

(a) The mercaptal was cyclized as previously described to yield the characteristic bright yellow needles in 56% yield which, without recrystallization, melted with decomposition at 142-150°C.

(b) To 17 mg (0.044 mmole) of the crystals in absolute EtOH (10 ml) was added $NaBH_4$ in excess. The mixture was stirred mechanically under N_2 for 1.5 h, during which time the yellow solution decolourized. The solvent was removed under vacuum, H_2O added (15 ml) and glacial acetic acid added with cooling to destroy unreacted $NaBH_4$. The solution was basified to pH > 10 with a saturated solution of NaOH, and extracted with ether (3 x 15 ml). The organic extract was shaken with 10% HCl (3 x 10 ml) and the aqueous layer basified as above. Extraction of this alkaline solution with ether (3 x 10 ml) was followed by drying

the organic layer over Na_2SO_4, and concentrating it under vacuum. A white crystalline residue was isolated (9 mg, 0.025 mmole, 58%) m.p. 145-147°C.

M.S.: The mass spectrum showed a parent peak at m/e = 355 (Intensity = 65%) corresponding to $C_{21}H_{25}O_4N$, and a base peak at m/e = 164, corresponding to $C_{10}H_{12}O_2$.

^1H NMR: 2.61-4.35 (9H, m, $C(5)H_2$, $C(6)H_2$, $C(8)H_2$, $C(13)H_2$, C(13a)H), 3.86 (12H, s, 4 x OCH_3), 6.62 (1H, s, arom.), 6.74 (1H, s, arom.), 6.82 (1H, s, arom.), 6.85 (1H, s, arom.).

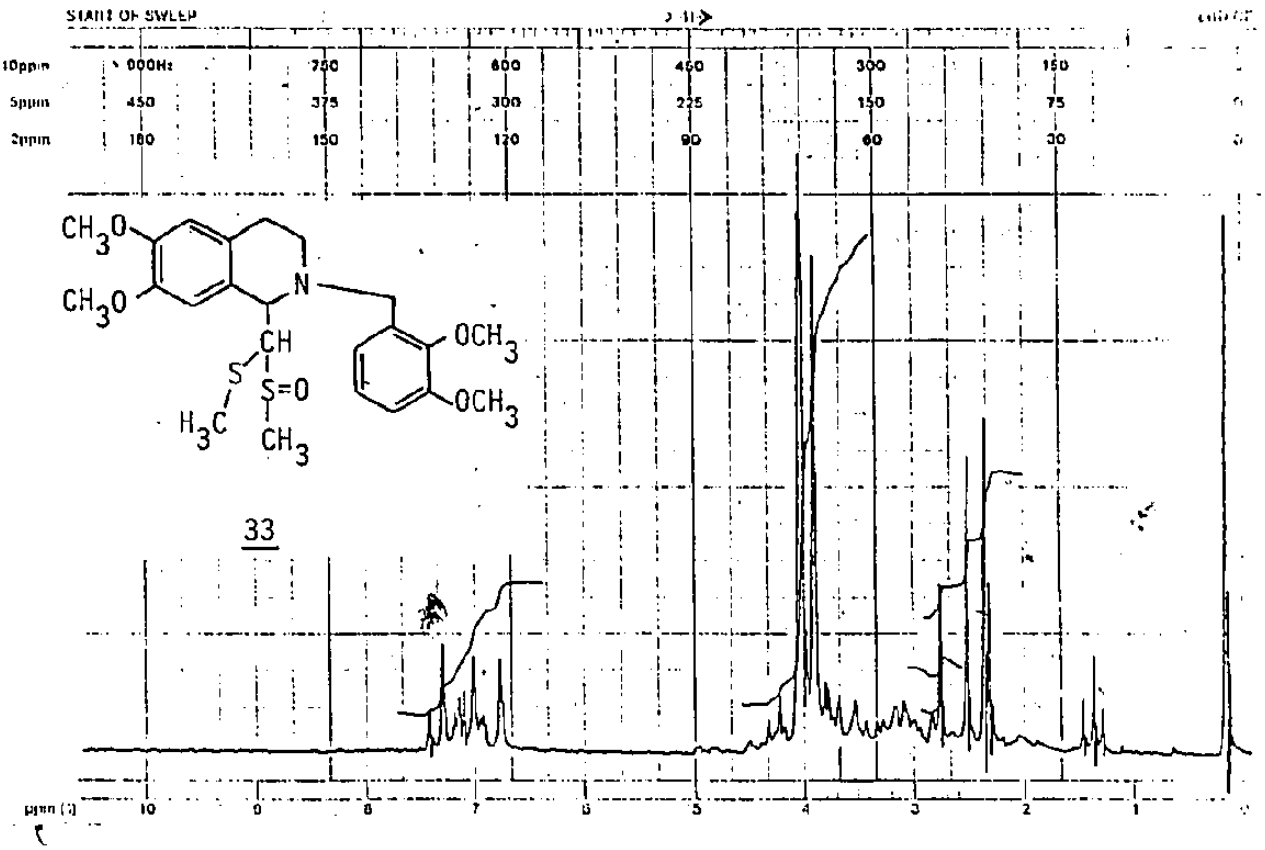


FIGURE 8: ^1H NMR of Mercaptal 33, R_f = 0.33

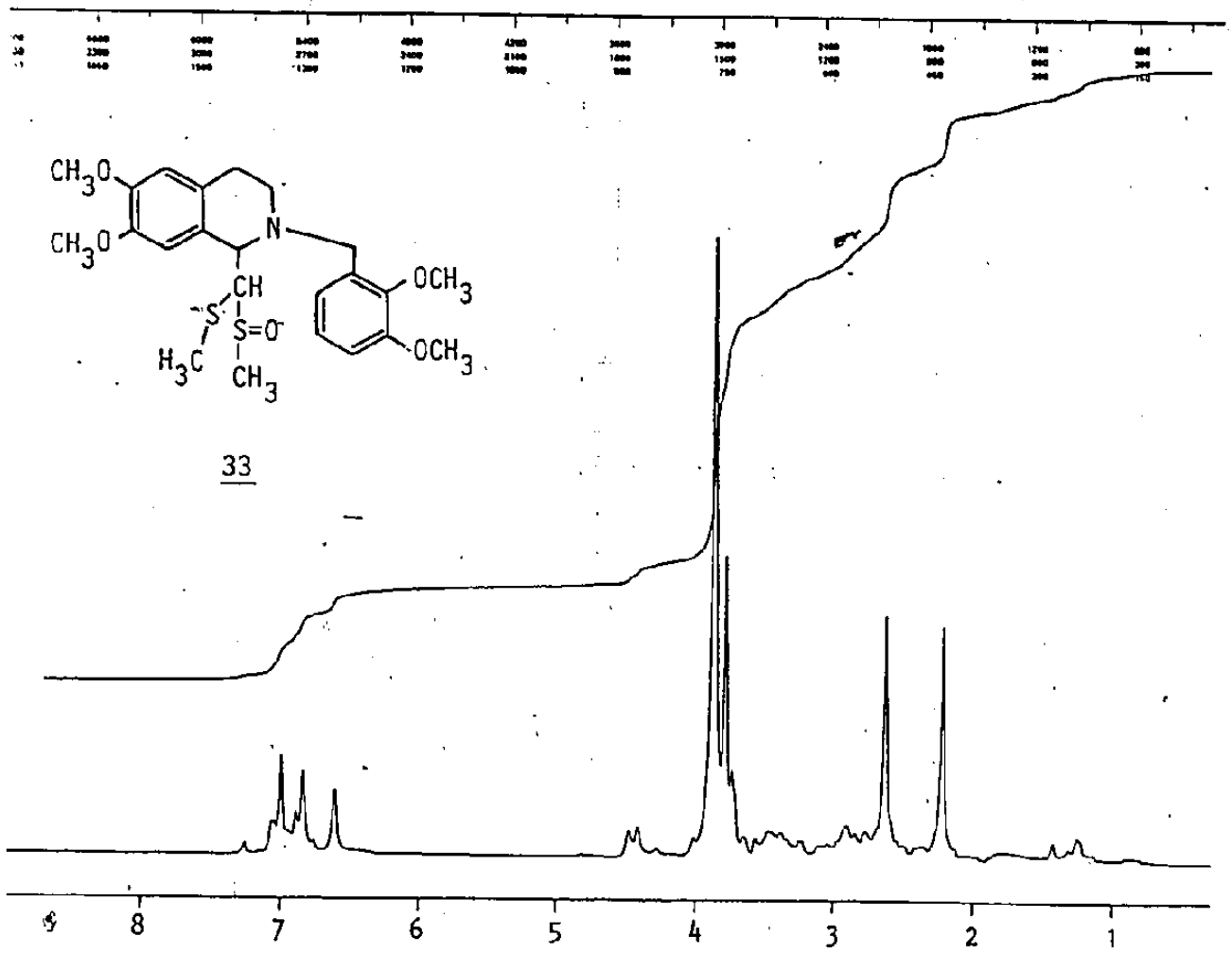


FIGURE 9: ^1H NMR of Mercaptal 33, R_f = 0.20

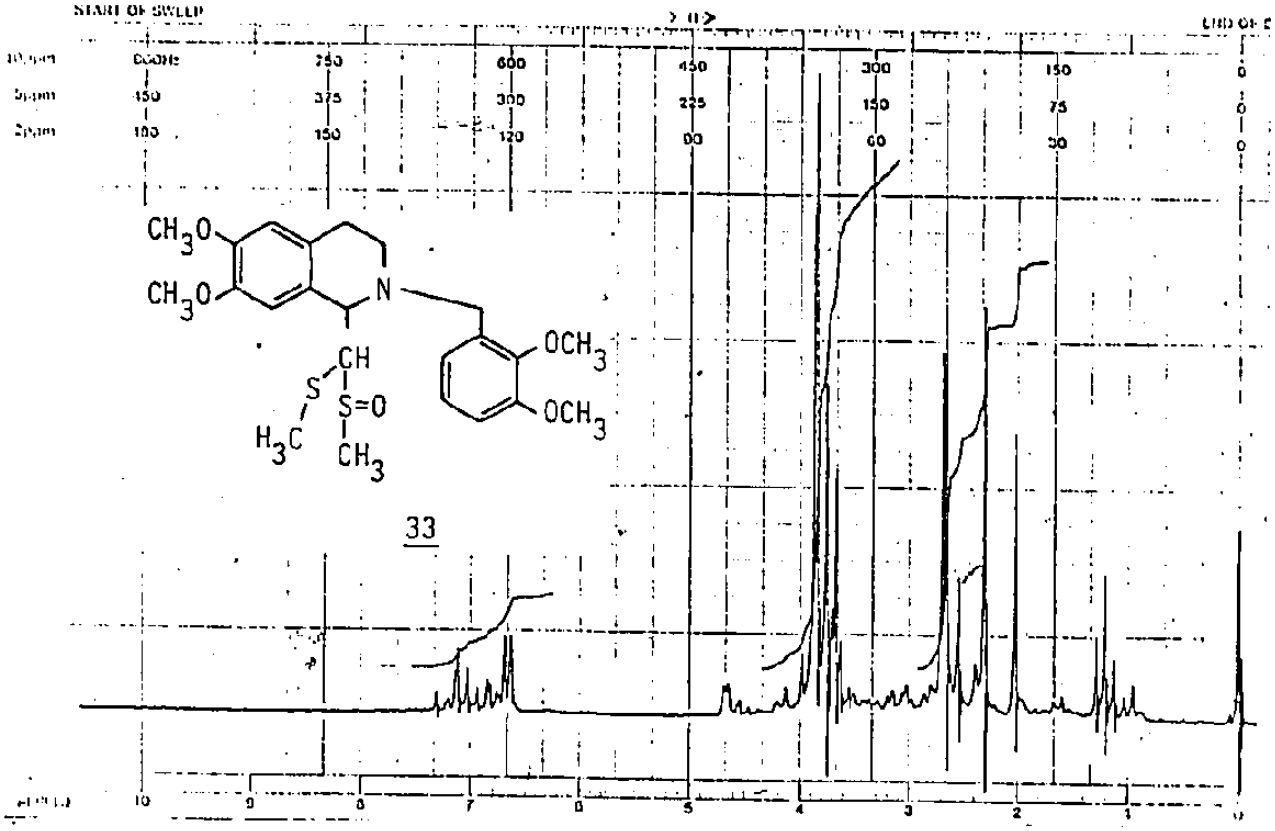


FIGURE 10: ^1H NMR of Mercaptal 33, R_f = 0.16

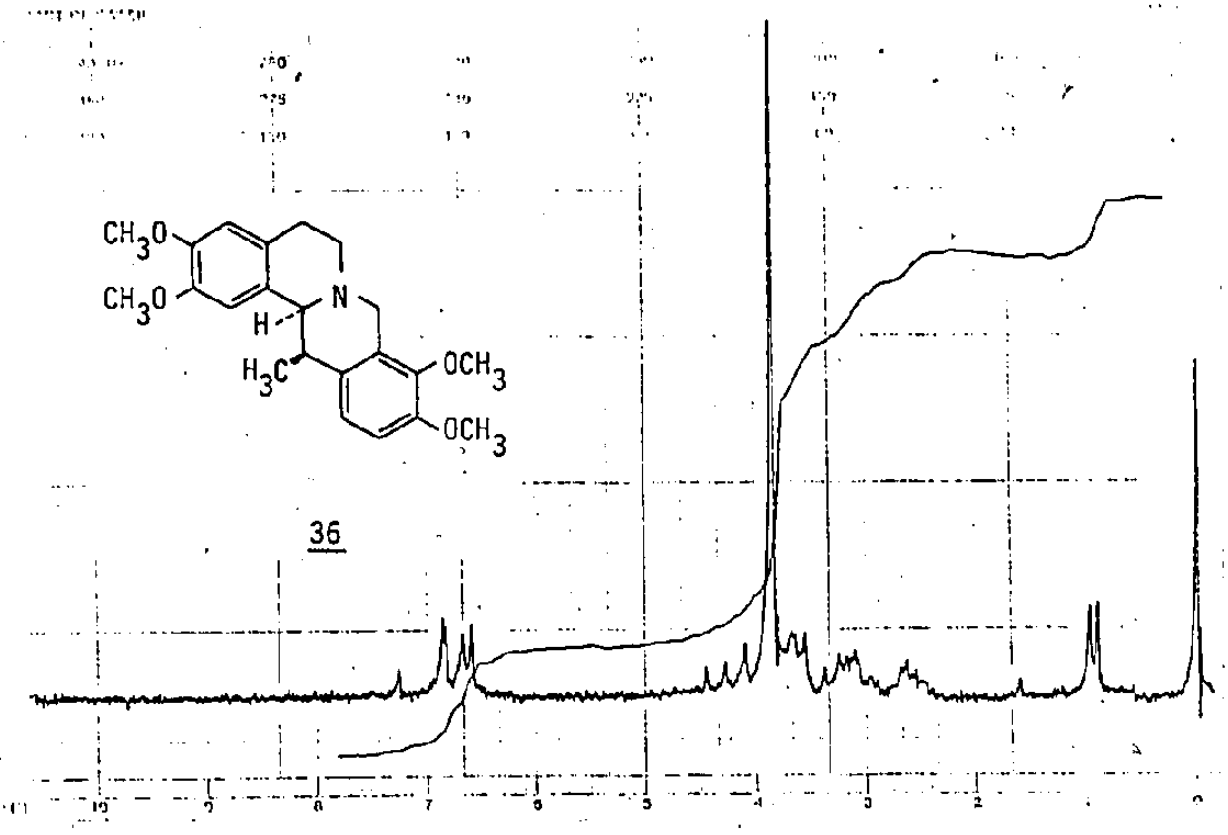


FIGURE 11: ^{1}H NMR of Corydaline 36 (synthetic sample)

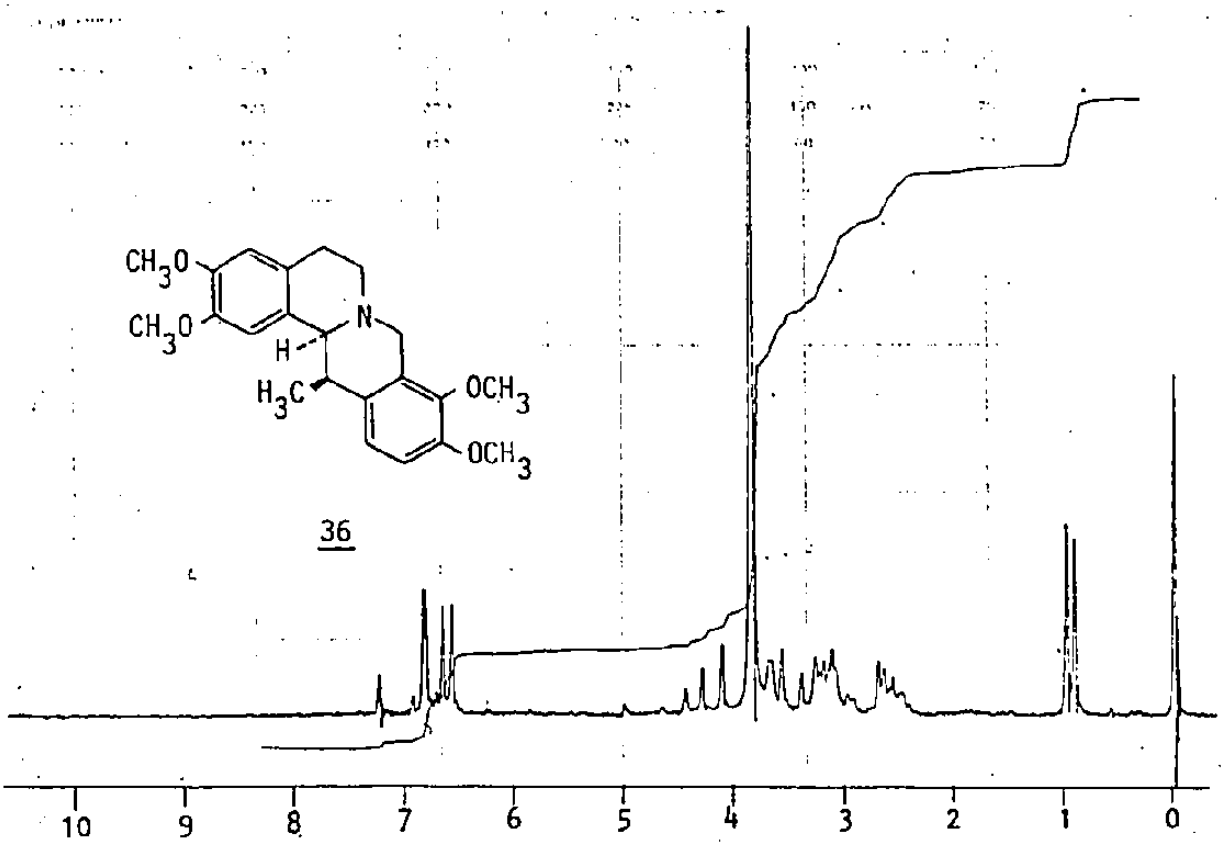
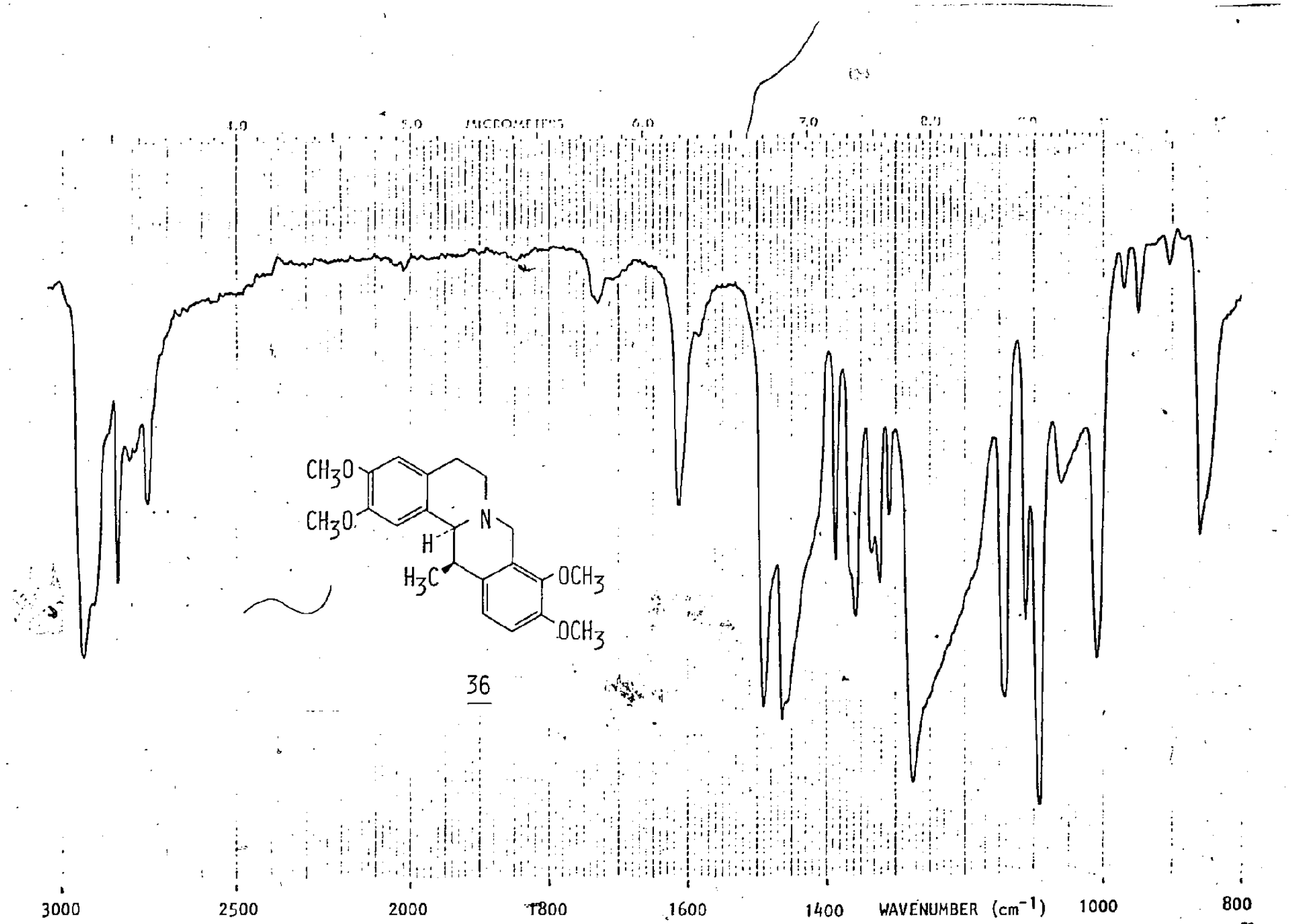


FIGURE 12: ^{1}H NMR of Corydaline 36 (authentic sample)



36

FIGURE 13: I.R. Spectrum of Corydaline 36 (synthetic sample)

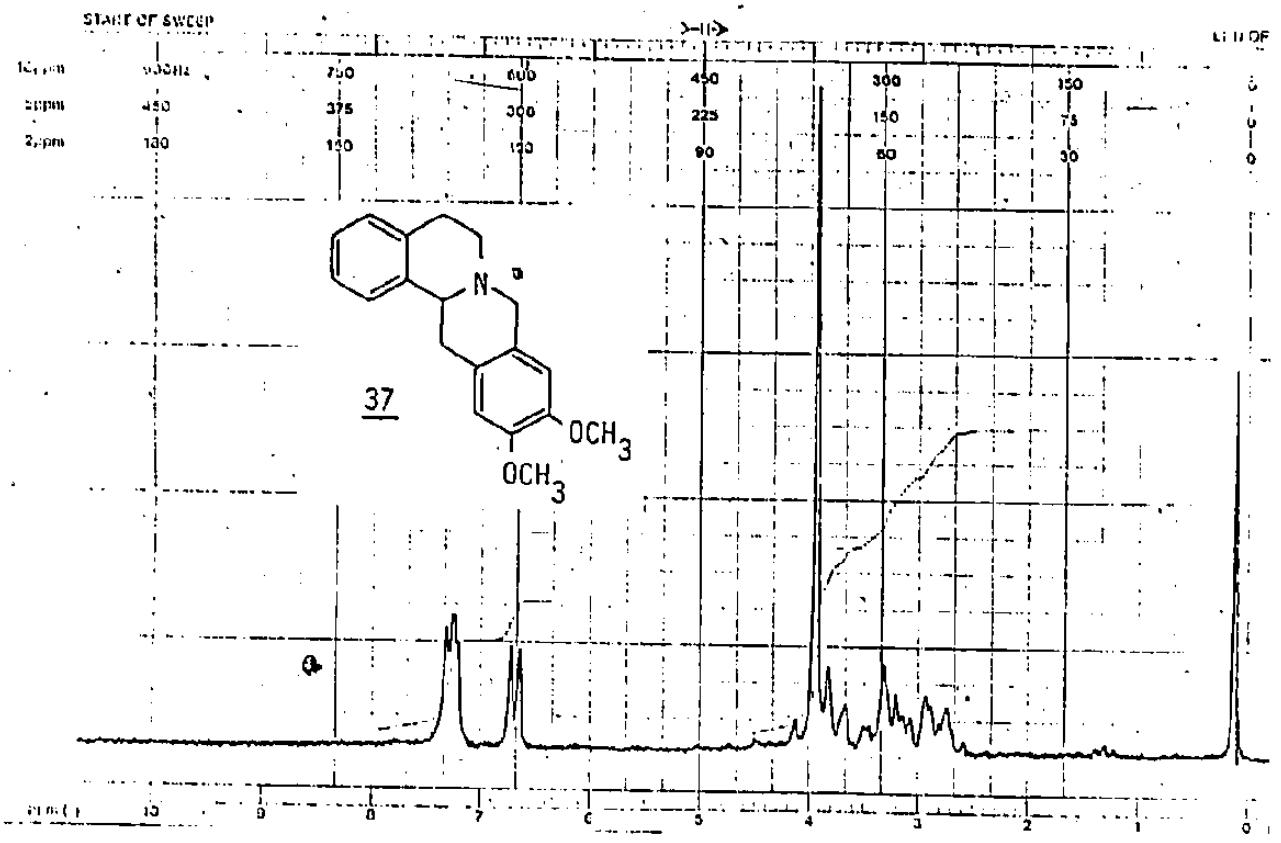


FIGURE 14: ^{1}H NMR of Protoberberine 37

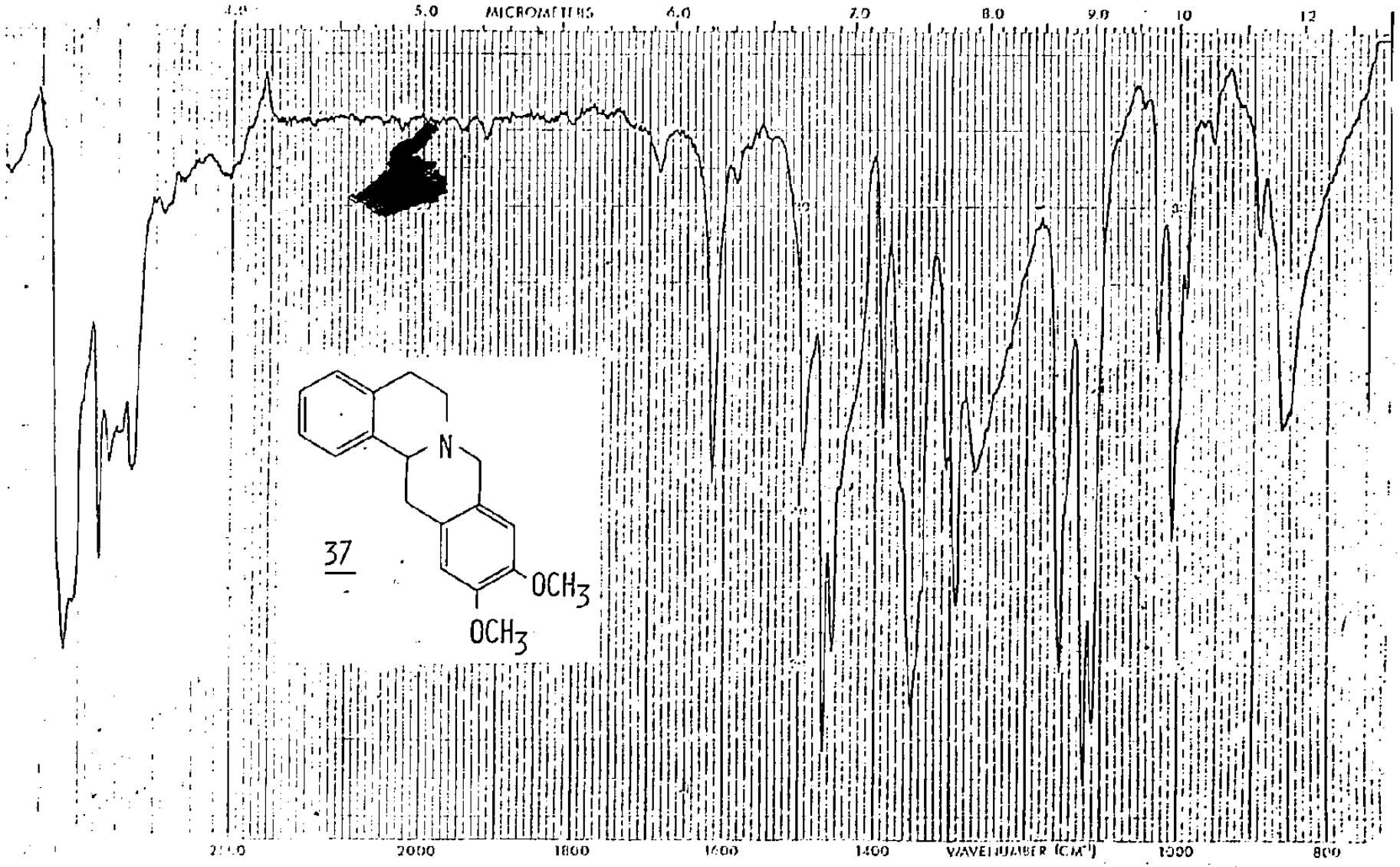


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FIGURE 15: I.R. Spectrum of Protoberberine 37

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