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REVIEW

The Syntheses of Isoquinoline Alkaloids and Related Compounds by Biogenetic Type Reactions

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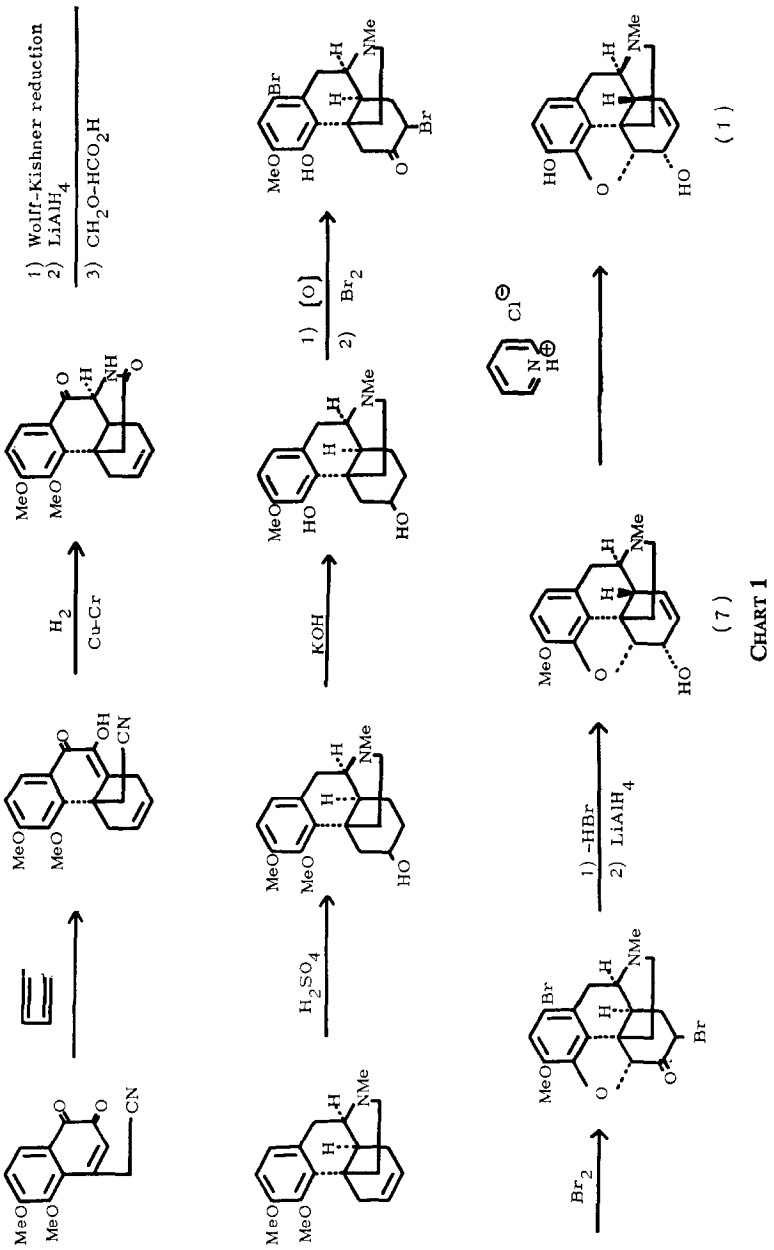
This contribution describes the biogenetic-type syntheses of some isoquinoline alkaloids and related compounds which,, without duplicating our previous review (*1*), is based on papers published after 1970.

INTRODUCTION

Many natural products have been isolated from nature, and their structures have been determined by the systematic use of chemical and spectroscopic methods. More recently, spectroscopy connected to a computer system (*2*) and also X-ray analysis have played an important role in structure determination. In contrast, there is no systematic method available for the synthesis of natural products, and as a result their total synthesis had depended on the original ideas of the chemist themselves (*3*).

There are the proverbs: "There is no royal road to learning" and "Practice makes perfect." However, nature provides a splendid method for the synthesis of natural products, which we call biogenesis (*4*). For example, morphine (**1**), whose structure was determined in 1925 by Sir Robert Robinson, was synthesized in 1952 in many steps as shown in the following chart by Gates (*5*), after many unsuccessful attempts by chemists throughout the world (see Chart 1). On the other hand, biochemical studies proved that morphine (**1**) was biosynthesized from reticuline (**2**) by phenol oxidation (*6*) *via* the intermediates salutaridine (**3**), salutaridinol (**4**), thebaine (**5**), codeinone (**6**), and codeine (**7**) (*4*). On the basis of this biogenetic mechanism, Barton (*7*) achieved the total synthesis of morphine (**1**) from reticuline (**2**). Thus, mild oxidation of reticuline (**2**) with manganese dioxide gave salutaridine (**3**) which was reduced to salutaridinol (**4**) with sodium borohydride followed by an acidic rearrangement to afford thebaine (**5**). Since thebaine had previously been converted, *via* codeine (**7**), to morphine (**1**), this work constituted a total synthesis of morphine (**1**) (see Chart 2).

The mild oxidation of reticuline to salutaridine is an example of phenol oxidation which plays such an important role in the biogenesis of isoquinoline and related alkaloids. Therefore, the synthesis of natural products *via* routes which are operable, or thought to be operable in nature is very fascinating to organic chemists; and, moreover, biogenetic-type synthesis is the simplest and most logical route to such natural products. In this connection, simple natural product synthesis along biogenetic lines is described in this review.


1) Wolff-Kishner reduction
2) LiAlH4
3) CH2O-HCO2H
H2
Cu-Cr
KOH
1) (O)
2) Br2
H2SO4
1) -HBr
2) LiAlH4
Br2
MeO
HO
NMe
Br
Cl
CN
OH

(7) (1)

CHART 1

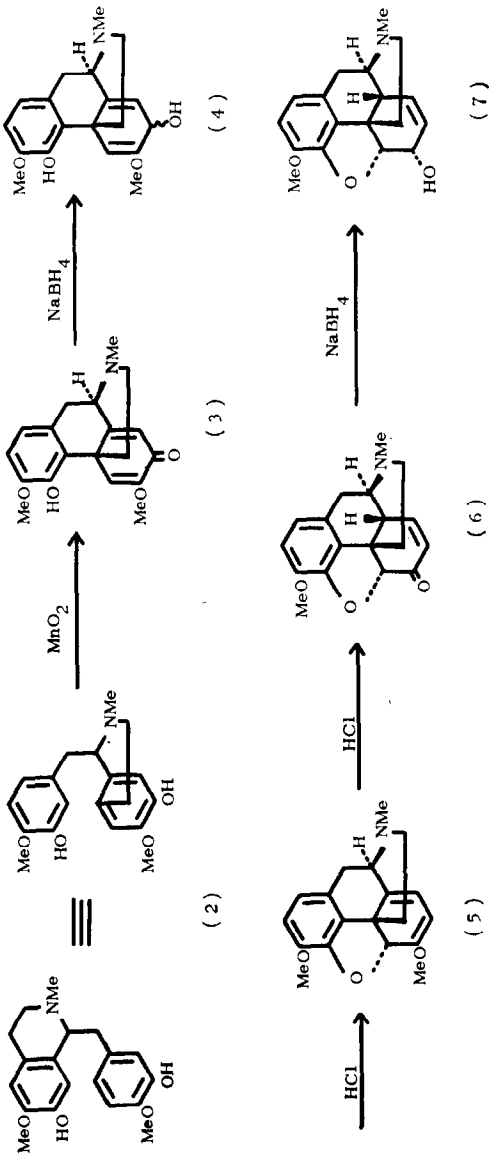
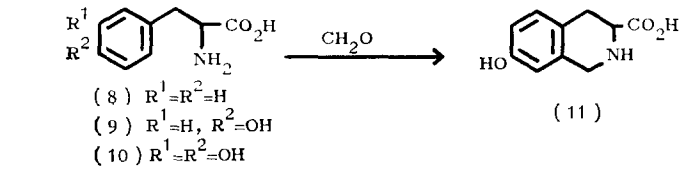


CHART 2

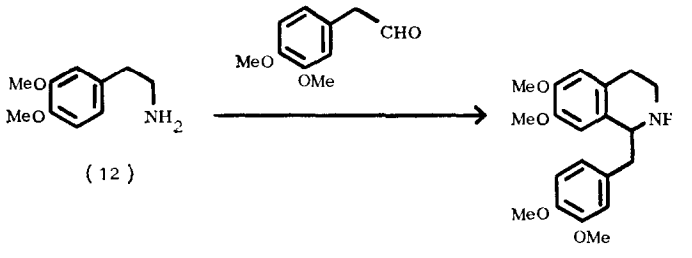
ISOQUINOLINE SYNTHESES

It is a matter of general agreement that the tetrahydroisoquinoline alkaloids are derived from phenylalanine (**8**), tyrosine (**9**), and 3,4-dihydroxyphenylalanine (L-dopa) (**10**). The process by which these phenethylamines cyclize to tetrahydroisoquinolines has been a matter of speculation since 1911, when Pictet and Spengler (*8*), on the basis of the formation of **11** by the condensation of β-phenethylamine with methylal in hydrochloric acid, proposed that an analogous condensation leads to tetrahydroisoquinoline alkaloids in plants (see Chart 3).



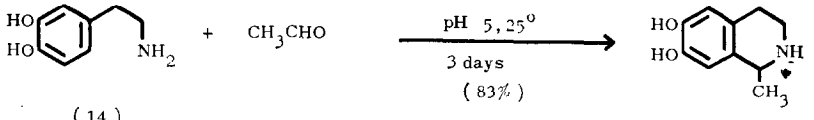
(8) $R^1=R^2=H$
(9) $R^1=H$, $R^2=OH$
(10) $R^1=R^2=OH$

(11)



(12)

(13)



(14)

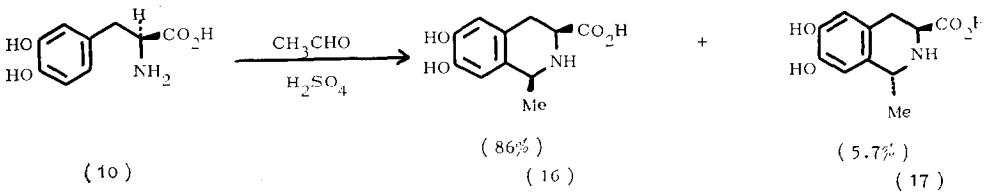
(15)

CHART 3

Winterstein and Trier (*9*) put forward a similar proposal for the biogenesis of the tetrahydroisoquinoline alkaloids (**13**) from dimethoxyphenethylamine (**12**) and the appropriate aldehydes. In 1934, these biogenetic proposals were achieved *in vitro* by the condensation of acetaldehyde with 3,4-dihydroxyphenethylamine (**14**) under physiological conditions of pH, temperature, and concentration to produce the tetrahydroisoquinoline (**15**) in 83% yields (*10*). Later, many tetrahydroisoquinoline alkaloids were synthesized under such physiological conditions (*11*).

Recently, a new alkaloid (**16**) isolated from *Mucuna deeringiana* was synthesized stereoselectively by this method from L-dopa (**10**) by two groups (*12, 13*). Thus, treatment of L-dopa (**10**) in aqueous suspension with acetaldehyde in the presence of 0.5 *N*

sulfuric acid at 50° for 2 hr and then at room temperature for 24 hr under nitrogen provided a 95:5 mixture of two isomeric amino acids, which was separated by crystallization to give the alkaloid (**16**) as the major product and its epimer (**17**) (see Chart 4).



(10) (86%) (16) (5.7%) (17)

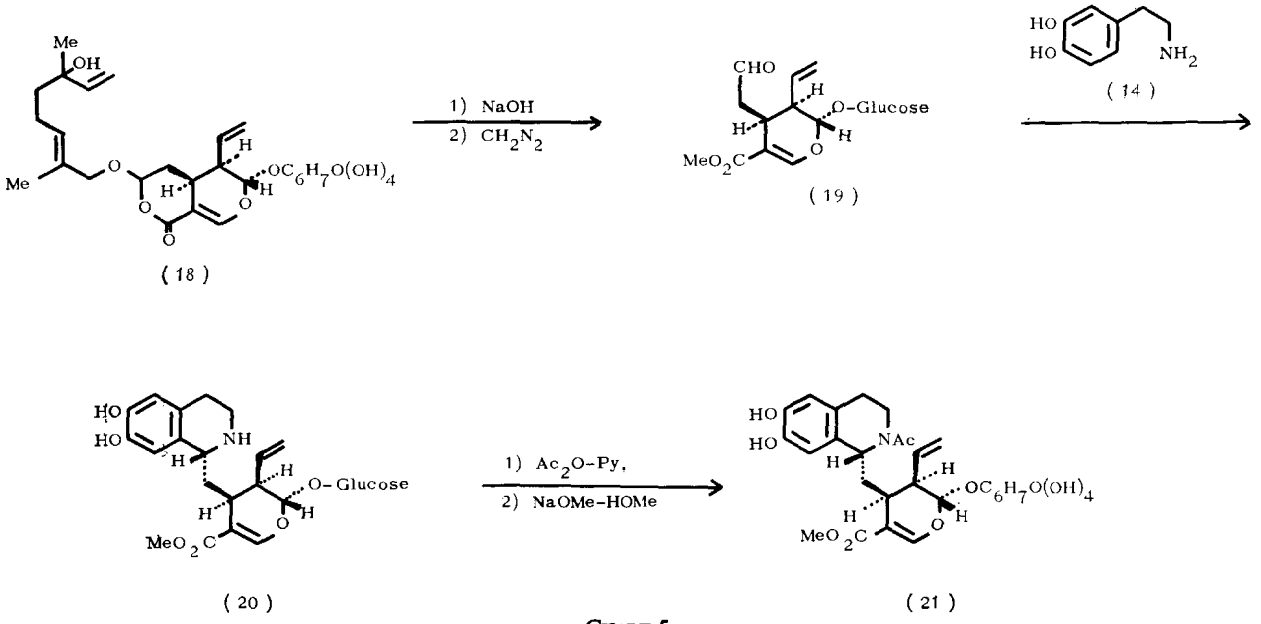
CHART 4

Similarly, ipecoside (**21**) was obtained by the condensation of dopamine (**14**) with secologanin (**19**) as shown in Chart 5 (*14*). Controlled, mild hydrolysis of menthiafolin (**18**) with sodium hydroxide, followed by methylation with diazomethane, afforded (−)-secologanin (**19**). The condensation of (**19**) with dopamine (**14**) hydrochloride in water at 20° for 3 days at pH 5.0 yielded two products, desacetylipecoside (**20**) and its epimer, which were separated by countercurrent distribution. Acetylation of desacetylipecoside with acetic anhydride in the presence of pyridine, followed by Zemplen *O*-deacetylation of the resulting hexa-*O*-acetylipecoside with sodium methoxide, furnished (−)-ipecoside (**21**).

Moreover, a biogenetic-type synthesis of *S*(+)-laudanosine (**32**) from L-dopa derivatives using 1,3-asymmetric induction was also achieved in 1972 by Yamada (*15*). The condensation of L(+)-dopa methyl ester hydrochloride (**22**) with sodium 3-(3,4-dimethoxyphenyl)glycidate (**23**), a chemical equivalent to 3,4-dimethoxyphenylacetaldehyde, at pH 4 and 35° gave in 44% yield a mixture of the tetrahydroisoquinolines, which was separated by a combination of silica-gel chromatography and crystallization into the expected compound (**24**) and its epimer in a 2.4:1 ratio. Methylation of (**24**) with diazomethane gave the amine (**25**) in 87% yield accompanied by the *N*-methylated amine (**26**) in 5% yield. Treatment of (**25**) and (**26**) with methanolic ammonia afforded the amides (**27**) and (**28**) in 94% and 41% yield, respectively. The former amide was converted into the latter in 97% yield by treatment with methyl iodide in the presence of potassium carbonate in boiling methanol. Dehydration of (**28**) with phosphorous pentoxide in hot pyridine, followed by reductive decyanization of the unstable nitrile (**30**) with sodium borohydride in ethanol-pyridine gave *S*(+)-laudanosine (**32**).

Similarly, the *N*-benzyl amide (**29**), obtained from (**27**) by treatment with benzyl chloride, was dehydrated to give the *N*-benzyl nitrile (**31**) in 55% yield, which was subjected to reductive decyanization to afford *N*-benzylnorlaudanosine (**33**) in 87% yield. Catalytic hydrogenation of this product with 5% palladium-carbon in the presence of hydrochloric acid gave *S*-norlaudanosine (**34**), which was converted into *S*(+)-laudanosine (**32**) by the Eschweiler–Clarke reaction (see Chart 6).

On the other hand, Hahn (*16*) regarded the carbonyl group of α-keto acids such as pyruvic acid as the source of C-1 in tetrahydroisoquinoline alkaloids, rather than the more reactive aldehydes indicated in the earlier proposals. His hypothesis was supported by the preparation of 1-benzyl-1-carboxy-1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (**35**) under conditions which were considered to be biologically plausible



(18) (19) (14) (20) (21)

CHART 5

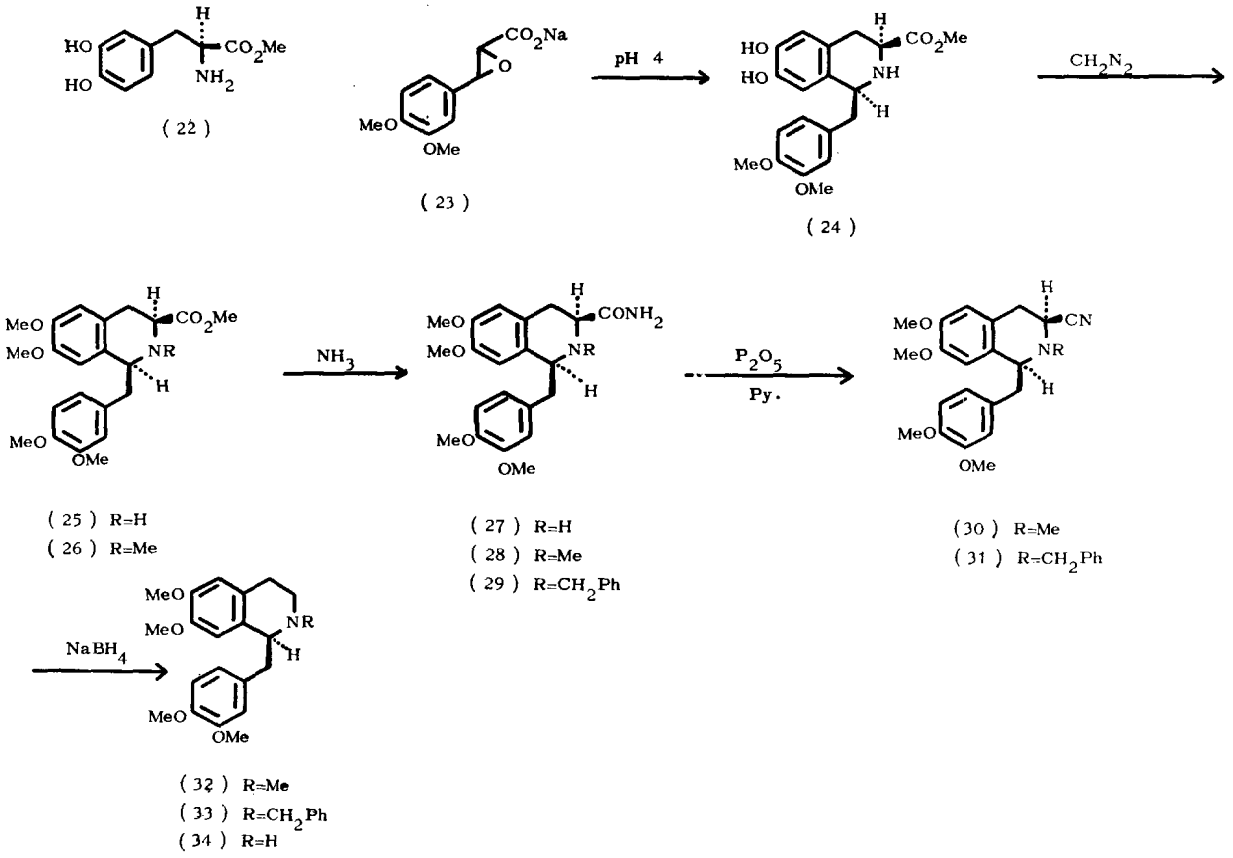
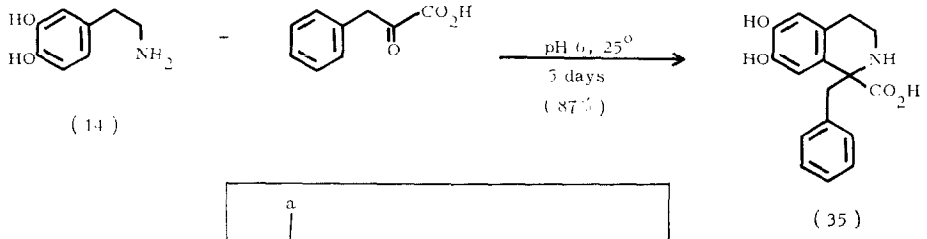
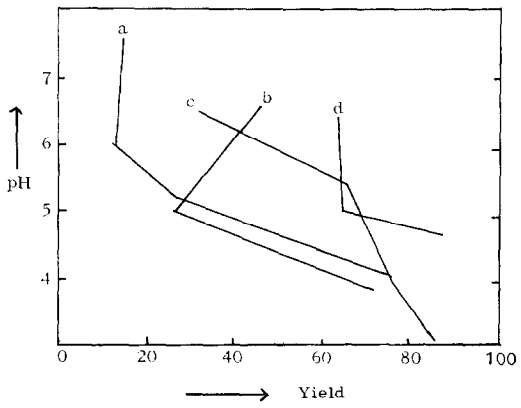

HO
HO
CO2Me
NH2
H
(22)
CO2Na
O
MeO
OMe
(23)
pH 4
HO
HO
CO2Me
NH
H
MeO
OMe
(24)
CH2N2
MeO
MeO
CO2Me
NR
H
MeO
OMe
(25) R=H
(26) R=Me
NH3
CONH2
(27) R=H
(28) R=Me
(29) R=CH2Ph
P2O5
Py.
CN
(30) R=Me
(31) R=CH2Ph
NaBH4
(32) R=Me
(33) R=CH2Ph
(34) R=H

CHART 6

(see Chart 7). There were many reports on the synthesis of other isoquinolines under physiological conditions from β-phenethylamines and α-keto acids (*11*). The relationship between pH and yields in a reaction of dopamine (**14**) with several α-keto acids is shown in Chart 7 (*11*).

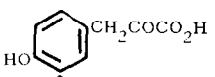


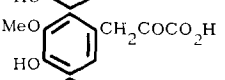
(14) (35)



Reaction of dopamine (14) with α-keto acids at 25°.

a: $C_6H_5CH_2COCO_2H$ 24 hr x 5

b:  24 hr x 4

c:  42 hr

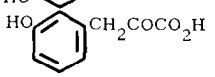
d:  24 hr x 6

CHART 7

However, Whaley and Govindachari (*11*) considered α-keto acids, which were the precursors in Hahn's hypothesis, to be unlikely ones, because the reaction of pyruvic acids is much slower than the reaction of aldehydes and the resulting condensation products were not decarboxylated under mild conditions. But such reactions occur easily in the presence of some enzymes; and, in fact, the recent identification of peyoglutam (**39**) and mescalotam (**40**), which evidently contain the α-ketoglutaric acid moiety, appear to support Hahn's theory. Further, the fact that peyoglutam (**39**) and its C-11 carboxyl precursor (**38**) formed spontaneously on admixture of 3-demethylmescaline (**36**) and α-ketoglutaric acid (**37**) further substantiates this theory (*17*) (see Chart 8). Moreover, the possibility of direct involvement of α-keto acids in the formation of isoquinoline alkaloids was suggested by the fact that 3-demethylmescaline

(36) reacts with pyruvic acid (41) at pH 4.0–4.5 and room temperature to form the amino acid (43) in quantitative yield. Similarly, the reaction of (36) with glyoxylic acid (42) under the same conditions gave the cyclization product (44) in good yield (*18*). Further support was provided by incubation of (43) in fresh peyote slices. Carbon dioxide was evolved, and on work-up the decarboxylation product was found to be the imine (45). The production of the imine rather than the tetrahydroisoquinoline suggests that decarboxylation may be occurring by an oxidative process.

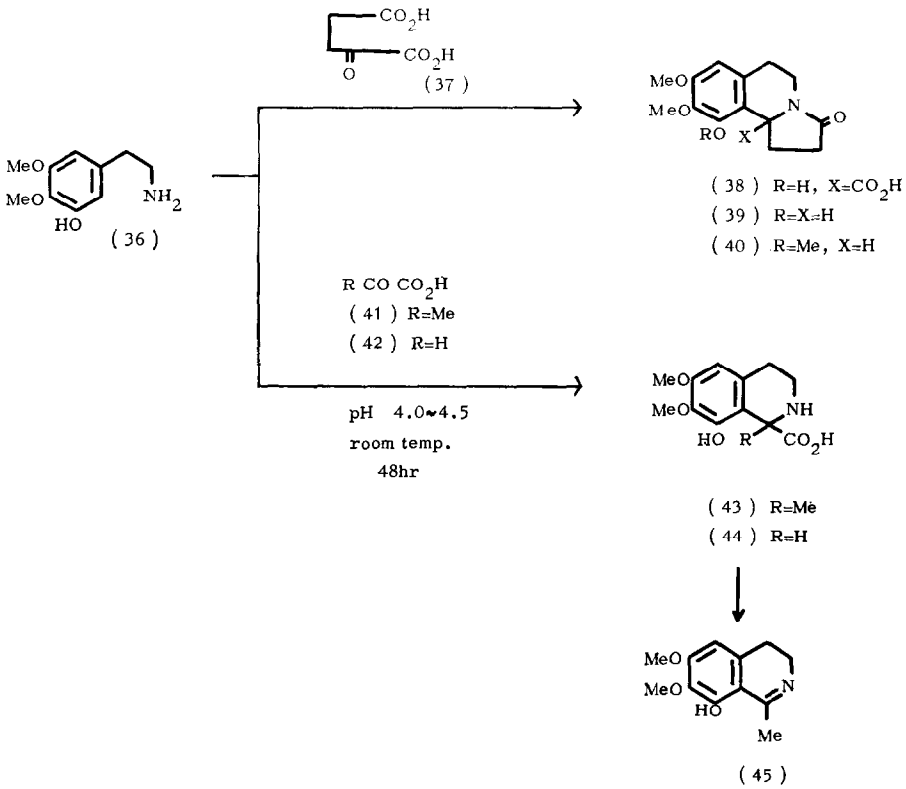


CHART 8

As an extension of Hahn's hypothesis that α-keto acids were involved rather than aldehydes, Robinson (*19*) suggested the possible involvement of tyrosine combined in a peptide linkage. On the ground of this suggestion and the presence of peptide alkaloids as well as the evolving chemistry of intrapeptide reactions, Lawton (*20*) proposed a new hypothesis that suitably orientated and modified amino-acid moieties on a peptide chain could interact to afford the alkaloid precursors. In the sequence for benzylisoquinoline-type alkaloids, the hydroxylation of tyrosine residues on proteins and peptides by tyrosinase is a probable first step (**46**) → (**47**). If transamination or *N*-acyloxidative cleavage of this amino acid occurred so as to give a 4-hydroxy- or 3,4-dihydroxyphenylpyruvoyl end group (**48**), the peptide could undergo spontaneous intrapeptide closure to form a peptide-benzylisoquinoline alkaloid precursor (**49**). A parallel pathway could involve interaction of a 3,4-dihydroxyphenylalanine moiety on the peptide

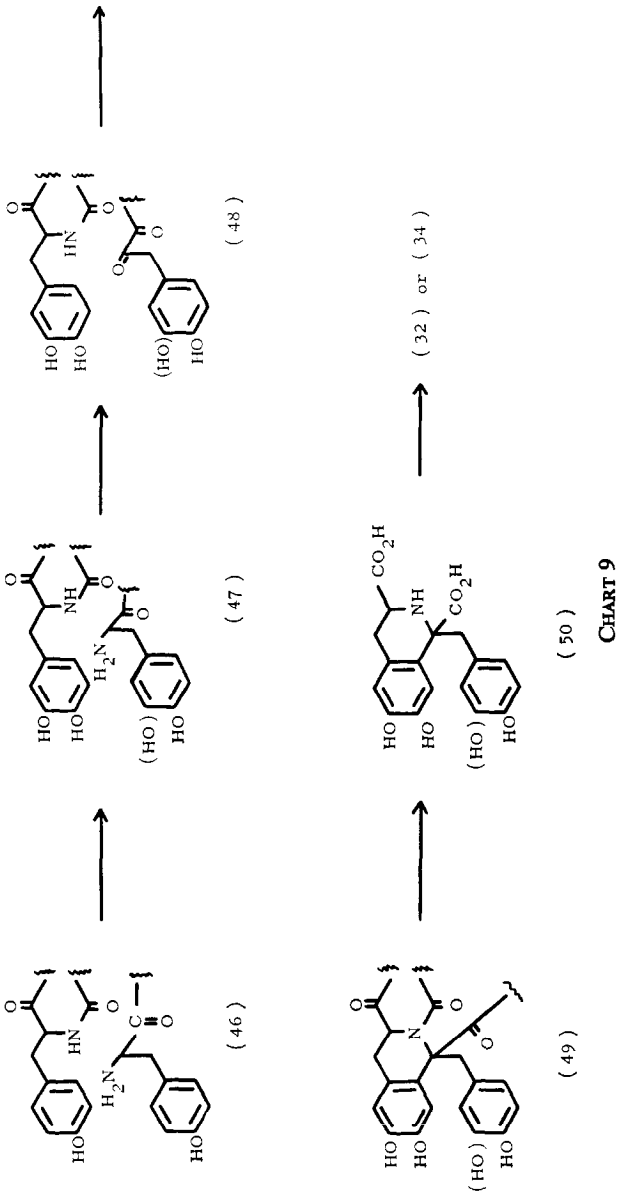


CHART 9

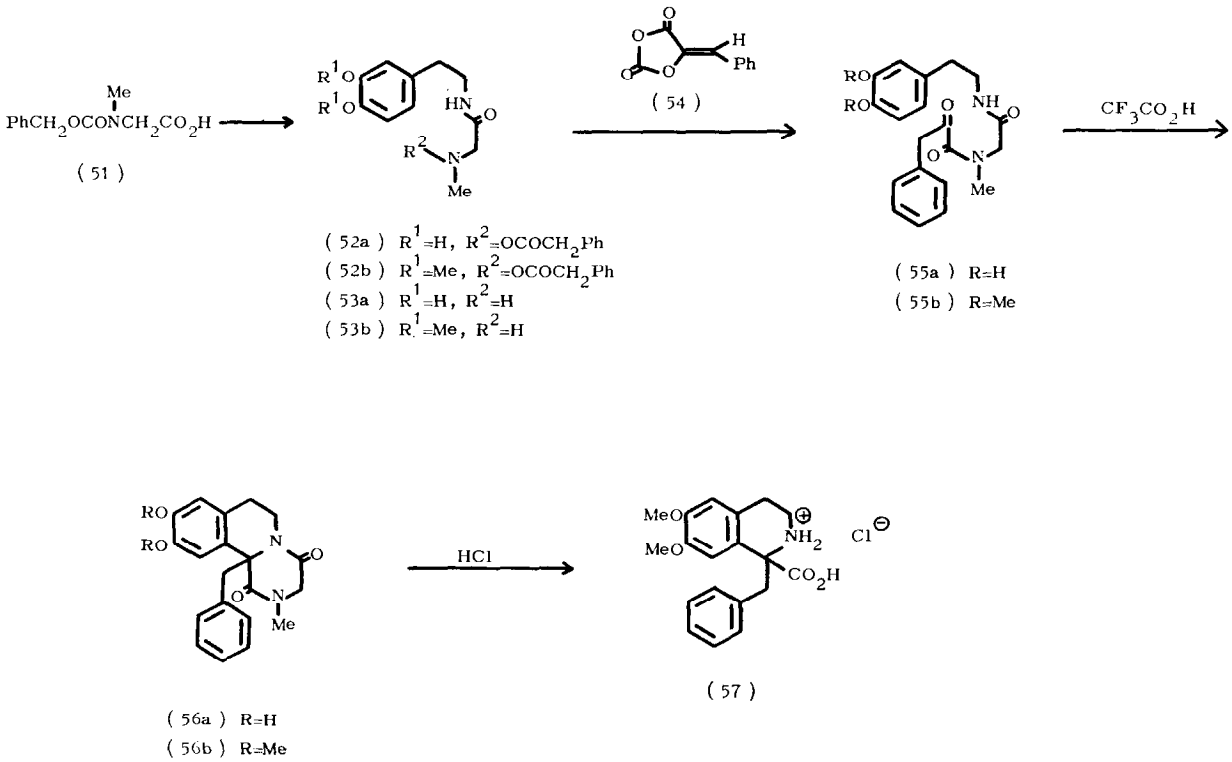

PhCH2OCONCH2CO2H
Me
(51)
R1O
R1O
HN
O
R2
N
Me
(52a) R1=H, R2=OCOCH2Ph
(52b) R1=Me, R2=OCOCH2Ph
(53a) R1=H, R2=H
(53b) R1=Me, R2=H
(54)
H
Ph
RO
RO
NH
(55a) R=H
(55b) R=Me
CF3CO2H
(56a) R=H
(56b) R=Me
HCl
MeO
MeO
NH2
Cl
CO2H
(57)

CHART 10

chain and a second phenylpyruvoyl derivative which is attached by its keto- or carboxy-group to some amino acid functionality or prosthetic group on the peptide. The succeeding steps would require digestion of the irregularly annulated peptide (**49**) and conversion of the resultant amino acid (**50**) to the various alkaloid systems (**32** or **34**) having the benzylisoquinoline framework (see Chart 9).

To simulate such a process, the model sequence delineated below was carried out *in vitro*. The peptide analogues (**53**) were prepared by reaction of *N*-benzyloxycarbonyl-sarcosine (**51**) with phenethylamines, followed by removal of the blocking group in (**52a**) and (**52b**). Reaction of each of the peptide analogues (**53a**) and (**53b**) with the reactive enol carbonic anhydride (**54**), 5-benzylidene-1,3-dioxolane-2,4-dione, in acetonitrile or aqueous acetonitrile gave with concomitant loss of carbon dioxide the respective phenylpyruvoyl derivatives (**55a**) and (**55b**), which were smoothly transformed with trifluoroacetic acid in benzene at room temperature to the cyclic benzyl-isoquinolines (**56a**) and (**56b**). Hydrolysis of (**56b**) with 10% hydrochloric acid gave the amino acid (**57**). The sequence (**51**–**57**) exemplifies the use of a peptide backbone for directing reactions, followed by its removal (see Chart 10).

It is known that *N*-oxides may also be intermediates in the biogenesis of some alkaloids (*21*). For example, the berberine bridge carbon atom is derived oxidatively from an *N*-methyl group in reticuline-type precursors (*22*). There are several possible mechanisms for this transformation (*23*), one of which could involve the *N*-oxide (**58**), its conversion into an immonium ion (**59**), followed by cyclization to give the proto-berberine (**60**) (see Chart 11).

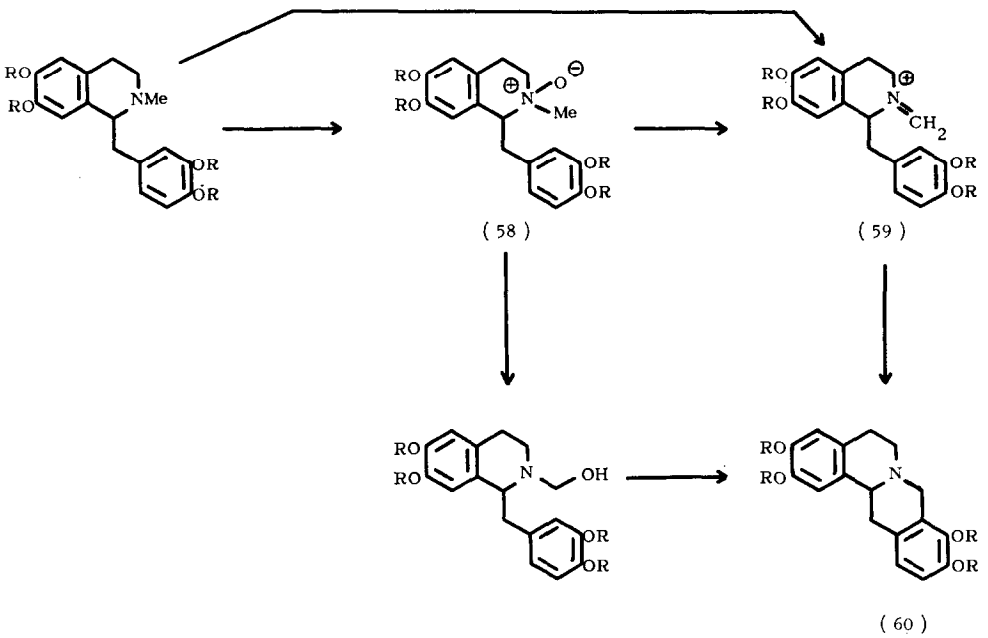


CHART 11

On the grounds of formation of immonium ion (**62**) by treatment of the tertiary amine *N*-oxide (**61**) with sulfur dioxide, this means has been used *in vitro* (*24*) to form

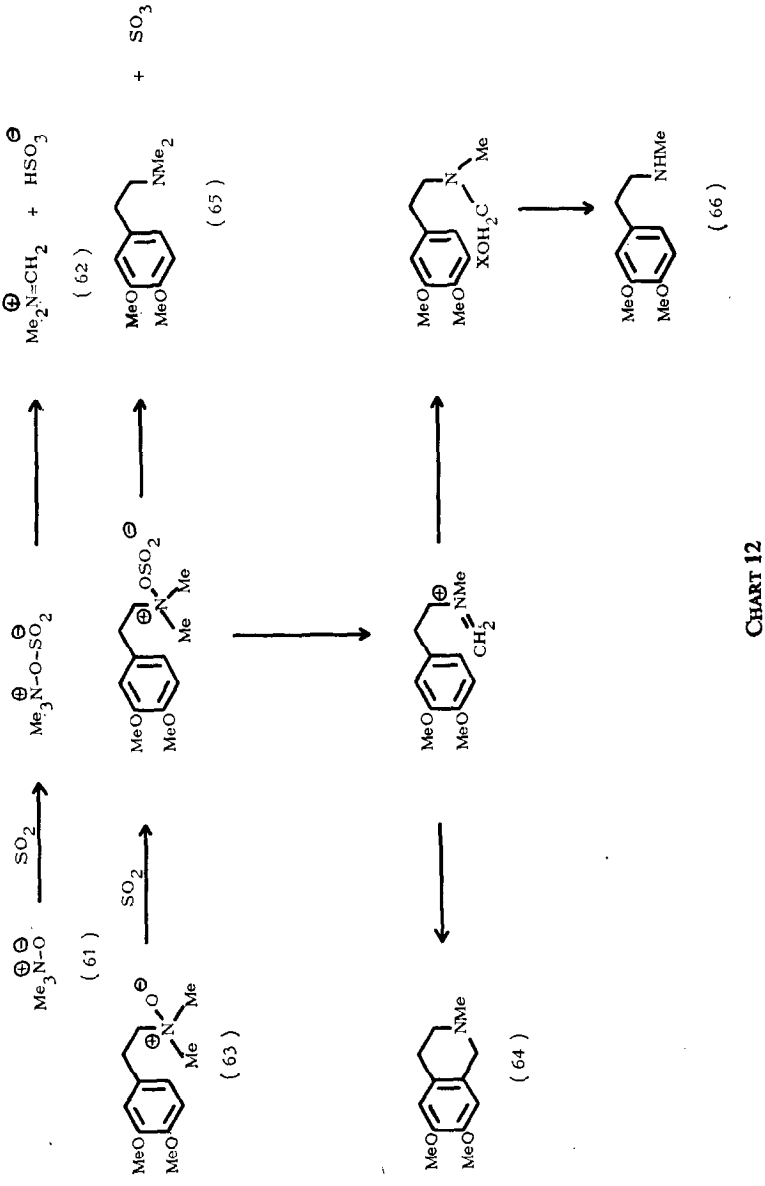


CHART 12

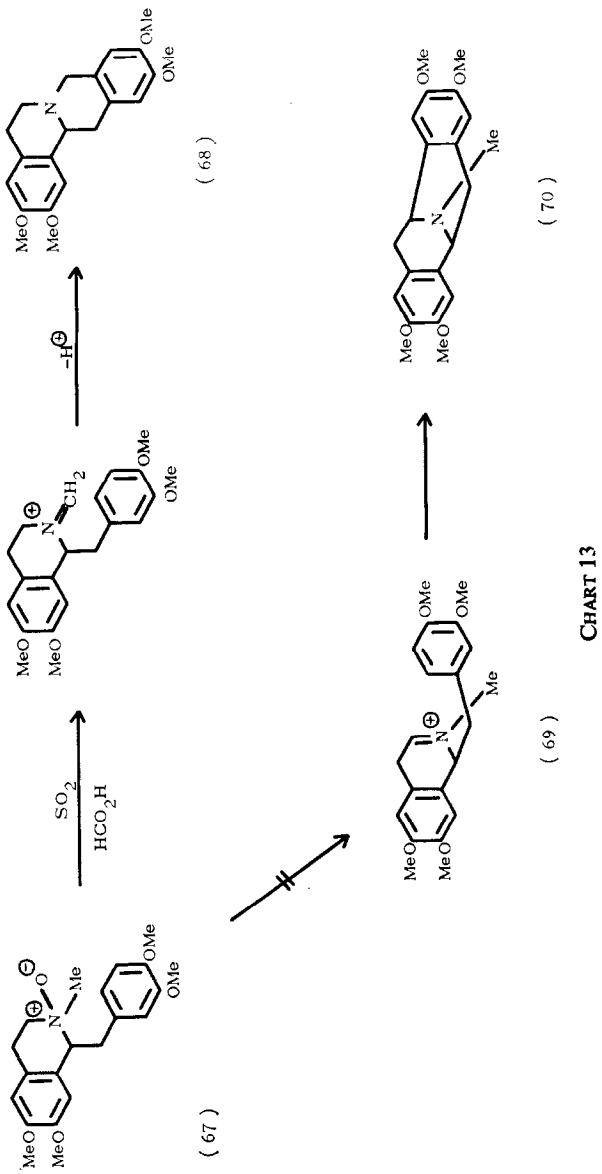


CHART 13

the tetrahydroisoquinoline (**64**) and protoberberine (**68**) (see Chart 12). Thus, in formic acid solvent, sulfur dioxide effects the dehydrative cyclization of 3,4-dimethoxy-*N*,*N*-dimethylphenethylamine *N*-oxide (**63**) to give the 2-methyltetrahydroisoquinoline (**64**) in 61% yield with the tertiary amine (**65**) as a minor product (29% yield), whereas only the secondary (**66**) and/or tertiary amine (**65**) is formed in water or acetic acid, the more nucleophilic solvent. The course of these reactions is interpreted in terms of the formation, when the ionizing power of the solvent is great enough, of an iminium ion, which can undergo either intramolecular aromatic substitution or solvolysis, depending on the nucleophilicity of the solvent used. Reaction of the *N*-oxide (**63**) with trifluoroacetic anhydride gave 33% of the cyclized product (**64**) with polymers as the main product.

The successful use of formic acid as a solvent for sulfur dioxide-induced cyclization of the above *N*-oxide (**63**) was applied to the biogenetic-type synthesis of a protoberberine alkaloid. Laudanosine *N*-oxide (**67**) gave 14.5% of xylopinine (**68**) in addition to 31% of laudanosine (**33**) with the sulfur dioxide-formic acid system, and 2.5% of the cyclized product (**68**) with trifluoroacetic anhydride system, indicating mediation of the methylene-containing iminium ion in each case (see Chart 13). Argemonine (**70**), which could in principle be formed from the second iminium ion (**69**), was not detected in either case.

Cherylline, a phenolic 4-phenyltetrahydroisoquinoline alkaloid, has recently been isolated from several *Crinum* species and assigned structure (**71**). Although cherylline is structurally unique for an *Amaryllidaceae* alkaloid, its biogenesis likely follows a pathway similar to that operative in the formation of the other alkaloids of this class,

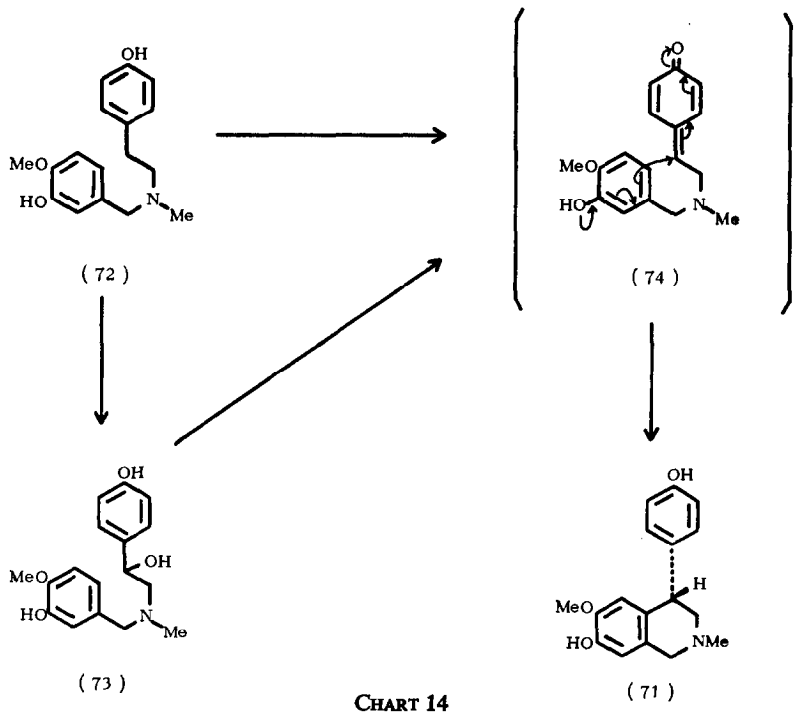


CHART 14

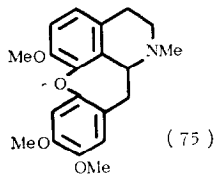
i.e., oxidation and cyclization of a suitable derivative of norbelladine (*4*). Such a pathway can be envisioned as shown in Chart 14. Direct two-electron oxidation of *O,N*-dimethylnorbelladine (**72**) could yield an intermediate quinone methide (**74**) which subsequently cyclized to cherylline (**71**); alternatively, hydroxylation of (**72**) could give the heretofore unknown hydroxy-*O,N*-dimethylnorbelladine (**73**), which would yield the same intermediate upon dehydration (see Chart 14). In terms of the feasibility of this scheme, the latter mechanism was investigated (*25*) *in vitro* as a synthetic route to the cherylline (**71**). When hydroxy-*O,N*-dimethylnorbelladine (**73**) was refluxed in aqueous ammonia, the reaction proceeded very smoothly to give (±)-cherylline (**71**) in 79% yield.

OXIDATION

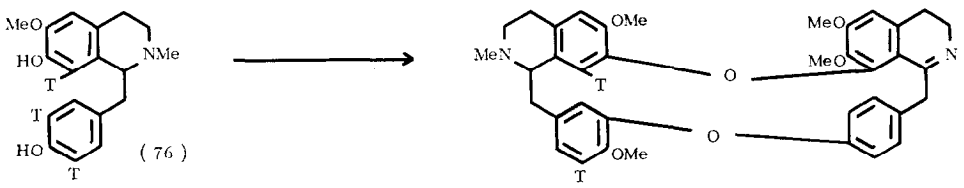
Phenolic Oxidation (*1, 6*)

Phenolic oxidation has become one of the new research areas of synthetic organic methodology during the past ten years, although it has long been recognized that a dimeric product can be derived from the oxidation of phenols with such reagents as ferric chloride and potassium ferricyanide.

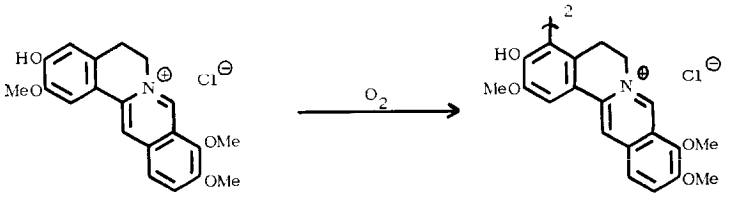
The concept that some isoquinoline alkaloids are built up in nature by oxidative coupling within a benzylisoquinoline molecule is not new: Gadamer (*26*) in 1911 drew



(75)



(76) (77)



(78) (79)

CHART 15

attention to the relationship between laudanosoline and glaucine, and similar ideas were promulgated by Robinson (*19*) and Schöpf (*27*). In 1957, Barton and Cohen (*28*) proposed that the new C–C or C–O bond in isoquinoline alkaloids was formed by pairing of radicals from the substrate involved in the oxidative step. Very detailed knowledge of the biosynthetic pathway to the isoquinoline alkaloids has been gained from extensive tracer experiments (*4*), which showed that phenolic oxidation is an important step in the biogenesis of isoquinoline alkaloids.

Since 1960, phenolic oxidation in the synthesis of isoquinoline alkaloids has been repeatedly investigated, and total syntheses of a number of isoquinoline alkaloids have been achieved using biogenetic-type reaction steps. This type synthesis was surveyed in detail by the present author (*1*). This paper will describe the data reported after our earlier review had been published.

Although an intramolecular oxidative coupling of diphenolic isoquinoline affords cularine (**75**) type alkaloids (*29*), intermolecular coupling of two *N*-methylcoclaurine units (**76**) by phenolic oxidation should afford bisbenzylisoquinoline alkaloids. This was confirmed by Barton (*30*) through feeding experiments showing that half of the epistephanine molecule (**77**) is derived exclusively from D-(–)-*N*-methylcoclaurine (see Chart 15).

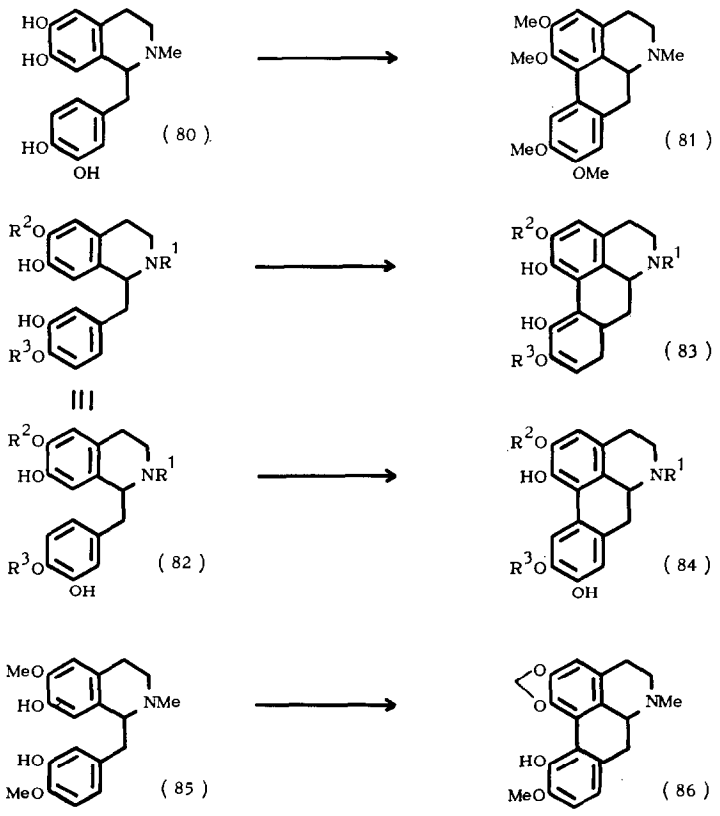


CHART 16

The laboratory conversion of a benzylisoquinoline into a bisbenzylisoquinoline, by catalytic oxidation has been reported. Thus, bisjatrorrhizine (**79**) was obtained in good yield by an oxygenation of jatrorrhizine chloride (**78**) in the presence of platinum (*31*).

The relationship between laudanosoline (**80**) and glaucine (**81**) was noted at the beginning of this century (*32*). In 1957, Barton (*28*) proposed the theory of phenol oxidation in biogenesis of aporphine alkaloids; thus, the majority of the aporphine bases can be regarded as being formed by phenolic coupling from phenolic base (**82**). This type of compound may be oxidized to corytuberine type alkaloids (**83**) and glaucine type alkaloids (**84**) (see Chart 16).

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 (**85**) into radioactive bulbocapnine (**86**) (*33*) and magnoflorine (*34*). The laboratory analogy for this type of biogenesis has been realized by a conversion of reticuline (**85**) into isoboldine (**84**, $R^1 = R^2 = R^3 = Me$) and then glaucine (**81**) by many groups (*35–40*).

On the other hand, several aporphine alkaloids, exemplified by roemerine (**94**) and anonaine (**92**), are constructed in such a way that their biogenesis by direct phenolic oxidation is not reasonable or involves unlikely precursors. Barton (*28*) therefore proposed that a coclaurine analog would initially be oxidized to the dienone proaporphine (**88**), which would be subjected to dienone-phenol rearrangement to generate

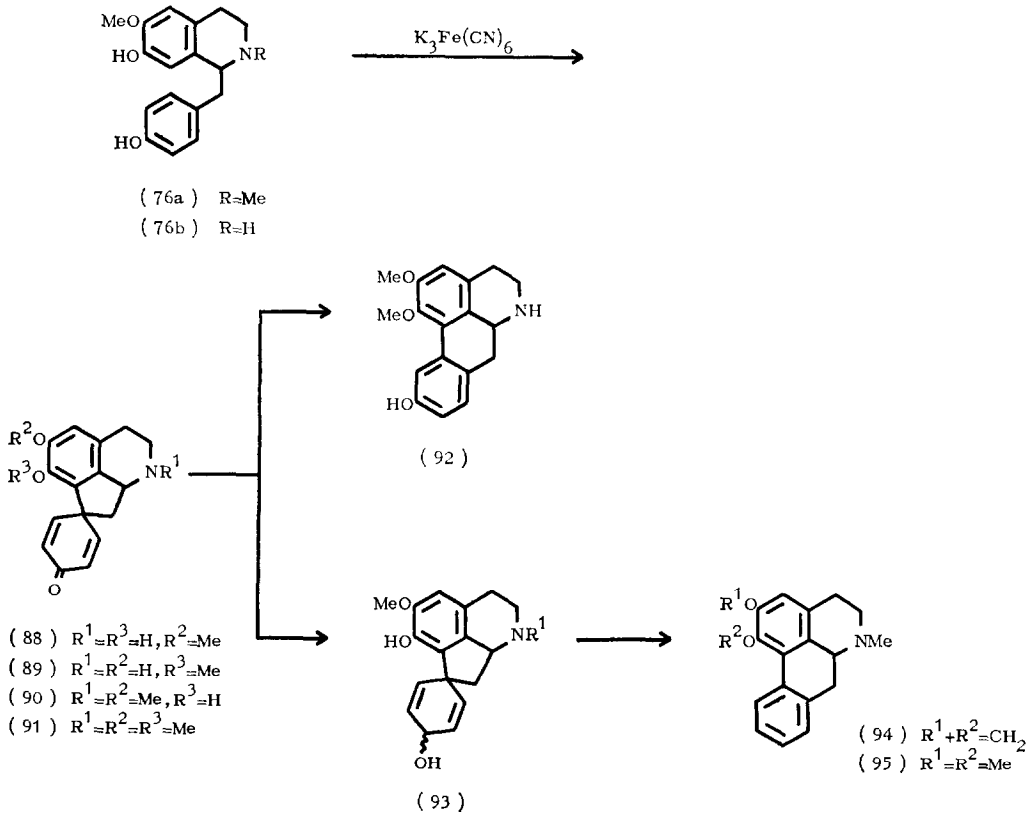


CHART 17

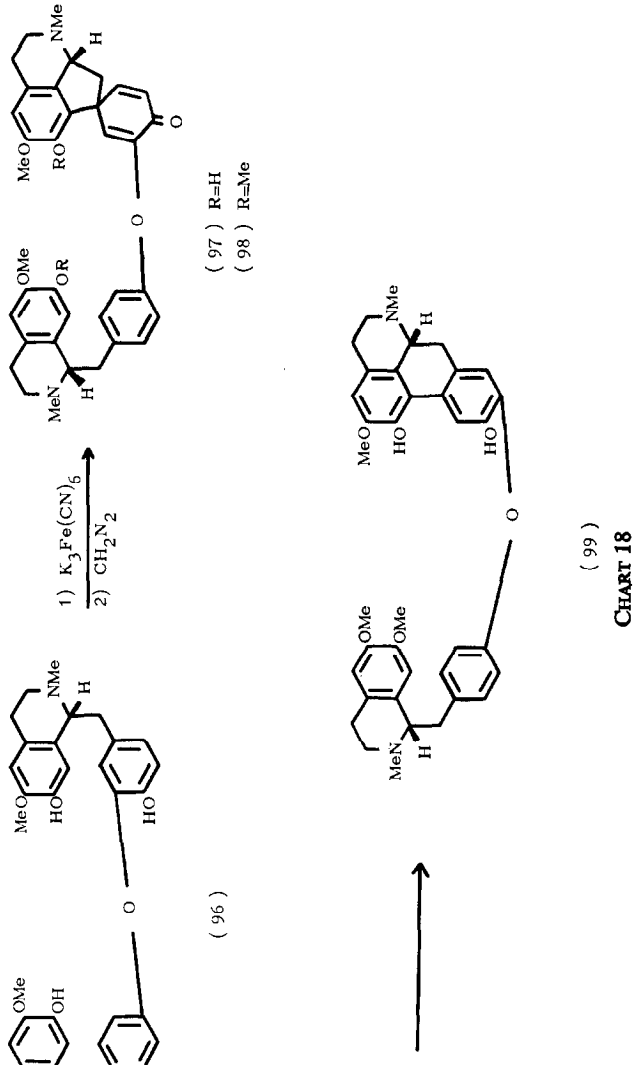


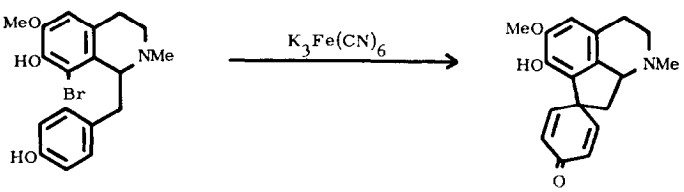
CHART 18

anonaine (**92**), and that reduction of dienone (**88**) to dienol (**93**), followed by dienol-benzene rearrangement, would then furnish roemerine (**94**). This hypothesis has been confirmed by feeding experiments showing that (+)-coclaurine (**76b**) is incorporated into crotonosine (**89**) (*41*) and moreover, that orientalinone [biosynthesized from orientaline] is incorporated into isothebaine *via* orientalinol in *Papaver somniferum* (*42*).

This coupling process was reproduced in the laboratory in the case of the *N*-methylcoclaurine (**76a**), which underwent phenolic oxidation with potassium ferricyanide in 1 *N* ammonium acetate solution to give glaziovine (**90**) (*43*, *44*). This was converted into pronuciferine (**91**) by methylation, and the latter (**91**) in turn could be transformed into nuciferine (**95**) (*43*, *45*). Similarly, tritium-labeled (±)-, (−)- and (+)-*N*-methylcoclaurines were converted into the corresponding proaporphines, respectively (*44*) (see Chart 17).

Pakistanamine (*98*) could be biosynthesized from the bisbenzylisoquinoline (**96**) (which is derived from a coclaurine-type precursor) by phenolic oxidative coupling, and transformed into the co-existing alkaloid, pakistanine (**99**). In the laboratory, a successful oxidation of (±)-berbamunine (*96*) to (±)-pakistanamine (*98*) has been brought about by an oxidation with potassium ferricyanide, followed by methylation (*46*). Natural pakistanamine was subjected to *in vitro* dienone-phenol rearrangement, giving a pakistanine-type dimer (*47*) (see Chart 18).

Phenolic oxidation of 8-bromo-2-methylcoclaurine (**100**) was examined in the expectation that glaziovine (**90**) would be formed in better yield than in the oxidation of *N*-methylcoclaurine (**76a**), since isoboldine (**84**, $R^1 = R^2 = R^3 = Me$) could be obtained in better yield by oxidation of 6′-bromoreticuline than by oxidative coupling of reticuline itself (*35*). Treatment of (**100**) with potassium ferricyanide, however, afforded glaziovine (**97**) in the same yield as the case of *N*-methylcoclaurine (*48*) (see Chart 19).



(100) (90)

CHART 19

Erybidine (**103**), a new protostephanine-type alkaloid, could be biosynthesized from proerythrinadienone (**102**), which would be formed from the protosinomenine type base (**101**) (*49*) or from morphinandienone (**104**) by the Franck (*50*) and Battersby mechanism (*51*). However, *O*-methylerybidine is synthesized, along the imagined biogenetic route, from the secondary amine (**107**) *via* the erythrinadienone (**106**) (*52*) (see Chart 20). Erythrinadienone (**106**), which had been already synthesized from the secondary amine (**107**) with ferricyanide oxidation in the presence of 5% sodium hydrogen carbonate (*49*, *53*, *54*), was cleaved reductively with chromous chloride (*49*), followed by *N*-methylation with formalin and sodium borohydride, and then *O*-methylation to give *O*-methylerybidine.

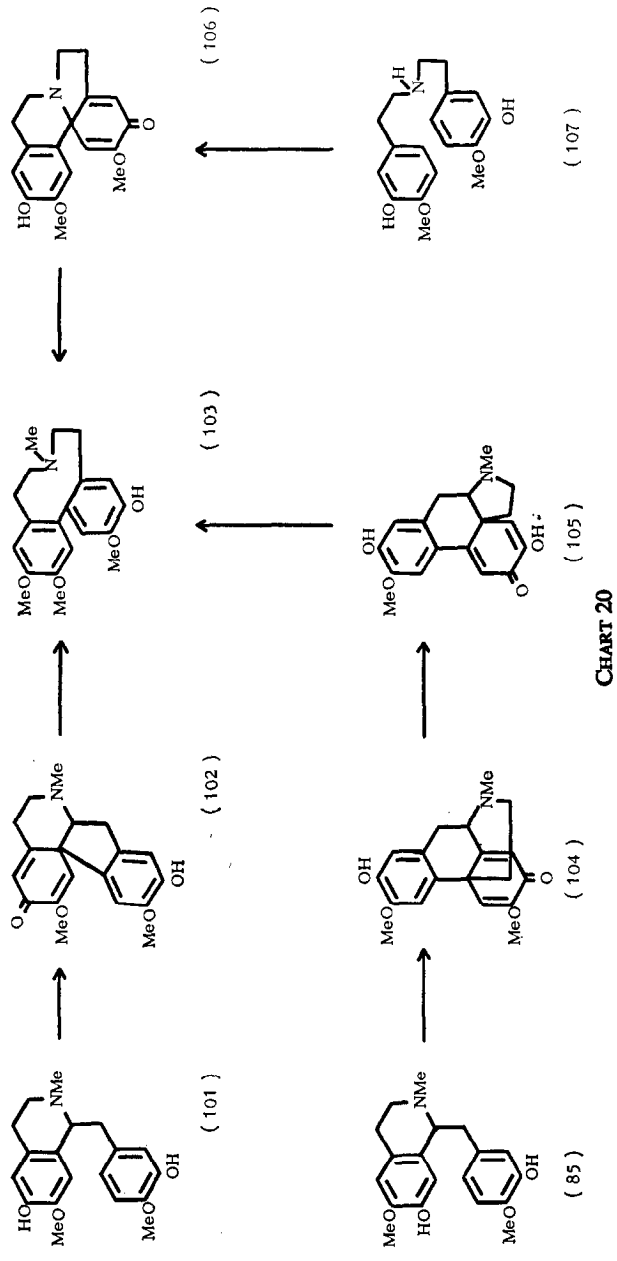


CHART 20

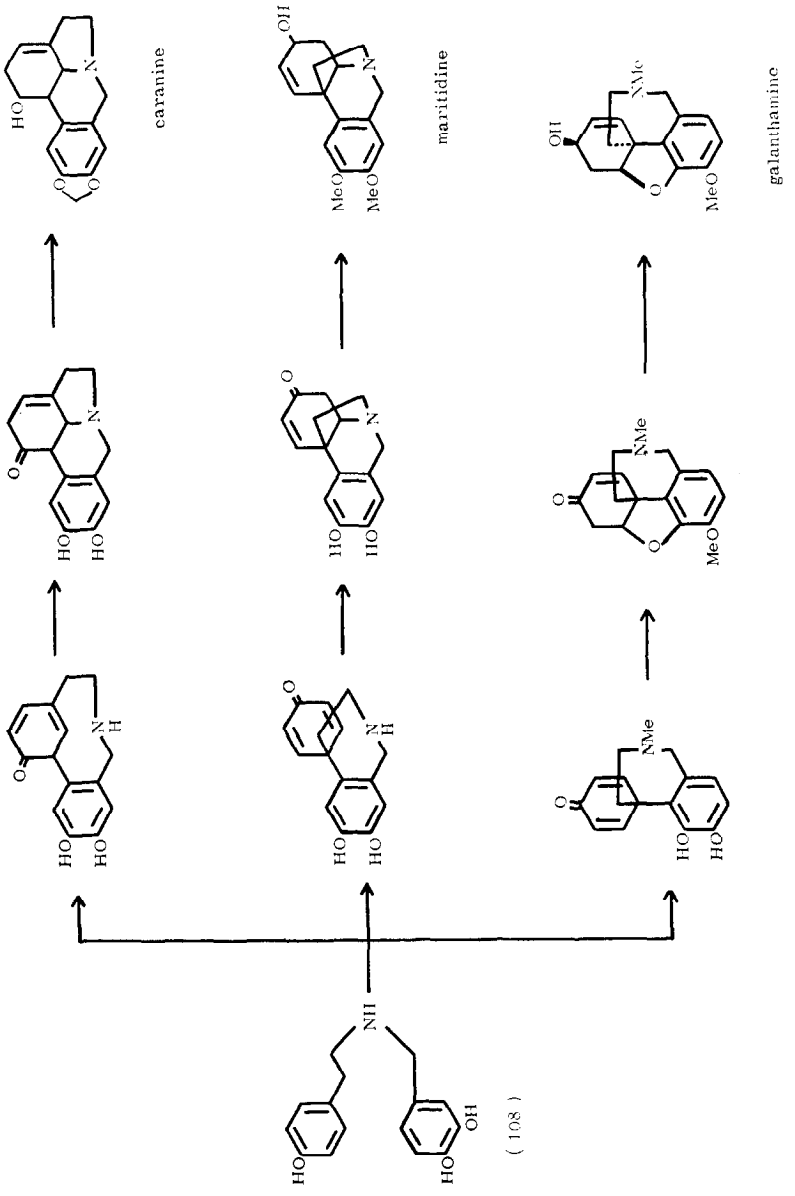
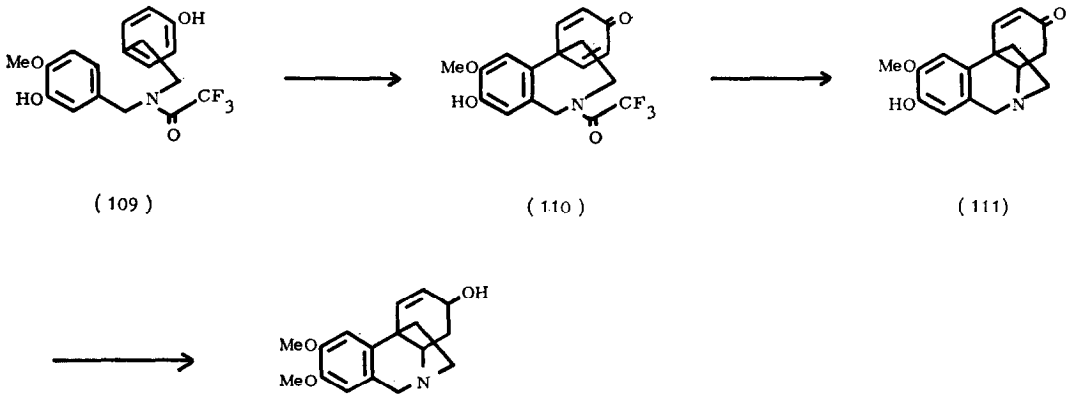


CHART 21

Barton and Cohen (*28*) suggested that a phenolic precursor such as amine (**108**), now known as the natural product norbelladine, represents a single precursor for the main three types of the *Amaryllidaceae* alkaloids. The validity of this proposal (Chart 21) has been conclusively demonstrated by independent investigators (*4*). Of the three types of alkaloids obtained by phenolic oxidation of norbelladine, crinan- and galanthamine-type alkaloids have been obtained by biogenetic-type synthesis (*1*).

Recently, maritidine (**112**), a crinan-type alkaloid, was synthesized along above biogenetic lines through the use of new oxidizing reagent, an iron complex $[Fe(DMF)_3Cl_2][FeCl_4]$ prepared from ferric chloride and dimethylformamide (DMF) (*55*). Oxidation of *N*-trifluoroacetylnorbelladine (**109**) with 10 mole equivalent of the complex in a two-phase system (ether and water) under refluxing with stirring gave the dienone (**110**), which on alkaline hydrolysis with potassium carbonate afforded enone (**111**). The enone (**111**) had already been converted into maritidine (**112**) by Schwartz (*56*), and thus this work constitutes the biogenetic-type synthesis of maritidine (**112**) (see Chart 22).

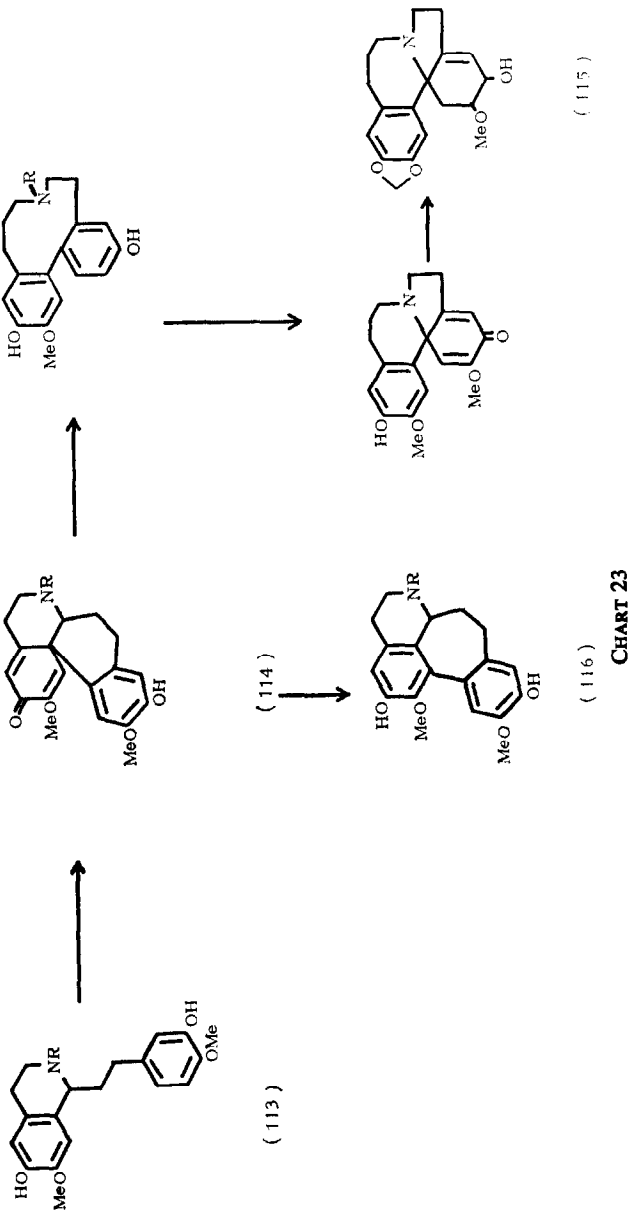


(109) (110) (111) (112) CHART 22

It is likely that the ring system of the homoerythrina alkaloids (**115**) derives from homoprotosinomenine (**113**) by a route analogous to that involved in the biogenesis of the erythrina alkaloids, for which a protosinomenine precursor has been established. An attempt in the laboratory based on this mechanism led to successful formation of prohomoerythrinadienone (**114**) (*57*). Thus, *N*-trifluoroacetylisoquinoline (**113**, $R = COCF_3$) on oxidation with vanadium oxychloride (2.5 equiv) in methylene chloride gave the dienone (**114**, $R = COCF_3$) in 35% yield, which, interestingly enough, rearranged to the homoaporphine type base (**116**) by treatment of boron trifluoride-etherate—reminescent of a mechanism of aporphine alkaloid biogenesis suggested by Battersby (*58*) (see Chart 23).

Two Electron Oxidation

Aporphine alkaloids could be biosynthesized by oxidative coupling of the 1-benzylisoquinolines by one of three different mechanisms; the first one is a direct coupling of the benzylisoquinolines (*33*, *34*); the second, *via* the proaporphines (*41*, *42*); and the



(113) (114) (115) (116)

CHART 23

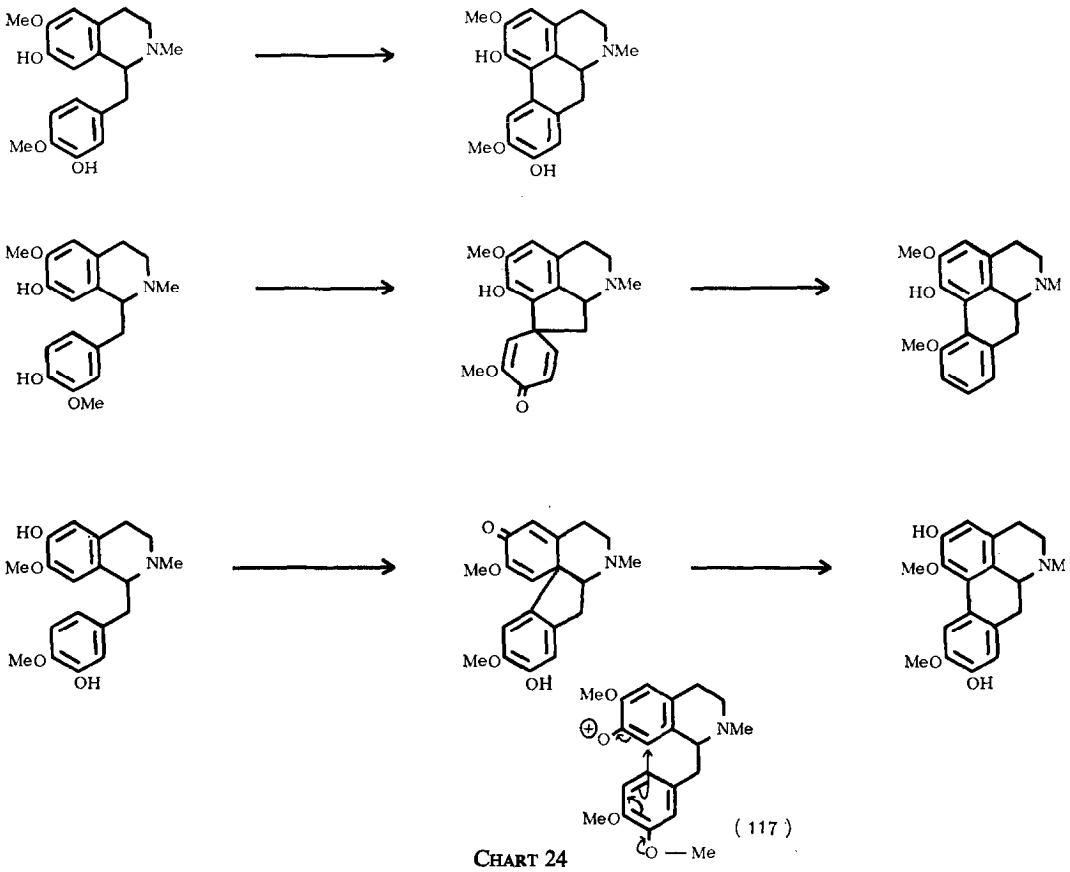
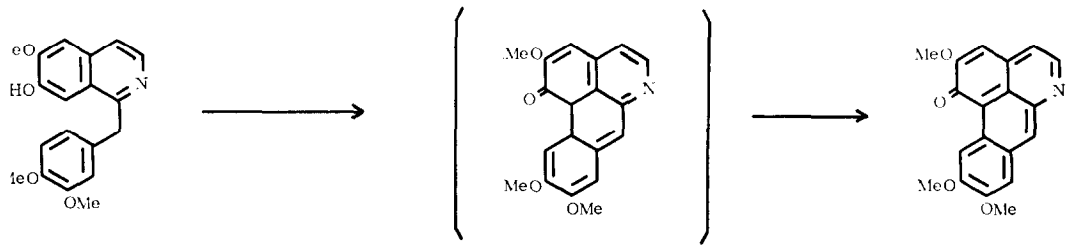


CHART 24

third, through the proerythrinadienones (*58*). It is necessary to locate phenolic hydroxy groups at the *ortho* or *para* position to the coupling site in these biogenetic sequences. The benzylisoquinolines which have non-phenolic or monophenolic hydroxy group and possess two phenolic groups in unsuitable positions for the above pathways could not be transformed into the aporphine alkaloids in nature. This fact shows that new bond formation proceeds through radical pairing and provides some evidence against a mechanism in which substitution by the phenoxonium cation (**117**) or a similar phenoxy radical attack is envisaged (see Chart 24).

However, valuable, biomimetic synthetic work based upon this phenoxonium cation or its similar mechanism has been carried out, involving an intramolecular oxidation of monophenolic benzylisoquinolines with two electron oxidation system. Thus, vanadium oxyfluoride (22 mmole) was added to a solution of 7-demethylpapaverine (**118**) in trifluoroacetic acid (which was a valuable medium for moisture-sensitive oxidations) at 0° under protection from moisture, and the mixture was stirred for 3 hr to give a quinonoid oxoaporphine (**119**) in 59 % yield. Other reagents were also utilized in this reaction, as shown in Chart 25. The reaction may proceed by abstraction of hydrogen atoms from the activated diarylmethylene function and the phenolic hydroxyl group to yield intermediate (**120**) and subsequent further oxidation to (**119**), although other mechanisms can not be precluded (*59*).



(118) (120) (119)

Oxidant	Medium	Temp. (°C)	Yield (%)
$Ce(SO_4)_2$	10% aq. H_2SO_4	0	25
$Co(OH)_3$	10% aq. H_2SO_4	25	15
MnO_2	CF_3CO_2H	0	30
CrO_3	aq. H_2SO_4-AcOH	0	25
$Tl(OCOCF_3)_3$	CF_3CO_2H	25	12
Pb_3O_4	CF_3CO_2H	0	22
VOF_3	CF_3CO_2H	0	59
$MoOCl_4$	CF_3CO_2H-$CHCl_3$	25	62

CHART 25

The biomimetic synthesis of crinan and androcymbine-type alkaloids by a phenoxonium ion (or equivalent) mediated intramolecular coupling from the monophenolic amines was also reported (*60*). The trifluoroacetyl norbelladine derivative (1 mmole) (**121**) was oxidized with thallium (III) trifluoroacetate (3 mmole) in anhydrous methylene chloride at room temperature for 20 hr to give dienone (**122**) in 19% yield. Hydrolysis of this with sodium carbonate in aqueous methanol afforded oxocrinine (**123**). Similar treatment of *N*-trifluoroacetylphenethylisoquinoline (**124**) with the above oxidant gave the dienone (**127**) in 10% yield. This type of coupling reaction has been achieved under phenolic oxidation conditions in very low yield (*61*). Interestingly, the phenethylisoquinoline (**125**) was treated with diborane in tetrahydrofuran-methylene dichloride, and the resulting protected amine (**126**) was oxidized wtih 2–3 molar equivalent of thallium trifluoroacetate in methylene dichloride at 25° for 24 hr to give *O*-methylandrocymbine (**128**), in 20% yield after removal of the blocking group with anhydrous sodium carbonate in refluxing methanol (see Chart 26).

Recently, Kupchan (*62*) achieved the synthesis of several types of alkaloids by intramolecular and intermolecular coupling of non-phenolic benzylisoquinolines by vanadium oxytrifluoride oxidation. Thus, laudanosine (**32**) was treated with this oxidant in trifluoroacetic acid-methylene dichloride-fluorosulfonic acid at −30° to give glaucine (**81**) in 43% yield, but papaverine (**129**) afforded the $C_{6'}$–$C_{6'}$ linkage dimer (**130**) in 80% yield. The absence of intramolecular coupling of papaverine under the reaction conditions employed could be attributed to protonation of the nitrogen, resulting in a general deactivation of the isoquinoline moiety. Moreover, a solution of *N*-formylnorlaudanosine (**131**) in methylene dichloride-tetrahydrofuran was treated with vanadium

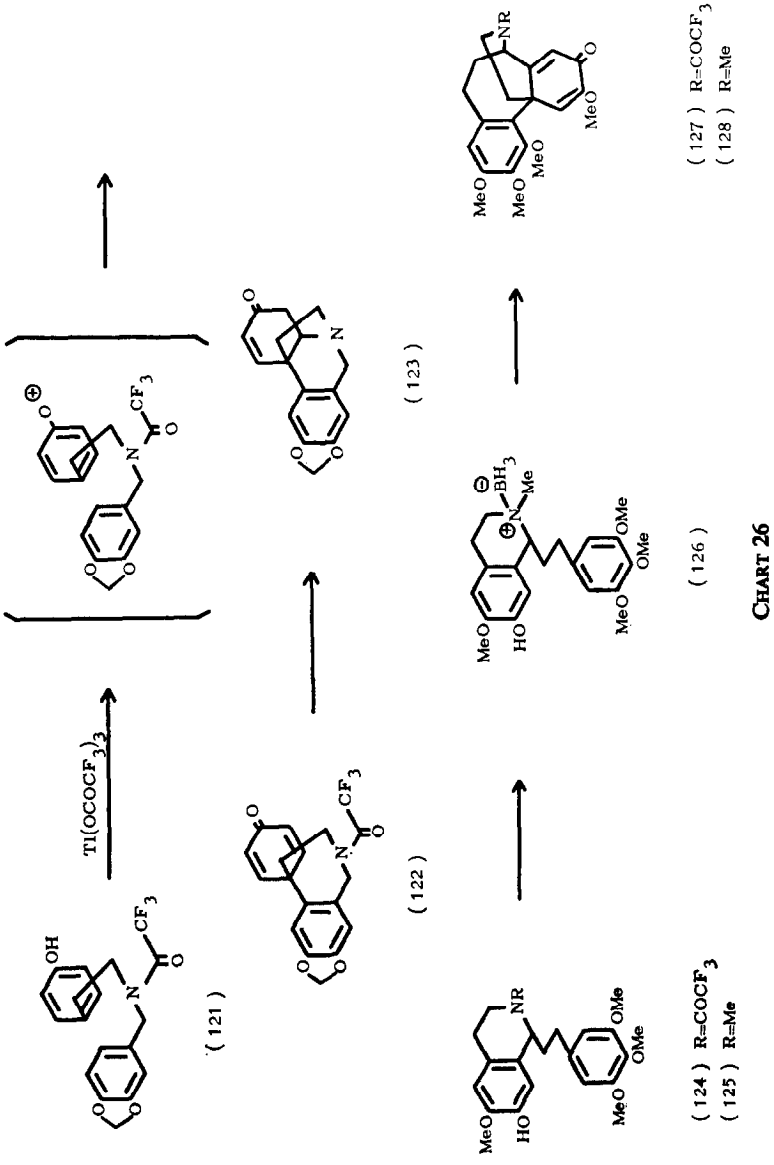

Tl(OCOCF3)3
(121)
(122)
(123)
(124) R=COCF3
(125) R=Me
(126)
(127) R=COCF3
(128) R=Me

CHART 26

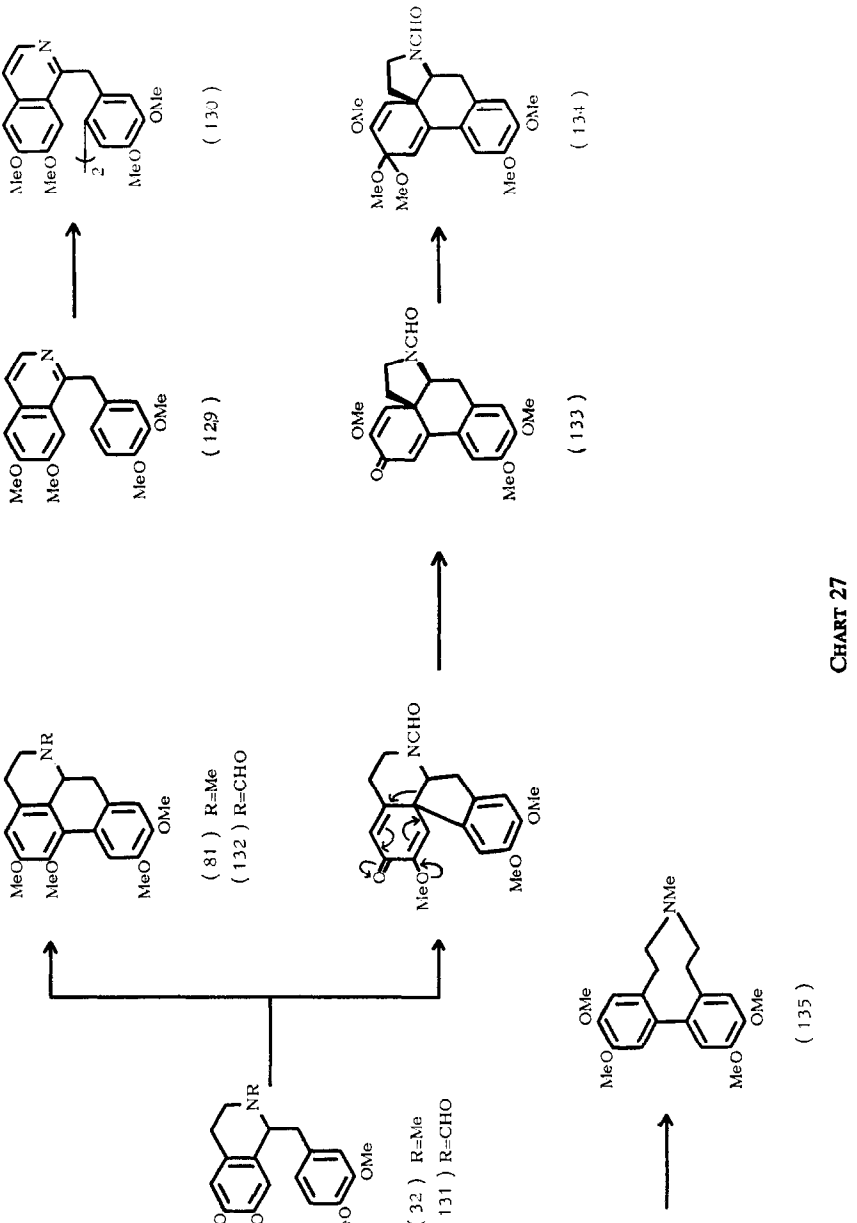

MeO
MeO
MeO
OMe
NR
(32) R=Me
(131) R=CHO
(81) R=Me
(132) R=CHO
NCHO
(133)
(134)
(129)
(130)
NMe
(135)

CHART 27

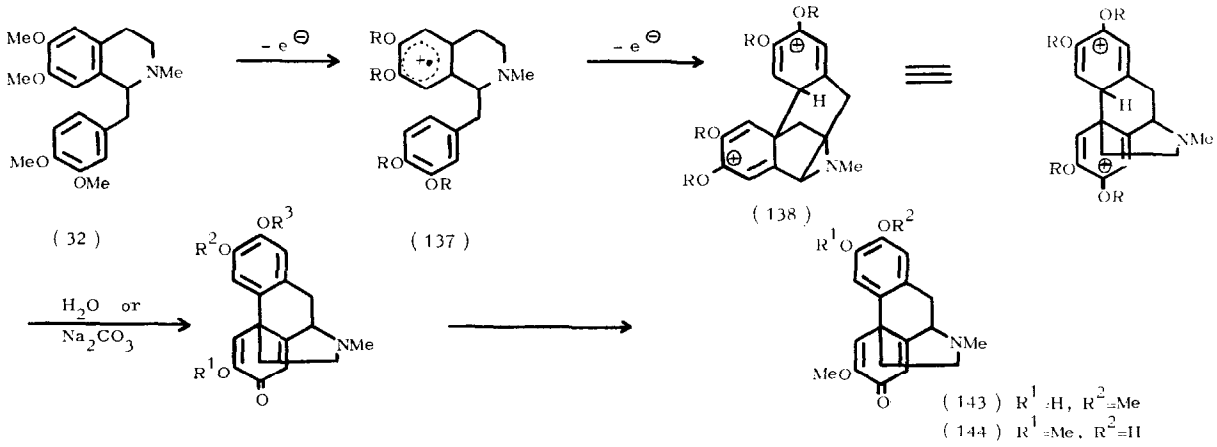
trifluoride at −30° to afford *N*-formylnorglaucine (**132**) (6% yield) and spirodienone (**133**) in 55% yield. The latter was treated with methanolic hydrochloric acid, followed by lithium aluminum hydride reduction of resulting ketal (**139**) to give *O*-methylerybidine (**135**). This reaction scheme may not be biogenesis-based, but the facile conversions of the benzylisoquinolines (**63**) to neoproerythrinadienone (**133**) and then to dibenzoazonine (cf. **103**) may have important implications for the biosynthesis of the erythrina alkaloids (see Chart 27).

Electro-oxidative Cyclization (64)

Phenolic oxidative coupling reactions (*1*, *6*) have long held a prominent position in the synthesis of isoquinoline and related alkaloids from relatively simple precursors, and this reaction is interesting and important as the synthetic analog of the biogenetic mechanism. Inorganic oxidants and some enzymic systems have been used in this synthesis, but this method suffers from very low yields and often leads to complex mixtures. In addition, other deficiencies in the method are apparent. First, the need for several additional synthetic steps to prepare the appropriate diphenolic isoquinolines lowers the overall yield. Secondly, it is necessary to locate a phenolic hydroxy group at a position *ortho* or *para* to the coupling site. Thirdly, in some cases, the coupling product seems to be more rapidly oxidized than the substrate. On these grounds, intramolecular coupling of monophenolic and nonphenolic benzylisoquinolines with two-electron oxidants is an important reaction from the synthetic chemical point of view, although this type of reaction is not biogenetic.

Recently, several types of isoquinoline alkaloids were synthesized in high yield from the non-phenolic benzylisoquinolines, available easily by an electro-oxidative intramolecular cyclization, which has the following valuable synthetic features. Controlled potential oxidation employing the powerful but selective oxidant such as an anode has eliminated the necessity for utilizing easily oxidized phenolates (*65*). Thus, laudanosine (**32**) was oxidized at the platinum electrode in acetonitrile at 1.1 V in the presence of sodium carbonate at 0° with either lithium perchlorate or tetramethylammonium tetrafluoroborate as the electrolyte. In this reaction, a three-compartment cell separating the cathode, anode, and $Ag/AgNO_3$ reference electrode solutions was utilized. The product, *O*-methylflavinantine (**136**) was isolated from the anolyte in 52% yield. Chart 28 shows a mechanistic rationale for the formation of this product (**136**). First, oxidation of the 1-benzyltetrahydroisoquinoline (**32**) to a cation radical (**137**), followed by cyclization and loss of another electron, forms (**138**). Loss of a proton, rearomatization of the initial benzyl moiety and alkyl cleavage from the initial isoquinoline aromatic ring forms the final morphinandienone product. The oxidative cleavage of alkyl groups from suitable alkyl phenyl ethers has analogy, but the timing of electron loss, cyclization, and cleavage as well as the cleavage mechanism remain unelucidated.

When the above oxidation was performed on an equimolar mixture of (**32**) and bis(acetonitrile)palladium (II) chloride, the yield of (**136**) was raised to 63%. Similar oxidation of (±)-*O*-benzylcodamine, (±)-*O*-benzylpseudocodamine, (±)-*O*-benzyllaudanine, and (±)-*O*-benzylpseudolaudanine yielded *O*-methylflavinantine (**136**) (53%), *O*-benzylflavinantine (**139**) (53%), O-benzylisoflavinantine (**140**) (43%), and 2,3-dimethoxy-6-benzyloxymorphinandienone (**141**) (44%), respectively.



				Yield (%)	
	R^1	R^2	R^3	Miller[65]	Tobinaga[66]
(136)	Me	Me	Me	53	
(139)	Me	CH_2Ph	Me	53	86(98)[a]
(140)	Me	Me	CH_2Ph	44	78(90)[a]
(141)	CH_2Ph	Me	Me	43	
(142)	Me	$-CH_2-$			70(80)[a]

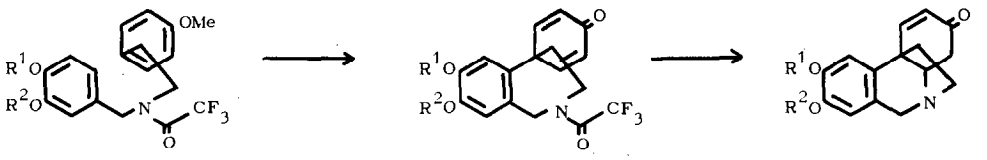
(a): Yield based on recovered starting material.

CHART 28

In this oxidation, the use of phenol ethers may provide specificity for carbon–carbon coupling which is not found in phenol oxidations. The wide and variable oxidation power of the anode is an important attribute *vis-à-vis* the usual chemical oxidant. By controlling the potential one can perform selective oxidations and, indeed, can selectively oxidize certain functionalities. In particular, electrochemistry allows us to oxidize nonphenolic materials (ferricyanide will oxidize phenolate ions but will not affect aryl ethers).

As discussed above, an intramolecular oxidative coupling reaction by electrochemical method is superior to other chemical methods in several respects. However, Miller's method needs to set to rather strict conditions for the electrolysis of the substrate. Later, Tobinaga (*66*) modified these conditions and obtained morphinandienones in better yield than in the case of Miller's method. The reactions were carried out with an H-type one-compartment glass cell at room temperature in a concentration of reactant 0.02 *M* in acetonitrile using a $Hg–HgCl_2$ reference electrode. Electrolysis was done at the current 100–120 mA maintaining the potential at 1.0 V for 15 min, using platinum electrodes. Nonphenolic benzylisoquinolines were oxidized in the manner mentioned above to give the morphinandienones, which on debenzylation gave respectively flavinantine (**143**), pallidine (**144**), and amurine (**142**) in surprising yields.

This method has also been applied in the biomimetic synthesis of *Amaryllidaceae* alkaloids (*67*), phenanthroquinolizidine alkaloids (*68*), and colchicine (*69*) by the same authors. Thus, nonphenolic *N*-benzylphenethylamines (**145** and **146**) were oxidized in acetonitrile with fluoroboric acid as an electrolyte using platinum electrodes at a current of 1.10–1.18 V for 1 hr to give the dienones (**122**) and (**147**), both in 62% yield, which on alkaline hydrolysis afforded oxocrinine (**123**) and oxomaritidine (**148**), respectively, which have already been converted to crinine and maritidine. The yields of the dienones (**122**) and (**147**) by an oxidation with tetraethylammonium perchlorate electrolytic and a carbon anode-platinum cathode were generally low (30 and 52%, respectively) (see Chart 29).



(145) $R^1+R^1=CH_2$
(146) $R^1=R^2=Me$

(122) $R^1+R^2=CH_2$
(147) $R^1=R^2=Me$

(123) $R^1+R^2=CH_2$
(148) $R^1=R^2=Me$

CHART 29

Cryptopleurine (**153**), a phenanthroquinolizidine alkaloid from *Cryptocarya pleurosperma*, is co-existent with pleurospermine (**149**). Tracer experiments have not been carried out, but it is very probable that this type of alkaloid is biosynthesized by phenolic oxidation of the quinolizidine derivatives (cf. **150**, **152**) by direct coupling or rearrangement of the dienone (cf. **151** and dienol **154**) formed by oxidative coupling (see Chart 30).

In the laboratory, a successful oxidation of quinolizidine (**155**) to dienone (**156**) has been brought about by manganese dioxide in 20% yield; and the conversion of dienone

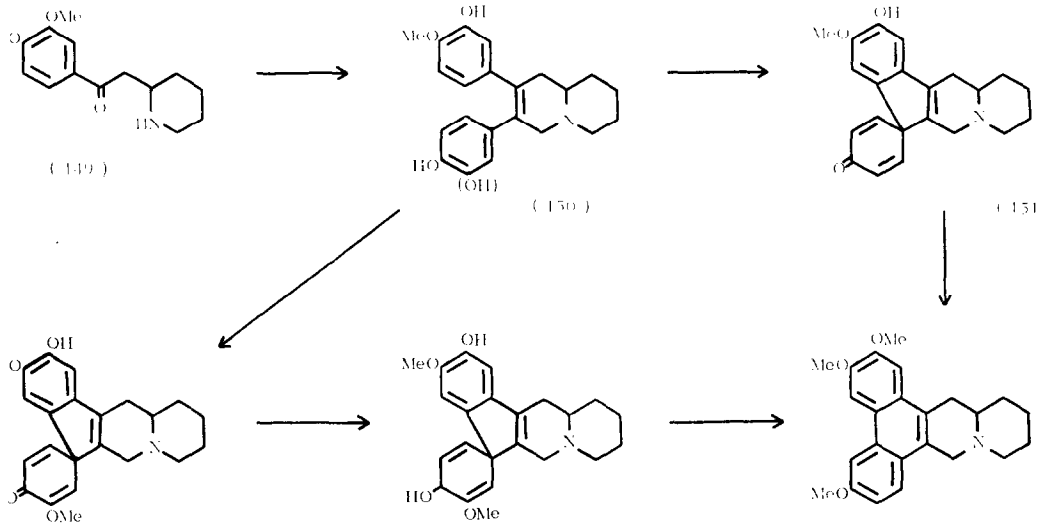


CHART 30

(**156**) into cryptopleurine (**153**) was carried out by dienone-phenol rearrangement, followed by *O*-methylation and reduction (*70*) (see Chart 31).

Alternatively, cryptopleurine (**153**) was synthesized from nonphenolic base (**157**) through electro-oxidation. The oxidation of the quinolizidinone (**157**) under the same conditions as the case of *Amaryllidaceae* gave the spirodienone (**158**) (60% yield) and ketocryptopleurine (**159**) (31% yield). The former was converted into the latter by acid-catalyzed dienone-phenol rearrangement, followed by hydrolysis and methylation.

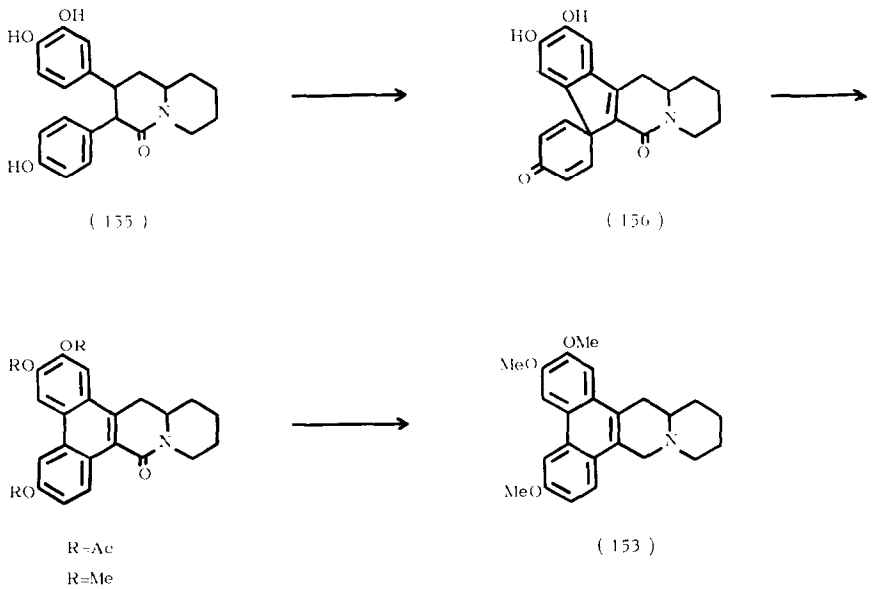


CHART 31

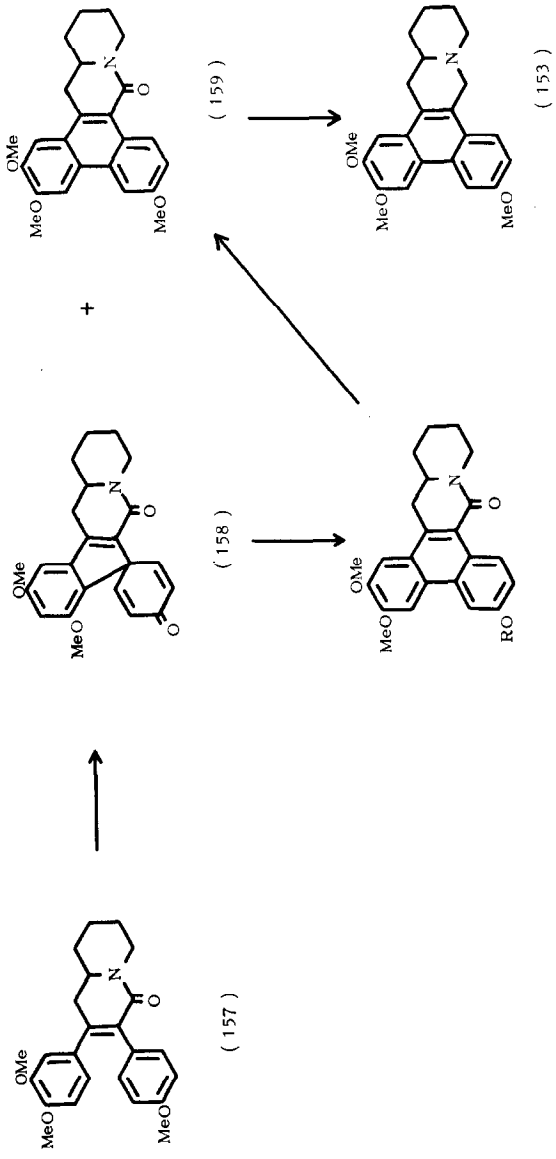
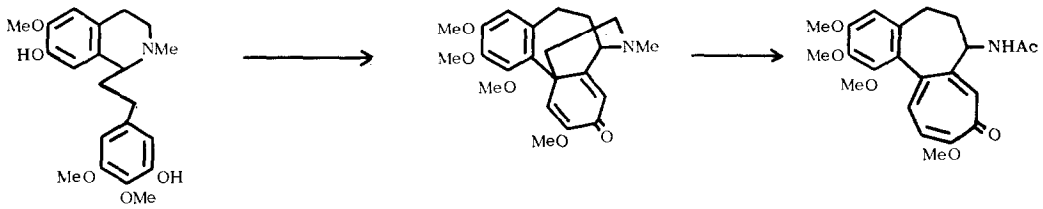


CHART 32

Reduction of ketocryptopleurine with lithium aluminum hydride afforded cryptopleurine (**153**) (see Chart 32).

O-Methylandrocymbine (**128**), the first example of a 1-phenethylisoquinoline alkaloid, is biosynthesized by phenolic oxidation of autumnaline (**160**) and transformed biogenetically into colchicine (**161**), as shown by tracer experiments (*71*) (see Chart 33).



(160) (128) (161)

CHART 33

An earlier scheme (*19*) for the biosynthesis of colchicine (**161**) proposed by Robinson and Anet envisaged the coupling of two aromatic rings followed by ring expansion as 162 → 163 → 164 → 165 → 161. The tracer results now show that this idea is not correct, but valuable synthetic work based upon it has been carried out by electro-oxidation (*69*). Thus, electro-oxidation of (**162**) (R = Me) as usual produced the dienone (**163**, R = Me) in 80% yield, which was subjected to the Simons–Smith reaction, followed by acetic acid-sulfuric acid treatment of the resulting enone (**164**), to give desacetylaminoisocolchicine (**165**). This sequence amounts to a synthesis of colchicine (**161**), as the remaining steps have been carried out previously (see Chart 34).

Lead Tetraacetate Oxidation

Isopavine-type alkaloids have been found as the minor bases in *Roemeria genus* and are characterized by the presence of an azepine ring system. The biosynthesis of this group of alkaloids may simply involve the oxidative C–C coupling between C_4 and $C_{2'}$ positions in the benzylisoquinolines. Brown (*72*) suggested that the intermediate in this coupling is the 4-hydroxybenzylisoquinoline base (**168**) derived from the benzylisoquinolines, since *N*-dimethoxybenzyl-4-hydroxyisoquinolines (**166**) are readily cyclized to (**167**) in acids (see Chart 35).

In support of this view it has been found that *O*-methylthalisopavine (**173**) and reframine (**174**) were synthesized from 6-hydroxytetrahydroisoquinolines (**169**) and (**170**) *via* the corresponding 4-acetoxy derivatives (**171**) and (**172**). Thus, 6-hydroxyisoquinoline (**169**) was oxidized with lead tetraacetate in chloroform under ice-cooling for a few min to give a diastereoisomeric mixture of 4-acetoxytetrahydroisoquinoline (**171**), which was treated with hydrochloric acid in ethanol at room temperature for 12 hr, followed by diazomethane methylation, to yield *O*-methylthalisopavine (**173**). Similarly, reframine (**174**) was obtained from (**170**) *via* its 4-acetoxy derivative **172** (*73*) (see Chart 36).

Nonbiogenetic-type synthesis of isopavine alkaloids through the 4-hydroxy isoquinolines was also achieved by Dyke. The first method is the conversion of the acetal (**175**) into amurensine (**177**) with hydrochloric acid at room temperature for 5 days, presumably by way of a base such as 4-hydroxyisoquinoline **176** (*72*). A similar type reaction is applied in the synthesis of isopavine (*74*, *75*) and thalisopavine (*76*). In the

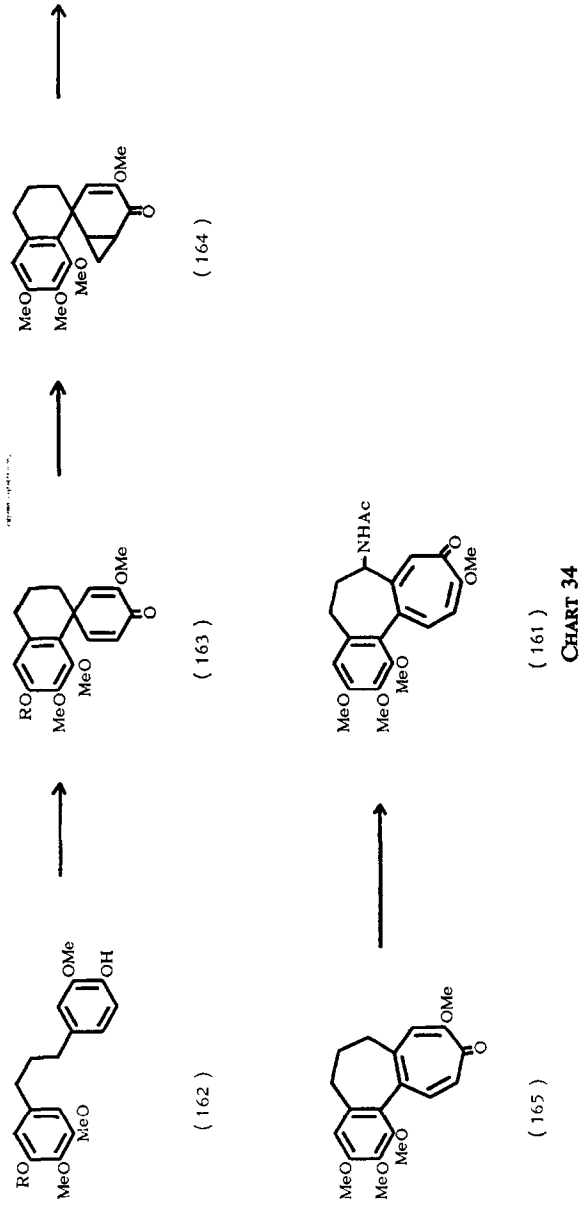
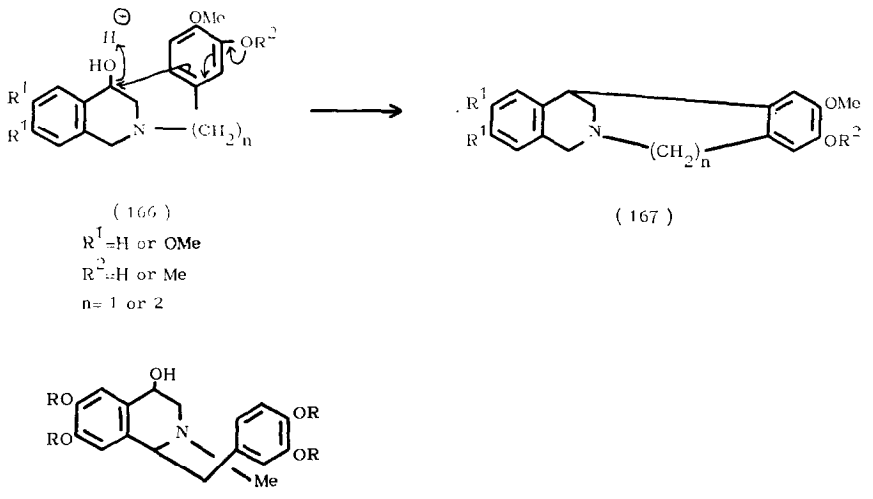

RO
MeO
MeO
OMe
OH
MeO
(162)
RO
MeO
MeO
OMe
O
MeO
(163)
MeO
MeO
MeO
OMe
O
O
(164)
MeO
MeO
MeO
OMe
O
(165)
MeO
MeO
MeO
NHAc
OMe
O
(161)

CHART 34



(166)
R¹=H or OMe
R²=H or Me
n=1 or 2

(167)

(168)

CHART 35

second method, the 1,2-dihydroisoquinoline (**178**) is hydrated with diborane-hydroperoxide, and the resulting 4-hydroxyisoquinoline (**179**) was cyclized with acid to *O*-methylthalisopavine (**173**) (*77*) (see Chart 37).

Moreover, lead tetraacetate oxidation of the benzylisoquinolines and phenethylisoquinolines was applied to the synthesis of aporphine and homoaporphine alkaloids. Thus, reaction of codamine (**180**) with lead tetraacetate in acetic acid at room temperature for 0.5 hr gave the *p*-quinol acetate (**181**), which was, without purification, treated with acetic anhydride and sulfuric acid at room temperature for 1 hr to yield 4-acetoxy-*O*-acetylthaliporphine (**182**) and *O*-acetylthaliporphine (**183**). Hydrolysis of (**183**) gave thaliporphine (**184**), which could be converted into glaucine (**81**). Thaliporphine (**184**) was also obtained from (**182**) by reduction with lithium aluminum hydride. Umezawa proposed the following mechanism for the formation of *O*-acetylthaliporphine: Michael-type addition of the 6-position in the veratryl group to the 9-position in *p*-quinol acetate (**181**) and concerted elimination of the 10-acetoxy group followed by 1,2-shift of the C_6–C_9 bond to the 8-position and aromatisation. The mechanism of the formation of 4-acetoxy derivative (**182**), however, remains obscure (*78*). The similar acid treatment of *p*-quinol acetate (**186**) derived from the monophenolic phenethylisoquinoline (**185**) by lead tetraacetate oxidation gave *O*-acetylkreysigine (**187**) in 18% yield (*79*) (see Chart 38). Furthermore, rearrangement of (**186**) with trifluoroacetic acid at room temperature gave kreysigine (**188**), but treatment with trifluoroacetic acid in boiling methylene dichloride or trifluoroacetic acid in acetic acid yielded *O*-methylandrocymbine (**128**) in addition to kreysigine (**188**). *O*-Methylandrocymbine (**128**) could be obtained directly from the phenethylisoquinoline (**185**) by an oxidation with lead tetraacetate in trifluoroacetic acid and acetic acid at room temperature (*80*).

Enzymic Oxidation

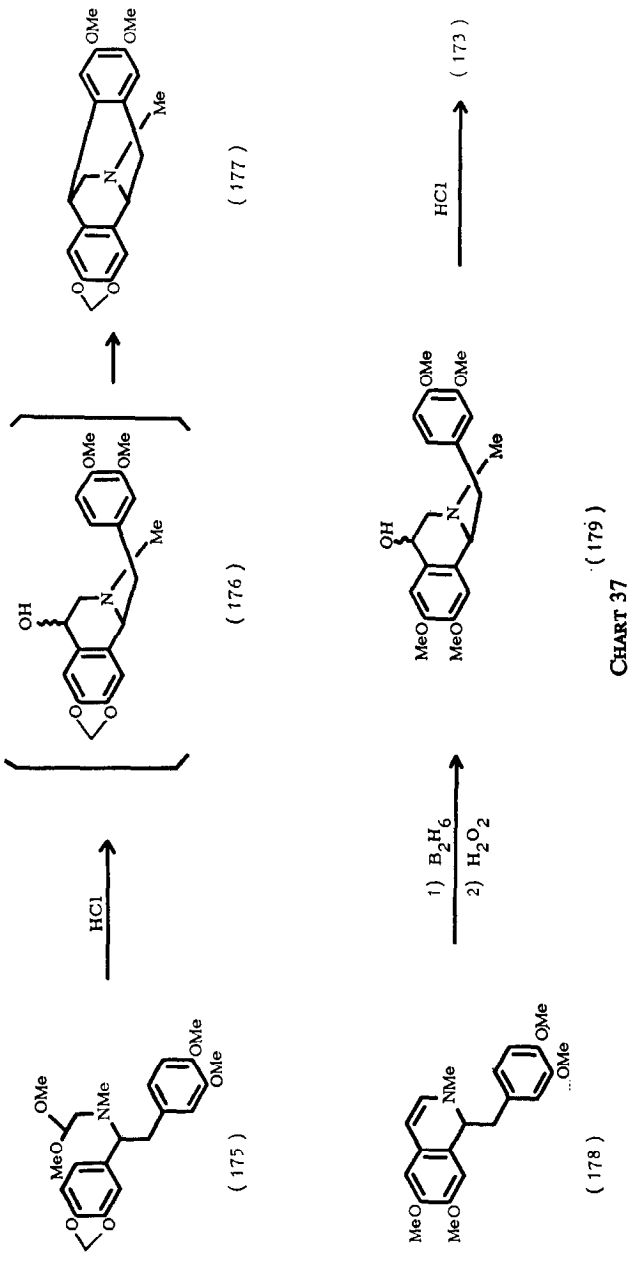
Many isoquinoline and related alkaloids are in principle derived from phenolic benzylisoquinoline precursors by carbon–carbon, carbon–oxygen, or carbon–nitrogen

(169) $R^1=R^1=Me$
(170) $R^1+R^2=CH_2$

(171) $R^1=R^2=Me$
(172) $R^1+R^1=CH_2$

(173) $R^1=R^2=Me$
(174) $R^1+R^2=CH_2$

CHART 36



(175) (176) (177) (178) (179) (173)

CHART 37

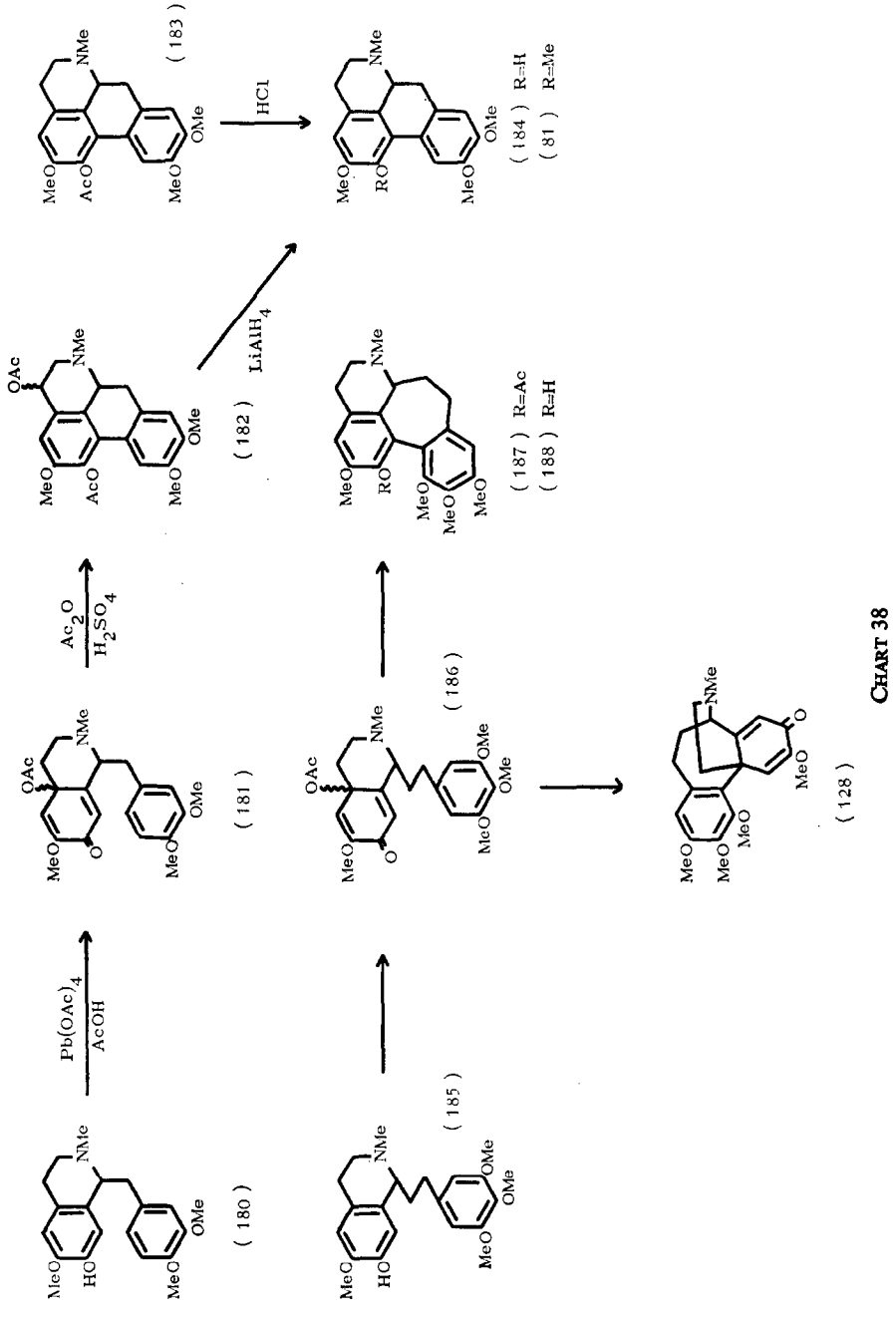
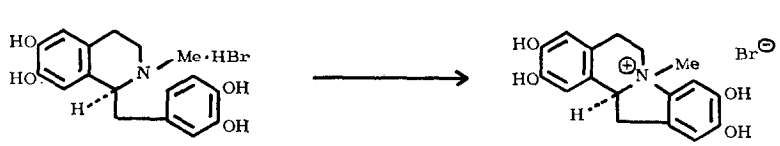

Pb(OAc)4
AcOH
Ac2O
H2SO4
LiAlH4
HCl
(180)
(181)
(182)
(183)
(184) R=H
(81) R=Me
(185)
(186)
(187) R=Ac
(188) R=H
(128)

CHART 38

coupling with the probable assistance of enzymes (*4*, *81*). While the use of enzymes and enzyme extracts in the synthesis of isoquinoline alkaloids has been reported by Kametani and co-workers (*82*), Inubushi and associates (*83*) and Fromming (*84*), this approach has been of little preparative value due to formation of complicated mixtures or poor yields. It is therefore not surprising that chemical oxidations have remained the method of choice. For example, ferric chloride has been used to effect the transformation of racemic laudanosoline (**80**) into the quaternary dibenzopyrrocoline (**189**) as well as the conversion of racemic laudanosoline methiodide (**190**) into the quarternary aporphine (**191**) (*85*).

In contrast, Brossi and associates reported that by the use of the purified enzyme horseradish peroxidase under controlled reaction conditions, oxidative coupling of (1S)-(+)-laudanosoline hydrobromide (**80**) and (1R)-(−)-laudanosoline methiodide (**190**) could be effected with great facility and in a preparative manner at pH 5 to afford the quaternary dibenzopyrrocoline (**189**) (81 % yield) and the quaternary aporphine (**191**) (60 % yield) respectively, with retention of configuration (*85a*) (see Chart 39).



(80) (189)

(190) (191)

CHART 39

Investigations on the biotransformation of the benzylisoquinoline to the protoberberine in the living animal have been carried out; thus, a solution of *S*(+)-reticuline (**2**) in propylene glycol was injected intraperitoneally (200 mg/kg) into five female rats, and the urine was collected in bottles containing a few drops of toluene for 4 days after the injection to give coreximine (**192**) (*86*). In this transformation, nonphenolic bases or orientaline type bases could not form the corresponding protoberberines, which fact showed this reaction to be occurring through a phenolic oxidative coupling mechanism (see Chart 40).

On the other hand, treatment of reticuline (**2**) with horseraddish peroxidase in the presence of hydrogen peroxide at pH 7.5 gave thalifoline (**193**) (*87*). As thalifoline could be biosynthesized by the oxidative cleavage of 1-benzylisoquinolines (*88*), this

work constituted a synthesis of thalifoline (**193**). The same cleavage proceeded during oxidation of reticuline with potassium ferricyanide (*87*). The oxidation of reticuline with homogenized *Papaver rhoeas* and hydrogen peroxide afforded β- hydroxyreticuline

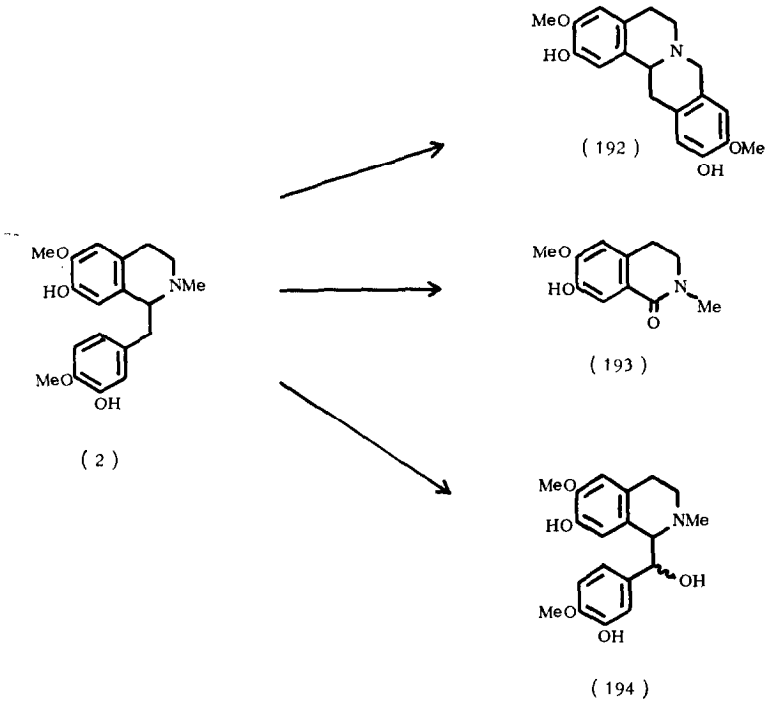


CHART 40

(**194**), which might offer an initial clue to the biosynthesis of rhoeadine and phthalide-isoquinoline alkaloids (*89*).

Other Oxidations

Protopine-type bases are formed in nature by oxidation of protoberberine as shown by an incorporation of reticuline (**2**) into protopine (**195**) (*90*, *91*) (see Chart 41).

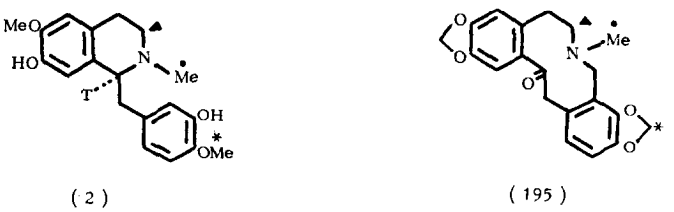


CHART 41

Chemical conversion of protoberberines into protopine-type bases had been achieved by Haworth and Perkin (*92*) before the biogenesis of protopine was made clear. Hofmann degradation of tetrahydroepiberberine (**196**) gave the polycyclic base (**197**),

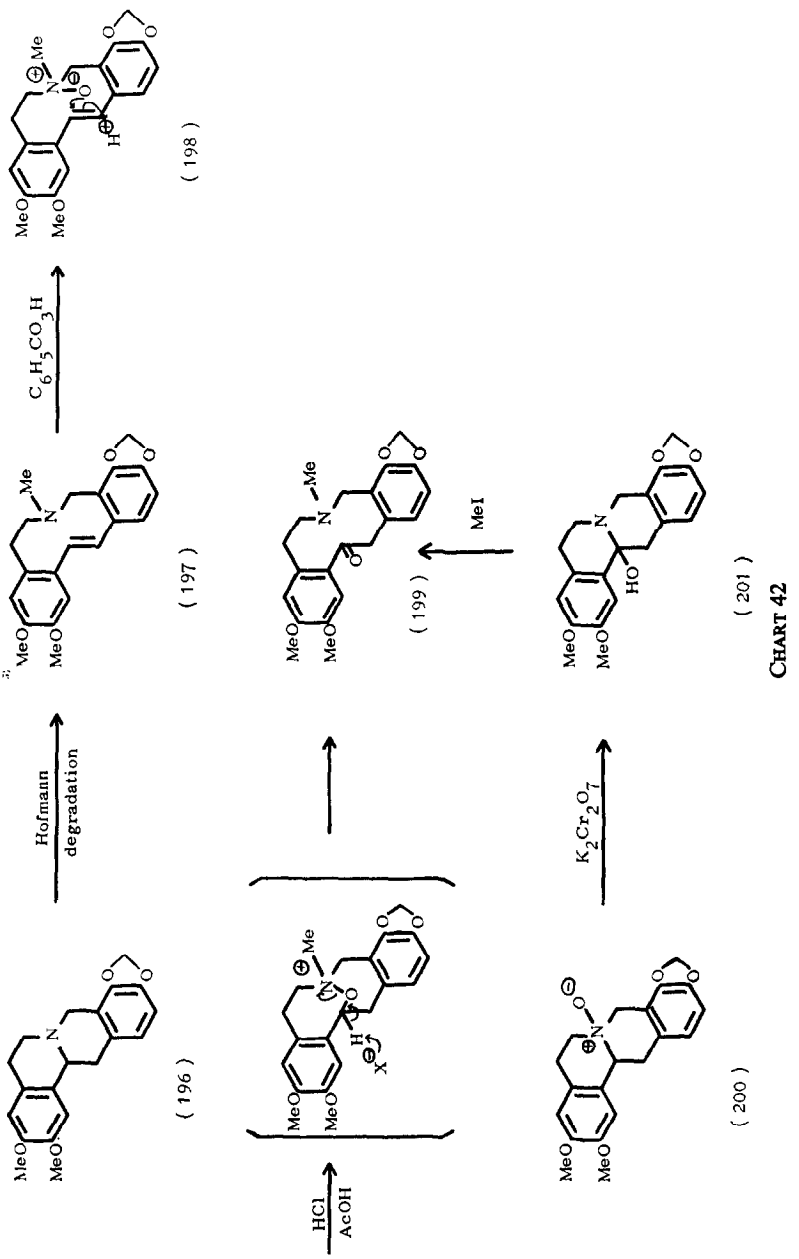


CHART 42

which was treated with perbenzoic acid to give the *N*-oxide (**198**), followed by acid-catalyzed rearrangement, to lead to cryptopine (**199**) (see Chart 42). Bentley presented an alternative synthesis of cryptopine (**199**) from tetrahydroepiberberine *N*-oxide (**200**) through the carbinolamine (**201**) (*93*).

PHOTOCHEMICAL REACTION

Some aporphine alkaloids are biosynthesized by direct oxidative C–C coupling of the appropriate diphenolic benzylisoquinolines in Nature, as described above. This coupling process has been achieved *in vitro* by chemical, electronic and enzymic oxidations. Recently, a photochemical oxidation, involving a kind of modified photolytic electrocyclic reaction (*94*), was also carried out to form the biphenyl system.

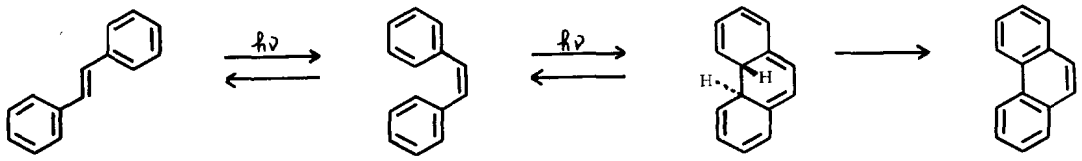
Conjugated polyene systems often undergo photolytic electrocyclization. Thus, *trans*-stilbene (**202**) undergoes a rapid cis–trans isomerization under the influence of ultraviolet light, and *cis*-stilbene (**203**) then cyclizes to the *trans*-dihydrophenanthrene (**204**) upon further irradiation. Mild oxidation of the latter with air or iodine produces phenanthrene (**205**) (*95*, *96*). This type of hexatriene–cyclohexadiene isomerization has been widely applied to the synthesis of several types of isoquinoline alkaloids (see Chart 43). In that this reaction has been applied to the synthesis of aporphine alkaloids, it has biogenetic relations.

Thus, ultraviolet irradiation (Hanovia 450 W mercury lamp housed in a water-cooled quartz insert) of 1-benzylidene-2-ethoxycarbonylisoquinoline (**206**) in the presence of iodine and cupric acetate in ethanol gave in 35% yield the dehydronuciferine analog (**207**) (*97*, *98*), which was converted into nuciferine (**208**) by a standard method. Moreover, the *N*-ethoxycarbonylstilbene derivatives (**209**, **210**) gave the dehydroaporphine (**211**, **212**) (*98*, *99*) which was converted to glaucine (**81**) (*98*) and neolitsine (**213**) (*100*) (see Chart 44).

Molecular orbital calculations on 1-benzylidene-2-ethoxycarbonylisoquinoline call for localization of electron density at the ortho position of stilbene in the excited state. The aromatic system is thus activated in the excited state, and intramolecular acylation occurs. In fact, the irradiation of *cis*-benzylidene-2-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (**213**) gave the dehydroprotoberberine (**214**) in 10–12% yield in addition to the dehydroaporphine (**215**) (*101*) (see Chart 45).

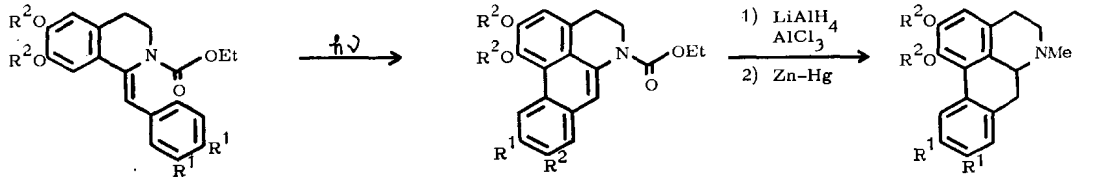
The synthesis of protoberberine bases according to this sequence also has been carried out; thus the urethan (**217**) was irradiated in the presence of iodine and hydriodic acid to give dehydro-β-coralydine (**218**) in 75% yield. Presumably the acid protonated the amide group to give the immonium alcohol (**219**), which increased the carbon to nitrogen double bond character, so that it reacted as a hexatriene system. Reduction of (**218**) with sodium borohydride afforded the protoberberine alkaloid, β-coralydine (**220**) (*102*) (see Chart 46).

The biogenesis of tylophorine (**223**), as in that of cryptopleurine (**153**), involves formation of the biphenyl system by oxidative C–C coupling. The process has been carried out photochemically: irradiation of 3,4-dimethoxy-α-(3,4-dimethoxyphenyl)-cinnamide (**221**) in the presence of iodine gave a phenanthrene derivative (**222**), which was converted into tylophorine (**223**) by the usual methods (*103*) (see Chart 47).



(202) (203) (204) (205)

CHART 43

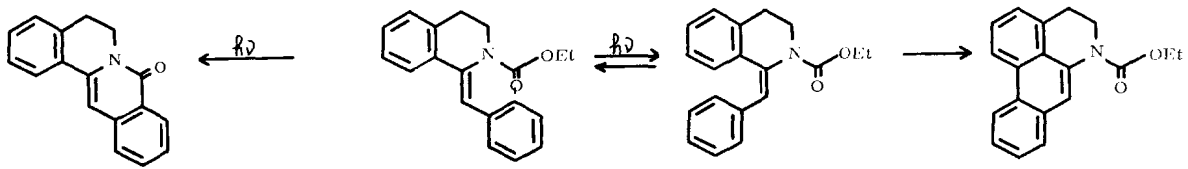


(206) R^1=H, R^2=Me
(209) R^1=OMe, R^2=Me
(210) R^1+R^1=OCH_2O, R^2+R^2=CH_2

(207) R^1=H, R^2=Me
(211) R^1=OMe, R^2=Me
(212) R^1+R^1=OCH_2O R^2+R^2=CH_2

(208) R^1=H, R^2=Me
(81) R^1=OMe, R^2=Me
(213) R^1+R^1=OCH_2O R^2+R^2=CH_2

CHART 44



(215) (214) (216)

CHART 45

CHART 46

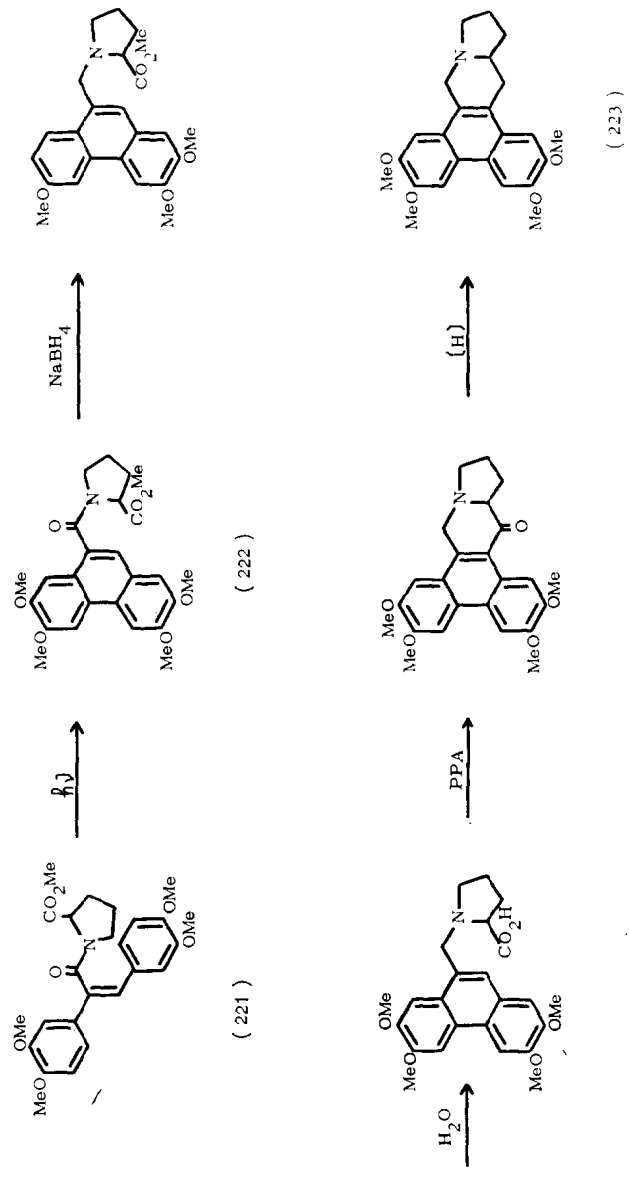


CHART 47

The hypothesis by Robinson (*19*) that the benzophenanthridine alkaloids are formed in plants though cleavage of C_6–C_7 bond of protoberberines followed by joining of C_6 to C_{13} has been supported by tracer experiments (*104*). In the laboratory, the synthesis of the benzophenanthridine base through fission of C_6–C_7 bond (see Chart 48), followed

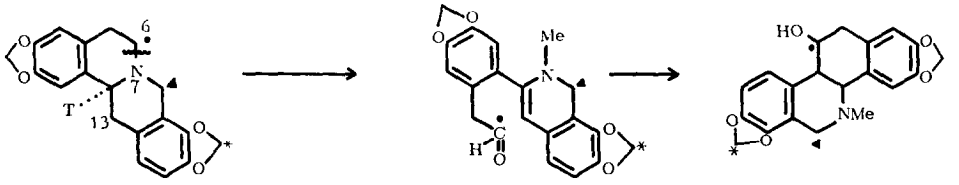


CHART 48

by bond formation of C_6–C_{13} linkage are reported. Thus, Onda synthesized chelerythrine (**228**) and sanguinarine (**229**) by a photolytic electrocyclic reaction from the methine bases (**226**) derived from the protoberberine (**224**) and protopine alkaloids (**225**). Irradiation of (**226a**) and (**226b**) in benzene gave the cyclized products (**227a**)

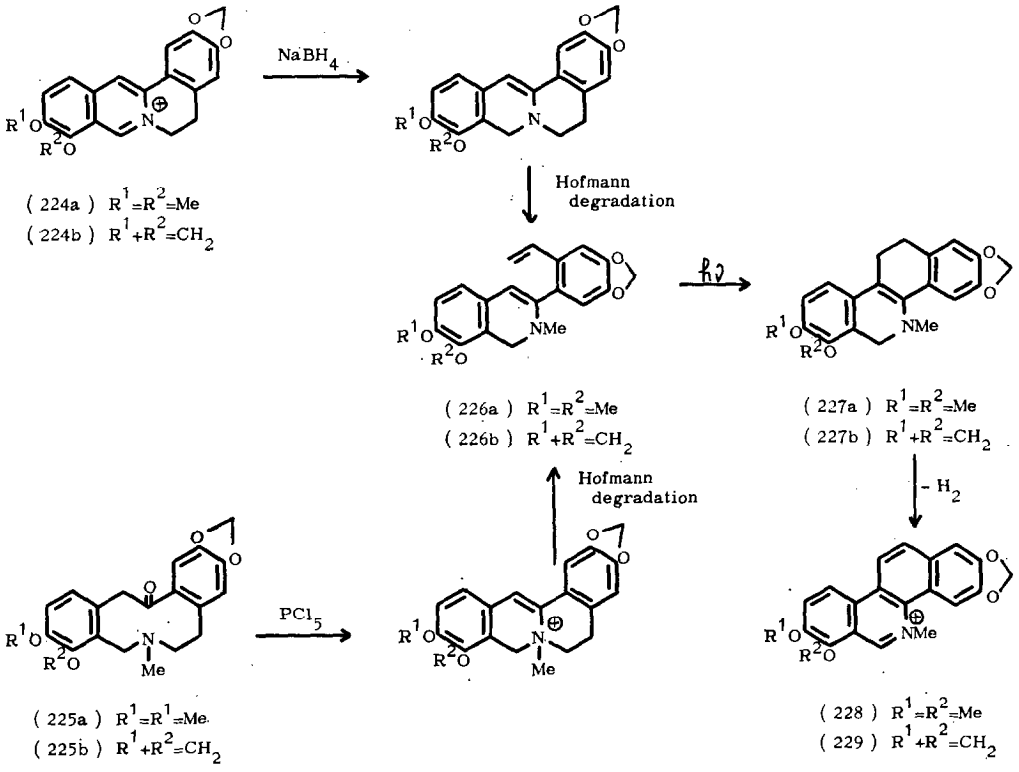
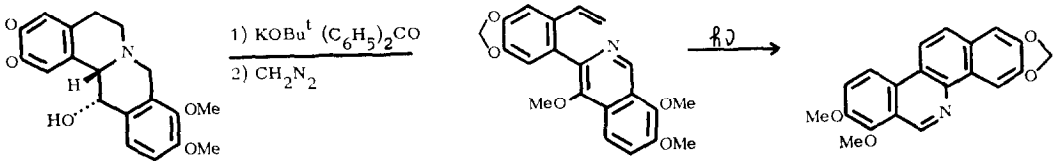


CHART 49

and (**227b**), respectively, which were converted into chelerythrine (**228**) and sanguinarine (**229**) (*105*) (see Chart 49).

Furthermore photolysis of the methyl ether of the isoquinoline (**231**) obtained from ophiocarpine (**230**) by Oppenauer oxidation, also produced *N*-norchelerythrine (**232**)

(*106*). A similar type reaction is applied in the synthesis of chelerythrine analog (**233**) (*107*) (see Chart 50). On the other hand, direct photolysis of 13-ketotetrahydro-



(230) (231) (232)

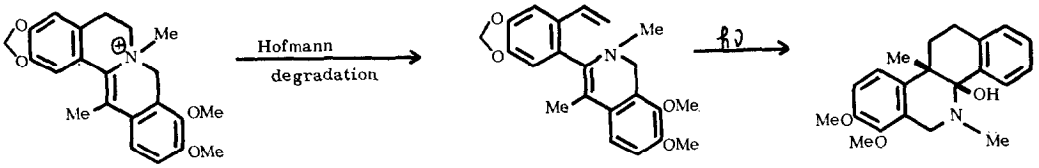
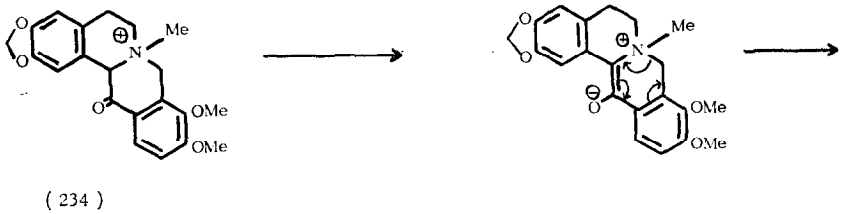
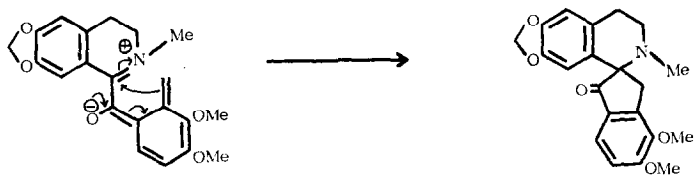


CHART 50 (233)

protoberberine (**234**) was achieved in basic medium (sodium hydroxide in ethanol) under nitrogen at 3500 Å for 24 hr to give the spirobenzylisoquinoline **236** (*107a*). The *o*-quinodimethane (**235**) is suggested as an intermediate, and this transformation is closely similar to the biogenesis of ochotensine-type alkaloids proposed by Shamma (see Chart 51).



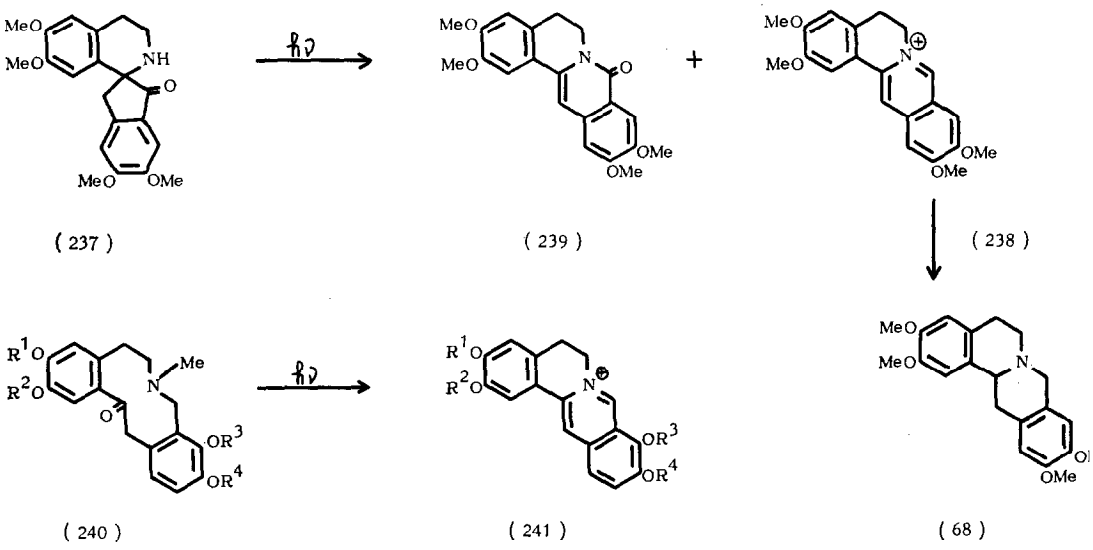
(234)



(235) CHART 51 (236)

Interestingly, retro-biogenetic type synthesis of the protoberberine alkaloids is reported as shown in a photolysis of the spirobenzylisoquinoline and protopine type bases. Irradiation of the spirobenzylisoquinoline (**237**) with high pressure mercury lamp in tetrahydrofuran gave a mixture of the berberinium salt (**238**) (85% yield) and the lactam (**239**) (8% yield), and then reduction of the former product with sodium borohydride furnished xylopinine (**68**) (*108*).

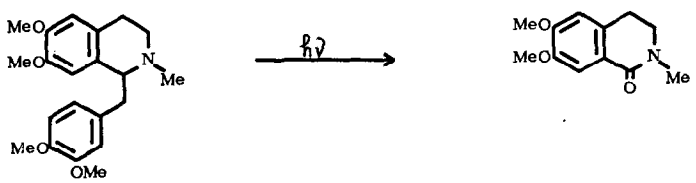
The conversion of the protopine alkaloids into the berberine alkaloids has been accomplished by the photochemical transannular reaction of a carbonyl with a tertiary amine function in a ten-membered ring. Irradiation of cryptopine (**240a**) in 95% ethanol afforded epiberberine (**241a**) in moderate yield. The same reaction with protopine (**240b**) and α-allocryptopine (**240c**) gave coptisine (**241b**) and berberine (**241c**), respectively (*109*) (see Chart 52).



a R^1=R^2=Me, R^3+R^4=CH_2
b R^1+R^2=CH_2, R^3+R^4=CH_2
c R^1+R^2=CH_2, R^3+R^4=Me

CHART 52

The biogenetic type synthesis of *N*-methylcorydaldine (**242**) is carried out by an irradiation of laudanosine (**32**) with uv light in the presence of oxygen (*110*) (see Chart 53).



(32) CHART 53 (242)

HO
MeO
NMe
MeO
OH
(243)
(244)
(245)
(246) R=Me
(247) R=H
(81)
(248) R=H
(249) R=H
(250)
(251)
$K_3Fe(CN)_6$
$NaBH_4$
FSO_3Me
NCO_2Et
OMe

CHART 54

REARRANGEMENT

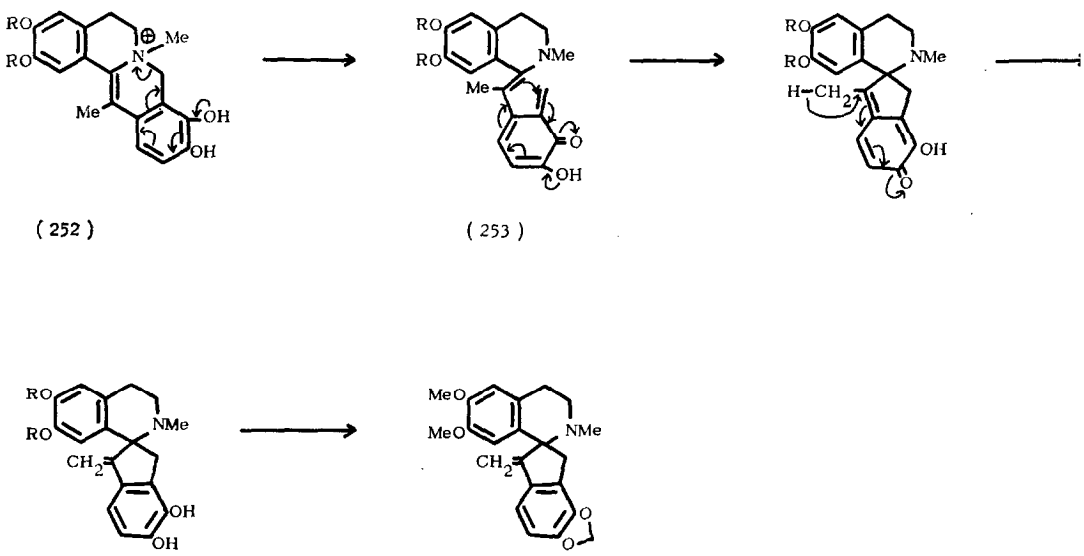
In the previous sections, we discussed some rearrangements found in the biogenesis of the isoquinoline alkaloids and here wish to survey the conversion of one type of alkaloid into the other types by means of such rearrangements.

Proerythrinadienone → Aporphine

Battersby (*58*) elucidated, as described above, a new biogenetic route to glaucine (**81**) and corydine (**246**) by means of tracer experiments. Thus, phenolic oxidation of a protosinomenine (**243**)-type isoquinoline yields dienones (**244**) and (**245**). Dienone-phenol rearrangement of dienone (**244**) yields boldine, glaucine (**81**) and the aporphine (**247**), which in turn leads to corydine (**246**), formed from the dienone (**245**). Dienone (**249**) has been synthesized in the laboratory by phenolic oxidation of *N*-ethoxycarbonyl-*N*-norprotosinomenine (**248**) with potassium ferricyanide in the presence of dilute ammonia and ammonium acetate, and the rearrangement of similar type dienol (**250**) with methyl fluorosulfonate gave aporphine **251** (*111*) (see Chart 54).

Protoberberine → Ochotensine Type Base

Although the biogenesis of the spirobenzylisoquinoline alkaloids such as ochotensimine (**254**) still remains to be established by *in vivo* experiments using labeled precursors, the knowledge that the protoberberine alkaloids coexist with the spirobenzylisoquinoline alkaloids suggests that the latter type of alkaloids **254** may be derived in plants from the former **252** (which has a C_{13}-methyl and a C_{13}–C_{13a} double bond) through the quinonoid intermediate (**253**) by the rearrangement as shown in Chart 55 (*112*).



(252) (253) (254)

CHART 55

(255) (256) (257)

CHART 56

To test this hypothesis *in vitro*, the related phenolic salts were synthesized and indeed found to rearrange under basic conditions to the spiro compounds in good yield. Treatment of the diphenolic base (**255**) with boiling aqueous ethanolic sodium hydroxide produced the quinone methide (**256**), which was tautomerized to the expected diphenolic spirobenzylisoquinoline (**257**) in dimethylsulfoxide (*112*) (see Chart 56). An alternative biogenetic model (**258**), in which the phenolic groups are in different rings, gave (**259**) directly by prolonged heating with sodium hydroxide (*113*). In a similar manner, base-catalyzed rearrangement of the monophenolic bases (**260**) and (**261**) leads to the spirobenzylisoquinolines (**262**) and (**263**) (*113*) (see Charts 57a, b).

On the other hand, *o*-quinonoid intermediate (**253**) in the above biogenetic type synthesis would be electronically equivalent to the *o*-quinodimethane structure (**265**) which seems to be easily available by thermolysis (*114*) of the 1-benzocyclobutenyl-3,4-dihydroisoquinolines (**264**). On the basis of this suggestion, the ochotensine-type compound has been synthesized as follows (*115*) (see Chart 58). Bischler–Napieralski reaction of the tertiary amide (**266**) with 2 mole equivalent of phosphoryl chloride in boiling benzene afforded directly the ochotensine-type compound (**269**) *via* the 3,4-dihydroisoquinolinium salt (**267**) and then *o*-quinodimethane (**268**) (see Chart 59).

Interestingly, the 1-benzocyclobutenyl-3,4-dihydroisoquinoline (**277**) hydrochlorides, derived from the primary amides, did not yield the ochotensine analog (**271**), but afforded the protoberberine alkaloids, xylopinine (**272**) and discretine (**273**) in good yields after reduction of thermolytic products. This reaction would be one kind of retrobiogenesis of ochotensine-type alkaloids (*116, 117*). However, the free bases of (**270**) on standing for 24 hr at room temperature in chloroform afforded the ochotensine-type base (**271**) (*118*) (see Chart 60).

Phthalideisoquinolines → Rhoeadine Type Bases

Because of the resemblance of the rhoeadine type bases (**227**) to the phthalideisoquinoline alkaloids (**274**), the following two mechanisms are proposed for the biogenesis of the rhoeadine alkaloids (*119, 120*). One proposal features the narceine type compound (**275**) as a key intermediate (*119*), and the other one (*120*) the aziridine intermediate (**276**). The biomimetic-type synthesis of rhoeadine (**287**) has been achieved according to the former mechanism by Brossi and his associates (*121*), but trials based on the latter failed (*120*) (see Chart 61).

Reaction of the phthalideisoquinoline, (–)-bicuculline (**278**) with phenyl chloroformate in the presence of diisopropylamine, followed by dehydrohalogenation with a mixture of dimethylsulfoxide and diisopropylamine, yielded the urethan (**279**), which was treated with 2N sodium hydroxide to afford the dihydrobenzazepine (**281**) through the narceine analog (**280**). Acidification of an aqueous solution of (**281**) with acetic acid effected cyclization to the spirolactone (**282**), which was not isolated but dissolved in ethanol and readily oxidized by air to provide the keto-lactone (**283**). Reduction of (**283**) with lithium borohydride in tetrahydrofuran followed by acidification with acetic acid afforded, *via* the transient *cis*-hydroxy acid (**284**), the *cis*-lactone, (±)-oxyrhoeagenine (± –**285**).

Resolution of (± –**285**) with (+)-10-camphorsulfonic acid in methanol and neutralization of the precipitated diastereomeric salt, provided (–)-oxyrhoeagenine. Treatment of

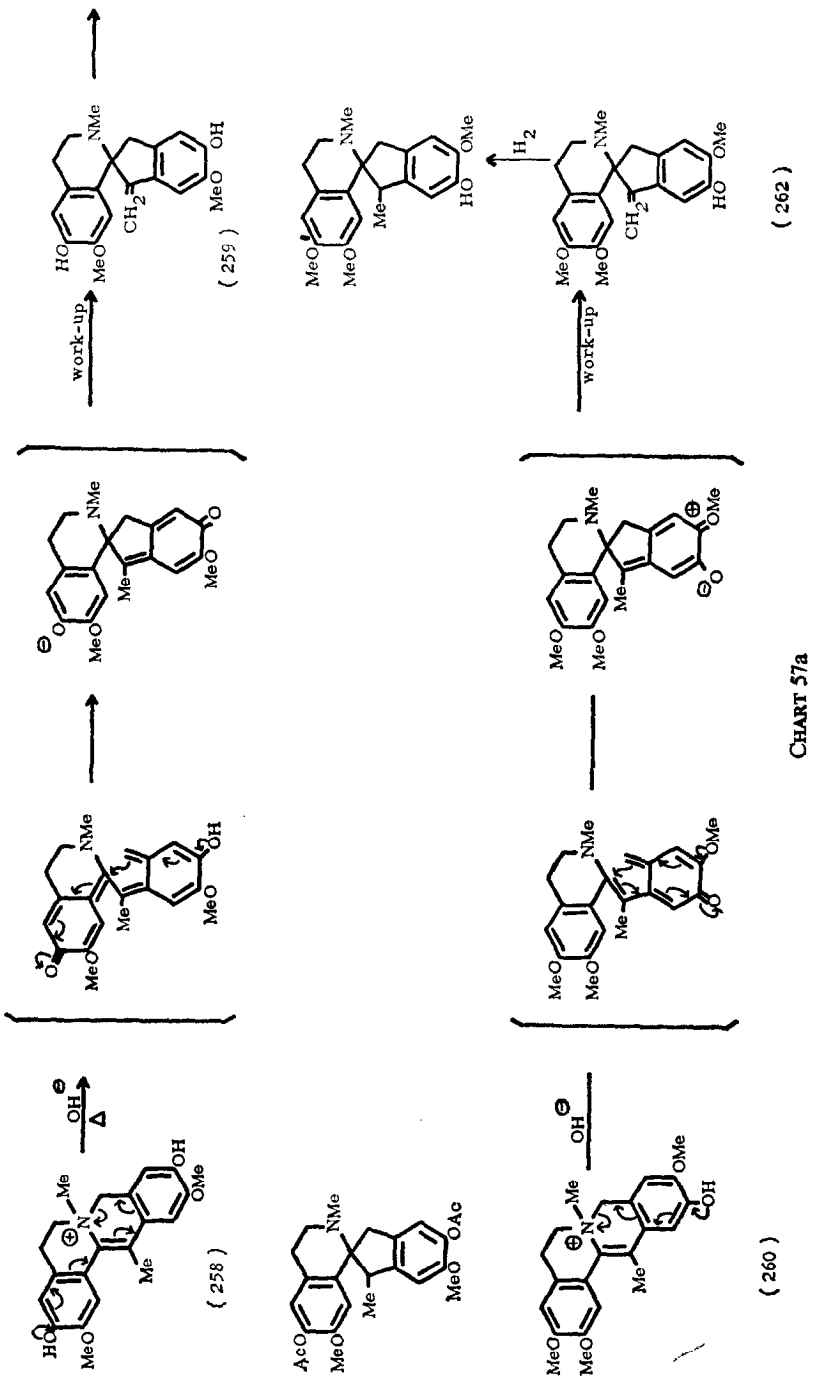


CHART 57a

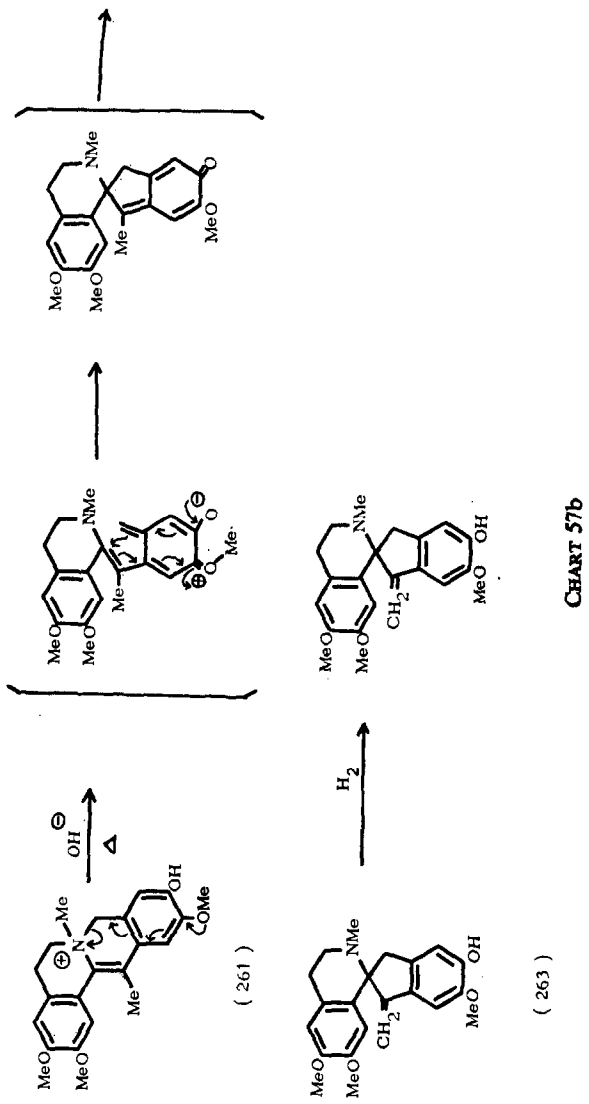


CHART 57b

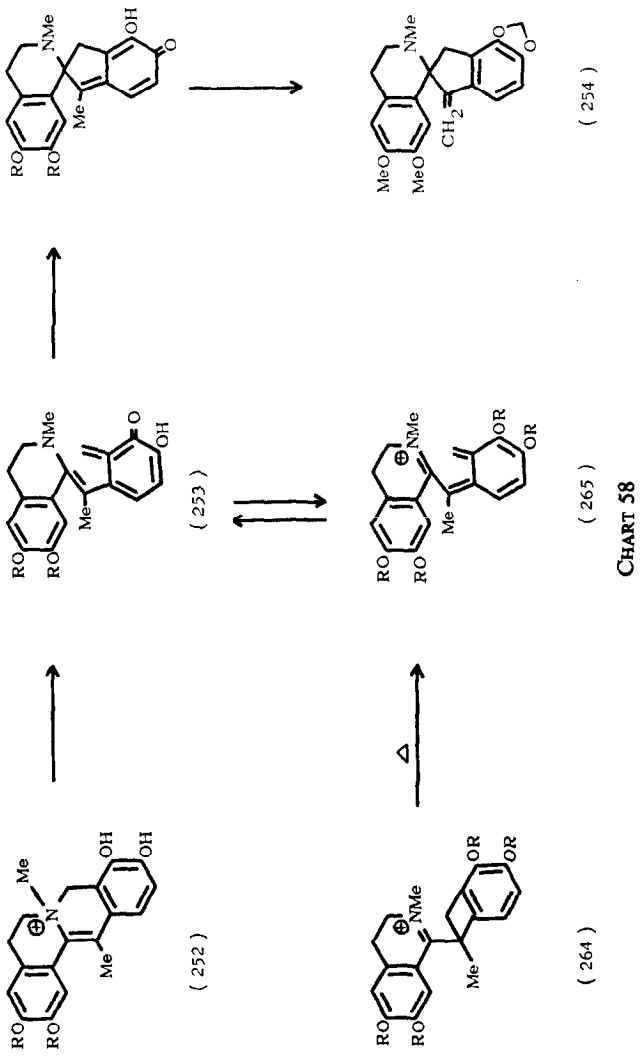


CHART 58

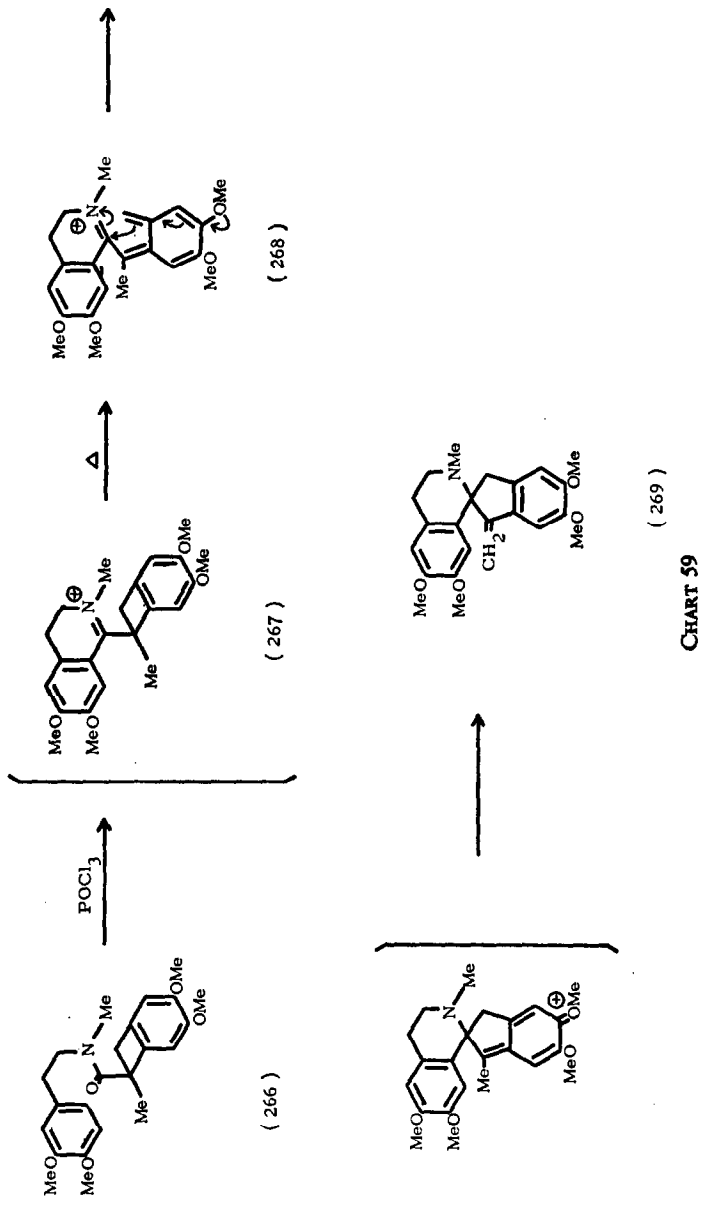


CHART 59

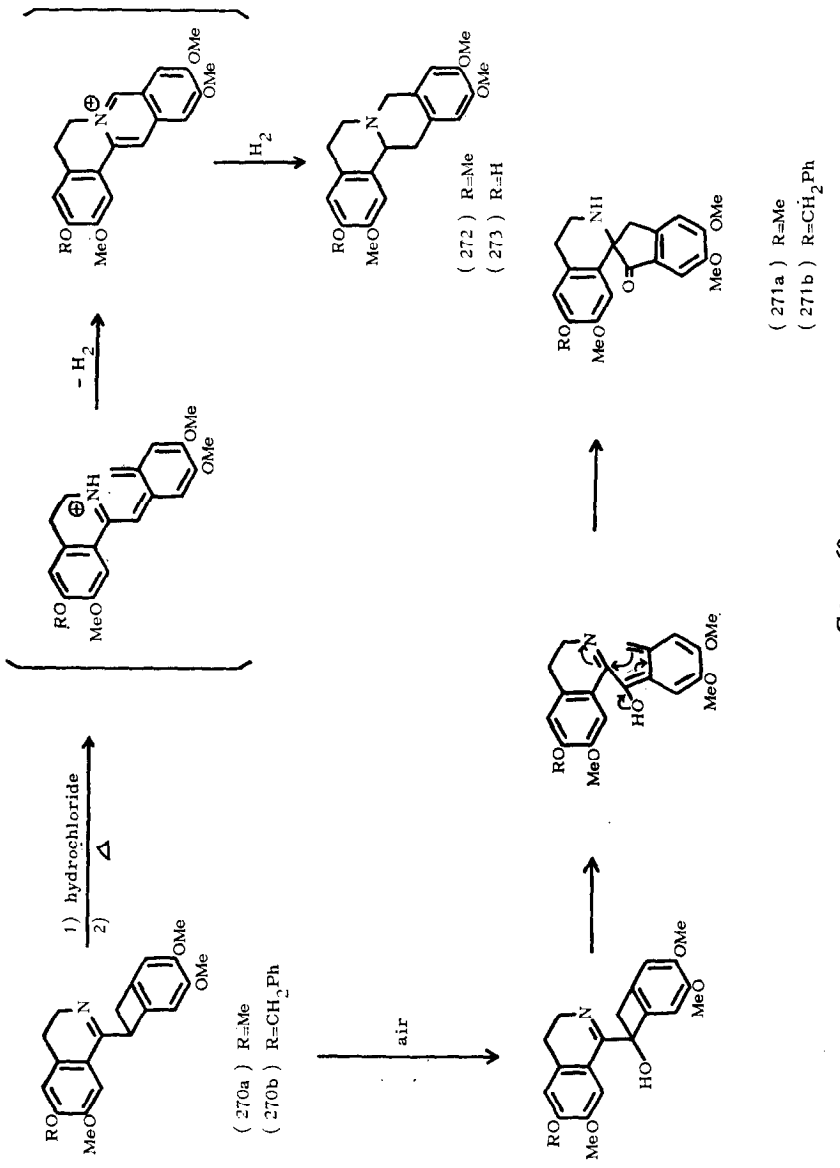


CHART 60

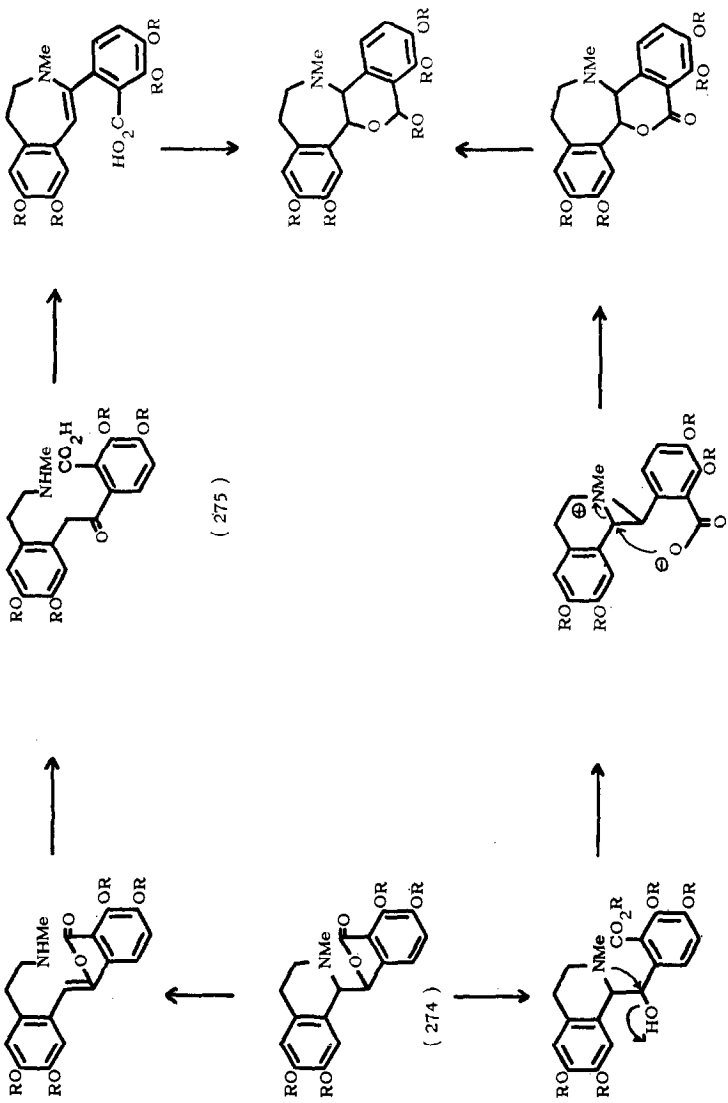


CHART 61

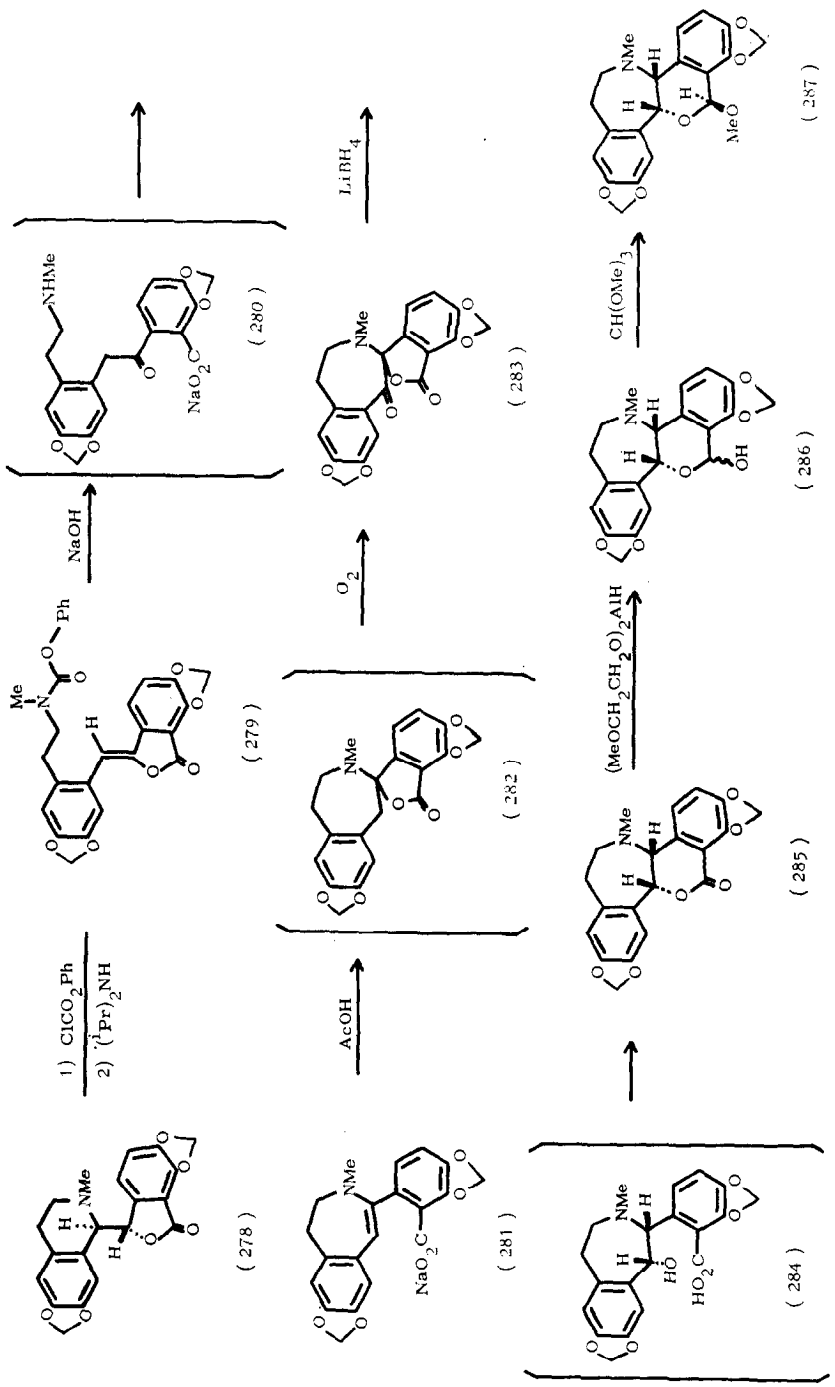


CHART 62

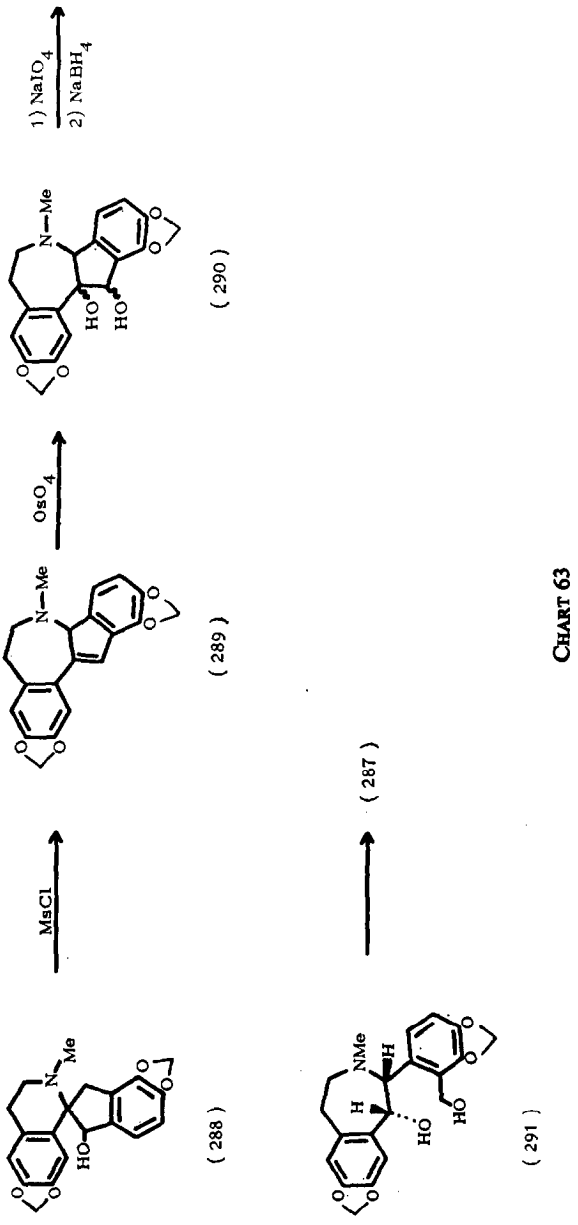
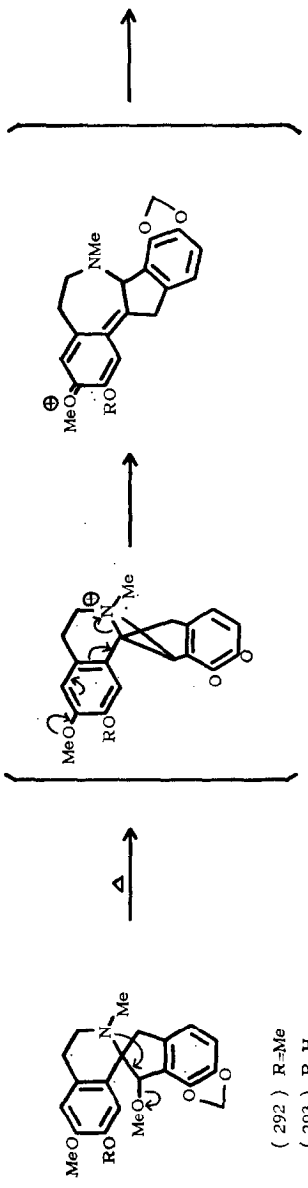


CHART 63



(292) R=Me
(293) R=H

(294) R=Me
(295) R=H

CHART 64

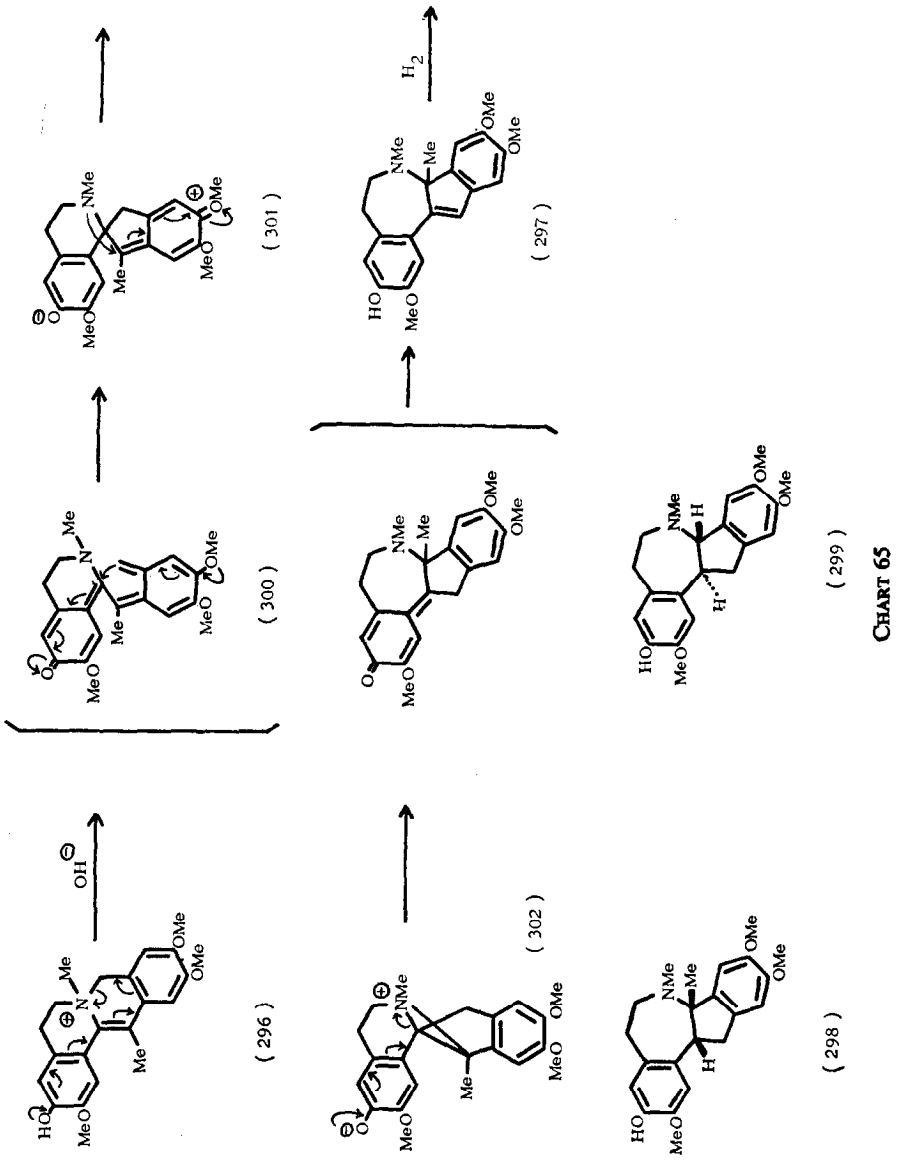


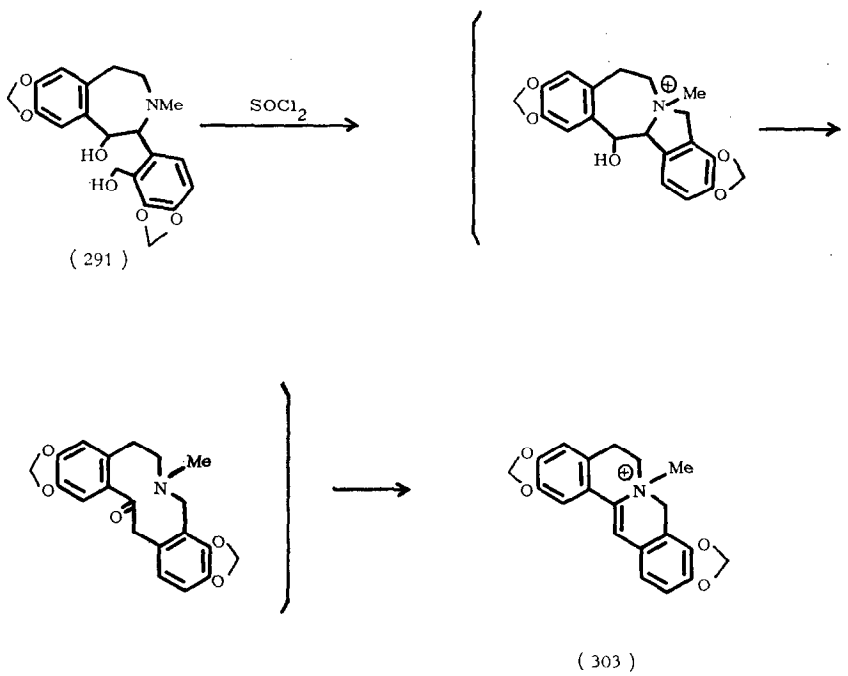
CHART 65

the mother liquors (as the free base) with (–)-10-1camphorsulfonic acid, followed by neutralization of the resulting diastereomeric salt, yielded (+)-oxyrhoeagenine.

Partial reduction of a pyridine solution of (**285**) at –70° with sodium bis-(2-methoxyethoxy)-aluminum hydride, followed by storage overnight at –20° and column purification, yielded a mixture of anomeric lactols (**286**) which were etherified in methanol with trimethyl orthoformate catalyzed by mineral acid, to afford (+)-rhoeadine (**289**) (see Chart 62).

Moreover, rhoeadine type bases are obtained from the ochotensine-type compound (**288**) (*122*) and the protoberberine compound (**289**) (*113*) by the rearrangement reactions, which may be a part of the rhoeadine biogenesis. Wagner–Meerwein rearrangement of (**288**) with mesyl chloride gave the benzazepine (**289**), which on oxidation with osmium tetraoxide afforded the diol (**290**). This was converted into rhoeagenine diol (**291**) with sodium periodate, followed by sodium borohydride, which had been correlated with rhoeadine (**287**) (*122*) (see Chart 63).

In another instance, pyrolysis of the new spirobenzylisoquinoline alkaloids fumaritine (**292**) and fumaritridine (**293**) was reported to furnish dibenzocyclopent[b]azepines (**294**) and (**295**) respectively (see Chart 64). Also, monophenol (**296**), when treated with sodium hydroxide for 4 days, did not yield a spirobenzylisoquinoline, but furnished instead the olefinic dibenzocyclopent[b]azepine (**297**), which was reduced catalytically to a mixture of diastereoisomeric amines (**298**) and (**299**). In this reaction sequence, cyclization of the quinone methide (**300**) leads to the spirobenzylisoquinoline intermediate (**301**) which possesses a net positive charge spread between rings C and D. This charge induces formation of the aziridinium ion (**302**), which can readily be trans-



(291)

(303)

CHART 66

formed into product (**297**) (*113*) (see Chart 65). Interestingly, dihydroprotoberberine (**303**) was generated from rhoeagenine diol (**291**) by treatment with boiling thionyl chloride (*124*) (see Chart 66).

The present survey is concerned with simple synthesis of the isoquinoline and related alkaloids. The improvement of yield and the achievement of stereospecificity or stereoselectivity by modification of the reaction conditions results in synthetic methods simpler and more beautiful than the classic ways, which involve many steps and much time for execution.

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