NEWER METHOD IN THE TOTAL SYNTHESES OF NATURAL PRODUCTS

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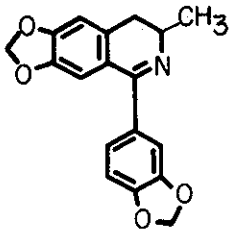
Total syntheses of natural products, such as isoquinoline, indole and diterpene alkaloids, terpenes and a steroidal compound by phenolic oxidation, Pschorr reaction, photolytic reaction, benzyne reaction and thermolysis of benzocyclobutene derivatives, which had been developed mainly in this laboratory, are described.

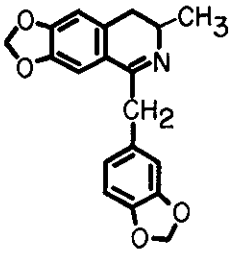
CONTENTS

I. INTRODUCTION

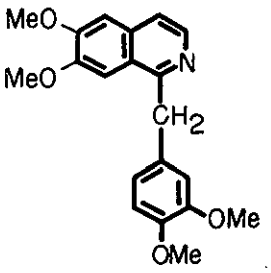
The studies focussed on the total syntheses of natural products based on systematic analysis started in the middle of 1960's with a biogenetic-type synthesis of glaziovine and



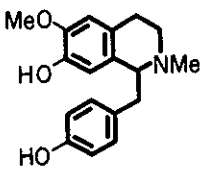
Neupaverine



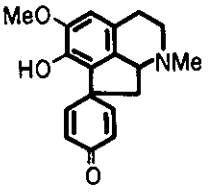
Eupaverine



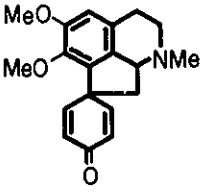
Papaverine



N – Methylcoclaurine



Glaziovine



Pronuciferine

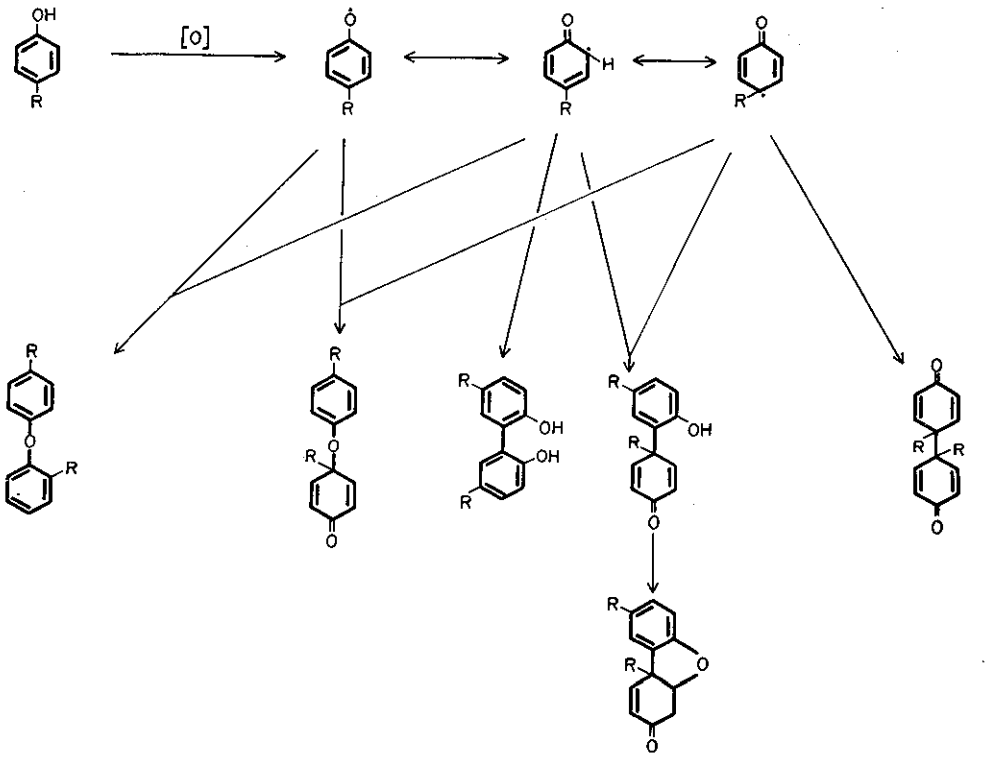
pronuciferine by phenol oxidation[1]. The key material in this synthesis was N-methylcoclaurine which has two phenolic hydroxy groups in a 1-benzylisoquinoline molecule. The most important synthetic step for the key material is the conversion of a non-phenolic base by O-dealkylation. However, O-dealkylation by our group is not new, although this work was started by one of the authors (T.K.) during the second world war. Thus, we had two main routs based on suggestions by Professor S. Sugasawa, Kametani's teacher at that time. One was the synthesis of papaverine-like compounds, neupaverine and eupaverine, from safrole that was easily available as a starting material. The other was the preparation of the water-soluble papaverine derivatives having phenolic hydroxyl groups by O-dealkylation of nonphenolic isoquinolines. The results of this work[2-4] established a general and effective method for O-deetherification of O-alkylated isoquinolines which has contributed much to finding several new synthetic reactions such as phenol oxidation or photolytic reaction in our laboratory. Here we wish to describe the total syntheses of natural products by several reactions developed in our laboratory. Firstly, we mention the total synthesis of isoquinoline alkaloids by phenolic oxidation in which phenolic isoquinolines were used as a starting material.

II. TOTAL SYNTHESIS OF ISOQUINOLINE AND RELATED ALKALOIDS BY PHENOL OXIDATION[5-7]

It has long been known that dimeric products can be formed by the oxidation of phenols with such reagents as ferric chloride

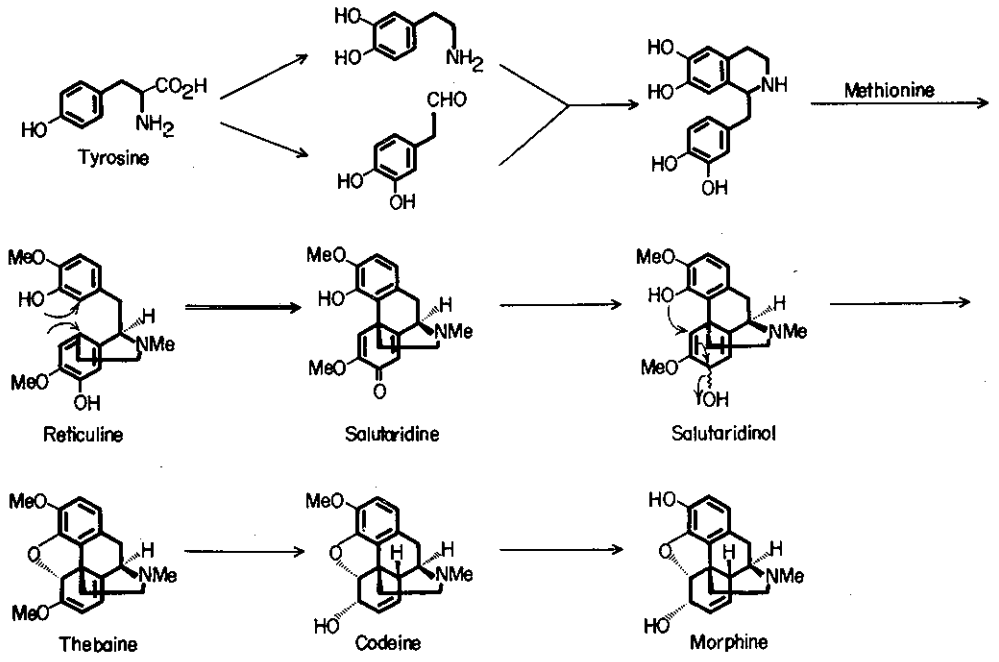
and potassium ferricyanide[8] as shown in the following chart.

Phenol Oxidation



In addition, the concept that some isoquinoline alkaloids are built up in nature by oxidative coupling within the molecule of a benzylisoquinoline is not new; Gadamer[9] in 1911 drew attention to the relationship between laudanosoline and glaucine, and similar ideas were promulgated by Robinson[10] and Schöpf[11]. In 1957, Barton and Cohen[12] proposed that the new C-C or C-O bonds in isoquinoline alkaloids were formed by pairing of radicals from the substrate involved in the oxidative step. A very detailed knowledge of the biosynthetic pathway to the isoquinoline alkaloids

has been gained from extensive tracer experiments,[13] which showed that phenolic oxidation is an important step in the biogenesis of isoquinoline alkaloids as shown below in the biogenesis of morphine. Thus, morphine is biosynthesised from salutaridine, formed via phenol oxidation of reticuline, through thebaine and codeine.



Since 1960, the biogenetical applicability of phenolic oxidation in the synthesis of isoquinoline alkaloids has been repeatedly investigated, and the total syntheses of a number of isoquinoline alkaloids have been achieved using biogenetic-type reaction steps.[14-19]

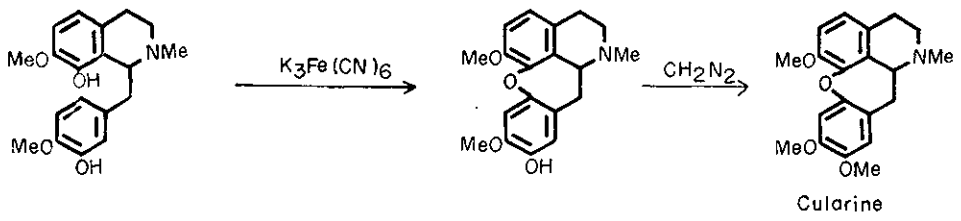
1. Chemical Oxidation

a) Cularine and Related Alkaloids

Cularine and related alkaloids[20] may be biosynthesised by

phenol oxidation of a 7,8-dioxygenated 1,2,3,4-tetrahydroisoquinoline. Thus, oxidative coupling of 1,2,3,4-tetrahydro-8-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-7-methoxyisoquinoline followed by O-methylation gives cularine. Alternatively, it is possible that phenol oxidation of the 1-(4-hydroxy-3-methoxybenzyl)-isomer, followed by conversion of the resulting dienone by dienone-phenol rearrangement[21] would also afford cularine.

Along this biogenetic pattern, the former diphenolic isoquinoline was oxidised with potassium ferricyanide in a two-phase system to afford O-demethylcularine in 2.5 - 8 % yield in addition to the ortho-coupling product. O-Demethylcularine was then transformed into cularine by methylation with diazomethane.[22] Thus, a biogenetic-type synthesis of cularine has been achieved. The same result was also obtained by Jackson.[23] Furthermore, the 1-(4-hydroxy-3-methoxybenzyl)isomeric isoquinoline on oxidation with the same reagent gave the dienone.[22]

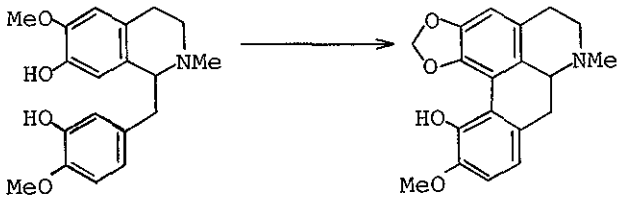


Cularine

b) Aporphine and Proaporphine Alkaloids

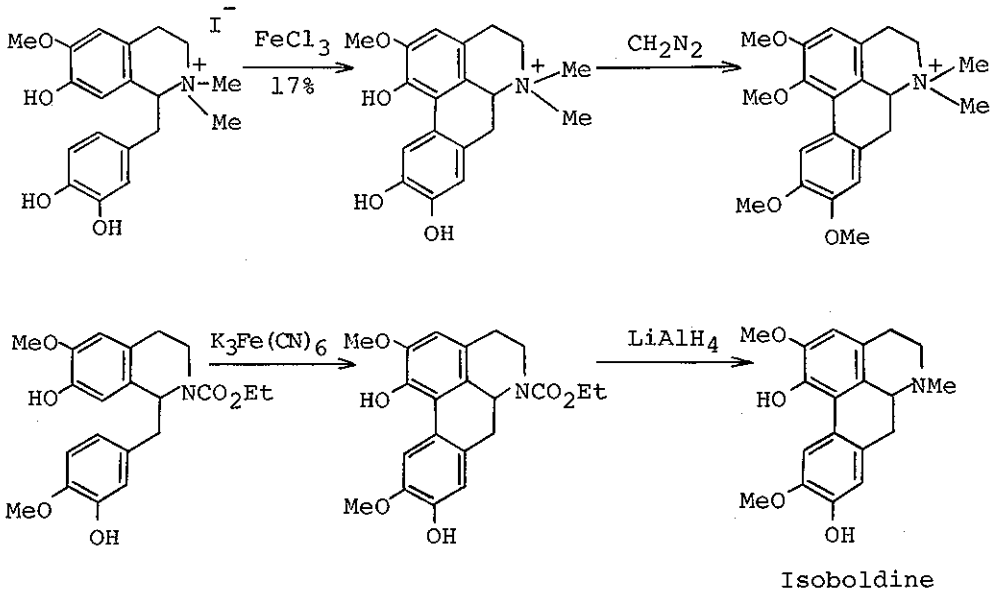
The relationship between laudanosoline and glaucine was noted at the beginning of this century.[9,24] In 1957, Barton[12] proposed the theory of phenol oxidation in the biogenesis of aporphine alkaloids. Thus, the majority of the aporphine bases such as isoboldine and glaucine, can be regarded as being formed by phenolic

coupling from the phenolic base reticuline or its biogenetic equivalent. The hypothesis that phenolic oxidation generates the bond between the two aromatic rings of the aporphines has been confirmed by conversion of a labeled reticuline into a radioactive bulbocapnine.[25,26]



Reticuline Bulbocapnine

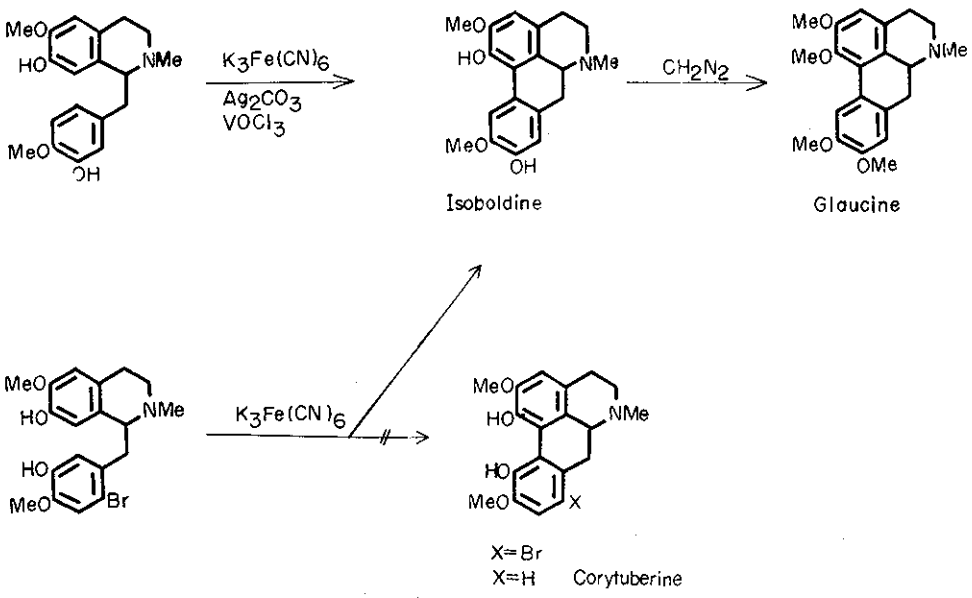
Until recently, no laboratory analogy of this type of biogenetic synthesis had been realized.[27,28] We postulated that the presence of the lone electron pair of nitrogen would prevent the C-C coupling, and thus accomplished the in vitro synthesis of the aporphine derivative in moderate yield via phenol oxidation of O-methyllaudanosoline methiodide where the lone electron pair on the nitrogen was protected by quaternisation, with ferric chloride.[29] Based this finding, N-ethoxycarbonylnorreticuline, whose lone electron pair on the nitrogen is also protected, was converted into an aporphine in 5 - 7 % yield, by phenolic oxidation with potassium ferricyanide in dilute ammonia; and lithium aluminium hydride reduction affords isoboldine.[30]



Isoboldine

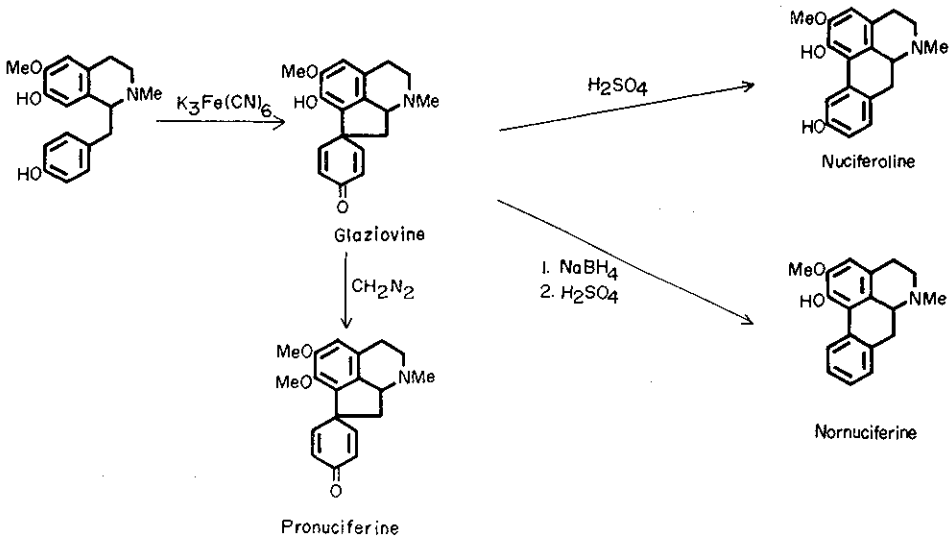
Later, we found that protection of the lone electron pair on the nitrogen is not necessary in a coupling reaction,[1] and reticuline has been converted into isoboldine on oxidation with potassium ferricyanide,[31,32] silver carbonate[33] or vanadium oxychloride,[33] in 5 - 10 % yield. Methylation of isoboldine afforded glaucine. The same work has been carried out independently by Jackson,[34] Chen,[35] and Franck[36]. Phenol oxidation of the diphenolic 2'-bromobenzylisoquinoline with potassium ferricyanide gave no corytuberine-type aporphine but isoboldine by an oxidative elimination of the bromine atom.[30] The difficulty in oxidizing reticuline or 6'-bromoreticuline-type compounds to corytuberine-type aporphines is probably due to the influence of

steric factors which prevent direct coupling of radicals ortho to both of the phenolic hydroxy groups.

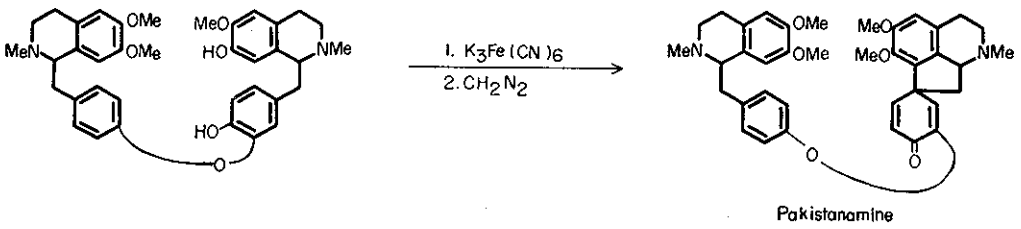


Several aporphine alkaloids, exemplified by nuciferoline and nornuciferine, are constructed in such a way that their biogenesis by direct phenolic oxidation is not reasonable or involves unlikely precursors. Barton[12] therefore proposed that a coclaurine analogue would initially be oxidised to the dienone proaporphine, which would then be subjected to dienone-phenol rearrangement to generate nuciferoline and that reduction of the dienone to dienol followed by dienol-benzene rearrangement, would then furnish nornuciferine. This hypothesis has been confirmed by feeding experiments[13].

This coupling process was reproduced in our laboratory. Thus, N-methylcoclaurine was oxidised with potassium ferricyanide in chloroform in the presence of 8 % ammonium acetate to give glaziovine which was converted into pronuciferine by methylation with diazomethane.[1] Glaziovine, in turn, could be transformed into nuciferoline and nornuciferine, and pronuciferine to nuciferine.

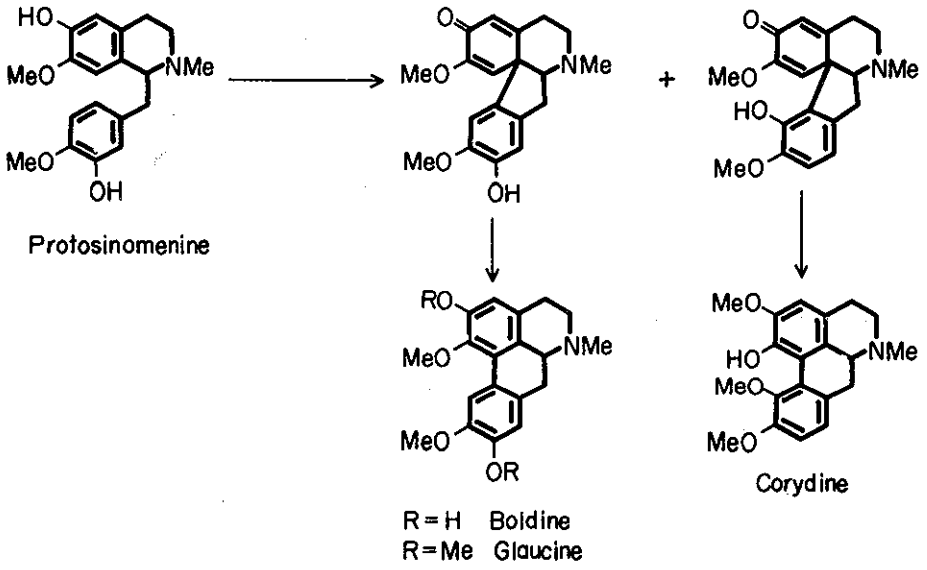


Pakistanamine is a bisbenzylisoquinoline alkaloids, whose proaporphine moiety would also be biosynthesised by this process.[37] Indeed, we obtained this compound as a diastereoisomeric mixture in the same manner as shown in the following chart.[38]



Pakistanamine

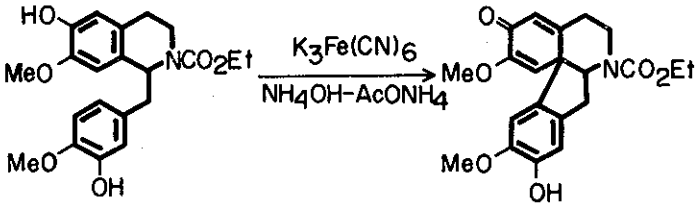
Recently, Battersby[39] elucidated a surprising biogenetic route to glaucine and corydine by means of tracer experiments. Thus, phenolic oxidation of a protosinomenine-type isoquinoline could yield a dienone. Dienone-phenol rearrangement of this first dienone could yield boldine, affording glaucine, and the second dienone which in turn leads to corydine. A related dienone has been synthesised in our laboratory, based on a



Protosinomenine

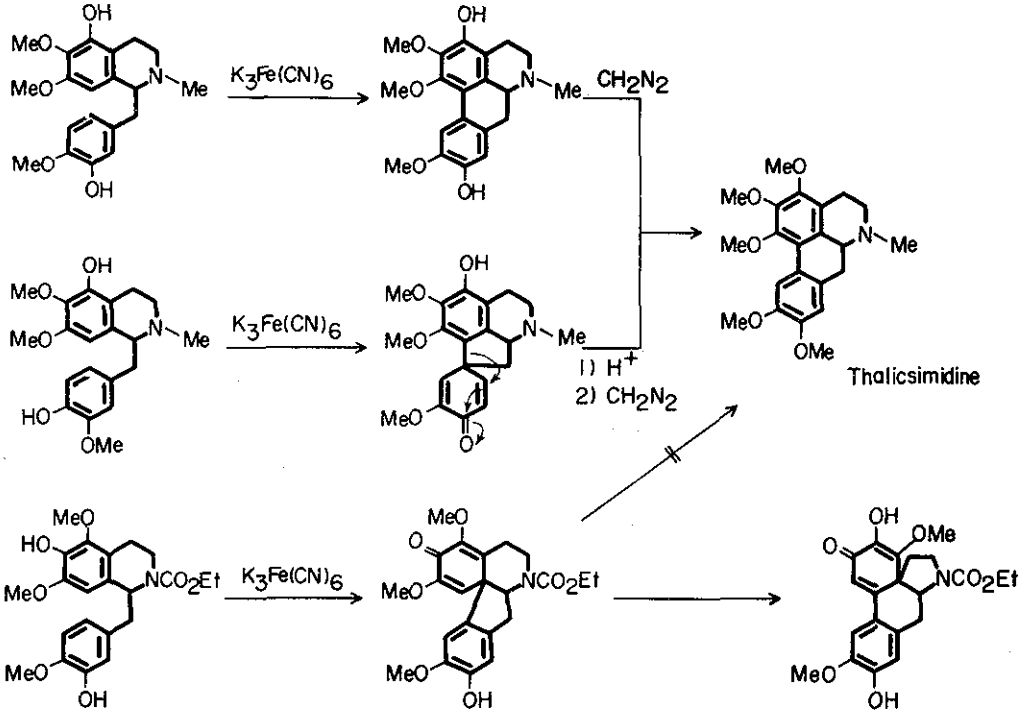
Corydine

R=H Boldine
R=Me Glaucine



hypothetical biogenesis of aporphine before presentation of this mechanism, by phenolic oxidation of N-ethoxycarbonyl-N-norprotosinomenine with potassium ferricyanide in the presence of dilute ammonia and ammonium acetate.

The synthesis of thalicsimidine was examined by the above three biogenetic routes,[41,42] and this alkaloid was obtained by two pathways, one *via* direct coupling and the other through proaporphine.[41]

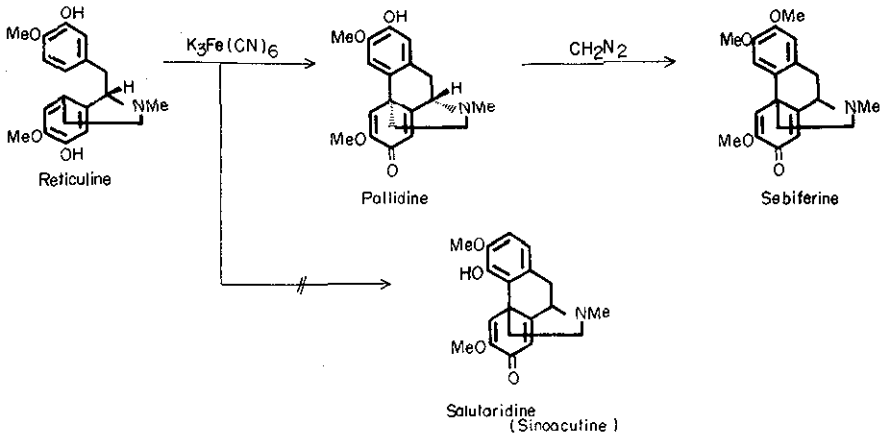


C) Morphine Alkaloids

Tracer experiments have shown that morphine is biosynthesised from salutaridine formed *via* phenolic oxidation of reticuline throuth thebaine and codeine[13] and this biogenetic route has been

duplicated by Barton.

Another coupling mode of reticuline would give a second morphinandienone, pallidine, which could be converted in nature into amurine or flavinantine by transmethylation and into sebiferine by methylation. We could convert reticuline into pallidine by an oxidative coupling with potassium ferricyanide in the presence of 50 % sodium hydrogen carbonate,[31-33] silver carbonate on celite[33] or vanadium oxychloride.[33] Pallidine is also transformed into sebiferine by treatment with diazomethane. In this oxidation, salutaridine could not be obtained.

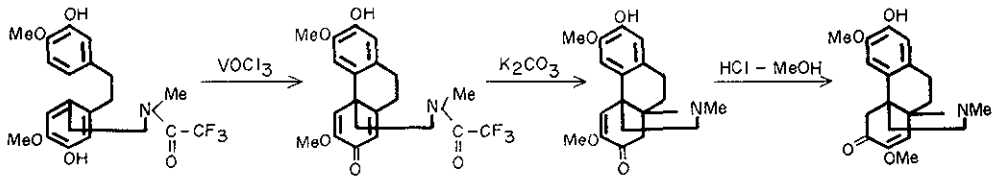


d) Hasubanan Alkaloids

Cepharamine, a hasubanan-type alkaloid from Menispermaceae, is probably biosynthesised by rearrangement of the proerythinadienone, a precursor to the aporphine alkaloids formed from protosinomenine by phenolic oxidation, although tracer experiments have not yet been carried out. In our laboratory, a dienone having the same molecular precursor skeleton was synthesised by phenolic

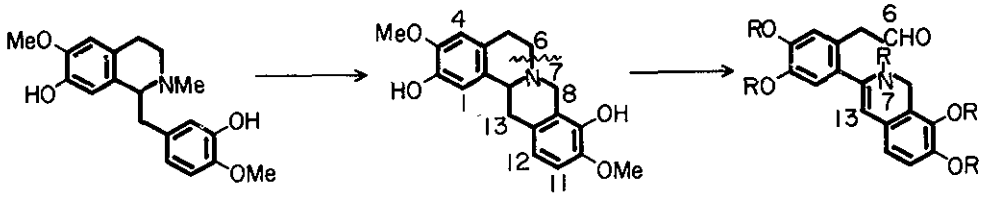
oxidation[40], but acidic rearrangement of the dienone gave no expected compound.

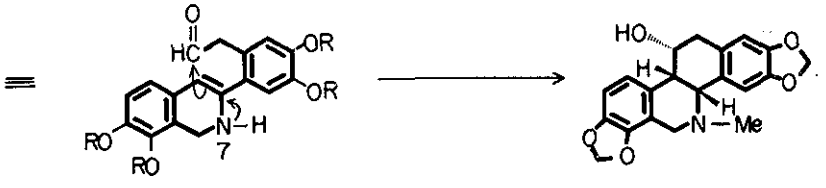
On the other hand, the hasubanan molecular skeleton was synthesised by a non-biogenetic route as shown in the following chart in which phenolic oxidation was a key step. Vanadium oxychloride oxidation of the diphenolic compound, followed by hydrolysis and isomerisation gave a hasubanan-type enone.[44]



e) Benzophenanthridine Alkaloids

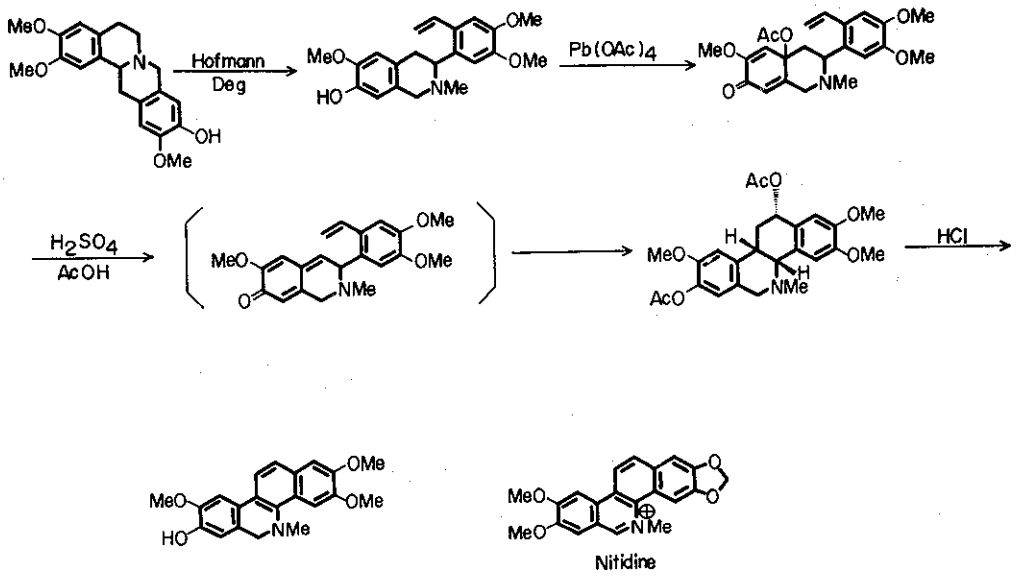
The benzophenanthridine alkaloids are biosynthesised through cleavage of the C_6-C_7 bond of berbines, formed in plants from reticuline or its biogenetic equivalents, followed by join-





ing of C_6 to C_{13}.

We have succeeded in the conversion of berbines into benzophenanthridine by using oxidative coupling with lead tetraacetate[46] as the key reaction[45]. Thus, oxidation of methine base, derived from the berbine, with lead tetraacetate gave the p-quinol acetate which was treated with sulphuric acid in acetic acid and then hydrolyzed to afford the benzophenanthridine.[45] Nitidine was synthesised by the same method from the corresponding 2,3-methylenedioxyberbine.[47]



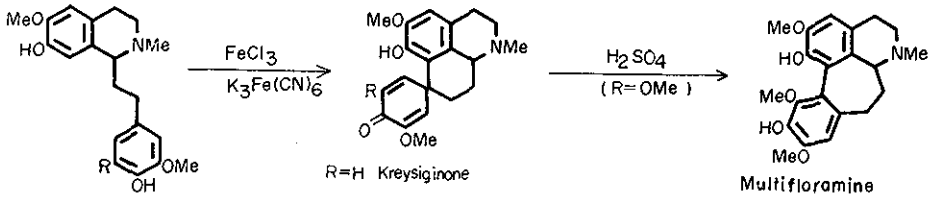
f) Phenethylisoquinoline Alkaloids

In the last decade, the phenethylisoquinoline alkaloids[20] have been isolated, characterised, and divided into five groups: bisphenethylisoquinoline, homoproaporphine, homoaporphine, homomorphinandienone, and homoerythrina alkaloids; corresponding to bis-

benzylisoquinoline, proaporphine, aporphine, morphinandienone, and erythrina alkaloids in the benzylisoquinoline series. These alkaloids are probably biosynthesised from autumnaline or its biogenetic equivalents by phenolic oxidation just as the benzylisoquinoline alkaloids could be formed from coclaurine or its analogue.

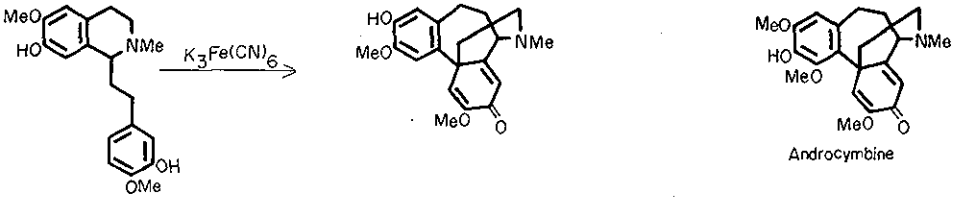
The homoaporphine alkaloids are known only in the form of their representative, kreysiginone, which is probably biosynthesised from homoorientaline (R=H). Laboratory experiments attempting the conversion of homoorientaline into kreysiginone have been carried out. Phenolic oxidation of homoorientaline with potassium ferricyanide[48,49] or ferric chloride[48,49] afforded a mixture of two dienones that differed in configuration at the spiro-center,[50] one of which was identical with kreysiginone.

Homoaporphine alkaloids such as floramultine, an isomer of multifloramine, may be biosynthesised by direct phenolic oxidation from autumnaline, as shown by tracer experiments, which ruled out a route involving a dienone-phenol rearrangement of the homoproaporphine.[51] On the other hand, the synthesis of homoaporphine by a non-biogenetic route through the homoproaporphine has been carried out as follows.[48-50,52] The diphenolic isoquinoline was oxidised with potassium ferricyanide or ferric chloride to give



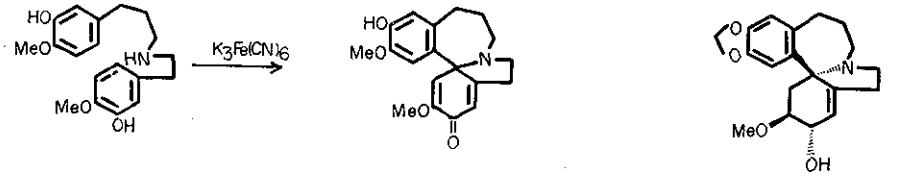
the homoproaporphine (R=OMe) in good yield, which was subjected to dienone-phenol rearrangement to afford multifloramine. Methylation of this furnished kreysigine.

Androcymbine, the first example of a 1-phenethylisoquinoline alkaloid, is biosynthesised by phenolic oxidation of autumnaline and transformed biogenetically into colchicine as shown by tracer experiments.[13] In the laboratory, the conversion of autumnaline into androcymbine by phenolic oxidation failed, but homomorphinandienone was obtained in low yield from homoreticuline by potassium ferricyanide oxidation.[53]



Androcymbine

It is likely that the ring system of the homoerythrina alkaloids, schelhammerine is derived from homoprotosinomenine by a route analogous to that involved in the biogenesis of the erythrina alkaloids, for which a protosinomenine precursor has been established. A trial in the laboratory resulted in failure,[54] but homoerythrinadienone has been obtained from the secondary amine *via* potassium ferricyanide oxidation.[55]

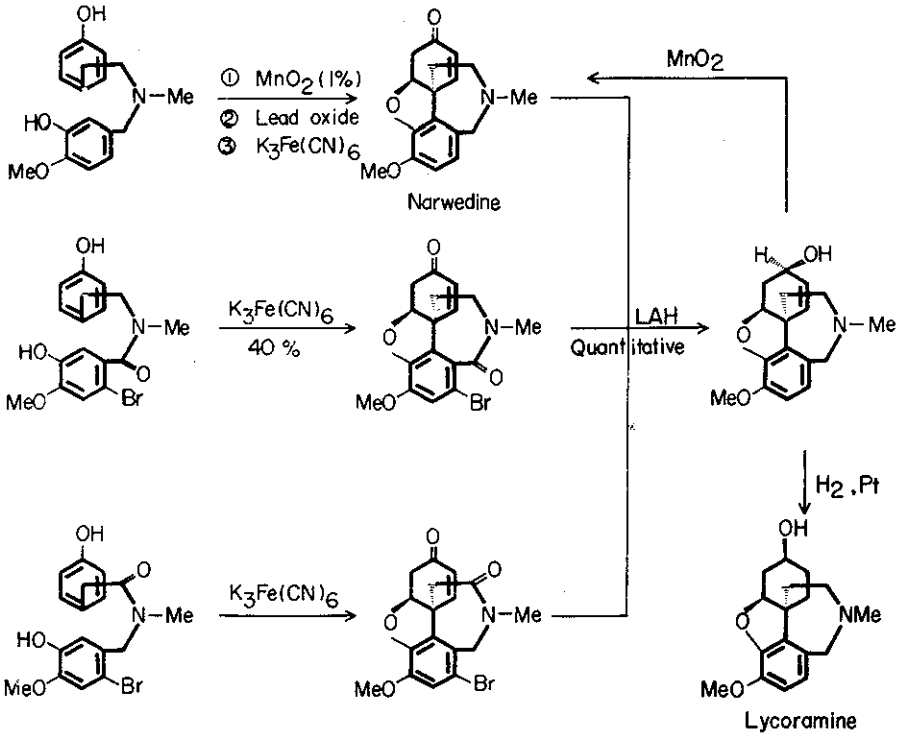


Schelhammerine

g) Amaryllidaceae Alkaloids

Barton and Cohen[12] suggested that a phenolic intermediate, such as the amine now known as the natural product norbelladine, represents a single precursor for galanthamine, the Amaryllidaceae alkaloid. The validity of this has been conclusively demonstrated by independent investigators.[13]

Narwedine, obtained in poor yield by manganese dioxide oxidation of belladine derivative, was reduced to galanthamine. Other oxidations, such as potassium ferricyanide or lead dioxide. were studied, but the yields, determined by the radiochemical dilution method, were very low.[56] However, we reported an improved method[57-59] involving the use of the bromoamide as a substrate for phenolic oxidation. Amidation protects the basic nitrogen



against oxidation and the bromine atom prevents oxidative coupling at an undersired position. Potassium ferricyanide oxidation of the amides in the presence of sodium hydrogen carbonate yielded the corresponding enones which were reduced to galanthamine by standard methods. Galanthamine was reduced to lycoramine and converted into narwedine by oxidation.

2. Enzymatic Oxidation

The enzymatic oxidation and coupling of phenols is a subject of great importance in biochemistry and organic chemistry. The three main classes of enzymes known as catalysts for phenol oxidation and coupling are the laccases, the tyrosinases, and the peroxidases, which involve a heavy metal as a coenzyme. For example, horseradish peroxidase consists of a protein together with an iron-porphyrin compound. The iron atom is thought to be surrounded octahedrally by the porphyrin, the protein, and another ligand, such as hydrogen peroxide.[19]

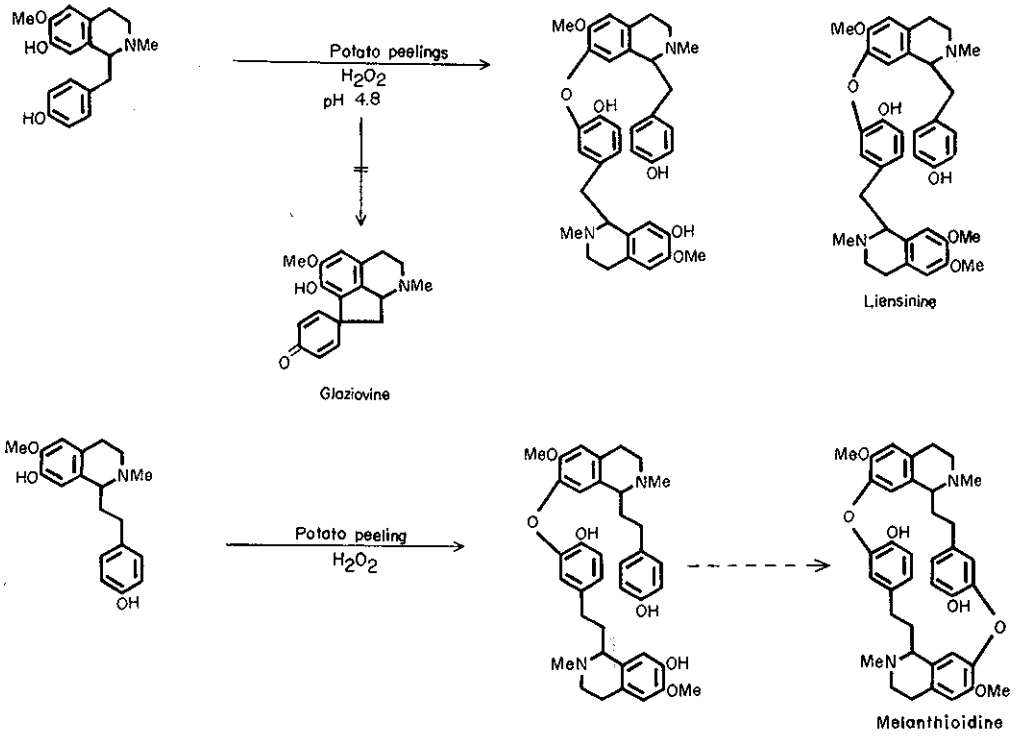
One outcome of a deeper knowledge of the mechanism of enzymatic oxidation and coupling of phenols will undoubtedly be to provide the organic chemist with more efficient chemical oxidations. The chemical oxidant that seems to come closest to the enzymatic oxidant is ferricyanide because the oxidation-reduction potential of ferricyanide (300mV) is reasonably close to that recorded for laccase (415 mV). Therefore we used potassium ferricyanide and a similar reagent, ferric chloride, as enzyme models for biogenetic-type synthesis of isoquinoline and related alkaloids by phenol oxidation.

Many types of isoquinoline alkaloids can be synthesised by phenolic oxidation with chemical oxidants along biogenetic lines. In this oxidation, the coupling reaction proceeds in an intramolecular manner, but not intermolecularly. On the other hand, enzymatic oxidation of phenolic isoquinoline differs from oxidations with chemical reagents.[60-65]

N-Methylcoclaurine, which furnished glaziovine by potassium ferricyanide oxidation as described above, on treatment with homogenised potato peelings and hydrogen peroxide at pH 4.8 for 8 days at room temperature afforded the liensinine-type compound in addition to a small amount of the trimer.[62] This reaction constituted a biogenetic-type synthesis of liensinine-type bisbenzylisoquinoline alkaloids. Similarly, treatment of N-methylhomococlaurine, which gives the homoproaporphine by potassium ferricyanide or ferric chloride oxidation, with homogenised potato peelings and hydrogen peroxide at pH 4.8 for 4 days at room temperature, gave promelanthioidine, a potential precursor of melanthioidine.[60] However, it was interesting that oxidation of N-methylcoclaurine with homogenised horseradish and hydrogen peroxide at pH 4.8 under the same conditions as those described above, afforded the isomeric bisphenethylisoquinoline.[61] On the other hand, monophenolic isoquinolines gave no oxidised products under the same reaction conditions.[61]

In the above reactions, C-C coupling products were not observed. Potato peel homogenates seem to contain the enzyme needed for head-to-tail coupling, while horseradish and Wasabia japonica

seem to contain the enzyme for head-to-head coupling. Therefore, the protein part of the enzyme which accepts the substrate seems to be different in the enzymes of potato and Wasabia japonica. It is interesting that no phenethylisoquinolines with two ether linkages have been observed in this enzymatic oxidation. It is possible that one pair of hydroxy groups in the 1-phenethyl groups participates in the approach to two isoquinoline molecules through the enzyme active site, whereas another pair of hydroxy groups in the isoquinoline nucleus seems to oxidise each other by phenol oxidation.



In summary, many differences were found in the behaviour of enzymatic models and enzymes; chemical reagents were more suitable for intramolecular C-C coupling than for intermolecular reaction, but enzymes led to intermolecular C-O coupling and intramolecular C-N coupling products. In order to understand these differences, it will be necessary to engage in thorough physicochemical and biochemical studies of the relationship between the metal ion, a type of enzymatic model, and the enzyme.

3. Biotransformation

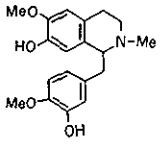
As mentioned earlier, reticuline plays an important role in the biogenesis of isoquinoline alkaloids. Direct oxidative intramolecular coupling of reticuline gives aporphine alkaloids (isoboldine and corytuberine), morphinandienone alkaloids (pallidine and salutaridine), and protoberberine alkaloids (coreximine and scoulerine), which may be precursors of benzophenanthridine alkaloids (chelidonine), phthalideisoquinoline alkaloids (narcotine), protopine alkaloids (protopine), spirobenzylisoquinoline alkaloids (ochotensimine), and rheadan alkaloids (roheadine). In order to investigate the biotransformation of reticuline in mammalian tissue, a solution of (+)-reticuline in propylene glycol was injected intraperioneally into rats and for 4 days after the injection, the urine was collected in a bottle containing a few drops of toluene. The pooled urine was adjusted to pH 5 with dilute sulphuric acid and then to pH 4.5 with 0.1 mole acetate buffer and incubated with ß-glucuronidase. The crude basic extract was separated by preparative tlc on silica gel to yield the starting reticuline and a protoberberine, the structure of which was shown

to be coreximine by tlc and gas chromatographic comparison and mass spectrometry.[66]

The biotransformation of 1-benzyl-1,2,3,4-tetrahydro-2-methyl-isoquinolines to tetrahydroprotoberberines was substantiated by tracer experiments.

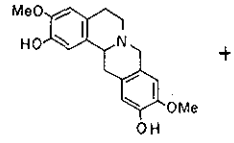
A solution of (±)-[N^{14}CH$_3$]reticuline was administered to a female rat of Wistar strain. After treatment of the collected urine and dilution with nonradioactive (±)-coreximine, radioactive (±)-coreximine was isolated in a pure state in 0.03 % yield.

The biotransformation was also demonstrated by incubating a 20 % homogenate of rat liver, prepared in phosphate buffer at pH 7.5, with (±)-[2',6',8-^{3}H]- and (±)-[N-^{14}CH$_3$]reticuline. After incubation at 37°C for 2 h, carrier alkaloid was added to each reaction mixture and then purified by preparative tlc, followed by recrystallisation to constant activity. Formation of coreximine and scoulerine from (±)-reticuline with homogenised rat liver was proved by experiments with (±)-reticuline labeled with carbon-14 or tritium. No radioactivity was found in pure sinoacutine.

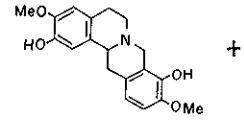


Reticuline

whole rat or
20 % homogenised
rat liver in phosphate
buffer at pH 7.4



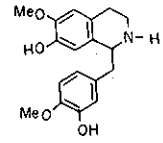
+



+

(±)-Coreximine 0.09 %
(+)-Coreximine 0.044 %
(−)-Coreximine 0.05 %

Scoulerine 0.034 %

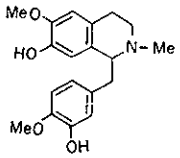


Norreticuline 0.41 %

The amount of alkaloids formed by the above enzymatic reaction was too small for measurement of optical rotation. Since the optically active coreximine was separable from the racemate by repeated recrystallisations, it was expected that, upon dilutions of a small amount of the optically active radioactive product with a large amount of the enantiomeric coreximine, repeated recrystallisations would eventually show no radioactivity. Thus, after incubation, the resulting homogenate was separated equally into three fractions, to which (-), (+), and (±)-coreximine were added. The radiochemically pure bases were obtained by rigorous preparative tlc followed by repeated recrystallisations. The yields, which were calculated on the basis of the amount of "cold" carrier added, are shown in the above chart. The radiochemical yield of the product from dilution with (±)-coreximine was nearly twice that obtained from dilution with (-)- or (+)-coreximine, respectively. This result suggests that the coreximine formed was racemic. It is interesting that the above enzymatic transformation of reticuline to coreximine was not stereospecific.[67]

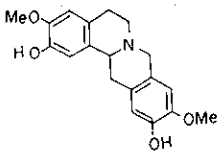
The transformation of (±)-reticuline was furhter studied using a 9000 g supernatant of rat liver homogenates. Without any cofactor, the radioactivity of (±)-[2',6',8-^{3}H]reticuline was incorporated into (±)-coreximine in 0.160 % and (±)-norreticuline in 0.410 % yield. Addition of NADPH (dihydronicotinamide adenine dinucleotide phosphate) to the supernatant increased the formation of (±)-coreximine and (±)-norreticuline to 3.31 and 1.35 %, respectively. Furthermore, the yield of coreximine was enhanced by the addition of magnesium chloride. Thus, in the presence of

NADPH and magnesium chloride, the incorporation of (±)-reticuline into (±)-coreximine was 11.6 %. When the supernatant together with glucose 6-phosphate, NADP, nicotinamide, and magnesium chloride was used, (±)-reticuline was converted to (±)-coreximine in 5.99 % yield.

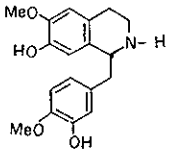


Reticuline

9.000 x g supernatant of rat liver



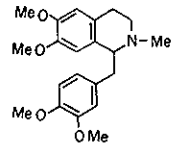
Coreximine



Norreticuline

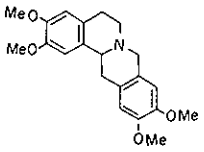
Cofactors	Coreximine	Norreticuline
Nil	0.16 %	0.41 %
NADPH	3.31 %	1.35 %
NADPH. $MgCl_2$	11.68 %	
NADP . $MgCl_2$, Nicotinamide, G-6-P	5.99 %	

In the case of nonphenolic tetrahydroisoquinolines, the radioactivity of (±)-[2',6',8-^{3}H]laudanosine was incorporated into (±)-



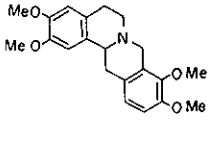
Laudanosine

9.000 x g supernatant of rat liver
+NADPH



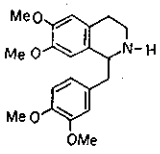
Xylopinine

0.02 %



Tetrahydropalmatine

0.007 %

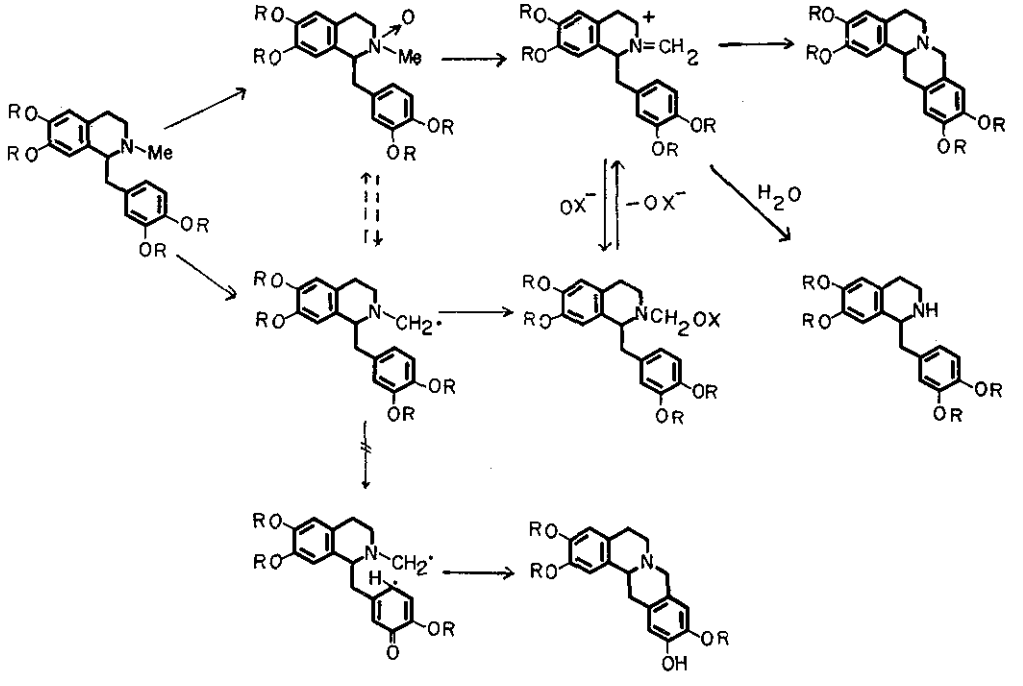


Norlaudanosine

14.13 %

norlaudanosine in 14.13 % yield in the presence of NADPH. The incorporations into (±)-xylopinine and (-)-tetrahydropalmatine were very small but not zero as shown in the above chart.

It is reasonable on the basis of the above results that 1-benzyl-1,2,3,4-tetrahydro-2-methylisoquinolines would give rise to immonium cations which afford tetrahydroprotoberberines by cyclisation or an N-demethylated product by hydrolysis. All possible mechanisms for the formation of the immonium cation are outlined in the following chart. The responsible rat liver enzyme would require NADPH and molecular oxygen as in the known enzymatic N-demethylation, suggesting the participation of the cytochrome P-450 enzyme system. The formation of xylopinine and tetrahydropalmatine from laudanosine would exclude the possibility that the radical is enzymatically oxidised to the diradical which affords a proto-



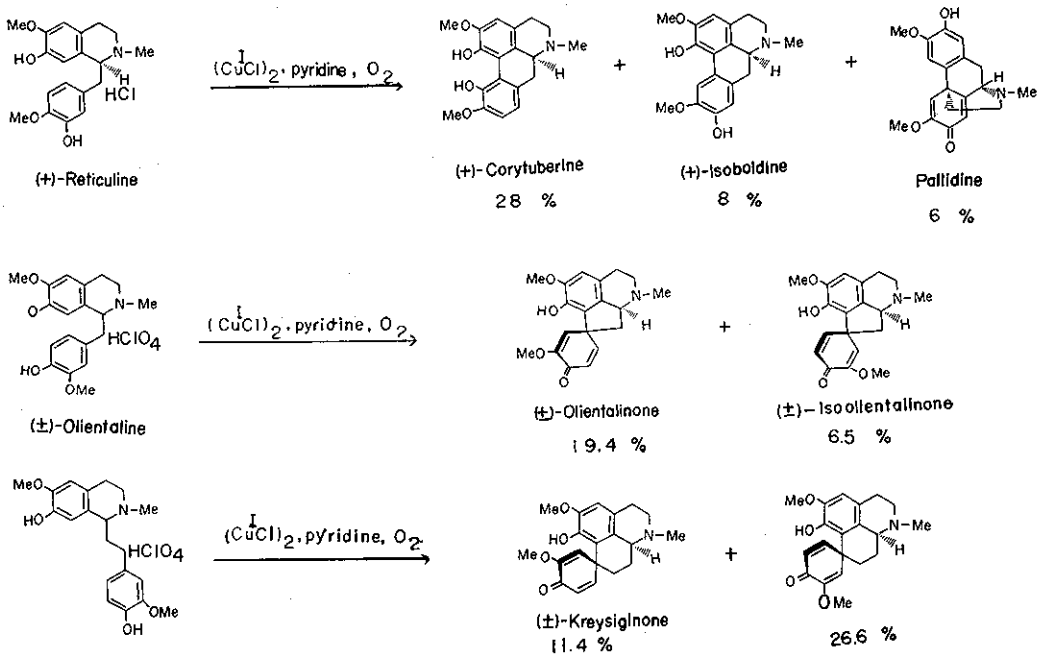
berberine by radical coupling. It is difficult to determine whether the cyclisation step of immonium cation is enzymatic or nonenzymatic.[67]

4. Phenol Oxidation with Enzymic Model

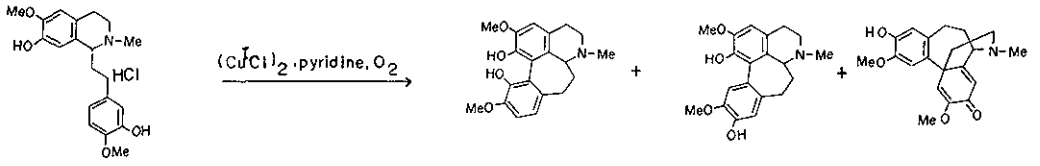
Reactions between atmospheric oxygen and phenols are of special interest in relation to autoxidation processes and enzymic processes. Oxidative reactions of phenols with molecular oxygen activated by metal salts are well known.[18,19] Many phenolic compounds in nature would also be oxidised with enzymes involving both metal and oxygen to afford complex natural products. The laccase and tyrosinase, two of the three main classes of enzymes known as catalysts for phenol oxidation and coupling, involve copper ion and oxygen. In connection with our interest in alkaloid synthesis under mild conditions, we studied phenol oxidation of some isoquinoline alkaloids by a mixture of cuprous chloride and molecular oxygen in pyridine[68,69] and related reaction systems as an enzymic model.

The suspension of cuprous chloride, Cu_2Cl_2, in pyridine absorbs oxygen rapidly under an oxygen atmosphere to give a dark green solution to which a solution of 1 molar equiv. of (+)-reticuline hydrochloride in pyridine was added dropwise at room temperature with efficient stirring. The colour of the solution changed to dark brown. The mixture was further stirred for 15 - 30 min, crystalline ammonium chloride added, and partitioned between chloroform and dilute ammonia. The chloroform extract was purified by preparative TLC on silica gel to afford (+)-corytuberine (28 %), (+)-isoboldine (8 %), and pallidine (6 %). The

same treatment of (±)-orientaline perchlorate and (±)-homo-orientaline perchlorate gave orientalinone and kreysiginone, respectively, in moderate yield.



Similarly, racemic 1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxyphenethyl)-6-methoxy-2-methylisoquinoline hydrochloride gave also ortho-ortho (5 %), ortho-para (2 %), and para-para (2 %) coupling products.

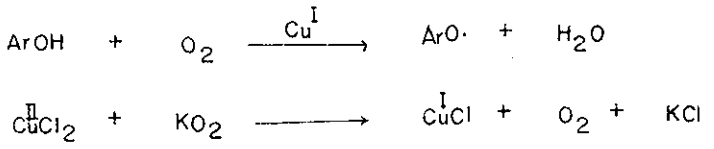


The above synthesis is the first example of the ortho-ortho oxidative coupling of reticuline to corytuberine and of the corresponding phenethylisoquinoline to the ortho-ortho coupling product with chemical reagents.

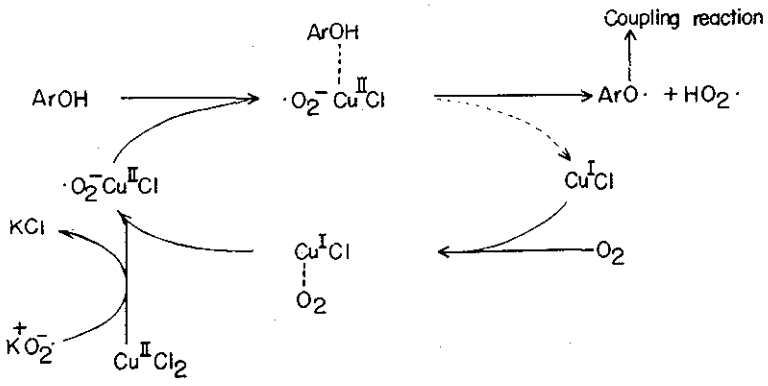
The use of dimethylformamide in place of pyridine for the above reaction gave poor results and needed longer reaction time. Cuprous bromide gave a similar result to cuprous chloride, but the use of divalent copper salts such as cupric chloride instead of cuprous chloride gave no oxidised product.

Two mechanisms could be considered for the above oxidation. The first resembles that of tyrosinase, in which copper would be in the cuprous state throughout the reaction and the phenols are oxidised directly with activated molecular oxygen to aryloxy radicals as in the following equation. The second is relevant to that of laccase in which one electron of the phenol group is transferred to molecular oxygen via copper, the valence of which changes during the reaction.

Tyrosinase like :



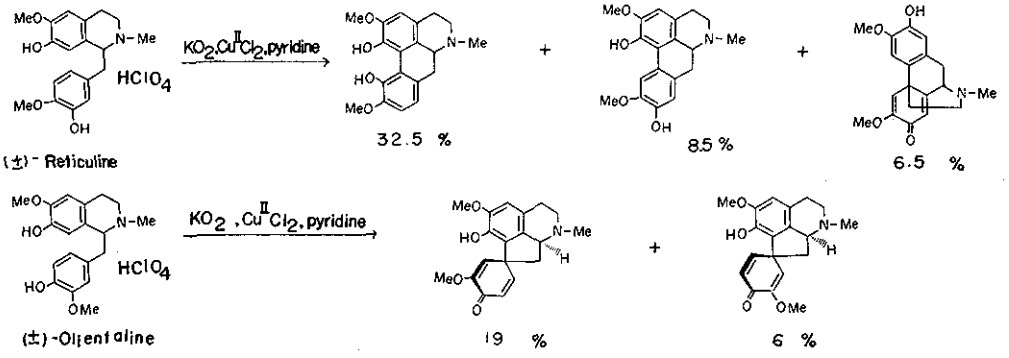
Laccase like



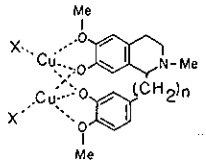
In order to clarify the mechanism of the above oxidation, the following reactions were studied. When a mixture of cupric chloride and an excess of potassium superoxide in pyridine was stirred for 12 hr at room temperature under nitrogen atmosphere the colour of the solution changed to dark green. With this mixture (+)-reticuline perchlorate was converted to (+)-corytuberine (32.5 %), (+)-isoboldine (8.5 %), and pallidine (6.5 %), whereas (±)-orientaline perchlorate was transformed to a mixture of (±)-orientalinone and its epimer (25 % yield), the ratio of the two components was nearly the same as in the case of oxygen-Cu_2Cl_2-pyridine, indicating that a cupric complex, $\cdot O_2^- Cu^{II}Cl$, in the above chart would operate in the above oxidative coupling. Neither potassium

superoxide in pyridine nor potassium superoxide and cuprous chloride in pyridine under a nitrogen atmosphere oxidised the above substrates; the starting material was recovered.

O_2-$(Cu^{I}Cl)_2$-pyridine	+
O_2-$(Cu^{I}Br)_2$-pyridine	+
O_2-$(Cu^{I}Cl)_2$-DMF	±
O_2-$Cu^{II}Cl_2$-pyridine	−
KO_2-$Cu^{II}Cl_2$-pyridine	+
KO_2-pyridine	−



Furthermore, on oxidation with two molar equiv. of a divalent copper complex [pyridine-CuClOMe]$_2$, prepared from cuprous chloride in pyridine in the presence of oxygen and methanol, in pyridine under nitrogen atmosphere, (+)-reticuline and (±)-orientaline perchlorates afforded the same reaction products as above. It is thus probable that cuprous salts are readily oxidised with molecular oxygen in pyridine to give certain cupric ions which are efficient catalytic systems for phenol oxidative coupling of some phenolic isoquinoline alkaloids.[70]

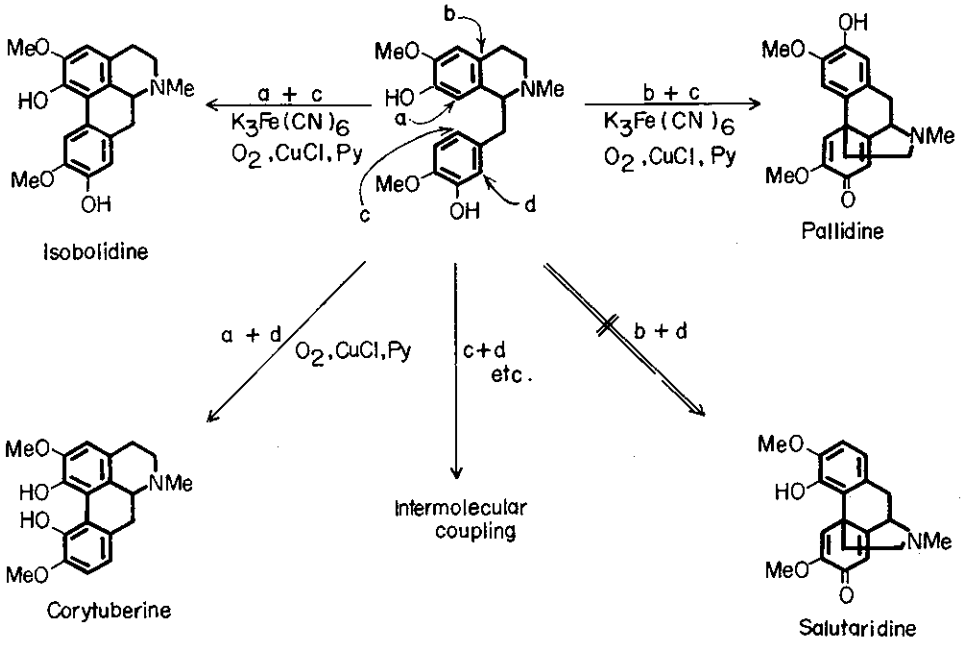


III. TOTAL SYNTHESIS OF ISOQUINOLINE ALKALOIDS BY MODIFIED PSCHORR REACTION[71]

1. Morphinandienone Alkaloids

Thus far, it has been demonstrated that phenol oxidation mimics one of the biogenetic pathway in Nature and provides a facile route to the synthesis of certain isoquinoline alkaloids. However, its utility is limited since intermolecular coupling also occurs to generate polymers which are formed from the starting material and/or its oxidation products. Moreover, intramolecular coupling always takes place at the ortho and para position to the phenolic hydroxyl group, and this fact reveals that phenol oxidation lacks regio-selectivity as shown in the following chart. Furthermore, phenol oxidation can not be employed in the synthesis of certain dienones, such as amurine where one hydrogen is ortho and the methylenedioxy group is meta and para to the coupling site, and flavinantine and androcymbine where the hydroxyl is meta to the coupling position.

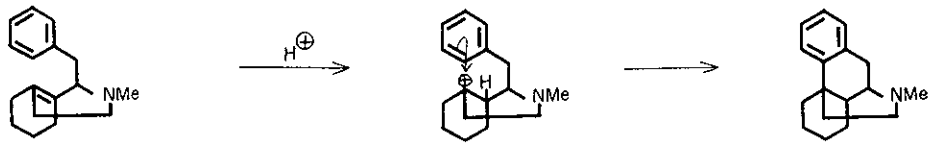
Furthermore, since oxidative coupling occurs preferentially at the para rather than the ortho position to the hydroxyl group, reticuline can be converted into isoboldine and pallidine but not into salutaridine.



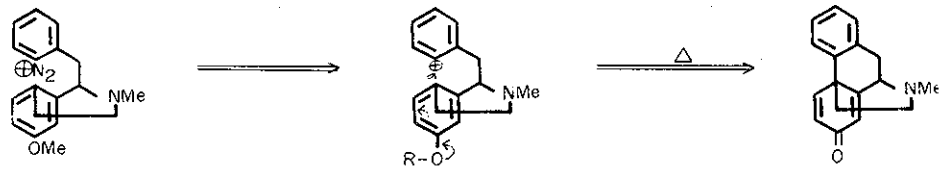
In view of these inherent limitation associated with phenol oxidation and connection with our interest in a general method for the synthesis of morphinandienone type compounds, we turned our attention to the use of the Pschorr reaction.[72]

It is well known that Grewe cyclisation[73] proceeds by a nucleophilic attack of the aromatic ring to the carbonium ion generated by protonation to an olefinic system as shown in the follwoing chart.

Grewe Cyclisation : Aromatic ring + $C^{\oplus}$



Based on this reaction, we supposed that if the angular carbon of the isoquinoline ring is activated by an appropriate substituent, the carbon could attack nucleophilically an aromatic cation generated in situ to form a morphinandienone-type compound. As usual a method for generation of an aromatic cation is decomposition of aromatic diazonium salt by an SN_1 mechanism. In this reaction the position of an aromatic cation is fixed at the position located by the diazonium group, so the reaction could proceed with high regioselectivity.



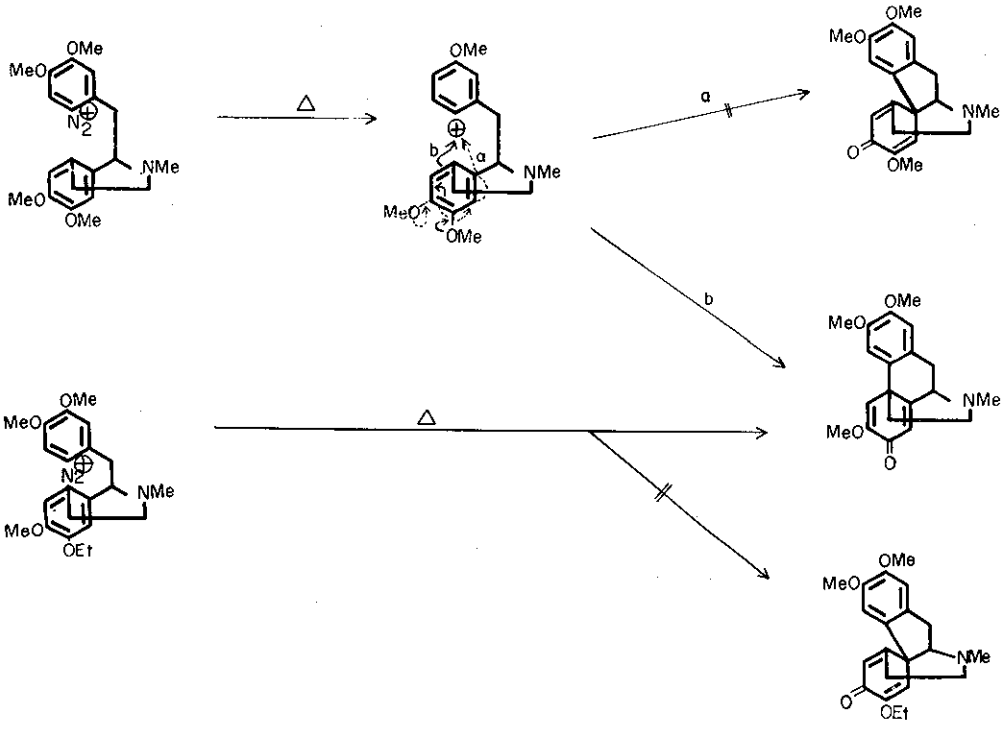
high regioselectivity

Thus when 2'-aminolaudanosine was diazotised with a slight excess of sodium nitrite in N-sulphuric acid and the resulting diazonium salt was decomposed thermally without a metal catalyst, we obtained a cyclohexadienone as the major product together with some laudanosine and glaucine.

The structure of this dienone was established as the morphinandienone by its spectral properties as well as by its alternate synthesis from the ethoxy analogue described below.

If 2'-aminolaudanosine had been converted into the unexpected dienone, proerythrinadienone, then the ethoxy derivative should

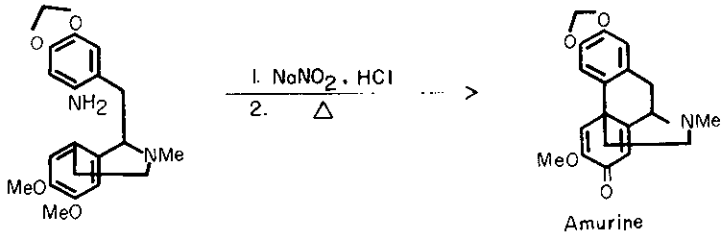
afford a second proerythrina dienone which has an ethoxy group. However, the products, obtained by diazotisation of the two amino-isoquinolines followed by decomposition, were identical in ir and nmr spectra as well as in mixture melting point of their methiodides. Unequivocal proof that the product was indeed the morphinandienone (±)-O-methylflavinantine was provided by the fact that its ir spectrum was superimposable with that of the O-methyl ether obtained from natural flavinantine and diazomethane.[74]



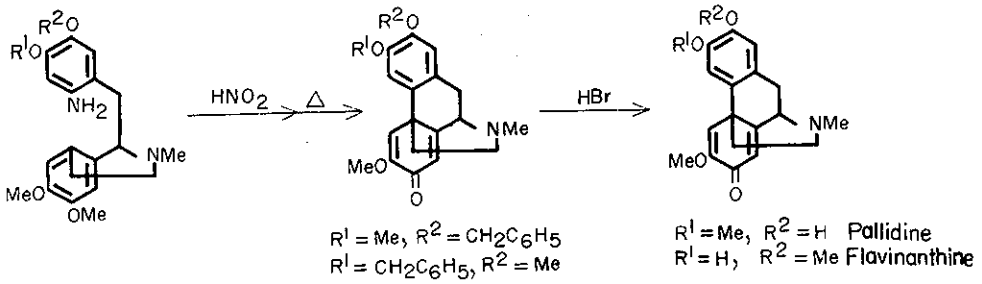
Thus, by applying the Pschorr reaction which had been widely used for the synthesis of aporphines, we discovered a general synthetic method for preparing morphinandienone-type alkaloids.

It is interesting that this reaction is particularly useful in the synthesis of morphinandienones which can not be prepared by phenol oxidation. Thus, since coupling in the Pschorr reaction occurs selectively at the position having the amino function, appropriately substituted morphinandienones can readily be prepared as desired.

Similarly, treatment of the isomeric precursors, followed by removal of the protecting group, gave the isomeric phenolic morphinandienones amurine,[75] flavinantine,[76] and pallidine.[77]



Amurine

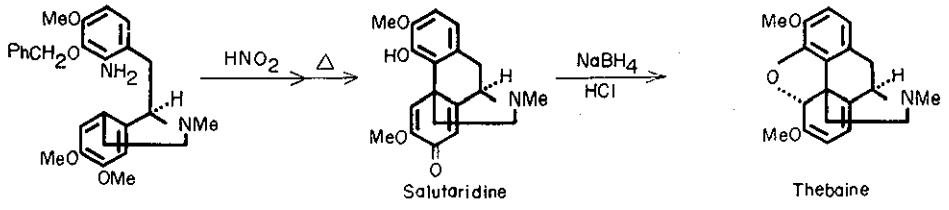


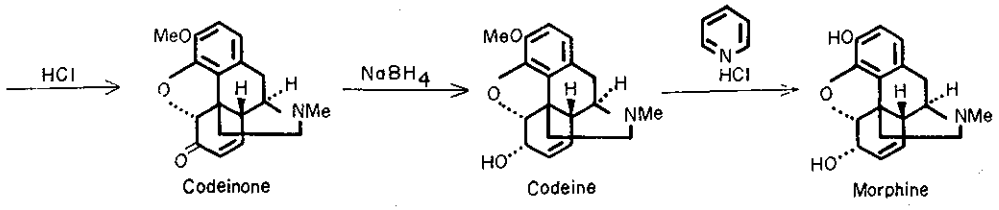
R^1 = Me, R^2 = $CH_2C_6H_5$
R^1 = $CH_2C_6H_5$, R^2 = Me

R^1 = Me, R^2 = H Pallidine
R^1 = H, R^2 = Me Flavinanthine

2. Morphine, Codeine and Thebaine

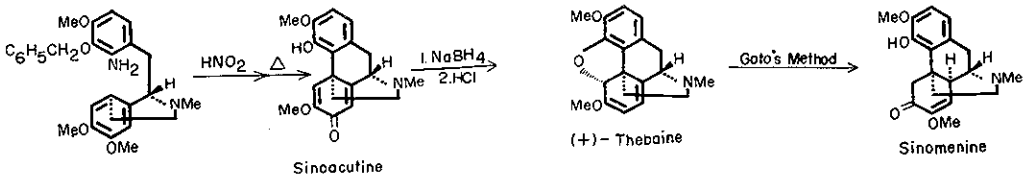
Based on this method, one of the most interesting and complicated isoquinoline alkaloid, morphine was also obtained by this modified Pschorr reaction. Optical resolution of the (±)-2'-aminobenzylisoquinoline *via* the salt of di-*p*-toluoyltartaric acid afforded the R-(−)-isomer which was diazotised with sodium nitrite and sulphuric acid and the resulting diazonium salt was decomposed thermally without a catalyst to give salutaridine. Reduction of salutaridine with sodium borohydride yielded the epimeric salutaridinols which were dehydrated in the presence of hydrochloric acid to furnish thebaine. Since thebaine has previously been converted into morphine *via* codeinone and codeine, a total synthesis of morphine and its related alkaloids was achieved.[78]





3. Sinomenine

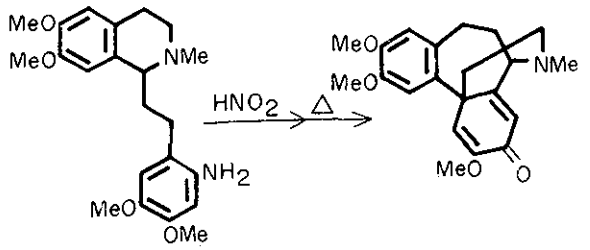
In a similar manner, S-(+)-2'-aminobenzylisoquinoline, obtained from its recemate by resolution with di-p-toluoyltartaric acid, was diazotised and thermally decomposed to give sinoacutine, an antipode of salutaridine, which was reduced to sinoacutinol and then dehydrated to afford (+)-thebaine, antipode of natural thebaine which had been transformed into the antipode of natural sinomenine. Moreover, sinomenine synthesis had been examined via several routes by the modified Pschorr reaction.[79-82]

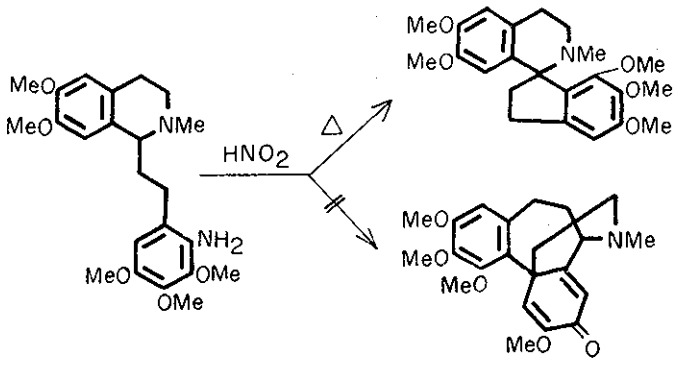


4. Homomorphinandienone Alkaloids

As an extension of the modified Pschorr reaction, the homomorphinandienone was synthesised from the 2'-aminophenethylisoquinoline under the same reaction conditions. The structure of the homodienone, supported by spectral data, was confirmed by its alternate synthesis from the benzyloxy-substituted aminoisoquinoline, thus ruling out the other possible coupling product, homoproerythrinadienone.[83]

However, the modified Pschorr reaction of the O-pentamethylated phenethylisoquinoline, which would be a precursor for O-methylandrocymbine, gave the abnormal spiro compound.[84] In contrast, C-norandrocymbine was formed from the corresponding benzylisoquinoline.[85]





O – Methylandrocymbine

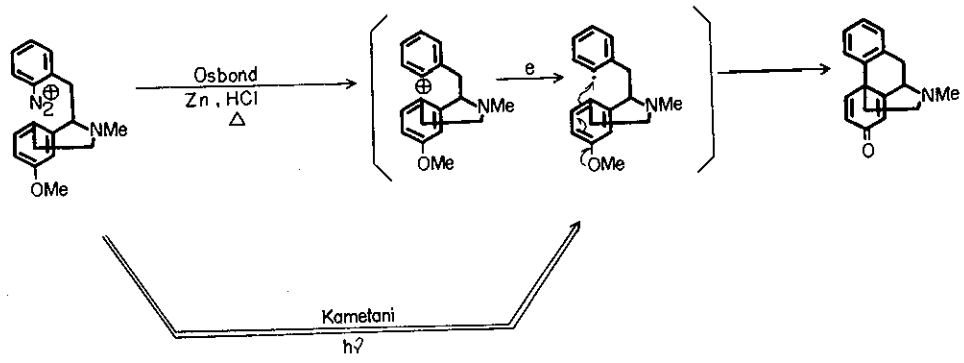
IV. TOTAL SYNTHESIS OF ISOQUINOLINE ALKALOIDS BY PHOTO-PSCHORR REACTION[71,86]

The photochemical reactions of organic compounds started to be investigated in the early years of this century but only in the last decade has photochemistry become a sophisticated field. Improved methods for the isolation of products and for the determination of structure which have been developed since World War II have overcome the former reluctance of organic chemists to utilize photochemical methods of synthesis. Photochemical synthe-

ses of strained or complicated molecules are widely employed. In particular, a number of alkaloids have been synthesised by photochemical reactions, often from starting materials of rather simple structure. In this review, we wish to describe the total synthesis of isoquinoline and related alkaloids by photolytic Pschorr reaction and then by photolytic cyclodehydrohalogenation developed in our laboratory.

1. Benzylisoquinoline Series

Osbond[87] reported that the diazonium salts derived from 2'-aminobenzylisoquinolines transformed into the morphinandienone by treatment with zinc and warm hydrochloric acid after we had described a morphinandienone synthesis by the modified Pschorr reaction. Soon thereafter, Ishiwata[88] reported a new synthesis of proaporphines by the Pschorr reaction.

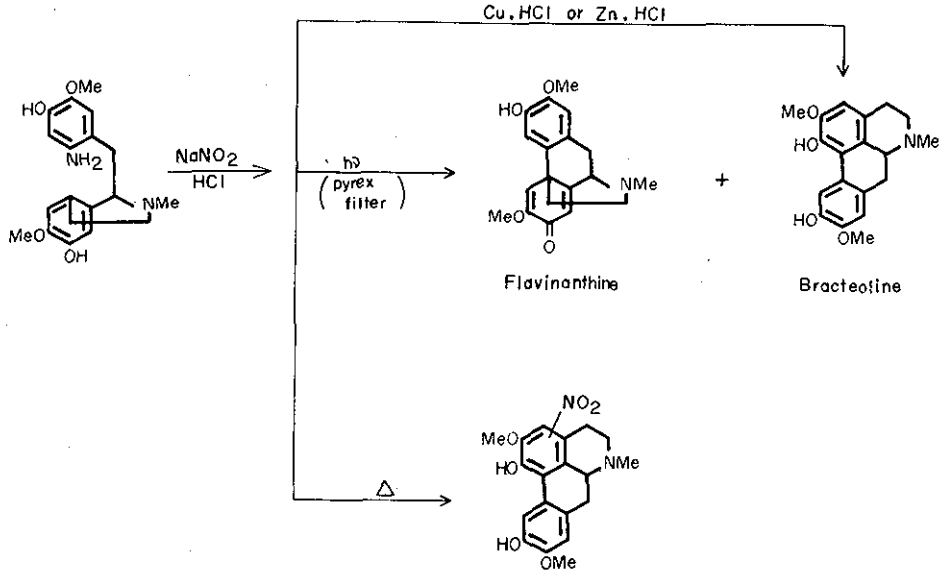


We supposed that morphinandienone formation in Osbond's work proceeded via radical mechanism as shown in the above chart. Thus, the aromatic cation, derived from a diazonium salt, is reduced with zinc and hydrochloric acid to form the aromatic radical which is attacked by the second aromatic nucleus.

Based on this idea, we assumed that photolysis of a diazonium salt would be a more efficient way of effecting homolysis of the carbon-nitrogen bond to form the postulated radical intermediate and thus examined the decomposition of diazonium salts under photolysis.

Irradiation of the diazonium salt, obtained from 6'-amino-orientaline by diazotisation, in dilute sulphuric acid at 5 - 10° for several hours afforded in moderate yield flavinantine and bracteoline.[89] To prevent the dienone-phenol rearrangement of the resulting dienone by $n-\pi^*$ transition, the photolytic reaction was carried out with a Hanovia 450 W mercury lamp surrounded by a pyrex filter to cut off the light below 310 nm and in the presence of acid to coordinate the lone electron pair on the oxygen.

On the other hand, the usual Pschorr reaction of the same isoquinoline gave only bracteoline in a low yield and the modified Pschorr reaction afforded the nitrobracteoline.



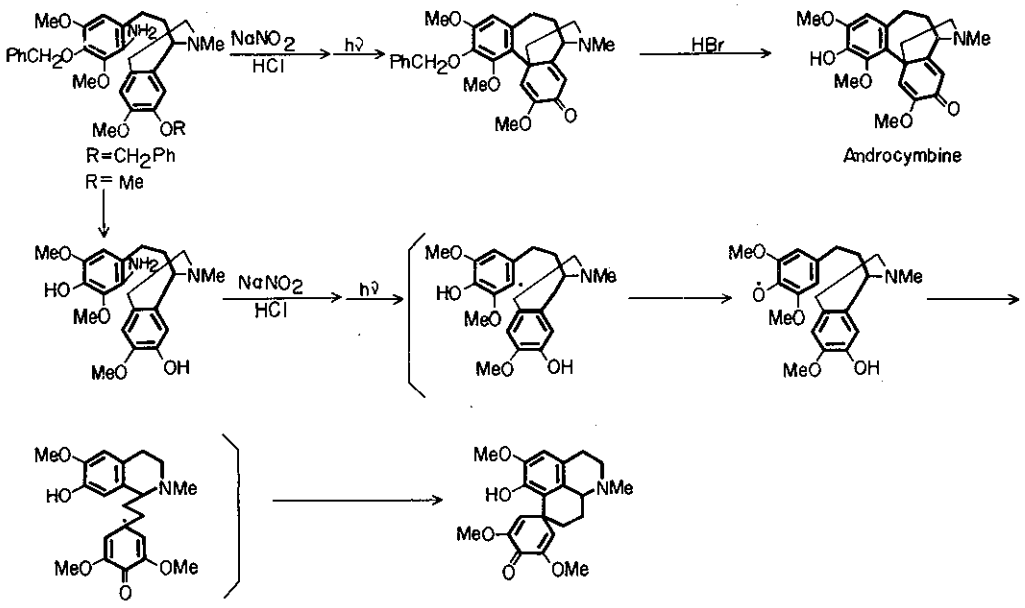
In a similar manner, N,O^{10}-dimethylhernovine,[90,91] N-methyllindecarpine[92] and corydine[92] have been prepared from the appropriate aminoisoquinolines. In these synthesis, diphenolic aporphines were directly obtained from the diphenolic precursors. These transformations demonstrate that, in contrast to the normal Pschorr reaction, side reactions, such as diazo coupling of the phenolic isoquinoline or loss of protecting groups, do not occur in the photo-Pschorr reaction.[92]

2. Phenethylisoquinoline Series

The photo-Pschorr reaction was also applied to the phenethylisoquinoline series under the same conditions as in the benzylisoquinoline series.

Photolysis of the diazonium salts of phenethylisoquinolines gave O-methylandrocymbine[93] but thermal decomposition of this diazonium salts afforded the abnormal spiro compounds.[93] Moreover, irradiation of the diazonium salt derived from 1-(2-amino-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline afforded O-methylandrocymbine and kreysigine.[91] The latter homoaporphine which could not be obtained by Pschorr reaction was also synthesised from a similar phenolic diazonium salt by a photo-Pschorr reaction.

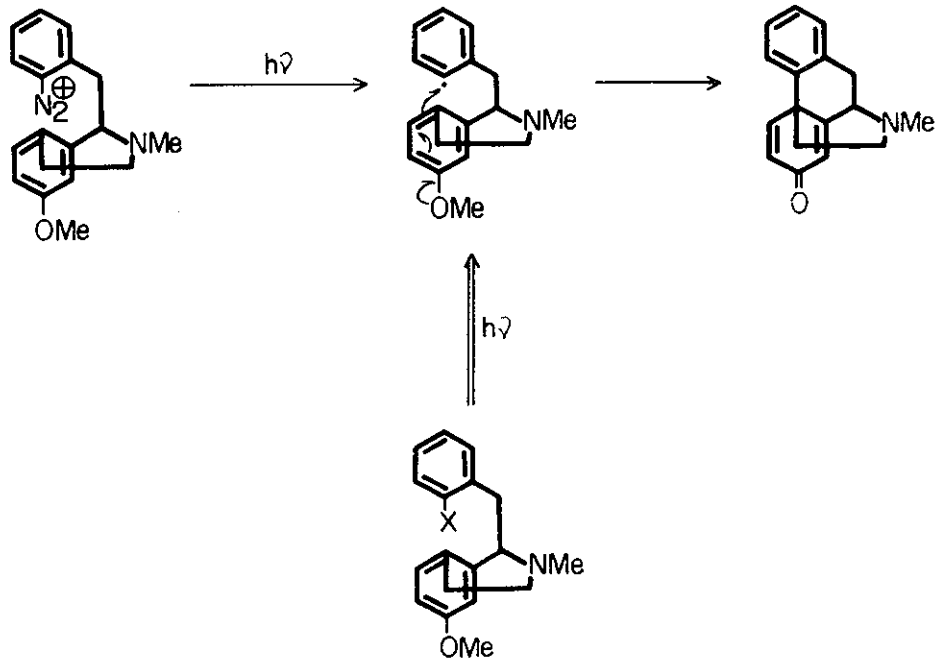
The total synthesis of androcymbine has been accomplished by an application of the photo-Pschorr reaction as follows. Photolysis of the monobenzyloxy diazonium precursor at 5 - 10° with a Hanovia 450 W mercury lamp using a pyrex filter provided O-benzylandrocymbine which was also obtained by treating the related dibenzyloxy intermediate in a similar manner. Treatment of the benzyloxy-dienone with 48 % hydrobromic acid at 55° for 45 min effected O-debenzylation to afford the desired dienone androcymbine.[94]



However, direct conversion of the diphenolic isoquinoline to androcymbine did not occur; instead this reaction produced the homoproaporphine, probably via radical intermediates as illustrated.[94]

V. TOTAL SYNTHESIS OF ISOQUINOLINE AND AMARYLLIDACEAE ALKALOIDS BY PHOTOLYTIC CYCLODEHYDROHALOGENATION[86]

It is well known that photolysis of aromatic halides in benzene results in the formation of biphenyl derivatives by reaction of the aryl radicals produced by homolytic cleavage of the carbon-halogen bond.[95] On the other hand, since the key intermediate in the photo-Pschorr reaction of the diazonium salt is probably the aromatic radical, it appeared likely that the latter could also be generated by radical formation at the C_2'-halo-substituted benzylisoquinoline to also afford the dienone. Based on this consideration, we investigated the potential utility of photolytic cyclodehydrohalogenation in the synthesis of morphinandienone and aporphine alkaloids.



1 Aporphine and Morphinandienone Alkaloids

In our initial studies, we irradiated the readily accessible 6'-bromolaudanosine (R=Me) in aqueous methanol with a Hanovia 450 W mercury lamp surrounded by a pyrex filter at room temperature in an atmosphere of nitrogen. However, the expected morphinandienone or aporphine was not obtained.

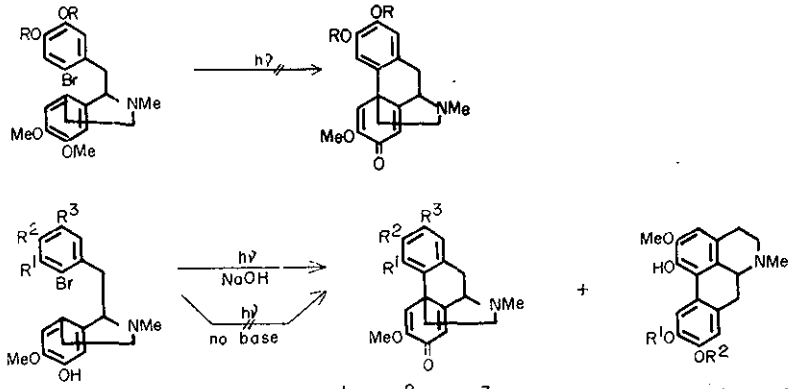
We then reasoned that coupling of the C_2,-radical with the isoquinoline ring would be favoured by the presence of a phenolic function which is more polar than a methoxyl group. Thus, the diphenolic isoquinoline 6'-bromoorientaline was irradiated in the usual way, but once again, no coupling products such as the aporphine or the morphinandienone could be obtained.

We next speculated that coupling of the radical would be favoured by a phenolate anion rather than a free phenolic function. This assumption proved to be correct and indeed irradiation of 6'-bromoorientaline (R^1=H, R^2=OH, R^3=OMe) for 7 h at room temperature in the presence of an excess of sodium hydroxide with a Hanovia 450 W mercury lamp using a pyrex filter afforded the aporphine bracteoline and the morphinandienone flavinantine in moderate yield. Since irradiation of the non-phenolic base in the presence of alkali resulted in no coupling product, we concluded that a phenolic hydroxyl group at the C_7-position of the isoquinoline ring as well as an excess of sodium hydroxide was necessary for C-C coupling.[96,97]

By this means, irradiation of 6'-bromoreticuline (R^1=H, R^2=OMe, R^3=OH) and its methylenedioxy analogue (R^1=H, $R^2 + R^3 = OCH_2O$) gave in moderate yield isoboldine and demesticine, respectively. In

addition, the corresponding morphinandienones pallidine and amurine were also obtained.[96,97]

It is apparent from the aforementioned examples that photocyclisation of phenolic bromoisoquinolines induced coupling at both the ortho and para position to the phenolic function to form the aporphines and morphinandienones, respectively. As an extension of the latter type coupling, photolysis of 2'-bromoreticuline (R^1=OH, R^2=OMe, R^3=H) in the presence of sodium iodide gave the morphinandienone salutaridine. Reduction of this product provided the corresponding dienol salutaridinol which was then rearranged by acid treatment to afford thebaine. Since thebaine had previously been converted by both Professors Gates and Rapoport *via* codeinone and codeine into morphine and sinomenine, our preparation of thebaine by photo-cyclodehydrohalogenation thus constitutes a total synthesis of morphine, codeine, and sinomenine.[98,99] Similarly, N-methyllaurotetanine, cassythicine and pukateine were obtained from the appropriate bromoisoquinolines.[99]

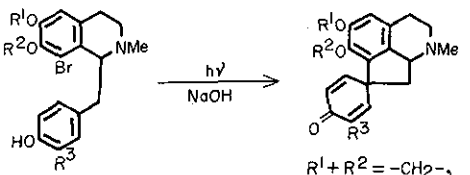


R^1 = H, R^2 = OH, R^3 = OMe Flavinanthine
R^1 = H, R^2 = OMe, R^3 = OH Pallidine
R^1 = H, R^2+R^3 = -OCH_2O- Amurine
R^1 = OH, R^2 = OMe, R^3 = H Salutaridine

R^1 = H, R^2 = Me Bracteoline
R^1 = Me, R^2 = H Isoboldine
R^1+R^2 = -CH_2- Domesticine

2 Proaporphine Alkaloids

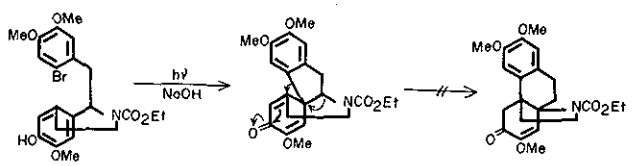
Having demonstrated the feasibility of preparing morphinandienones by photo-cyclisation, we then extended this study to the synthesis of proaporphine alkaloids. Thus, irradiation of the substituted 8-bromo-1-(4-hydroxybenzyl)isoquinolines in the usual manner in the presence of sodium hydroxide afforded the corresponding proaporphines mecambrine, pronuciferine and glaziovine. Moreover, photolysis of the trimethoxy-substituted intermediate gave O-methylorientalinone in addition to O-methylisoorientalinone, a spiro isomer which was separated by fractional crystallisation of the picrolonates.[97,99,100]



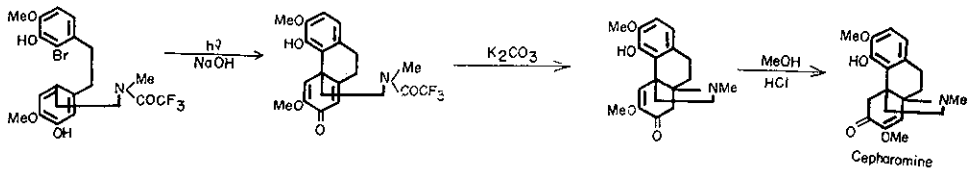
$R^1 + R^2 = -CH_2-$, $R^3 = H$ Mecambrine
$R^1 = R^2 = Me$, $R^3 = H$ Pronuciferine
$R^1 = Me$, $R^2 = R^3 = H$ Glaziovine
$R^1 = R^2 = Me$, $R^3 = OMe$ O-Methylorientalinone

3 Hasubanan Alkaloids

Using similar photolytic conditions, the phenolic bromocarbamate was cyclised to yield the proerythrinadienone-type compound but this was not transformed into the cepharamine-type compound.[101,102]



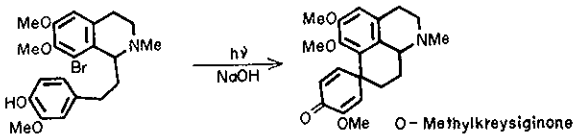
By a modification of the photo-cyclodehydrohalogenation reaction, the hasubanan alkaloid cepharamine was synthesised as its racemate in the following manner. 2'-Bromoreticuline was treated with trifluoroacetic anhydride in a sealed tube at 160° for several hours and the resulting stilbene was hydrogenated over Adams catalyst to give the dihydrostilbene. Irradiation of the latter in the presence of sodium iodide and sodium hydroxide gave a mixture of the dienone and the enone. Treatment of the dienone with weak base also afforded the enone which was then transformed by methanolic hydrochloric acid into cepharamine.[103]



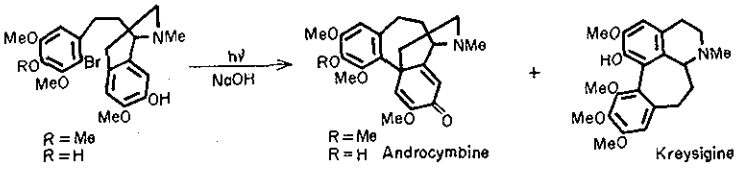
4. Phenethylisoquinoline Alkaloids

In addition to the conversion of phenolic bromobenzylisoquinolines into aporphines, morphinandienones, and proaporphines, photolytic cyclisation of related phenethylisoquinolines afforded the corresponding "homo" alkaloids.

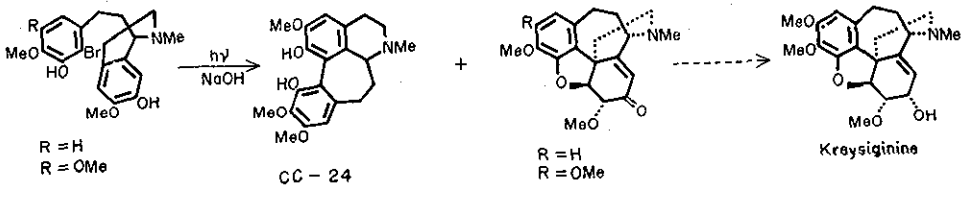
The 8-bromo-monophenol was converted by irradiation into the dienone O-methylkreysiginone and its spiro isomer, the former of which was identical with the methylation product of kreysiginone.[100]



Irradiation of the bromo-monophenol in the usual manner afforded a separable mixture of the homodienone alkaloid O-methylandrocymbine and the homoaporphine alkaloid kreysigine which were identical by ORD with the natural products.[104,105] Similarly, photolytic cyclisation of the bromo-diphenol gave androcymbine as well as multifloramine.[106]



The synthesis of kreysiginine was also examined. Photolysis of the diphenolic bromoisoquinoline gave alkaloid CC-24 and the enone. The latter one formed by a Michael-type addition of the phenolic hydroxyl group to the initial dienone system.[107]

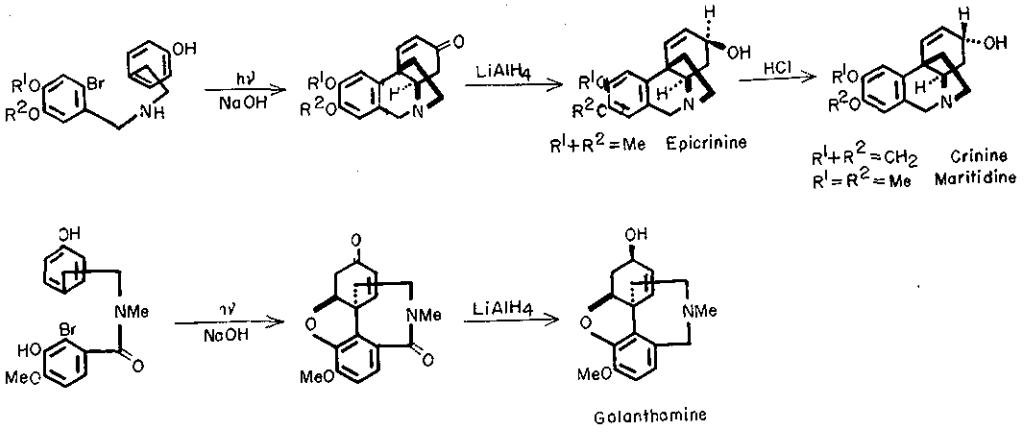


5. Amaryllidaceae Alkaloids

Finally, the spirodienone synthesis by photolytic cyclisation of phenolic bromo compounds was also applied to the total synthesis of certain Amaryllidaceae alkaloids. Thus, irradiation of phenolic bromo-amine (R^1=R^2=Me) in the usual manner afforded the

enone. Since this enone had previously been converted into maritidine, this sequence constituted an alternate route to the Amaryllidaceae alkaloid.[108] In a similar manner, (±)-epicrinine was synthesised by photolysis of the methylenedioxy-substituted amine followed by reduction of the resulting enone with lithium aluminium hydride.[109]

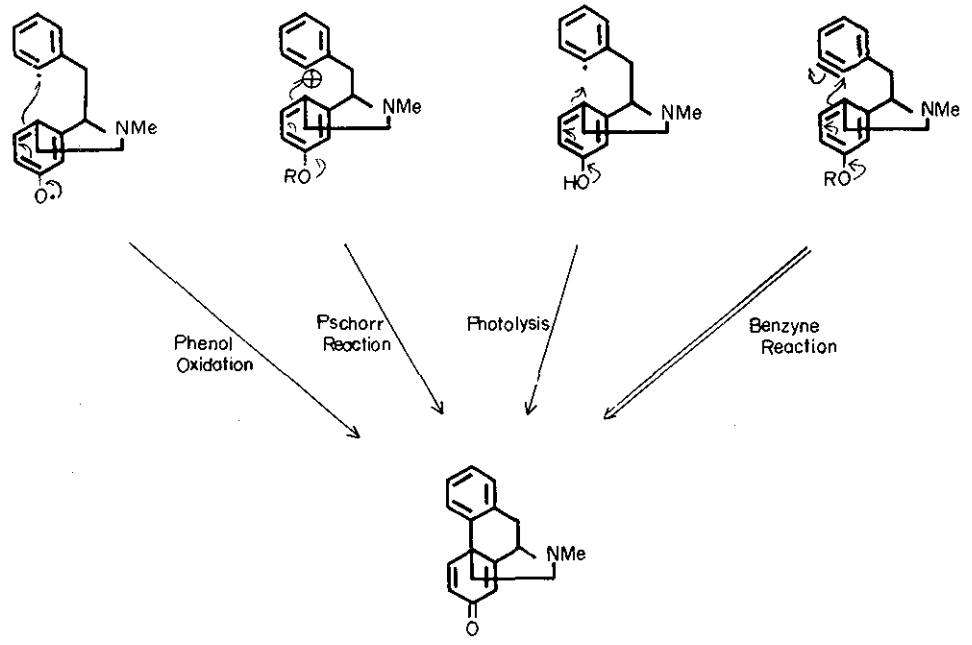
Utilizing a variation of this approach, we also achieved the synthesis of the Amaryllidaceae alkaloid galanthamine as its racemate. Irradiation of the phenolic bromo-amide effected cyclisation to the narwedine-type derivative which was then reduced with lithium aluminium hydride to afford (±)-galanthamine.[110]



VI. TOTAL SYNTHESIS OF ISOQUINOLINE ALKALOIDS BY BENZYNE REACTION

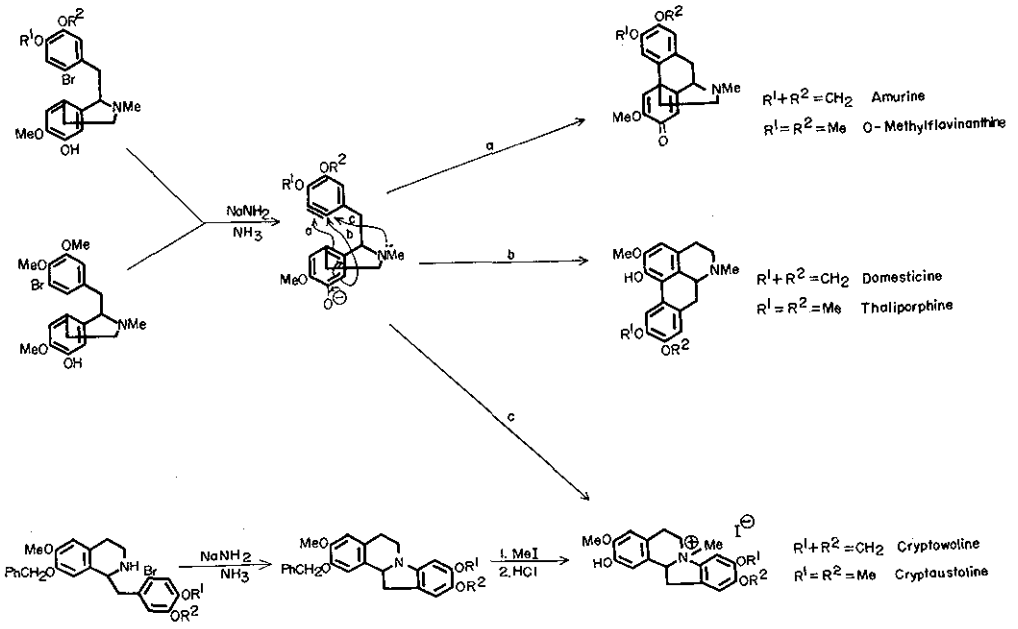
As the fifth approach to the total synthesis of isoquinoline alkaloids, we explored the utility of the benzyne reaction which involves another mechanism in the substitution reaction on an aromatic ring instead of the ionic reaction in Pschorr synthe-

sis and the radical reaction in phenolic oxidation and photolysis.



Firstly, 2'-bromocodamine (R^1=R^2=Me) was treated with sodium amide in liquid ammonia to give thaliporphine and O-methylflavinantine, both of which were also synthesised from 3'-bromocodamine by the same reaction. Thus, it was established that this reaction involved benzyne intermediates. In addition, racemic cryptaustoline was also obtained and was probably formed by the nucleophilic attack of the tertiary nitrogen atom to the benzyne position.[111,112]

In a similar manner, the methylenedioxy analogue (R^1 + R^2 = CH_2) afforded a mixture of domesticine, amurine, and the quaternary dibenzopyrrocoline, cryptowoline.[111,113]



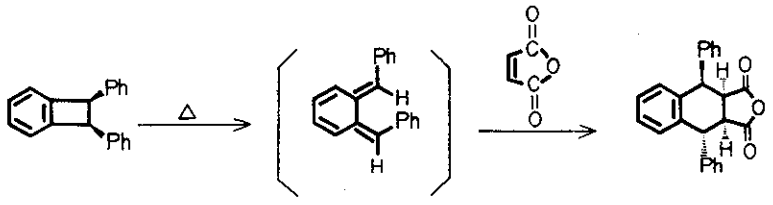
1-(2-Bromobenzyl)-1,2,3,4-tetrahydroisoquinoline was subjected to the benzyne reaction with sodium amide in liquid ammonia to provide the tetrahydrodibenzopyrrocoline. Proof that this type of reaction proceeded *via* a benzyne intermediate was provided by the *cine*-substitution observed in the conversion of the 3'-bromoisoquinoline into the dibenzopyrrocoline with sodium amide in liquid ammonia.[114]

Based on this finding, we synthesised cryptowoline and cryptaustoline from the 2'-bromoisoquinolines by the benzyne reaction. Treatment of the 2'-bromoisoquinolines with sodium amide in liquid ammonia gave the dibenzopyrrocolines which were converted into the methiodides followed by debenzylation to give the racemates of the alkaloids cryptowoline and cryptaustoline.[114]

VII. TOTAL SYNTHESIS OF NATURAL PRODUCTS VIA BENZOCYCLOBUTENES[115]

1. Introduction

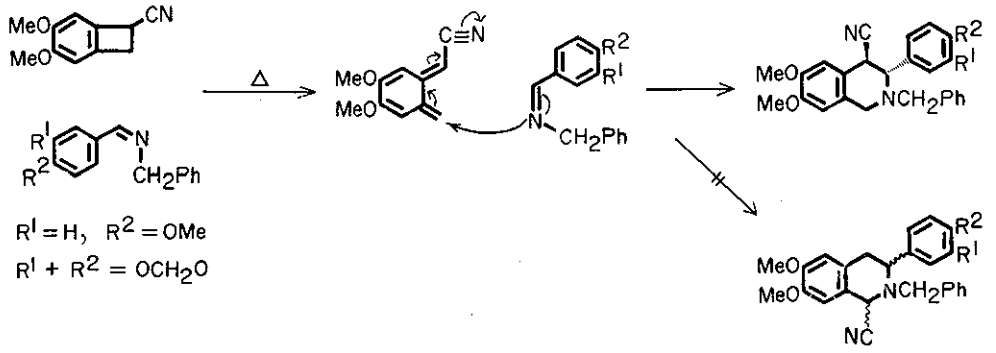
According to the Woodward-Hoffmann rule,[116] the application of photolysis and thermolysis to electrocyclic and cycloaddition reactions gives different products. This rule not only explains the mechanism of the photolytic and thermal reactions but also provides a useful route for the synthesis of organic compounds. For example, Huisgen[117] reported that thermolysis of the benzocyclobutene derivative[118] in the presence of the dienophile gave in a regioselective and stereoselective manner the tetralin derivative by the electrocyclic reaction followed by cycloaddition to the resulting o-quinodimethane. Based on this finding, we investigated the possibility of converting 1-benzocyclobutenes via ring-opened intermediates into natural products with a complicated ring system.



a) Isoquinoline Synthesis

Initially, we examined the thermolysis of benzocyclobutenes in the presence of imines as the dienophiles in order to develop a new method of isoquinoline synthesis. Thus, reaction of 1-cyanobenzocyclobutene with Schiff bases was carried out at 150 - 160°

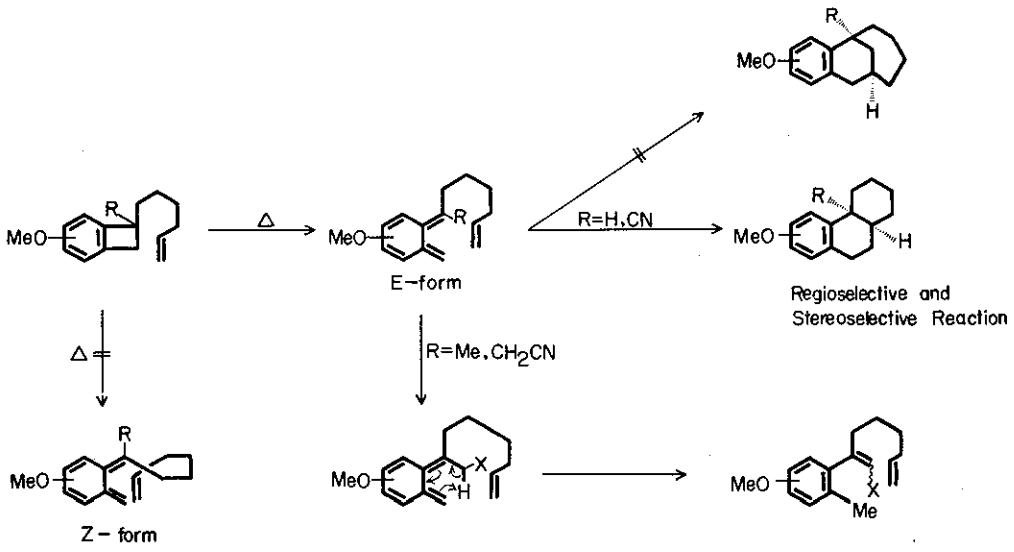
without solvent to give only the 3,4-disubstituted 1,2,3,4-tetrahydroisoquinolines whose structures were deduced from nmr spectral analysis. Although the stereochemistry of the C-3 and C-4 positions was unclear, we assumed that the trans-configuration was the preferred one since epimerisation at the C-4 position would give a more thermodynamically stable compound. Since the 3,4-disubstituted isoquinoline was obtained as a single stereostructure, it may be concluded that the cycloaddition proceeded in both a regioselective and stereoselective manner. Therefore, we developed a new and simple synthesis of the isoquinoline ring in a regioselective and stereoselective manner and also found that the o-quinodimethane reacted with an imine system.[119]



b) General Reaction of o-Quinodimethane

Usually, o-quinodimethanes are formed in situ by thermolysis of benzocyclobutenes and it is known that ring-opening of benzocyclobutene occurs in a conrotatory manner.[116] We also examined the direction of ring opening and found that o-quinodimethane takes the (E)-form which is more stable thermodynamically rather than the

(Z)-form due to the secondary effect of the substituent on cyclobutene ring.[120] Moreover, we also observed that o-quinodimethanes derived from 1,1-dialkylated benzocyclobutenes or 1-substituted 1-methylbenzocyclobutenes cause a new type of reaction, namely [1,5]sigmatropic hydrogen migration as shown in the following chart.[120]



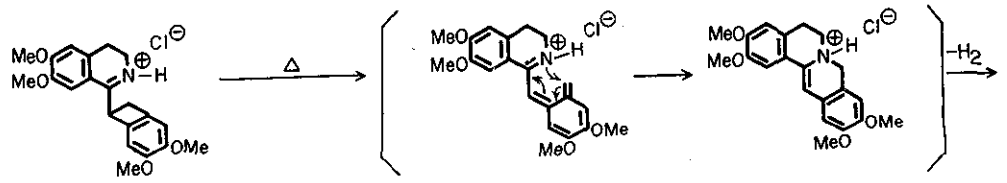
2. Total Synthesis of Isoquinoline Alkaloids

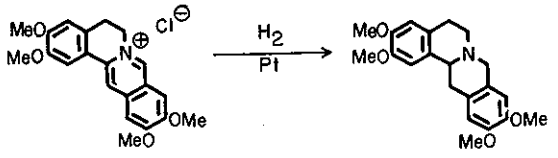
a) Protoberberine Alkaloids

As shown in the above chart, since o-quinodimethanes could react intramolecularly (electrocyclic reaction or intramolecular cycloaddition) and intermolecularly (cycloaddition), we investigated protoberberine synthesis by both methods.

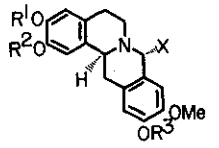
Thermolysis of the 1-benzocyclobutenyl-3,4-dihydroisoquinoline hydrochloride at 160 - 180° for 20 min gave the protoberberine. This probably involved an electrocyclic reaction of benzocyclo-

butene to form the o-quinodimethane which underwent a second electrocyclic reaction with the 3,4-dihydroisoquinoline system to yield the 7,8-dihydroprotoberberine intermediate which was then easily dehydrogenated in the air to give the protoberberine. Hydrogenation of the quaternary base thus afforded the alkaloid xylopinine. In the same manner, discretine,[122] coreximine[123] and O-methylcorytenchirine[124] have been synthesised from the appropriate benzocyclobutenes.





Xylopinine



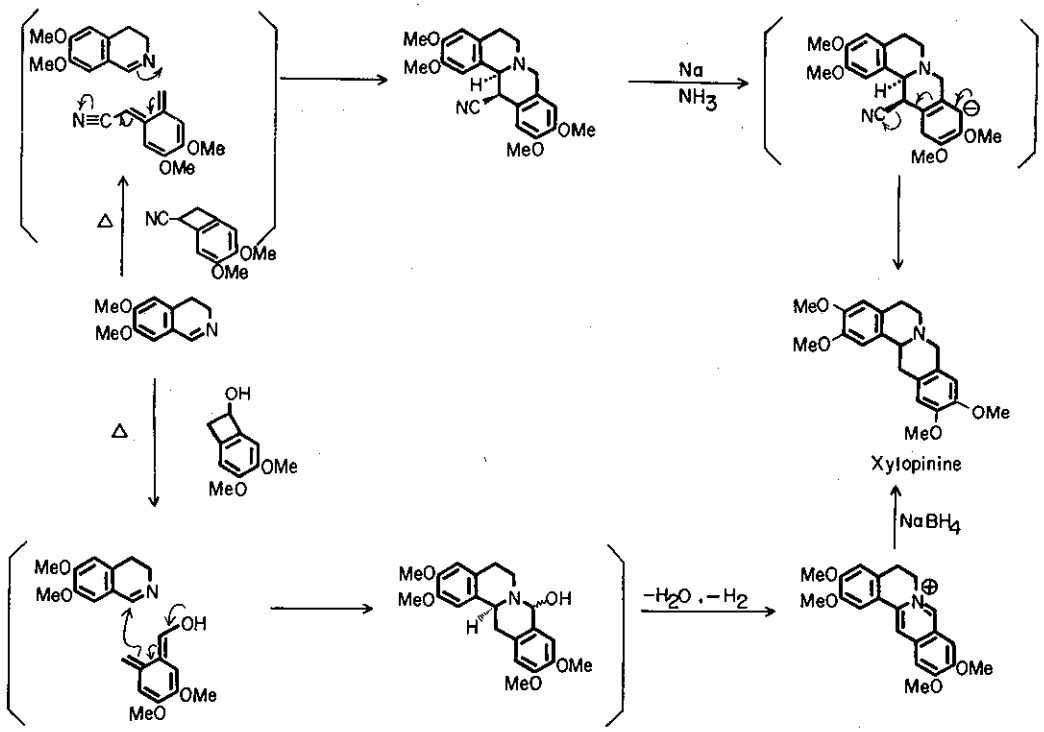
	R^1	R^2	R^3	X
Discretine	H	Me	Me	H
Coreximine	Me	H	H	H
O-Methyl-corytenchirine	Me	Me	Me	Me

The second approach is an application of intermolecular cycloaddition of benzocyclobutenes to 3,4-dihydroisoquinolines.[125]

Thus, heating the 1-cyanobenzocyclobutene with the 3,4-dihydroisoquinoline at 150 - 160° gave in good yield the 13-cyano-7,8,13,13a-tetrahydroprotoberberine with regio- and stereoselectively but

not the 8-cyano isomer. Moreover, 1-cyano-1-methylbenzocyclobutene also gave 13-cyanomethyltetrahydroprotoberberine.[126] Decyanation of the latter by a Birch-type reduction with lithium in liquid ammonia in the presence of isopropyl alcohol afforded xylopinine.[127]

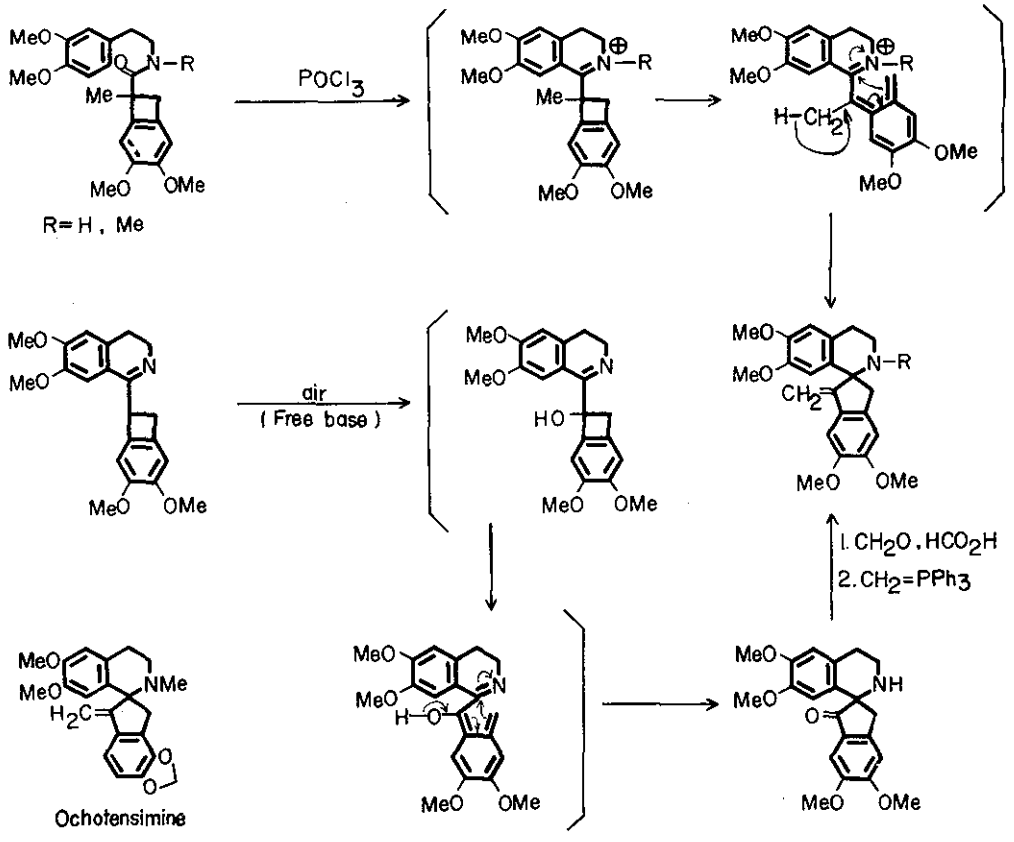
On the other hand, heating the benzocyclobutenol with 3,4-dihydro-6,7-dimethoxyisoquinoline in benzene at 80° for 5 h gave *via* the transient 8-hydroxyprotoberberine the quaternary protoberberine in 52 % yield. The later was then converted into the protoberberine alkaloid xylopinine in good yield by reduction with sodium borohydride.[128]



Thus, we found that the regioselectivity in cycloaddition of an o-quinodimethane depended upon an E-effect of the substituent on cyclobutene ring and also developed two new methods for protoberberine synthesis.

b) Spirobenzylisoquinolines

In connection with our protoberberine synthesis, a novel synthesis of the spirobenzylisoquinoline was achieved as follows. It was surprising that Bischler-Napieralski reaction of the amide with phosphoryl chloride in refluxing benzene for 22 h did not provide the expected 3,4-dihydroisoquinolinium salt. Instead, we



obtained directly the spirobenzylisoquinoline.[129] It is probable that the 3,4-dihydroisoquinolinium salt was initially formed and then rearranged thermally via o-quinodimethane and the spiro intermediate to yield the ochotensine-type compound.[129,130] The different chemical behaviour of the amide must arise from hyperconjugation and the steric effect of the methyl group on cyclobutene ring.

This finding provides a more direct route to the ochotensine-type alkaloids than the stepwise procedure heretofore reported, and this transformation also represents a convenient entry into the synthesis of the spirobenzylisoquinoline alkaloids.

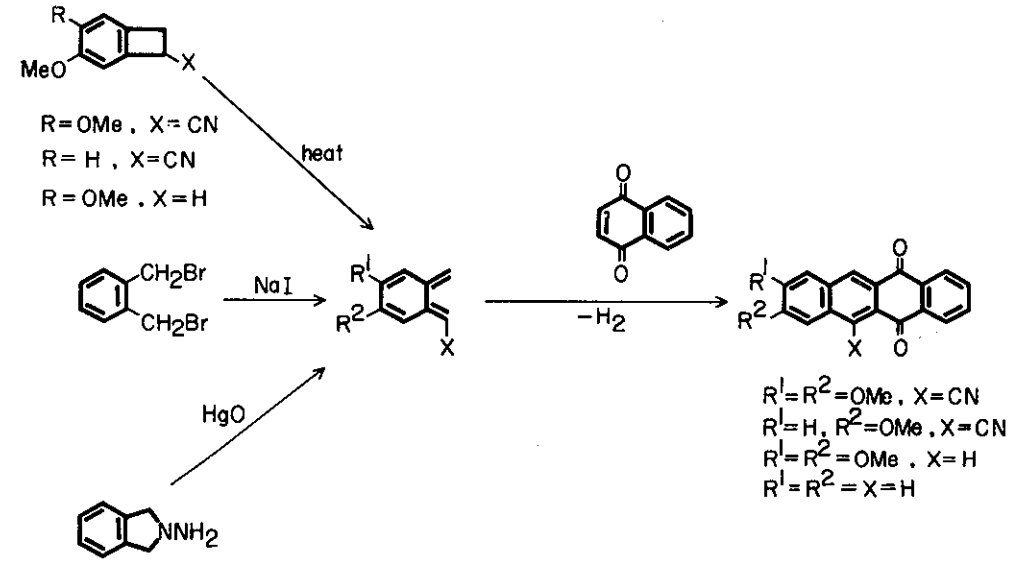
The hydrochlorides of the 1-benzocyclobutenyl-3,4-dihydroisoquinoline are stable at room temperature but the free bases of these compounds are unstable in air. A chloroform solution of the free base on standing at room temperature for 2 or 3 days was transformed, in good yield, into the ketospirobenzylisoquinolines. The mechanism of this reaction could be explained by air oxidation of the benzocyclobutenes to the benzocyclobutenols followed by ring opening to o-quinodimethanes and then electrocyclic reaction as shown in the above chart.[131,132]

3. Tetracyclines

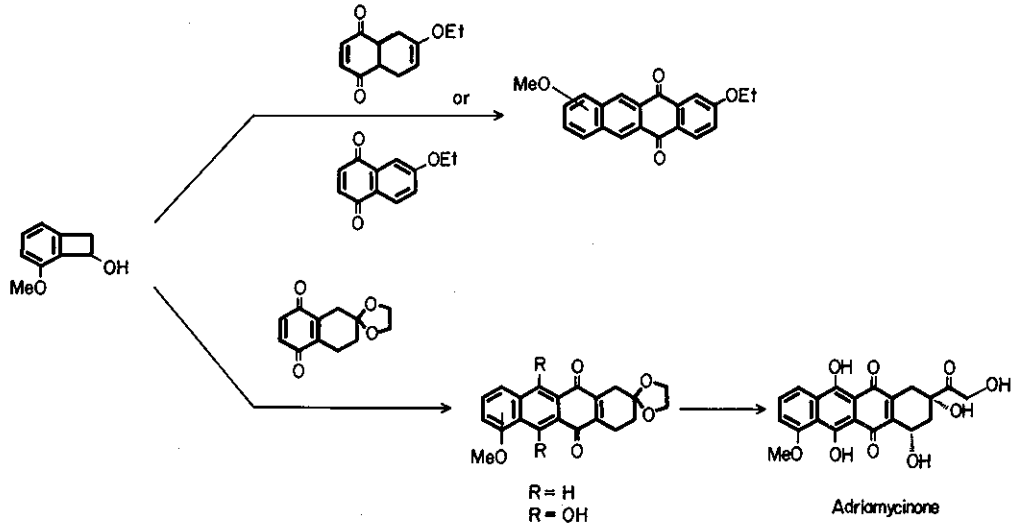
It is well known that p-quinone or naphthoquinone is an effective dienophile, and, therefore, the reaction of naphthoquinone with o-quinodimethanes was examined to develop a new and simple method for a synthesis of tetracycline-type compounds.

Heating naphthoquinone with o-quinodimethanes, which were generated in situ from latter benzocyclobutenes, o-xylyl dibromide

or N-aminodihydroisoindole, gave the tetracycline-type of compounds, naphthacene-5,12-quinones in moderate yield.[133]



Based this finding we have investigated the total synthesis of adriamycinone. Reaction of 6-ethoxy-5,8,9,10-tetrahydronaphthoquinone with 6-methoxybenzocyclobutenol at 150 - 160° afforded the tetracyclic compound, which was also obtained by treatment of the



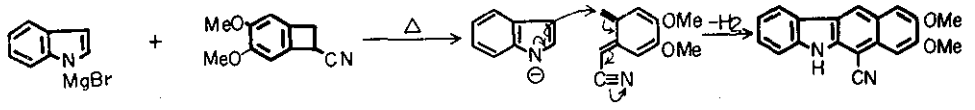
benzocyclobutenol with 6-ethoxynaphthoquinone. Similarly, the benzocyclobutenol was converted into 2-ethylenedioxy-1,2,3,4-tetrahydro-7- or 10-methoxynaphthacene-5,12-quinone by reaction with 6-ethylenedioxy-5,6,7,8-tetrahydronaphthoquinone. The resulting product can be considered as a potential precursor to adriamycinone since the related 6,11-dihydroxylated compound has been converted into adriamycinone.

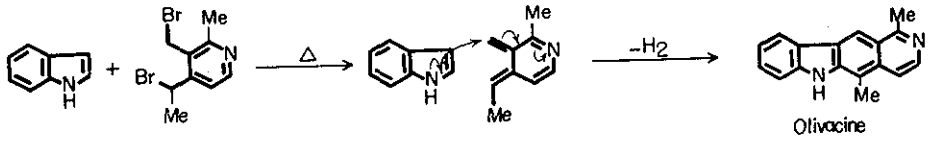
4. Olivacine

As a further extension of the intermolecular cycloaddition of o-quinodimethanes to the imines system, the possibility of obtaining an indolotetralin derivative by the reaction of an o-quinodimethane with indole was investigated. This was of particular interest as the expected cycloaddition product would be an analogue of olivacine or ellipticine which shows antitumor activity.

However, since reaction of indole with the cyanobenzocyclobutene in boiling dichlorobenzene afforded only the benzocyclobutene dimer, the more nucleophilic indolylmagnesium bromide was fused with the cyanobenzocyclobutene at 160° for 10 min to give regioselectively 6-cyano-8,9-dimethoxybenzocarbazole in 83 % yield.[134]

Based on this finding as well as several model experiments[135] using indole and pyridine derivatives, the total synthesis of olivacine was achieved as follow. Heating indole with 3,4-dibromoethylpyridine in dimethylformamide at 150° afforded regioselectively olivacine in 30 % yield. The regioselectivity was based on the nucleophilicity at the C_3 position in the indole ring and also on the electrophilic activity by C=N in the pyridine system.[136]





5. Quinazolone Alkaloids

As mentioned above, we exploited the novel synthesis of heterocyclic systems by an intermolecular cycloaddition of o-quinodimethane with imines. In addition we expected that if an iminoketene could be generated in situ from some suitable precursors, this species would react with imines to form a quinazolone system and that this type of cyclisation could be applied to the total synthesis of rutecarpine, evodiamine and related compounds.

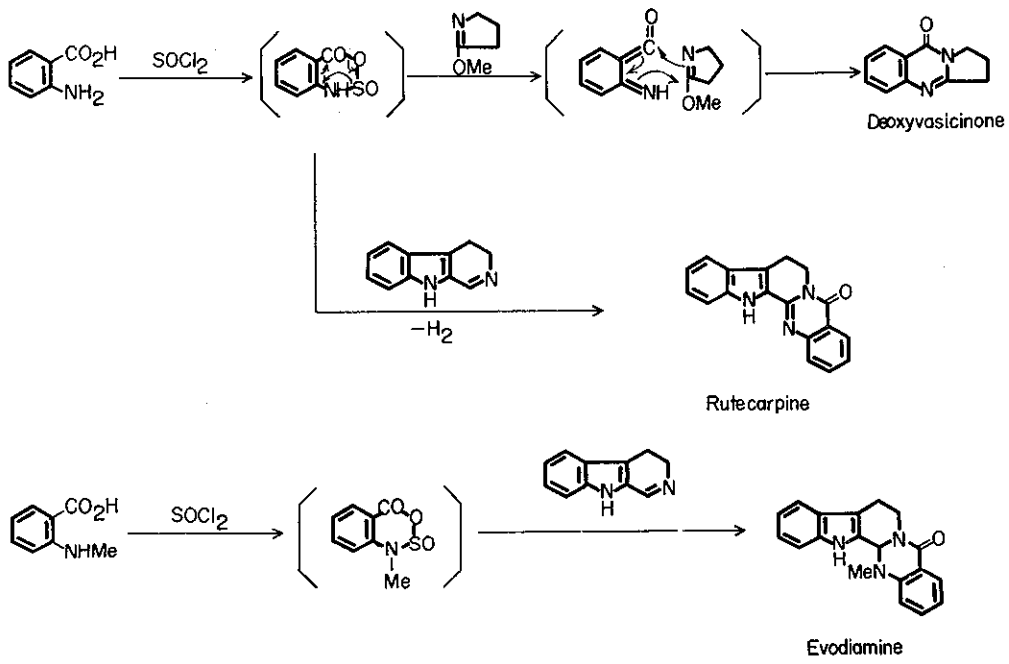
Firstly, we carried out model experiments in investigating the synthesis of the iminoketene. It has been reported that the reaction of isatoic anhydride with imines to form quinazolone required severe conditions. Since the mechanism had not been elucidated, we assumed that the intermediate would be the iminoketene, formed by elimination of carbon dioxide by a retrograde Diels-Alder type reaction. Since our experience, cycloaddition reaction with imines would be expected to proceed under mild conditions, sulfinamide anhydride was used as a possible precursor of the

iminoketene.

Heating anthranilic acid with thionyl chloride in dry benzene under reflux gave the unstable sulfinamide anhydride. Reaction of the latter with O-methylpyrrolidine, which was unstable on heating, was carried out in dry benzene at room temperature to afford regioselectively deoxyvasicinone in good yield. In this reaction, the sulfinamide anhydride could have been converted into the iminoketene by a retrograde cycloaddition, which would regioselectively react with the imine *via* a concerted ($_{\pi}4 + _{\pi}2$)cycloaddition pattern to form deoxyvasicinone.[137]

On the basis of this finding that the quinazolone system could be obtained in one-step and in a regioselective manner by cycloaddition of imines with iminoketene, we examined the synthesis of evodiamine and rutecarpine.

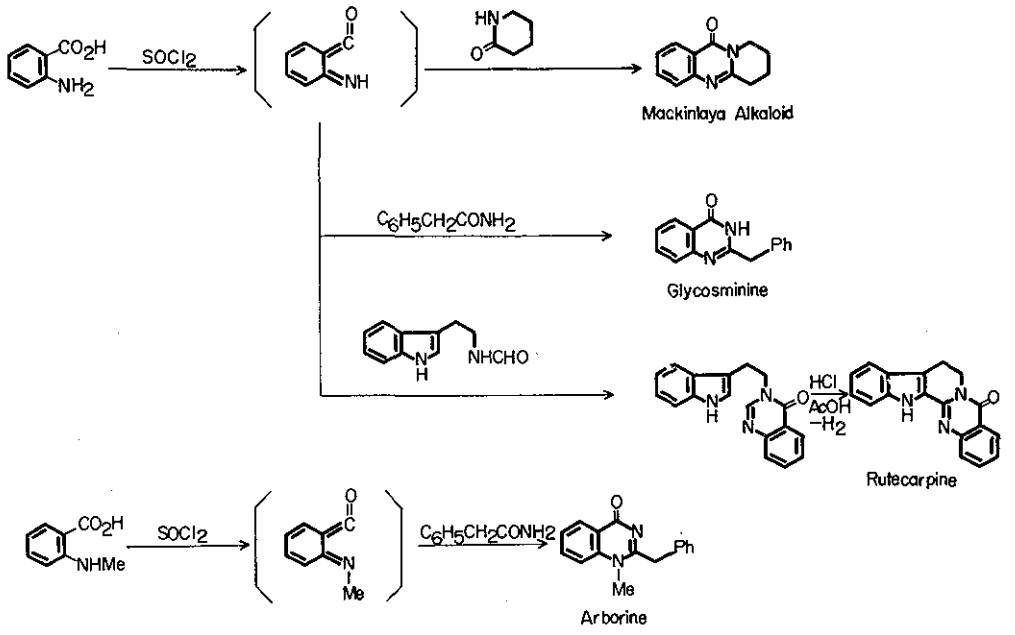
Heating N-methylanthranilic acid with thionyl chloride in dry benzene gave an unstable sulfinamide anhydride which on treatment with 3,4-dihydro-β-carboline in dry benzene at room temperature evolved sulphur dioxide to afford perhaps *via* a hypothetical intermediate N-methyliminoketene, regiospecifically evodiamine in 65 % yield.[137] In a similar manner, rutecarpine was also obtained in one step. Namely, treatment of the sulfinamide anhydride with 3,4-dihydro-β-carboline in dry benzene at room temperature gave, in 80 % yield, rutecarpine by a spontaneous dehydrogenation of the initial product.[137] Euxylophoricine A and C, the dimethoxy and methylenedioxy analogues of rutecarpine, respectively, were also obtained by the same method.[138]



Although we have proposed a concerted mechanism in the above type of cycloaddition reaction, a stepwise mechanism is also likely since the anhydride is prepared by heating at 80° without decomposition to the iminoketene. If the latter mechanism would be applicable, the formation of quinoazolones from the reaction of the iminoketene with amides would be possible. Based on this premise, we investigated the reaction of the sulfinamide anhydride with amides.[139]

Treatment of the sulfinamide anhydride with pyrrolidone or phenylacetamide at room temperature gave, in good yield, Machinlaya alkaloid and glycosminine.[139] Similarly, arborine,[139]

glycorine, glomerine and homoglomerine[138] have been prepared from N-methylanthranilic acid. This reaction was also applied to a total synthesis of rutecarpine from N-formyltryptamine via 3-indolylethylquinazolin-4-one as shown in the following chart.[139]



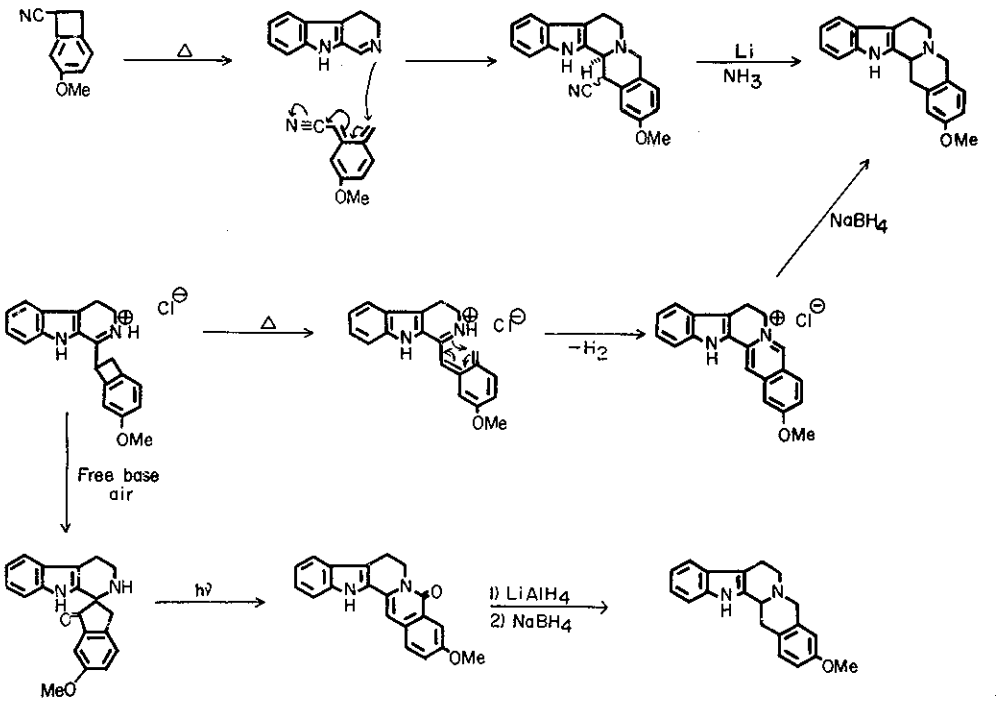
6. Yohimbine

The successful synthesis of a protoberberine-type compound from benzocyclobutenes by an electrocyclic reaction and an intermolecular cycloaddition reaction suggested that the decadehydroyohimbanes or yohimbones, possible intermediates to yohimbine, could be obtained by the same reaction of the appropriate o-quinodimethanes with 3,4-dihydro-β-carbolines. Based on this idea, we firstly investigated a yohimbone synthesis as follows.

An intermolecular cycloaddition of 1-cyanobenzocyclobutene to 3,4-dihydro-β-carboline was effected at 150 - 160° without solvent

over 2 h in a current of nitrogen to give regioselectively the 14-cyanohexadehydroyohimbane in 85 % yield which was decyanated by treatment with metallic lithium and liquid ammonia in the presence of isopropyl alcohol to afford in 65 % yield the hexadehydroyohimbane.[127] The regioselectivity of this reaction is rationalised by the electron-attracting power of the cyano group in quinodimethane system.

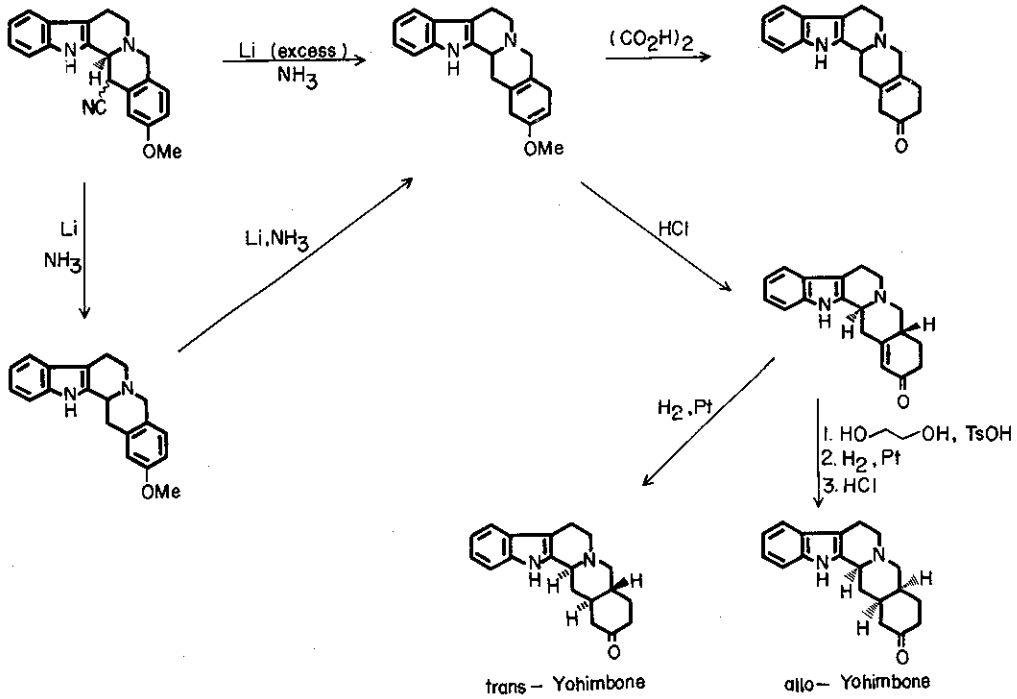
Moreover, thermolysis of 3,4-dihdyro-1-benzocyclobutenylcarboline hydrochloride at 155° in bromobenzene for 30 min in a current of nitrogen gave the expected decadehydroyohimbane in 70 % yield which was reduced with sodium borohydride to give the hexadehydroyohimbane, identical with the product formed <u>via</u> an intermolecular cycloaddition reaction.[140]



In addition, we synthesised another type of hexadehydroyohimbane differing only in the position of the methoxyl substituent by utilizing the difference in reactivity between the free base and the hydrochloride. Thus, the free base of the 1-benzocyclobutenyl-3,4-dihydrocarboline rearranged on standing for 3 days in chloroform at room temperature to the ketospirobenzyl-β-carboline followed by irradiation in dry tetrahydrofuran at room temperature for 3 h to give the lactam which had already been converted into 18-methoxyyohimbane.[127]

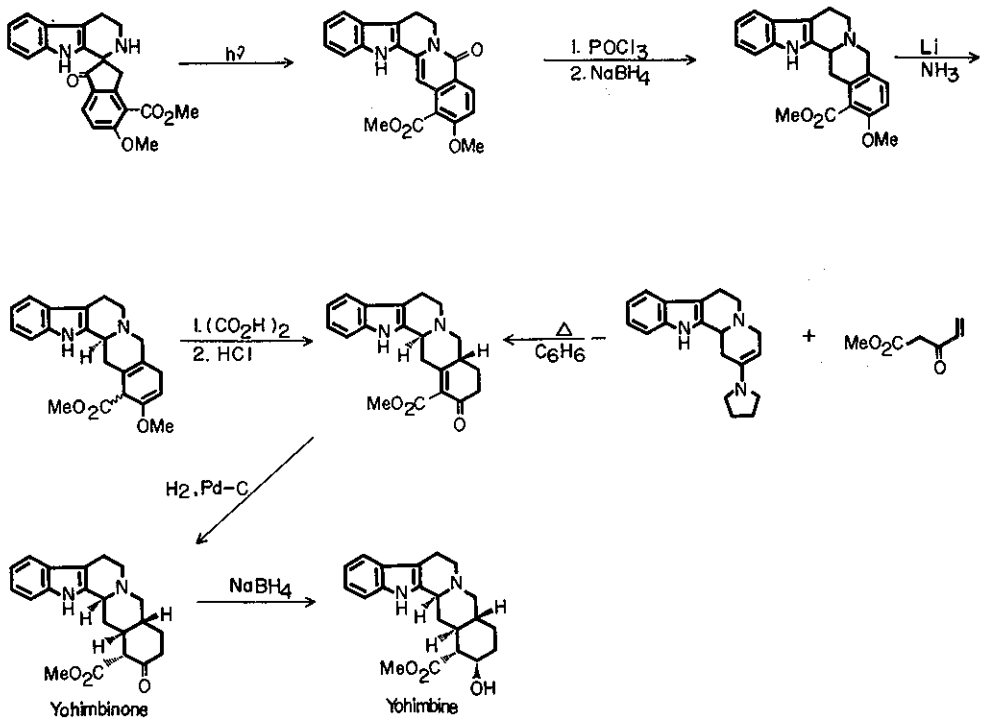
It is interesting that the same starting material gives the two yohimbanes which are position isomers as shown in the following chart.

Birch reduction of the hexadehydroyohimbane with the lithium and liquid ammonia-isopropyl alcohol system gave the enol ether. The



same enol ether was obtained by reduction of 14-cyanoyohimbane with a large excess of lithium in liquid ammonia and isopropyl alcohol. Finally, treatment of the enol ether with oxalic acid gave the β,γ-unsaturated dehydroyohimbone in good yield while reaction with hydrochloric acid by Swan's method afforded the dehydroyohimbones.[127]

Our methods would be specially useful for the synthesis of yohimbanes and yohimbones having an electron-withdrawing group on ring E since this type of compound could not be obtained by the usual Mannich reaction of 1-benzyl-1,2,3,4-tetrahydro-β-carboline with formalin while in our synthesis the key starting materials have already a "berberine bridge carbon" in the molecule.



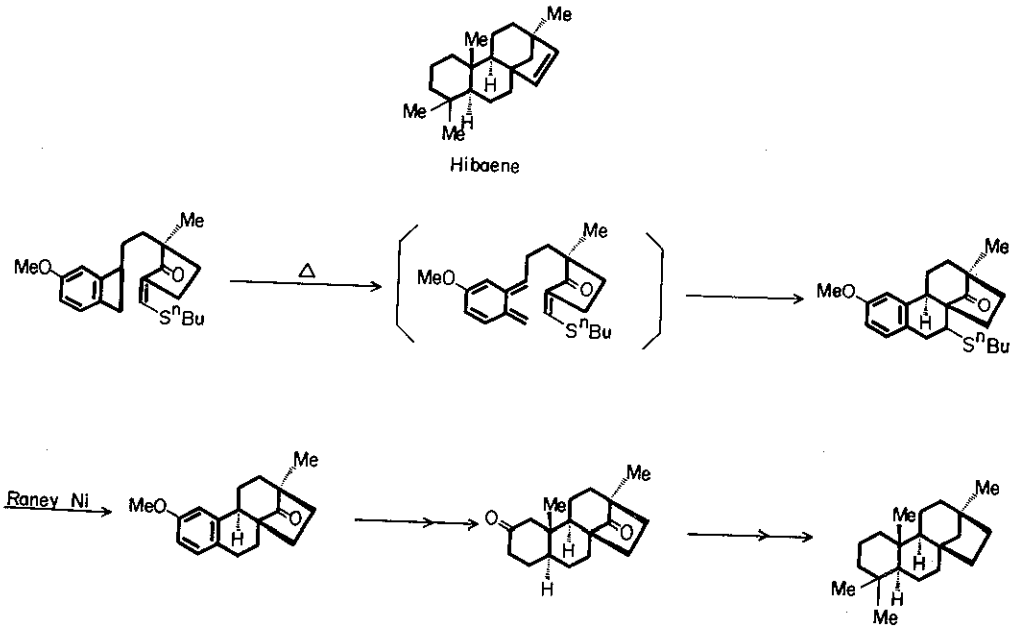
Based on the above model experiments, we have accomplished the total synthesis of yohimbine from the key intermediate 1-spirobenzyl-β-carboline via hexadehydroyohimbine as shown in the above chart. Photolysis of the spirobenzyl-β-carboline with a Hanovia 450 W mercury lamp in tetrahydrofuran yielded the decadehydroyohimbane and the decadehydroyohimban-21-one. Reduction of both products with sodium borohydride gave O-methylhexadehydroyohimbine.[141] Hydrolysis of this ester with aqueous methanolic potassium hydroxide followed by Birch reduction[141] of the resulting carboxylic acid, afforded the enol ether which was esterified with diazomethane to give the O-methyltetradehydroyohimbine. Treatment of the latter first with oxalic acid and then with dilute hydrochloric acid afforded dehydroyohimbinone which was catalytically hydrogenated with 30 % palladium on carbon to give (±)-yohimbinone, followed by sodium borohydride reduction to afford (±)-yohimbine and β-yohimbine. Thus, a total synthesis of (±)-yohimbine has been accomplished by a method developed in our laboratory.[142]

7. Diterpenes

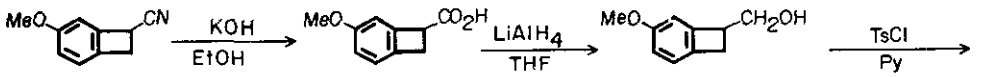
a) Tetracyclic Diterpene[143]

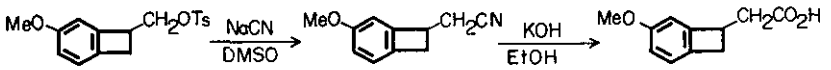
The bridged bicyclic[3.2.1]octane, which is found in hibaene, is an integral part of the structure of a large class of tetracyclic diterpenoids for which many types syntheses have been reported. One of the most difficult synthetic steps is to build the bicyclo-[3.2.1]octane system from appropriate precursors such as tetralin or hydrophenanthrene derivatives. In the early part of this section we described the formation of hydrophenanthrene ring by an intramolecular cycloaddition of an olefinic benzocyclobutene as

a general reaction of o-quinodimethanes. Thus, it should be possible to synthesise, in one step, the hibaene ring system if the benzocyclobutene substituted by a methylenecyclopentene unit is subjected to thermolysis. Based on this consideration, we planned a synthesis of dihydrohibaene as shown in the following chart.

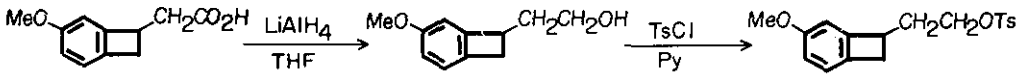


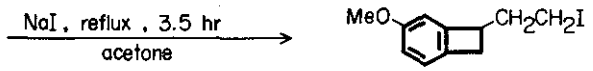
The benzocyclobutenylethyl group which forms ring A and a part of rings B and C was synthesised as follows. Hydrolysis of the cyano group gave the carboxylic acid which was reduced to the alcohol. The tosylate, prepared by the reaction of the alcohol with tosyl chloride, was converted into the homocarboxylic acid via the nitrile.





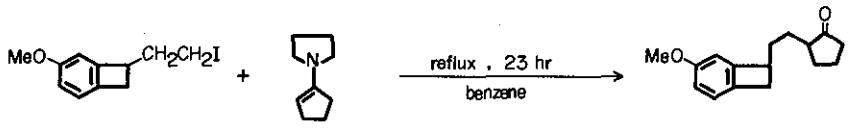
The homocarboxylic acid was reduced to the alcohol, whose tosylate was treated with sodium iodide to give the starting benzocyclobutenyl iodide.

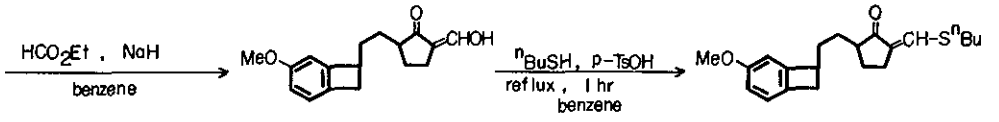




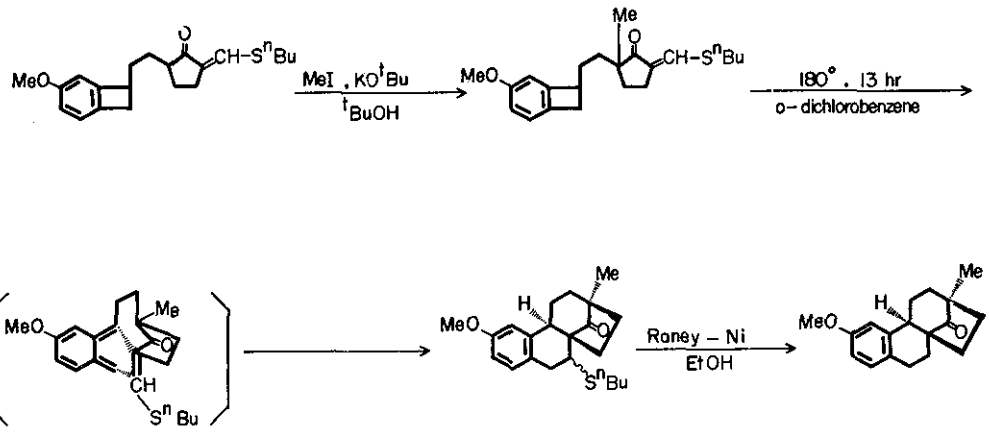
Condensation of this iodide with the pyrrolidine enamine of cyclopentanone in boiling benzene for 23 h gave the cyclopentanone in 60 % yield. Prior to introducing the methyl group at the C_2-position of cyclopentanone ring, the C_5-position was blocked by a protecting group which would react as a dienophile in a later stage. Reaction of this product with ethyl formate in the presence of sodium hydride in benzene followed by treatment of the

resulting hydroxymethylenecyclopentanone with butyl mercaptan in the presence of p-toluenesulphonic acid afforded the sulphide in 79 % yield.



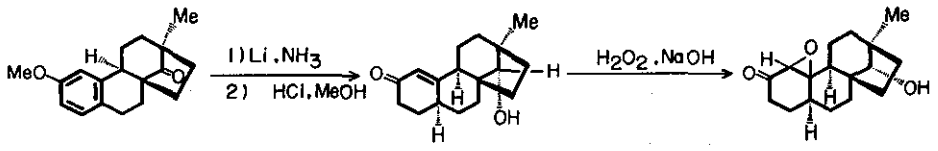


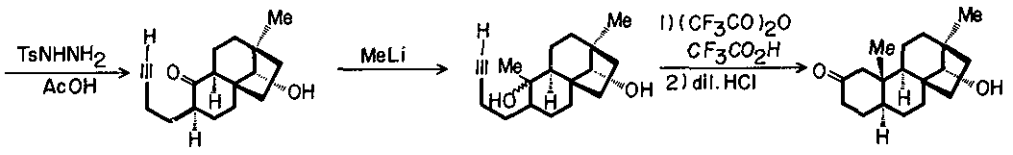
A methyl group was then introduced at the C_2-position by reaction with methyl iodide in tert-butanol in the presence of potassium tert-butoxide at room temperature for 17 h to give, in 48 % yield, the key intermediate. Heating the latter in o-dichlorobenzene at 180° for 13 h in a current of nitrogen afforded via the o-quinodimethane in a regioselective manner the tetracyclic compound in 65 % yield. Desulphurisation of this product with Raney nickel in ethanol gave, in 86.2 % yield, the potential intermediate whose 13-methyl signal in nmr spectrum was in the normal position. This showed that the relative configuration of the 13-methyl and 9-hydrogen was probably cis-configuration. The stereochemistry of this product was thus considered to the cis, although the alternative trans-structure cannot be ruled out.



The carbonyl group of this compound was converted into a methylene function by Wolff-Kishner reduction. Thus, we could establish a novel and short synthesis of the tetracyclic moiety which forms the framework in hibaene.

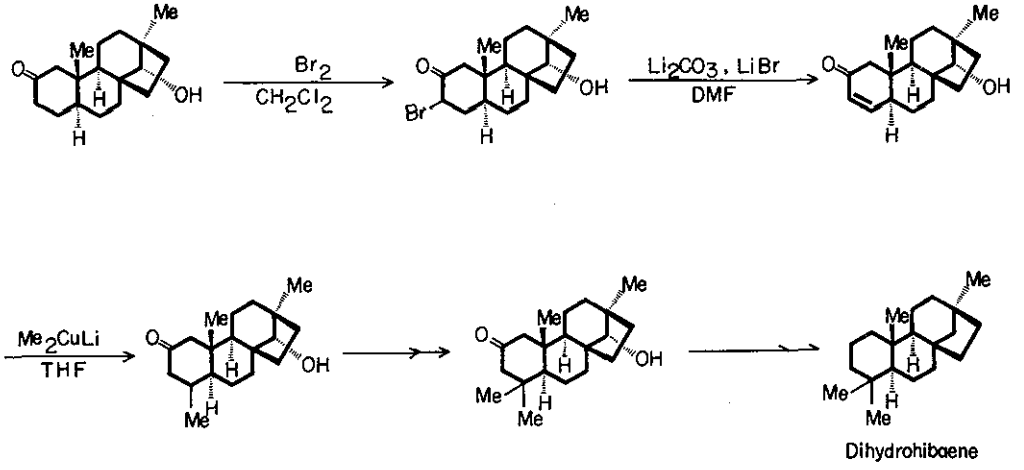
In order to introduce methyl groups on ring A, the following reactions were carried out. Birch reduction of the tetracyclic compound with lithium in liquid ammonia followed by hydrolysis gave the enone, in which the carbonyl group on ring-C was also





reduced to an α-hydroxyl group. Treatment of the cyclohexenone with hydrogen peroxide in sodium hydroxide followed by decomposition of the resulting epoxide with tosylhydrazine and acetic acid afforded the acetylenic ketone which on methylation and acidic treatment yielded stereoselectively the 10ß-methyl ketone.

A methyl group was introduced at the C_4-position as follows. Bromination of the ketone obtained by the above reactions followed by dehydrobromination with lithium carbonate and lithium bromide under mild conditions gave the 3,4-dehydro compound which was treated with dimethylcopper lithium at -30° to afford the expected C_4-methyl derivative. The final steps of introducing one more methyl group at the C_4-position and the conversion of O-functions to methylene groups are now under investigation.



b) Diterpene Alkaloids[144]

Nagata had achieved the total synthesis of the diterpene alkaloids, atisine, veatchine and garryine during 1964 - 1967.[145,146] In these syntheses the key and common intermediate was 16,17-imino-13-

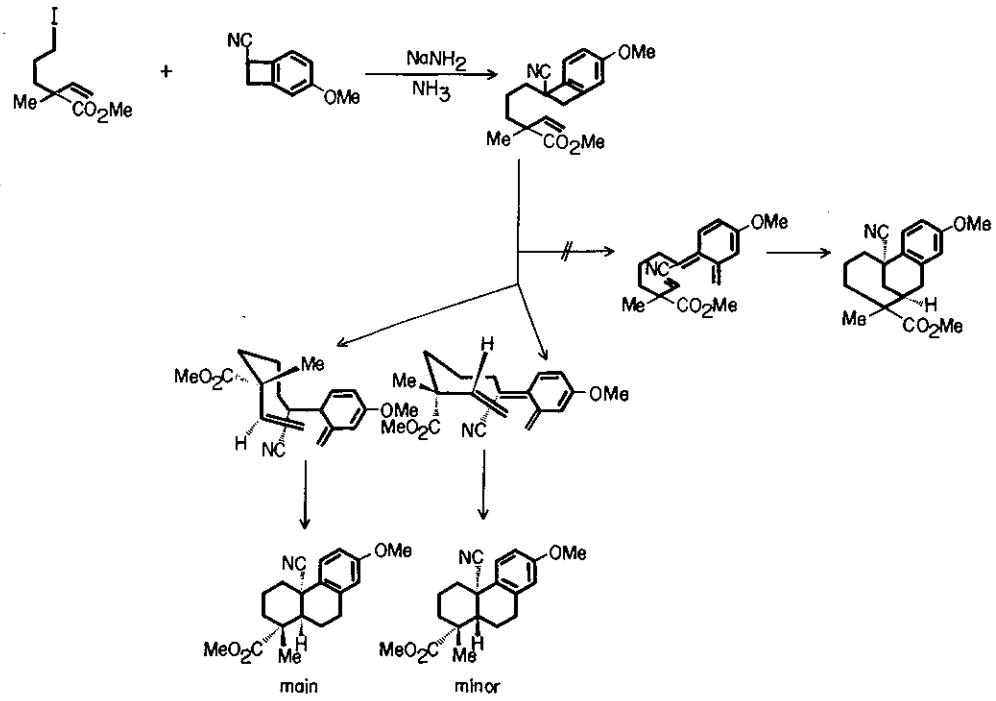
methoxy-5β,10α-podocarpane-8,11,13-triene. Wiesner also succeeded in a synthesis of atisine from the 15-carbonylpodocarpane derivative (shown in the chart after the next one).

Our synthesis was based on the idea that a hydrophenanthrene derivative which has two functional groups would be most effective for construction of the 16,17-iminobridge (D-ring) of Nagata's intermediate and that such an intermediate could be prepared in one step by an intramolecular cycloaddition reaction of an o-quinodimethane derivative. The benzocyclobutene was chosen as a suitable starting material because it forms an o-quinodimethane on heating and also has cyano and carbomethoxyl groups which are necessary for building up the ring D, although there are two regioselectively different routes for the intramolecular cycloaddition reaction of the o-quinodimethane as shown in the following chart. One is the formation of the expected hydrophenanthrene and the other generated the bicyclo[4.3.1]decane.

The iodide, obtained easily from methyl acetoacetate, was condensed with 1-cyano-4-methoxybenzocyclobutene in the presence of sodium amide in liquid ammonia to give in 75 % yield the 1-cyano-1-(4-vinylpentyl)benzocyclobutene. Heating the benzocyclobutene in dry toluene in a sealed tube at 180 - 230° afforded 4aα-cyano-7-methoxy-1α-methoxycarbonyl-1β-methyl-1,2,3,4,4a,9,10,10aα-octahydrophenanthrene in 40 - 50 % yield and the 10aβ-isomer in 10 % yield in a regiospecific and stereospecific manner. In this stage, the stereochemistry could not be determined but was evidenced by hydrogenation of these products over Raney nickel in ethanol under 115 atm of hydrogen at 80° to the lactams in quantitative yield.

This fact revealed the relative configuration of the cyano group to be cis and also ruled out another possible structure in the thermolysis of the benzocyclobutene derivative since the bicyclo-[4.3.1]decane could not from a stereochemical point of view form a lactam. The AB ring juncture of both products was determined by their conversion into known compounds.

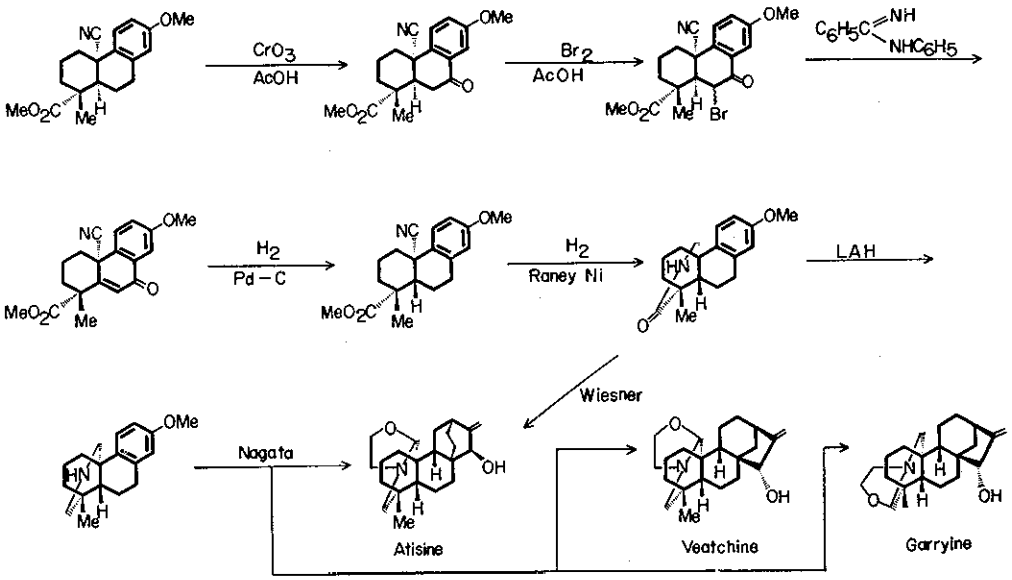
The stereocontrolled rearrangement of the benzocyclobutene into the hydrophenanthrene can be explained as follows. On thermolysis of the benzocyclobutene, which might be an epimeric mixture, the o-quinodimethanes are formed by an electrocyclic reaction of the cyclobutene ring where one has a steric repulsion



between the cyano and methoxycarbonyl groups while the other has no repulsion. Therefore, it is the latter epimer that gave the major product with the cis-AB ring junction while the former gave the minor product.

In order to obtain the trans fused octalin belonging to the natural series, thermolysis of the benzocyclobutene was carried out by refluxing in triglyme in the presence of 10 % palladium on carbon for 6 h, however the cis fused octalin was obtained. Further the direct epimerisation of the cis-product into the trans fused octalin by Pelletier's method was examined but once again the starting octalin was recovered. Therefore, the indirect conversion of the cis fused octalin into the trans isomer was investigated as follows. Oxidation of the cis fused octalin with chromium trioxide in acetic acid for 16 h and then at 60° for 1 h gave, in 45 - 50 % yield, the ketone which was treated with bromine in acetic acid at room temperature to produce the α-bromoketone in 98 % yield. Dehydrobromination of this compound was achieved by treatment with N-phenylbenzamidine in boiling xylene for 3 h to give, in 90 - 95 % yield, the α,β-unsaturated ketone which was subjected to catalytic hydrogenation on 10 % palladium on carbon in ethanol to afford the expected 4aα-cyano-1,2,3,4,4a,9,10,10aβ-octahydro-7-methoxy-1α-methoxycarbonyl-1β-methylphenanthrene. High-pressure reduction of this cyano ester under 115 atm of hydrogen on Raney nickel in ethanol at 80° gave the lactam in 80 % yield. Treatment of the lactam with lithium aluminium hydride in boiling dioxane for 7 h afforded 16,17-imino-13-methoxy-5β,10α-podocarpene-8,11,13-triene characterised as

hydrochloride which was identical with an authentic sample. Since our product had been correlated to atisine, veatchine and garryine by Nagata,[145] this work constituted a formal total synthesis of these alkaloids.



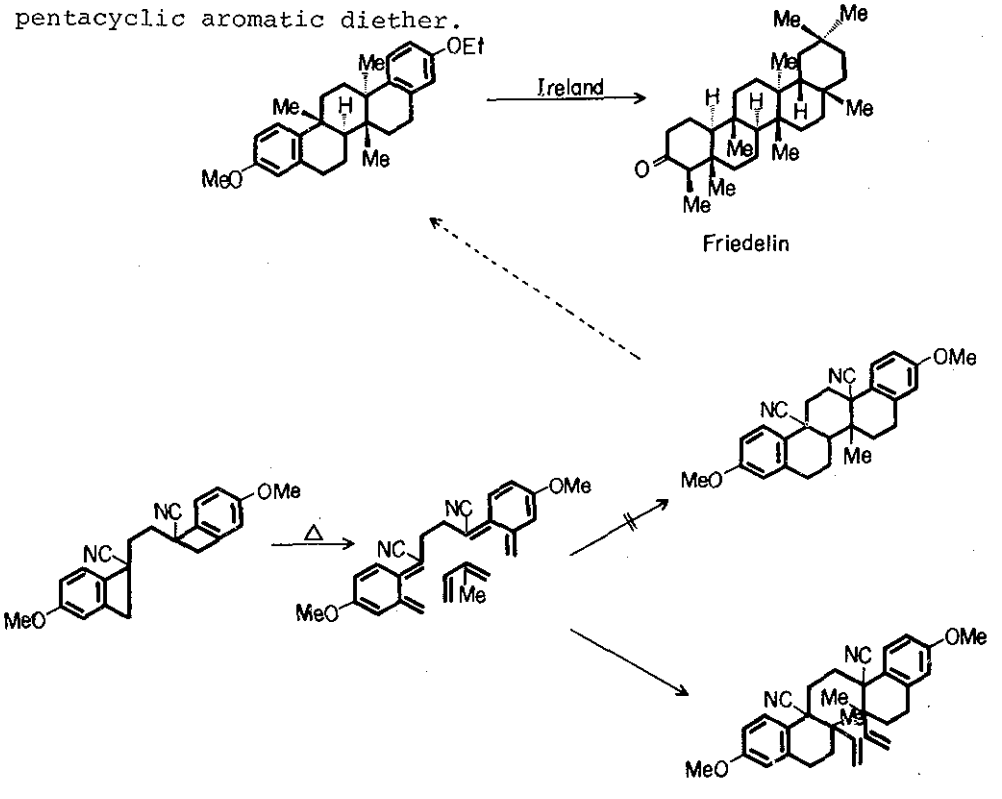
8. Triterpenes[147]

The pentacyclic aromatic diethers having the trans, anti, trans-BCD ring structure and the correct array of angular methyl groups, are important intermediates in the total synthesis of the pentacyclic triterpenes, as seen in the total synthesis of alnusenone and friedelin by Ireland.[148,149] A crucial step in the synthesis of this pentacyclic diethers is the introduction of methyl groups at angular positions with the required stereochemistry.

Since we found that intramolecular cycloaddition of an o-quinodimethane in the synthesis of diterpenes could proceed

stereoselectively as shown in above section, we investigated a novel synthesis of triterpenoids by this method. In this connection, a simple and stereoselective synthesis of the key intermediates for triterpenoid synthesis is described.

Our first trial was a one-step synthesis of the pentacyclic compound by a double intermolecular cycloaddition of the bis-o-quinodimethane to isoprene. This idea was based on the fact that the C_6,C_{6a},C_{6b} and C_7-unit correspons to isoprene. Attempted preparation of the pentacyclic compound by heating the bisbenzocyclobutene with a 10 molar excess of isoprene in an autoclave at 180° for 2 h gave instead the 1 : 2 adduct, bistetralin derivative, so we turned our attention to a stepwise synthesis of the pentacyclic aromatic diether.



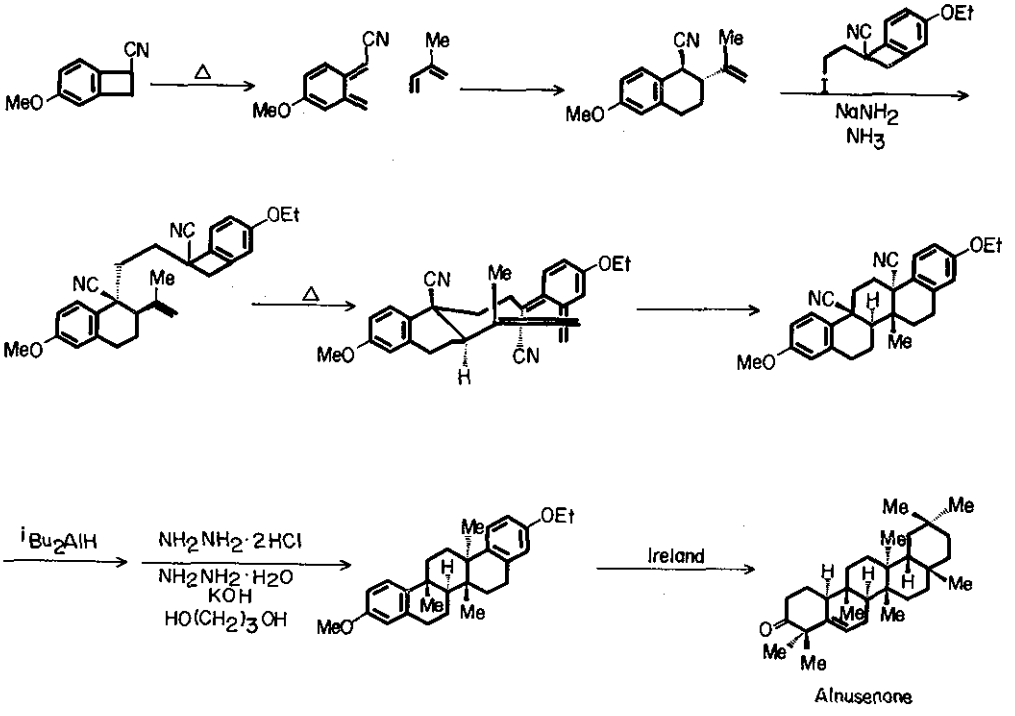
We selected 1-cyano-4-methoxybenzocyclobutene as a starting material for the stepwise synthesis since the corresponding 1-methyl analogue, which would be a more direct intermediate to alnusenone than the 1-cyano derivative, would rather form a 2-vinyltoluene by a [1.5]sigmatropic reaction than cycloaddition in a thermolysis.

Heating the 1-cyano-4-methoxybenzocyclobutene with isoprene in a sealed tube at 180° gave in 80 % yield a mixture of the 1-cyano-2-propenyltetralin and 1-cyano-2-methyl-2-vinyltetralin in a ratio of 1 : 1. Condensation of the former with benzocyclobutenylethyl iodide in the presence of sodium amide in liquid ammonia proceeded from the less hindered side of the C-1 position to give the key starting material in 88 % yield with the 1-cyano and 2-vinyl groups cis to each other.

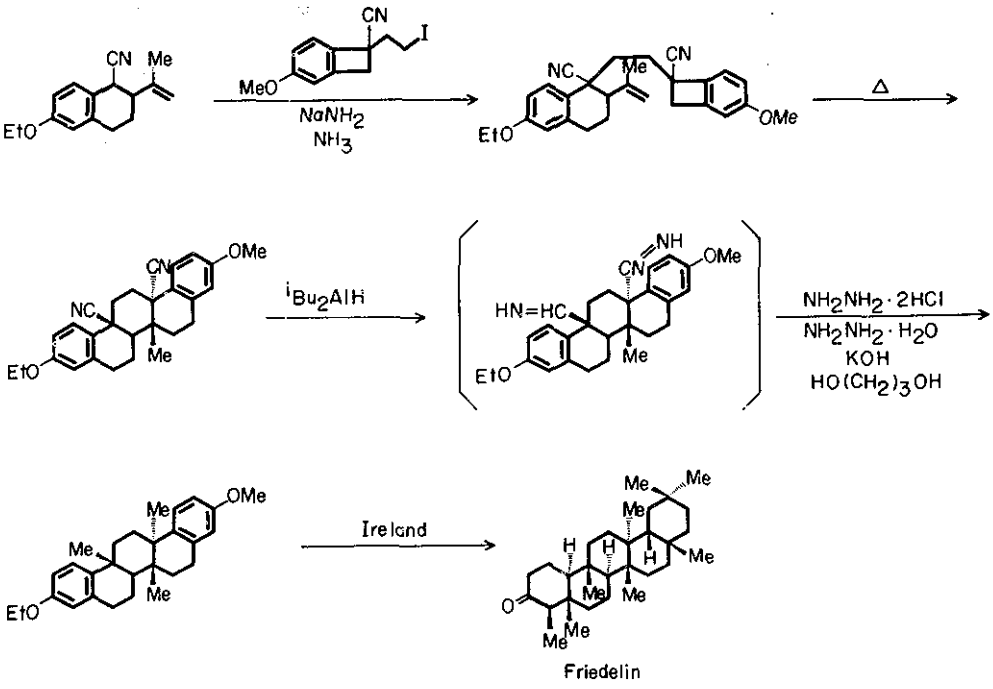
Heating this compound in dry toluene in a sealed tube at 210 - 215° for 3 h provided stereoselectively, in 58 % yield, the pentacyclic compound which was reduced with di-isobutylaluminium hydride in benzene at room temperature to give the diimine in 90 % yield. Wolff-Kishner reduction of the diimine with hydrazine hydrate and hydrazine dihydrochloride in triethylene glycol in the presence of potassium hydroxide at 160 - 165° gave in 44 % yield the expected the 6b,12bβ,14aβ-trimethylated pentacyclic compound, identical with that obtained by Ireland.

The stereoselective formation of the pentacyclic compound on the thermolysis of the benzocyclobutene derivative can be explained as follows. Conrotatory ring opening of the cyclobutene unit in

the benzocyclobutene would form the sterically favoured o-quinodimethane. Synchronous intramolecular cycloaddition of this intermediate would most favourably proceed through the exo-chair conformation shown to give the pentacyclic compound with the required stereochemical arrangement, rather than through the less stable "endo-chair" or "boat" forms which would produce the trans, anti,cis-BCD and trans,syn,trans-BCD ring stereoisomers of the pentacyclic compound.



By the same reaction using 1-cyano-4-ethoxybenzocyclobutene and 1-cyano-1-(2-iodoethyl)-4-methoxybenzocyclobutene, the pentacyclic aromatic diether, which had been converted into friedelin by Ireland, has been synthesised as shown in the following chart.



Thus, we obtained the key compounds, which have been correlated with the triterpenoid, alnusenone and friedelin in a simple stereoselective way, providing an effective method for the synthesis of pentacyclic diethers.

9. Total Synthesis of Estrone[150,151]

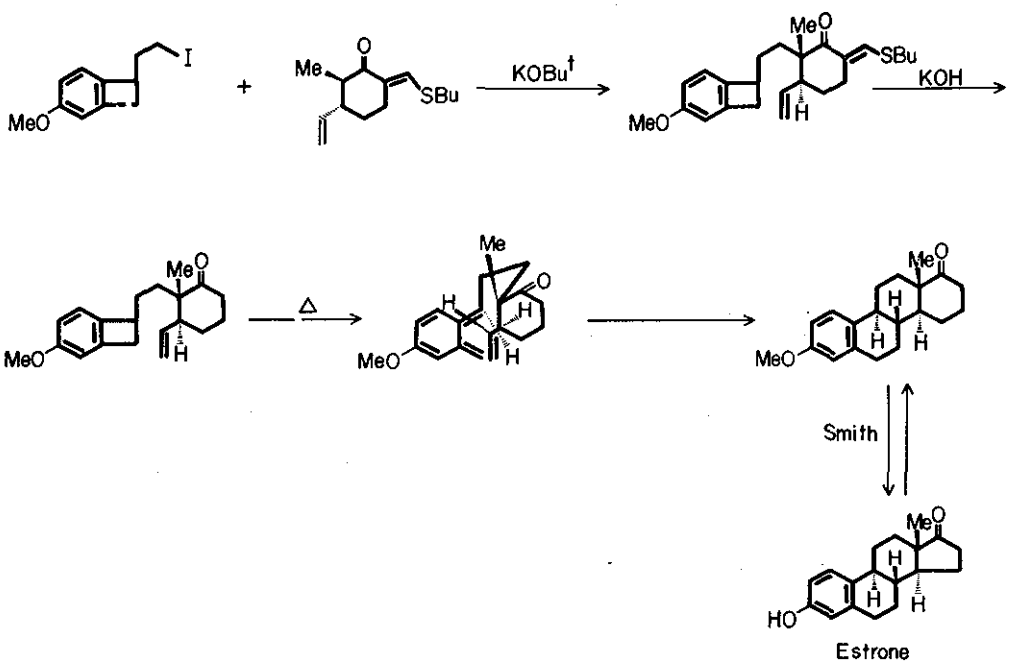
The synthesis of estrone has held a special fascination for organic chemists and many types of approaches have been reported toward this natural sex hormone. In the last decade, interest has focused on developing asymmetric syntheses of estrone and related compounds.

In connection with our interest in the synthetic development of cycloaddition of electrocyclic reaction starting from o-quinodimethanes based on benzocyclobutenes, we investigated a

new synthesis of estrone through O-methyl-D-homoestrone via the intramolecular cycloaddition reaction. The following description is a synthesis of D-homoestrone which constitutes a formal total synthesis of estrone by our method.

Condensation of the benzocyclobutenylethyl iodide with 2-methyl-3-vinylcyclohexanone which is protected by a 6-butylthiomethylene group in order to introduce regioselectively a methyl group at C_2-position, in the presence of potassium tert-butoxide afforded the 1,1-disubstituted cyclohexanone. Hydrolysis of this product with potassium hydroxide in diethylene glycol at 100° furnished the key intermediate by elimination of the protecting group. This compound transformed smoothly in boiling dichlorobenzene for 4 h to O-methyl-D-homoestrone, identical with an authentic sample, in 95 % yield.

The stereocontrolled formation of homoestrone can be explained as follows. The four-membered ring in the key intermediate benzocyclobutene derivative opens preferentially to form the sterically favoured E-oriented o-quinodimethane whose synchronous cycloaddition proceeds regiospecifically through the more stable exo transition state rather than the endo state which has steric repulsion between the aromatic and the cyclohexanone ring. Demethylation of O-methyl-D-homoestrone gave D-homoestrone. Since O-methyl-D-homoestrone has previously been correlated to estrone,[152] this work constitutes a total synthesis of estrone.



VIII. CONCLUSION

We would like to say that the synthetic organic chemistry will live forever supported by the splended development of physico-chemical tool and by the appearance of new reagents and the discovery of new reactions. Although a computer system for the synthesis of complex molecules is under examination, we believe that the systematic methodology for the synthesis of organic compounds, such as retro mass spectral synthesis,[153] will always be necessary. Synthetic studies must continue so that new and more efficient drugs become available for medicinal use.

A silk road is well known in Japan as a route for transportation of silk, a valuable good, from Orient to Europe, namely from

China to Rome through India, Afganistan, Iran, Turkey and Greek. Although this word involves many meanings, a silk road of our synthetic studies was not so easy. My work (T.K.) started from a very simple isoquinoline synthesis under Professor Shigehiko Sugasawa during the second world war. My first research subject from Professor S. Sugasawa caused me to develop the isoquinoline chemistry leading to the total synthesis of a variety of natural products. I believe that it is very important for our chemist to keep in mind the first research subject.

Finally I should greatly appreciate Professor Shigehiko Sugasawa's help and guidance for me. Thank you very much indeed for his warnest kindness.

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