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BIOGENETIC PATHWAYS FOR THE APORPHINOID ALKALOIDS

MAURICE SHAMMA and HÉLÈNE GUINAUDEAU[1]
Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, U.S.A.

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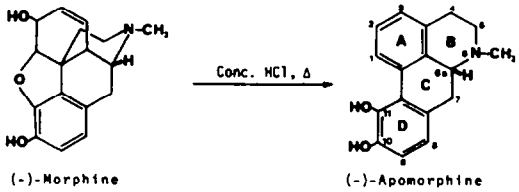
The aporphinoids are a broad class of isoquinoline alkaloids which includes the proaporphines and aporphines, and compounds derived naturally from them. The present review will cover the biogenesis of the proaporphines and aporphines, and will then consider some of the changes they can undergo in plants.

1. INTRODUCTION

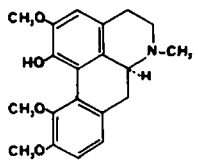
As early as 1869, it was noted that acid catalyzed rearrangement of (−)-morphine provided the new base (−)-apomorphine. In the early decades of the 1900s, the structure of apomorphine was determined by degradation, and then confirmed through synthesis.[2]



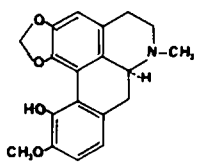
(-)-Morphine (-)-Apomorphine

Since that time, nearly 200 naturally occurring aporphine alkaloids have been recognized. All of these incorporate the tetracyclic nucleus present in apomorphine. Additionally, they are without

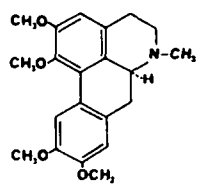
exception oxygenated at C-1 and C-2, and very often at other positions as well. The oxygenated substituents are usually OH, OMe or methylenedioxy groups. A few naturally occurring aporphines are shown below.[3]



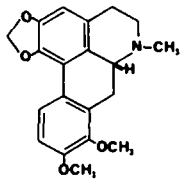
(+)-Corydine
(S configuration)



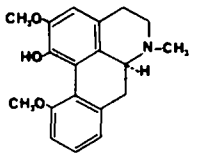
(+)-Bulbocapnine



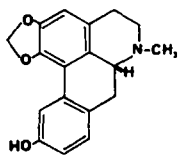
(+)-Glaucine



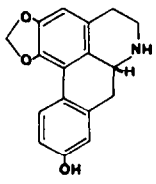
(-)-Crebanine
(R configuration)



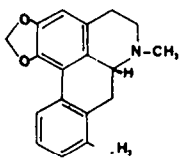
(+)-Isothebaine



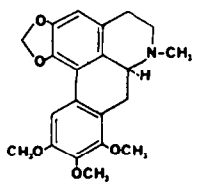
(-)-Mecambroline



(-)-Anolobine



(-)-Stephanine



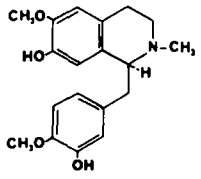
(+)-Ocopodine

Aporphine alkaloids are usually optically active, and possess either the *R* or the *S* absolute configuration. Worthy of note, however, is the trend, not without exception as in the case of (−)-crebanine, that naturally occurring aporphines possessing two or more oxygenated substituents in ring D belong to the *S*-configuration, while aporphines with one or no substituent on that ring may belong to either stereochemical series.[4]

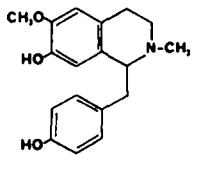
The biochemical problem thus presented by the aporphines is a challenging one since any rational biogenetic scheme or schemes would have to account for the variety of different oxygenation patterns encountered, as well as for the stereochemical preference that prevails based upon the substitution pattern of ring D.

2. MAIN BUILDING BLOCKS AND THE ROLE OF PHENOLIC OXIDATIVE COUPLING

The common building blocks for the aporphine alkaloids are the tetrahydrobenzylisoquinolines reticuline and N-methylcoclaurine. The tetraoxygenated reticuline usually acts as a precursor to the aporphines when it is in the *S* absolute configuration which is dextrorotatory. On the other hand, the trioxygenated N-methylcoclaurine may function as a precursor in the dextro or the levorotatory form.[5]

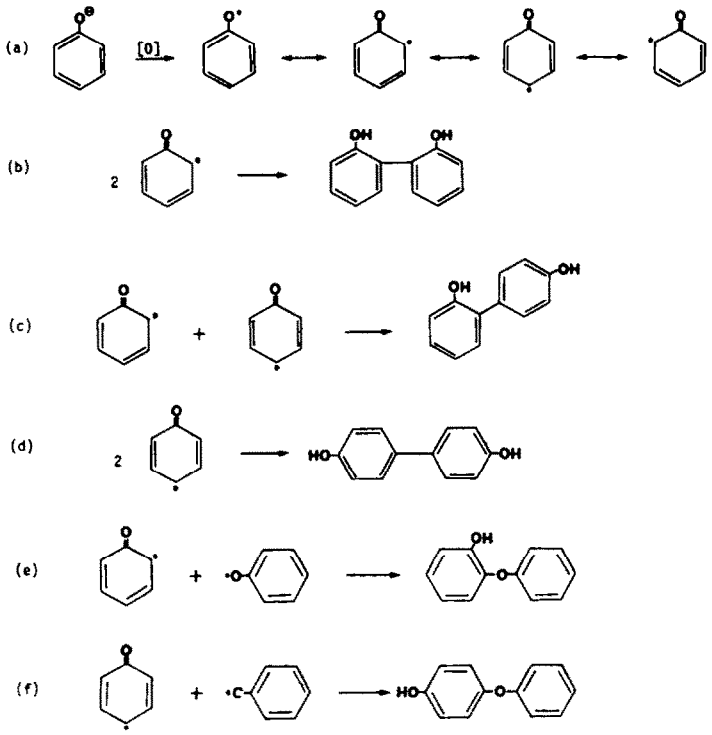


(+)-Reticuline



N-Methylcoclaurine

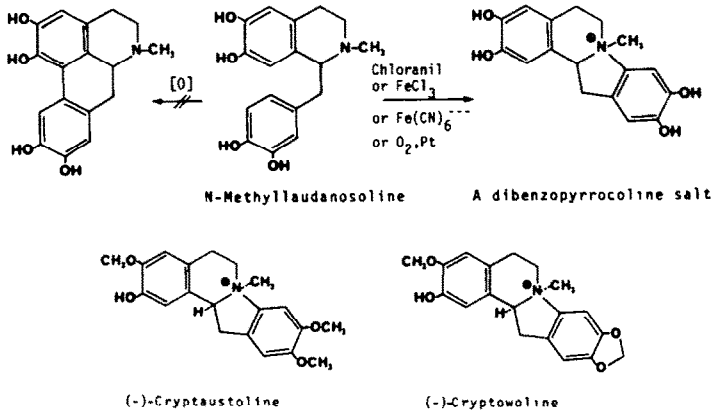
A key reaction in the *in vivo* formation of aporphines from tetrahydrobenzylisoquinolines is phenolic oxidative coupling. In its simplest form, this transformation may be looked upon as the oxidation of a phenoxide anion to a phenoxyl radical, which can then condense with another phenoxyl radical at sites *ortho* or *para* to the original phenolic group as shown. No condensation at a *meta* position can occur.



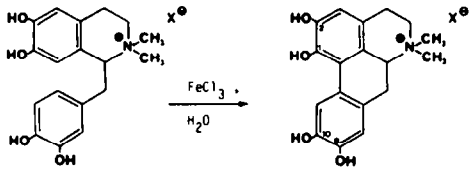
It has always been assumed that coupling occurs only between two phenolic entities. In other words, a key requirement for phenolic oxidative coupling is that two phenoxyl radicals be available for bonding.

3. APORPHINES BY DIRECT PHENOLIC OXIDATIVE COUPLING

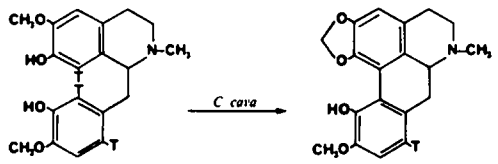
The biogenesis of the aporphines was first considered by Robinson[6] and by Schöpf[7] who independently reported in 1932 on their unsuccessful attempts to cyclize the tetrahydrobenzylisoquinoline N-methyllaudanosoline through intramolecular phenolic oxidative coupling into 1,2,9,10-tetrahydroxyaporphine. The product proved to be instead the dibenzopyrrocoline salt shown. Significantly, in 1952, the dibenzopyrrocolines (−)-cryptaustoline and (−)-cryptowoline were reported to be present in an Australian shrub belonging to the Lauraceae family, and these two alkaloids must indeed originate from oxidation of a tetrahydrobenzylisoquinoline precursor.[8]



It remained for Franck to report in 1962 the first *in vitro* synthesis of a quaternary aporphine by direct phenolic oxidative coupling of a tetrahydrobenzylisoquinoline N-metho salt.[9]



The thesis of direct phenolic oxidative coupling of a tetrahydrobenzylisoquinoline to an aporphine is now also supported by several experiments with labeled precursors. To cite just one example, feeding labeled (±)-reticuline to *Corydalis cava* (Fumariaceae) led to labeled (+)-bulbocapnine.[10]

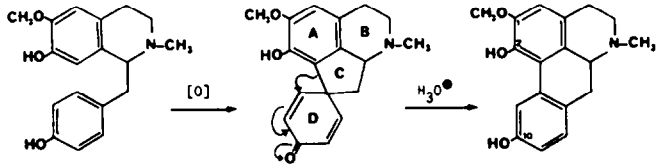


Labeled (±)-reticuline Labeled bulbocapnine

Direct phenolic coupling can thus explain the genesis of several 1,2,10,11- as well as 1,2,9,10-tetrasubstituted aporphines. It does not rationalize for us, however, the existence of other aporphines, such as those bearing a single oxygenated function in the D ring, or those devoid of oxygen on that ring.

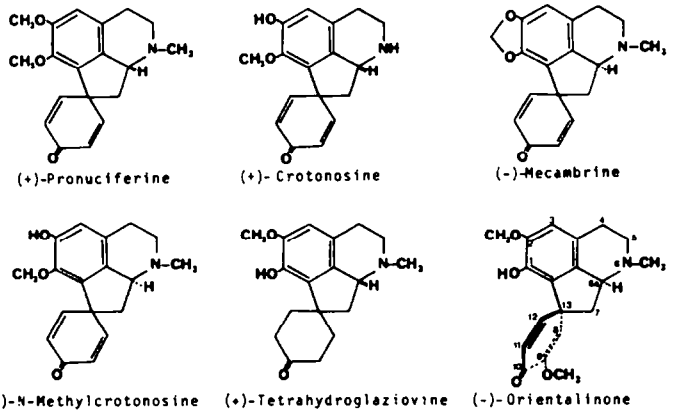
4. PROAPORPHINES AND THEIR ACID CATALYZED REARRANGEMENT

It is to Barton's credit that in 1957, in a nodal review on the role of phenolic oxidative coupling in plant metabolism, he predicted the existence of proaporphines in nature, even though none had been isolated at that time.[11] Proaporphines were postulated as tetracyclic molecules incorporating a cross-conjugated dienone system, and formed from intramolecular oxidative coupling of a tetrahydrobenzylisoquinoline such as N-methylcoclaurine. Their acid catalyzed dienone–phenol rearrangement would then lead to aporphines oxygenated at C-10.



N-Methylcoclaurine A proaporphine A 1,2,10-substituted aporphine

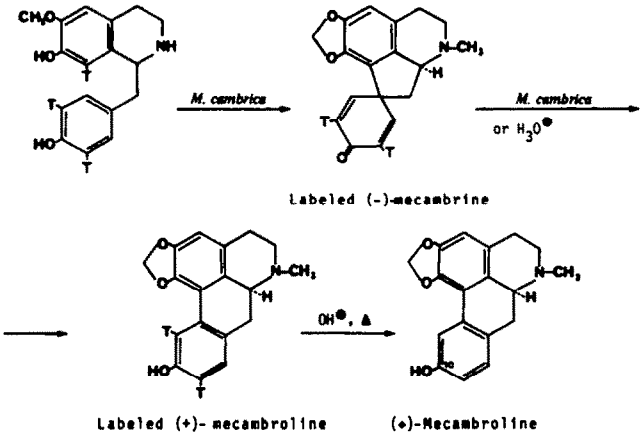
Vindication came in 1963 when the structures of the first two proaporphines, pronuciferine[12] and crotonosine,[13] were described. Since that time, more than twenty other naturally occurring proaporphines have been reported, and some of these are presented below. It will be noticed that ring D is sometimes reduced as in (+)-tetrahydroglaziovine.



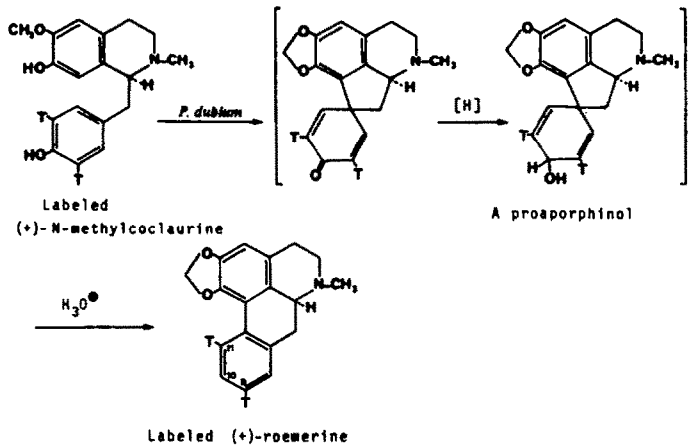
(+)-Pronuciferine (+)-Crotonosine (-)-Mecambrine

(-)-N-Methylcrotonosine (+)-Tetrahydroglaziovine (-)-Orientalinone

That proaporphines may act as biogenetic precursors to some of the aporphines has been confirmed by studies using labeled compounds. Thus, feeding tritiated (−)-mecambrine to *Meconopsis cambrica* (Papaveraceae) provided the tritiated aporphine (+)-mecambroline which bears a single oxygenated function at C-10 in the bottom ring.[14]



A variation on the theme of the dienone–phenol rearrangement is the dienol–benzene rearrangement, which proceeds by way of a proaporphinol, and which may occur both *in vivo* and *in vitro*. It has been established, for example, that tritium labeled (+)-N-methylcoclaurine when fed to *Papaver dubium* (Papaveraceae) is incorporated stereospecifically into the aporphine (+)-roemerine which bears no oxygenated substituent on ring D.[14] Parallel *in vitro* acid catalyzed rearrangements of proaporphinols into aporphines are known.[12]

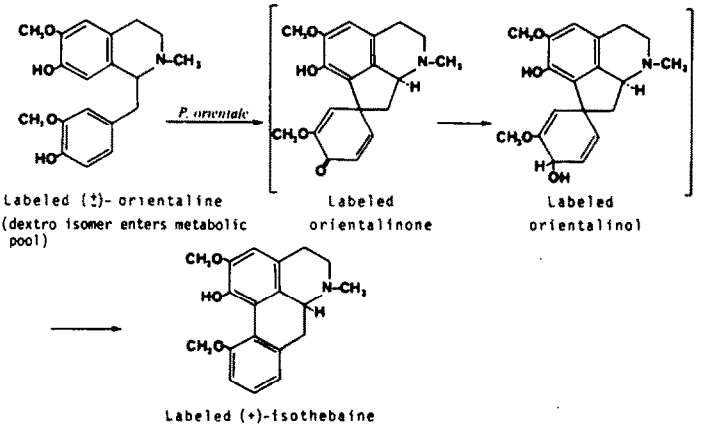


The dienone–phenol and dienol–benzene rearrangements can, therefore, explain for us the biogenesis of aporphines monoxygenated at C-10 in ring D, or non-oxygenated in that ring.

In retrospect, it is now easy to rationalize why aporphines dioxygenated in ring D usually belong to the S-configuration, while aporphines monooxygenated or non-oxygenated in that ring can belong to either absolute configuration. Reticuline, the precursor for many aporphines oxygenated at C-9 and C-10, or at C-10 and C-11, usually exists as mentioned above as the dextrorotatory isomer with the *S* absolute configuration. It follows that its biogenetic derivatives also partake of the *S*-configuration. On the other hand, the trioxygenated N-methylcoclaurine does not usually have a natural stereochemical preference. Since N-methylcoclaurine is the precursor for several aporphines monoxygenated or non-oxygenated on ring D, it follows that these aporphines may exist in either absolute configuration.

5. (+)-ORIENTALINE AS A BUILDING BLOCK

An interesting facet of the complexity of aporphine biogenesis concerns the proaporphine (−)-orientalinone. When the labeled racemic tetrahydrobenzylisoquinoline orientaline, a close analog of reticuline, was fed to *Papaver orientale* (Papaveraceae), the labeled C-11 oxygenated aporphine (+)-isothebaine was obtained. Obviously, *S*-(+)-orientaline had entered the metabolic pool, to furnish *S*-(+)-isothebaine through the intermediacy of *S*-(−)-orientalinone and *S*-(−)-orientalinol.[14,15] It is a fact, therefore, that some aporphines monooxygenated in ring D may originate from tetra- rather than from trioxygenated tetrahydrobenzylisoquinoline precursors. This is particularly true for S aporphines monooxygenated in ring D at either C-9 or C-11.

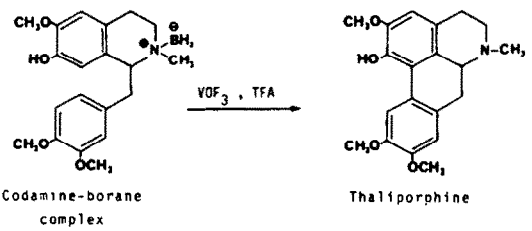


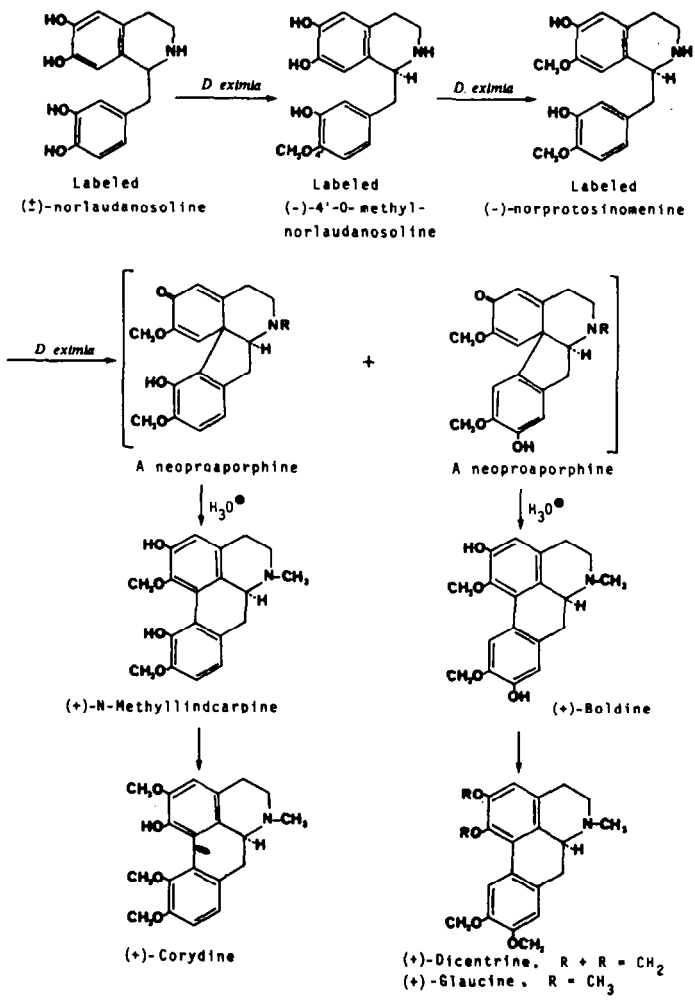
6. (−)-NORPROTOSINOMENINE AS A BUILDING BLOCK

It is sometimes difficult to predict what the principal building block for an alkaloid will be in a specific plant. This was dramatically and conclusively demonstrated by studies on *Dicentra eximia* (Fumariaceae) conducted by Battersby *et al.*[16] (±)-Reticuline and (±)-orientaline were found to be ineffective as precursors for the tetraoxygenated aporphines corydine, dicentrine and glaucine. But precursors which were readily incorporated in all three alkaloids proved to be 4′-O-methylnorlaudanosoline which originates from norlaudanosoline, as well as norprotosinomenine. 4′-O-Methylnorlaudanosoline is converted into norprotosinomenine which is incorporated into the three alkaloids. The logical intermediates postulated were the neoproaporphines shown at the top of p. 4801.[16]

Although the above pathway is the most rational to explain the metabolism prevailing in *D. eximia*, it should nevertheless be pointed out that to date no neoproaporphines have been isolated as natural products.

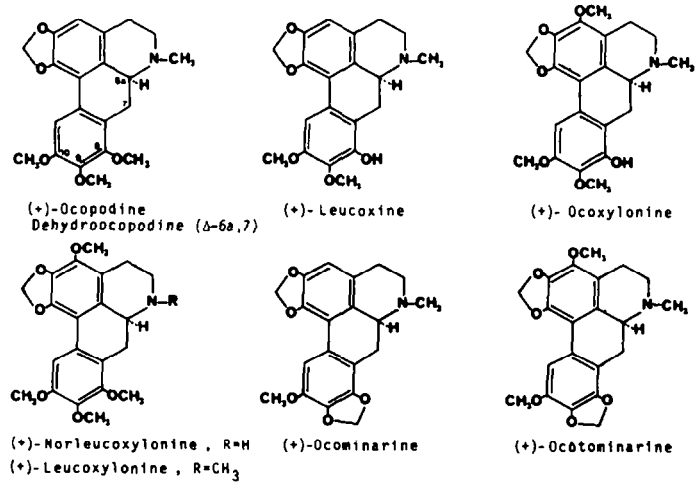
At this juncture, one would be justified in asking rhetorically: May direct coupling occur intramolecularly between a phenol on the one hand and a methoxylated ring on the other, rather than between two phenols? Such a process would obviate the necessity of a neoproaporphine intermediate. A chemical analogy exists of coupling between a phenol on the one hand, and a methyl aryl ether on the other. This involves the oxidation of the codamineborane complex using vanadium oxytrifluoride. The product, obtained in 80% yield, was the aporphine thaliporphine.[17] There is presently, however, no firm evidence that such a process obtains in nature.





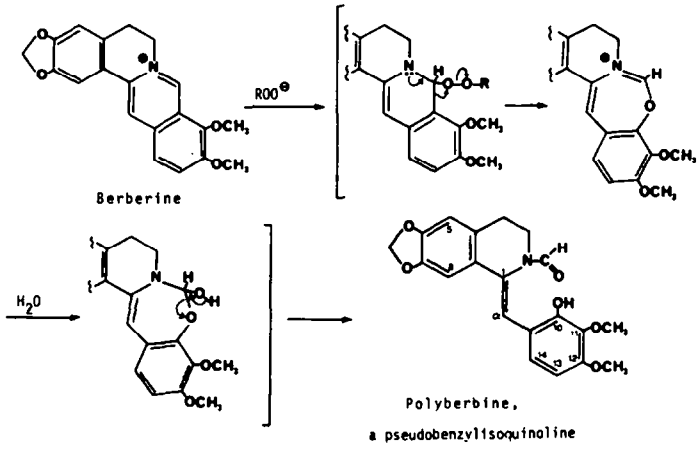
7. THE C-8,9,10-OXYGENATED APORPHINES

A category of alkaloids that concerns us at this stage is the C-8,9,10-substituted aporphines. Eight of these are known, namely ocopodine and its dehydro analog called dehydroocopodine, leucoxine, ocoxylonine, norleucoxylonine, leucoxylonine, ocominarine and ocotominarine. Most were found in *Ocotea* species (Lauraceae).[3,18] A significant feature of these bases is that if a phenolic function is present in ring D, it is always located at C-8. Another structural characteristic is that they possess the *S*-configuration at C-6a.

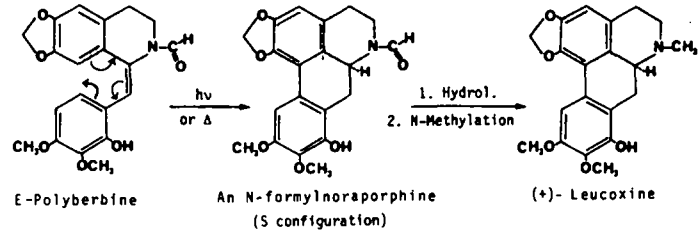


Three biogenetic schemes suggest themselves for the C-8,9,10-substituted aporphines. The first but rather pedestrian hypothesis is that a 1,2,9,10-tetraoxygenated aporphine, belonging as expected to the *S* configuration, suffers enzymatic oxidation *ortho* to the oxygenated substituent at C-9, thus yielding the desired product.

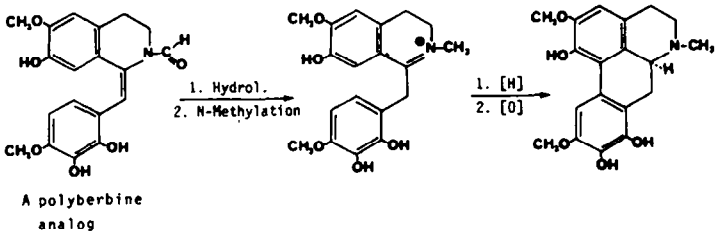
The second scheme is more intriguing, and almost equally likely. It would proceed through the intermediacy of the novel eneamide polyberbine, a member of the new class of pseudobenzylisoquinoline alkaloids, all of which by definition bear three oxygenated functions on the lower ring, located at C-10, C-11 and C-12.[19] Polyberbine must originate from the protoberberinium alkaloid berberine through oxidative rearrangement as shown below; and indeed such a transformation has been duplicated in the laboratory.[20]



Sunlight irradiation of polyberbine could easily induce a *Z* to *E* geometrical isomerization. Once formed, the *E*-isomer could undergo an electrocyclic process as indicated to provide an N-formylnoraporphine which could be transformed into an aporphine;[20] and indeed cases are known in the literature of such *in vitro* formation of aporphines from benzylisoquinoline eneamides.[21] A key requirement in the present context, however, is that the newly formed asymmetric center at C-6a of the N-formylnoraporphine possess the *S* absolute configuration due to enzymatic assistance. Such a scheme, incidentally, would explain why the C-8 oxygenated substituent in the aporphines in question appears sometimes in the form of a phenol. The sequence, if truly applicable in a natural process, would mean that some aporphines could originate from protoberberinium salts—a rather exciting possibility.

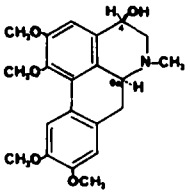


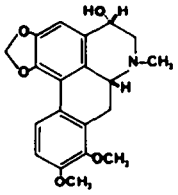
The third plausible avenue for the formation of C-8,9,10-substituted aporphines is by intramolecular phenolic oxidative coupling of tetrahydrobenzylisoquinolines of the *S*-configuration, oxygenated at C-10,11,12; i.e. which possess the same general oxygenation pattern as polyberbine in the lower ring. Such precursors would probably originate from the hydrolysis of the N-formyl group of polyberbine or a polyberbine analog, followed by N-methylation and stereospecific reduction to the tetrahydrobenzylisoquinoline stage. A hypothetical example is presented below.

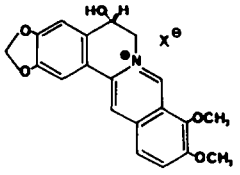


8. APORPHINES OXYGENATED AT C-4 OR AT C-7

Several aporphines are known which possess an alcohol function at C-4. The alcohol group may be syn or anti to the hydrogen at C-6a, and two of these aporphines, cataline and 4-hydroxycrebanine, are represented below.[3] No experiments have been carried out concerning their biogenesis. It is known, however, that in the case of the protoberberine alkaloid berberastine, which bears an alcohol at the corresponding site, the oxygen is introduced at an early stage, prior to protoberberine formation.[22] The same may, therefore, apply to the aporphine analogs, with the OH group introduced prior to generation of the aporphine skeleton.


(+)-Cataline


(-)-4-Hydroxycrebanine


(+)-Berberastine

Turning now to the C-7 oxygenated aporphines, the following generalizations have been drawn:[23]

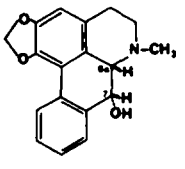
(a) Their occurrence is limited to the four botanical families Annonaceae, Menispermaceae, Magnoliaceae and Lauraceae.

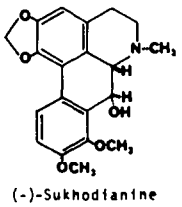
(b) They inevitably belong to the C-6a *R* configuration.

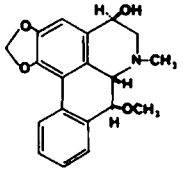
(c) The C-7 oxygenated substituent may by *syn* or *anti* to H-6a. It is found *syn* to H-6a only among some of the Annonaceae.

(d) The C-7 oxygenated substituent may be either an alcohol or a OMe group. It is solely among the Annonaceae that C-7 methoxylated aporphines are known to occur.

Nothing is known with certainty about the stage at which the C-7 oxygen is introduced. It may be, however, that this substitution pattern is due to oxidation of the enamine system of a dehydroaporphine precursor. Three representative C-7 oxygenated aporphines are ushinsunine, sukhodianine and pachystaudine, the last named being oxygenated at both C-4 and C-7.[3]


(-)-Ushinsunine


(-)-Sukhodianine

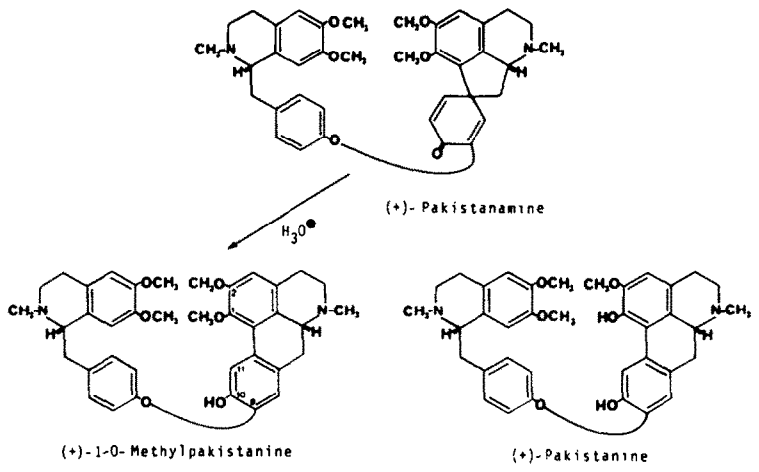

(+)-Pachystaudine

9. THE PROAPORPHINE- AND APORPHINE-BENZYLISOQUINOLINE DIMERS

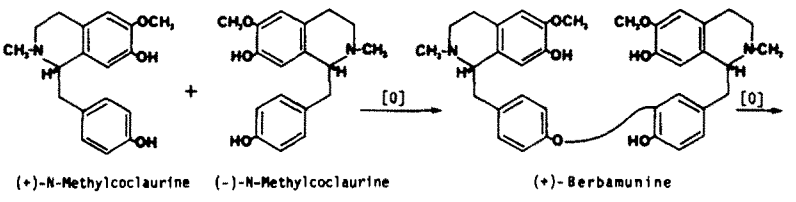
All proaporphine–benzylisoquinoline alkaloids known belong to the N-methylcoclaurine series. In contrast, aporphine–benzylisoquinolines are best subdivided into two broad classes, those made up of two N-methylcoclaurines, and those incorporating two reticulines or else one reticuline and one N-methylcoclaurine unit.[24] The subject of the biogenesis of the aporphine–benzylisoquinolines is a complex one since it involves not only the mode of formation of the aporphine moiety, but also the establishment of the exact sequence leading to the dimerization. Fortunately, sufficient information is available that it is possible to discuss this matter at some length. We shall consider the dimers of two N-methylcoclaurines first.

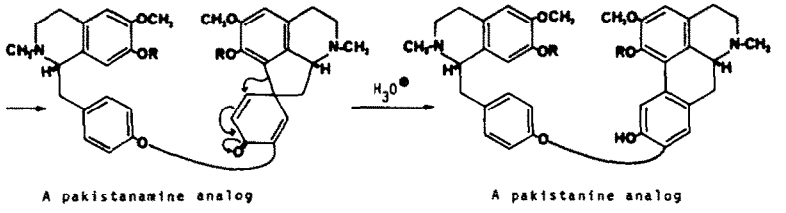
(i) *Proaporphine- and aporphine–benzylisoquinolines of the* N-*methylcoclaurine series*

In 1972, it was reported that an investigation of *Berberis baluchistanica* (Berberidaceae), a barberry collected in Pakistan, had yielded the novel alkaloids (+)-pakistanamine and (+)-pakistanine. Pakistanamine is a proaporphine–benzylisoquinoline dimer and pakistanine an aporphine–benzylisoquinoline. *In vitro* acid catalyzed rearrangement of pakistanamine furnished 1-O-methylpakistanine, later found as a natural product.[25]

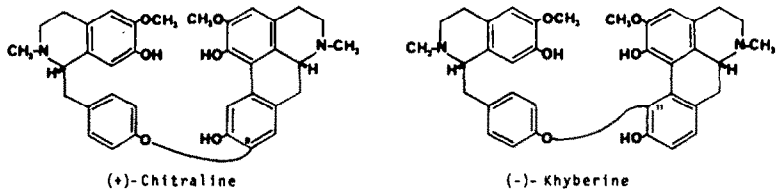


Since *Berberis* species as a rule also produce a variety of bisbenzylisoquinolines from the dimerization of N-methylcoclaurine, the following biogenetic sequence, involving the intermediacy of the known bisbenzylisoquinoline alkaloid (+)-berbamunine, immediately suggested itself.[25]





In subsequent work, a variety of pakistanine analogs were obtained, the two most important of which proved to be the triphenolic (+)-chitraline and (−)-khyberine. (−)-Khyberine was of particular interest because it is substituted at C-11 rather than at the more common C-9 position. It was isolated, however, in very small amounts.[26,27]



In the wake of the above results, an investigation of the barberries from South America was undertaken, given that that continent supports more than fifty different *Berberis* species. Specifically, a study of Chilean members of the Berberidaceae produced five phenolic analogs of the proaporphine–benzylisoquinoline pakistanamine, with the phenolic groups located either on rings A or A'.[28] Whereas pakistanamine tends to oxidize and decompose with time, and is best kept as the picrate salt, the phenolic analogs of pakistanamine proved to be quite stable as the free bases, probably due to inter or intramolecular H-bonding.

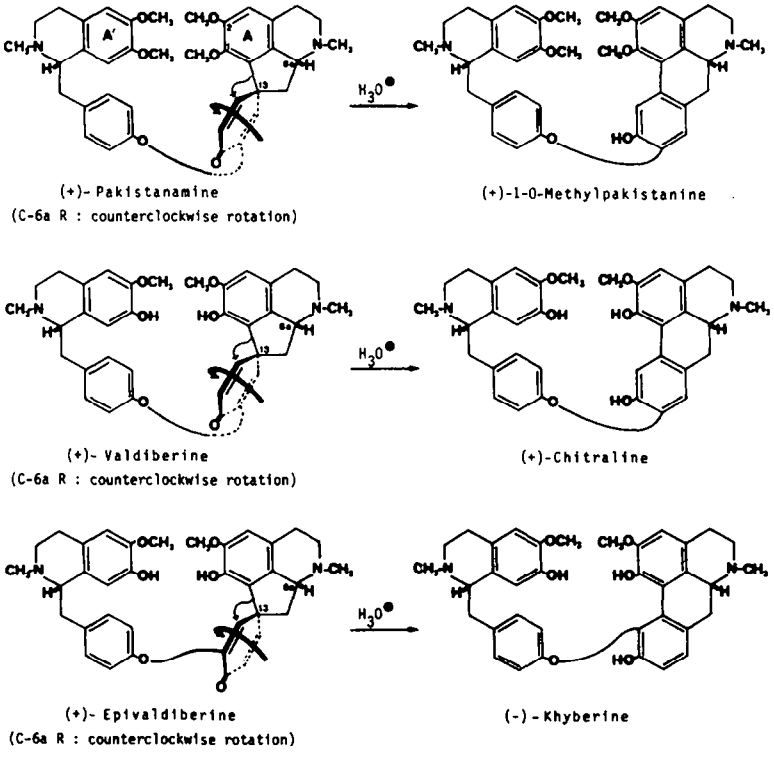
One of the new phenolic proaporphine–benzylisoquinoline dimers that concerns us here is (+)-valdiberine, whose ^{1}H-NMR spectrum, specific rotation, and CD curve clearly indicated that it possessed the same stereochemistry as (+)-pakistanamine. Its acid catalyzed dienone–phenol rearrangement furnished the aporphine–benzylisoquinoline (+)-chitraline of known absolute configuration. By a felicitous coincidence, one of the other new proaporphine–benzylisoquinoline dimers was (+)-epivaldiberine, a diastereomer of (+)-valdiberine, which was isolated in very small amounts, and whose acid catalyzed rearrangement gave rise to (−)-khyberine, also of known absolute configuration. Clearly, (+)-valdiberine and (+)-epivaldiberine had to be isomeric at the spiro C-13 center of the proaporphine moiety.[28]

The stereochemistry at C-13 of (+)-pakistanamine, which was available in sufficiently large quantities, was then elucidated by a detailed ^{1}H-NMR nuclear Overhauser enhancement study, and proved to be as indicated below. Its close relative, (+)-valdiberine, has the identical stereochemistry, while (+)-epivaldiberine differs at C-13 as shown.[28]

Several conclusions may be drawn from the above results. Firstly, from a biogenetic viewpoint, both (+)-valdiberine and its diastereomer (+)-epivaldiberine probably originate from the same bisbenzylisoquinoline, namely (+)-berbamunine. There is, nevertheless, a marked tendency for (+)-berbamunine to undergo enzymatic intramolecular oxidative coupling to furnish (+)-valdiberine rather than (+)-epivaldiberine, since the former is found in quantities about 50–100 times larger than the latter. Additionally, the other proaporphine–benzylisoquinoline dimers isolated from the Chilean barberries possess the same chirality as (+)-pakistanamine and (+)-valdiberine. (+)-Epivaldiberine thus incorporates the biogenetically somewhat less favored stereochemistry at its spiro C-13 center.[28]

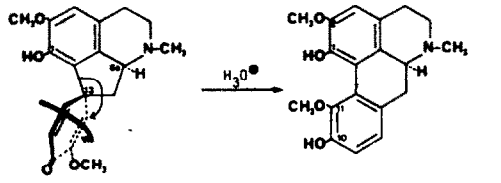
Secondly, it is steric factors—particularly the presence of a C-1 substitutuent on the proaporphine skeleton—that dictate that the dienone system in (+)-valdiberine and (+)-epivaldiberine will rotate preferentially in the same counterclockwise direction during the dienone–phenol rearrangement, as indicated above. A corollary is that proaporphines of the *S* rather than the *R* configuration at C-6a will rotate their dienone moiety in a clockwise direction during the dienone rearrangement. In other words, the rule can be enunciated that the aryl ring A of a proaporphine will migrate preferentially to that terminus of the dienone system which lies *syn* to H-6a.[28,29]

The above generalization was then applied to the case of the previously mentioned proaporphine (−)-orientalinone, whose stereochemistry at C-13 was unknown up to this stage. (−)-Orientalinone is a difficult alkaloid to isolate, so none was available for investigation. It was known from the litera-



ture, however, that acid catalyzed rearrangement of this proaporphine of the C-6a *S* configuration furnished (+)-1,10-dihydroxy-2,11-dimethoxyaporphine.[30] It thus follows that the stereochemistry of (−)-orientalinone at the C-13 spiro center is as indicated, since the dienone entity must suffer a clockwise rotation in the course of the rearrangement.

It should be noted, moreover, that the oxygenated substituent on the dienone systems of the biogenetically favored proaporphine dimers (+)-pakistanamine and (+)-valdiberine lies anti to H-6a. With (−)-orientalinone, however, the OMe substituent on ring D is *syn* to H-6a; while its diastereomer is unknown in nature. There is little doubt, however, that (−)-orientalinone analogs with the OMe group on ring D *anti* to H-6a will, some day, be found in nature.



(-)-Orientalinone (C-6a S : clockwise rotation)

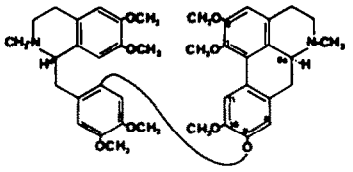
(+)-1,10-Dihydroxy-2,11-dimethoxyaporphine

As a final note concerning the aporphine–benzylisoquinoline dimers derived from N-methylcoclaurine, it should be stated that the oxygenated function at the aporphine C-10 site inevitably appears in the form of a phenolic hydroxyl. It is never O-methylated. This is because natural products often tend to bear the scars of their biogenesis. All of the dimeric alkaloids in question are formed through a dienone–phenol rearrangement, and the resulting phenolic function is not readily methylated.

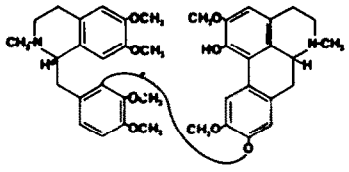
(ii) *Aporphine–benzylisoquinolines with either one or two (+)-reticuline moieties*

The biogenetic sequence followed by the aporphine–benzylisoquinoline dimers incorporating either one or two (+)-reticuline units bears little resemblance to the corresponding N-methylcoclaurine series discussed above. As a rule, the intermediacy of a proaporphine is not required, and a dienone–phenol rearrangement does not occur.

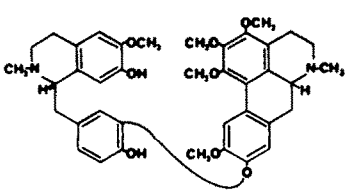
The first dimer of this series, (+)-thalicarpine, was reported in 1963.[31] Since that time, several other types of dimers incorporating (+)-reticuline have been described, and are presented below. (+)-Thalicarpine and (+)-fetidine encompass two reticuline units, while (+)-istanbulamine, (+)-uskudaramine and (+)-thalifaberine each possess an N-methylcoclaurine half.[24] Furthermore, in (+)-uskudaramine, the two units making up the dimer are linked directly through a C—C bond, whereas in all of the other dimers the bridging is through an ether oxygen. The left hand portion of the dimers (as drawn) is inevitably a tetrahydrobenzylisoquinoline of the *S*-configuration, and this generalization even carries over to the aporphine–benzylisoquinolines of the N-methylcoclaurine series previously discussed.



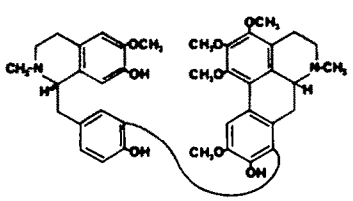
(+)-Thalicarpine



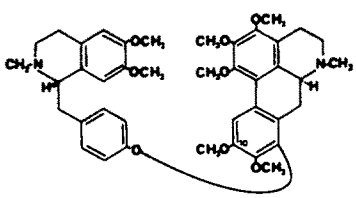
(+)-Fetidine



(+)-Istanbulamine



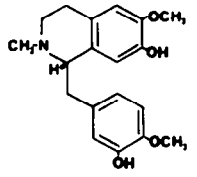
(+)-Uskudaramine



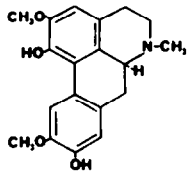
(+)-Thalifaberine

Whereas the aporphine–benzylisoquinolines derived from two N-methylcoclaurines always incorporate a phenolic function at the aporphine C-10 site, in the dimers presently under consideration it is a methoxyl group that is consistently present at that position. This fact, coupled with the realization that no proaporphine–benzylisoquinoline dimer incorporating a reticuline unit had ever been isolated, led to the generalization that *Thalictrum* aporphine–benzylisoquinolines involving either one or two reticuline-type units are formed through direct phenolic oxidative coupling of a fully formed 1,2,9,10-tetraoxygenated aporphine with a (+)-N-methylcoclaurine or a (+)-reticuline unit.[33]

Two recent studies with labeled precursors have indeed shown, using *Thalictrum minus* (Ranunculaceae) in one case,[34] and *Cocculus laurifolius* (Menispermaceae) in the other,[35,36] that the aporphine (+)-isoboldine is very efficiently incorporated into (+)-thalicarpine. Reticuline also is readily incorporated. These results strongly support the thesis of condensation between an aporphine on the one hand and a tetrahydrobenzylisoquinoline on the other to eventually produce (+)-thalicarpine.



(+)- Reticuline

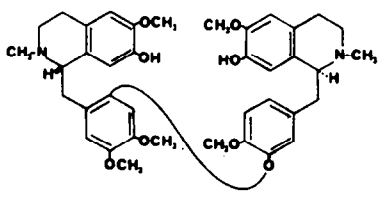


(+)- Isoboldine

Before leaving the subject of aporphine–benzylisoquinoline dimers, it is appropriate to point out that the dimers derived from two N-methylcoclaurines are found among members of the plant family Berberidaceae, while reticuline dimers are present primarily in the genus *Thalictrum* which belongs to the Ranunculaceae. Reticuline dimers are also sometimes found in the genus *Hernandia* (Hernandiaceae).[24,36]

In a most recent development, Bruneton *et al.* have reported the isolation of the new bisbenzylisoquinoline (+)-vanuatine from the bark of *Hernandia peltata* which grows on the Pacific island of Vanuatu (New Hebrides). This alkaloid is of special interest since it is the first known bisbenzylisoquinoline composed of two (+)-reticuline units.[37] Generally speaking, (+)-reticuline itself, being activated in the bottom ring by the presence of two oxygenated functions, tends to undergo intramolecular rather than intermolecular coupling to produce pavines, isopavines, dibenzopyrrocolines, aporphines or protoberberines. On the other hand, N-methylcoclaurine, which possesses only one oxygenated substituent in the bottom ring, cannot undergo intramolecular coupling except to furnish a proaporphine. It, therefore, has a distinct tendency to dimerize to supply bisbenzylisoquinolines. In fact, prior to the Bruneton findings, out of over 260 known bisbenzylisoquinolines, only 14 were known which incorporated one reticuline unit condensed with one N-methylcoclaurine.[38] All the others were dimers of N-methylcoclaurine, and none were known which incorporated two reticulines.

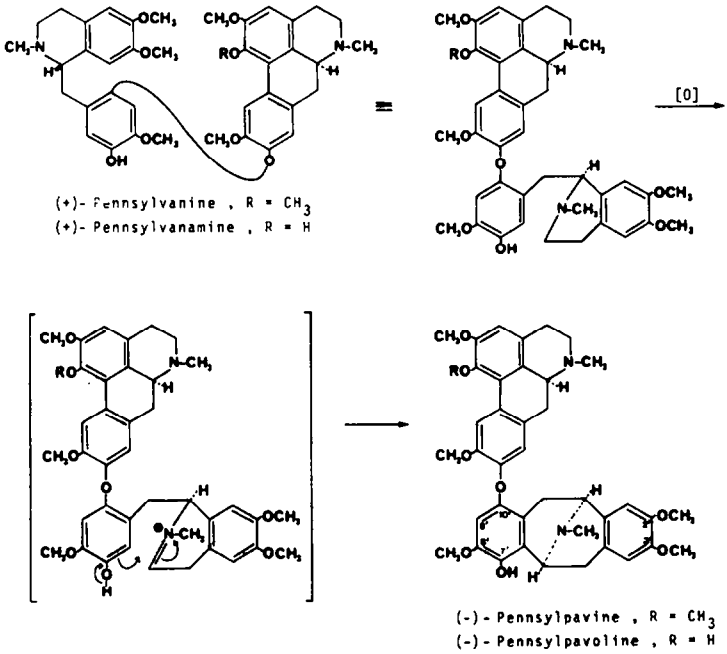
The bisbenzylisoquinoline vanuatine is of relevance in the present context since towards the end of the botanical growing season it was noticed that the amounts of vanuatine present in the bark of the tree had decreased drastically, to be replaced by substantial quantities of the aporphine–benzylisoquinoline (+)-thalicarpine.[39] It will be worthwhile, therefore, to carry out a study with *Hernandia peltata* using labeled precursors to determine exactly the origin of thalicarpine in this specific instance.[39a]



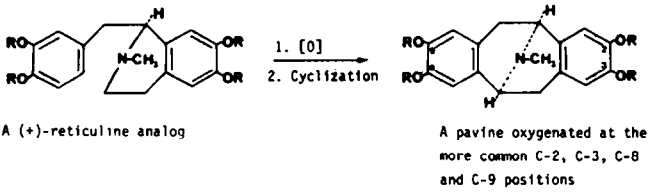
(+)- Vanuatine

10. APORPHINE–PAVINE DIMERS

One is justified at this stage of the discussion to raise the question: Do the aporphine–benzylisoquinoline dimers represent a final stage in the building up of aporphinoids, or is there a further anabolic stage that can be reached? This question was answered in 1974 when the two aporphine–pavines (−)-pennsylpavine and (−)-pennsylpavoline were described.[40] An investigation of the alkaloidal content of *T. polygamum* yielded not only the new aporphine–benzylisoquinolines (+)-pennsylvanine and (+)-pennsylvanamine which are related to (+)-thalicarpine, but also the novel aporphine–pavines (−)-pennsylpavine and (−)-pennsylpavoline. It is quite likely, therefore, that enzymatic oxidation of (+)-pennsylvanine and (+)-pennsylvanamine, followed by Mannich type cyclization, leads to (−)-pennsylpavine and (−)-pennsylpavoline, respectively.[40]

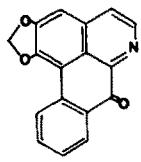


Thalictrum species are known to produce a variety of isoquinoline alkaloids, including simple pavines. These pavine monomers are mostly symmetrically substituted, at C-2, C-3, C-8 and C-9, and originate from the further oxidation and cyclization of (+)-reticuline or any of its close analogs. But in the case of the dimers (−)-pennsylpavine and (−)-pennsylpavoline, the oxygenation pattern is C-2′, C-3′, C-7′ and C-8′, probably due, as indicated above, to the specific biogenetic route that applies.[41]

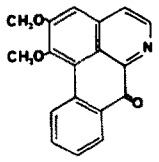


11. OXOAPORPHINES AND 4,5-DIOXOAPORPHINES

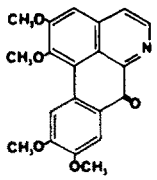
Over forty oxoaporphines are presently known. They are usually colored yellow, orange, or orange-red because of their high degree of aromaticity, and they are found to accompany aporphines in plants.[3] Six representative oxoaporphines are shown here.



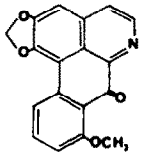
Liriodenine



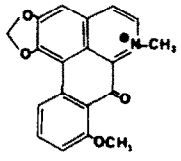
Lysicamine



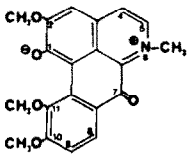
Oxoglaucine



Oxostephanine

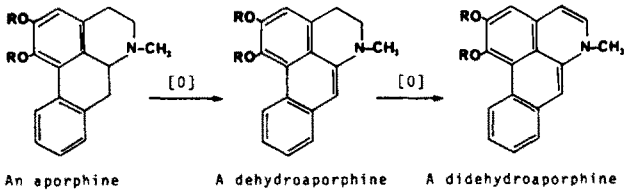


Thailandine

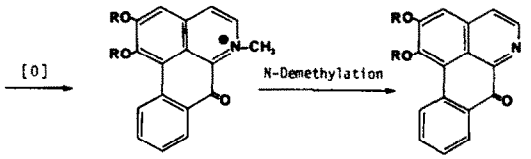


Glaunidine

A rational sequence of *in vivo* transformations leading from an aporphine to its corresponding oxoaporphine would be through the intermediacy of dehydro- and didehydroaporphines as delineated below.



An aporphine A dehydroaporphine A didehydroaporphine

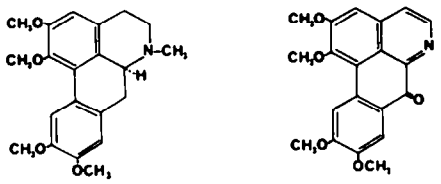


An N-methooxo-aporphinium salt An oxoaporphine

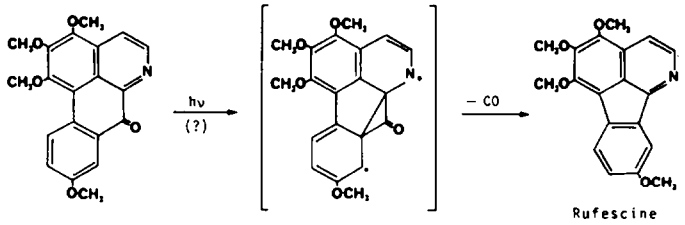
Although several naturally occurring dehydroaporphines are known,[3] didehydroaporphines are generally too unstable to be fully characterized. Whereas most aporphine alkaloids incorporate an N-methyl group, the corresponding oxoaporphines do not. This is because N-methooxoaporphinium salts undergo facile N-demethylation to the free base even on a TLC plate. Thus, the N-methooxoaporphinium salt thailandine was so labile that each attempt at purification by TLC produced substantial quantities of the corresponding N-demethylated free base oxostephanine.[42] The only N-methooxoaporphinium salts that appear to be fairly stable are those that include a phenolic function at C-1 such as glaunidine, in which case the alkaloid does not possess an overall positive charge, and is not as susceptible to nucleophilic attack. It can, therefore, be concluded that some of the oxoaporphines isolated as the non-phenolic free bases may actually exist in the plants as the N-metho salts which are then easily N-demethylated during the isolation–purification process.[42]

A relevant observation concerns the alkaloids of *Magnolia kachirachirai* (Magnoliaceae). The freshly collected powdered plant provided substantial quantities of the common aporphine (+)-glaucine. But a reinvestigation of the same powdered plant material after it had been allowed to stand for seven years supplied instead the corresponding oxoaporphine oxoglaucine. The oxidation of an

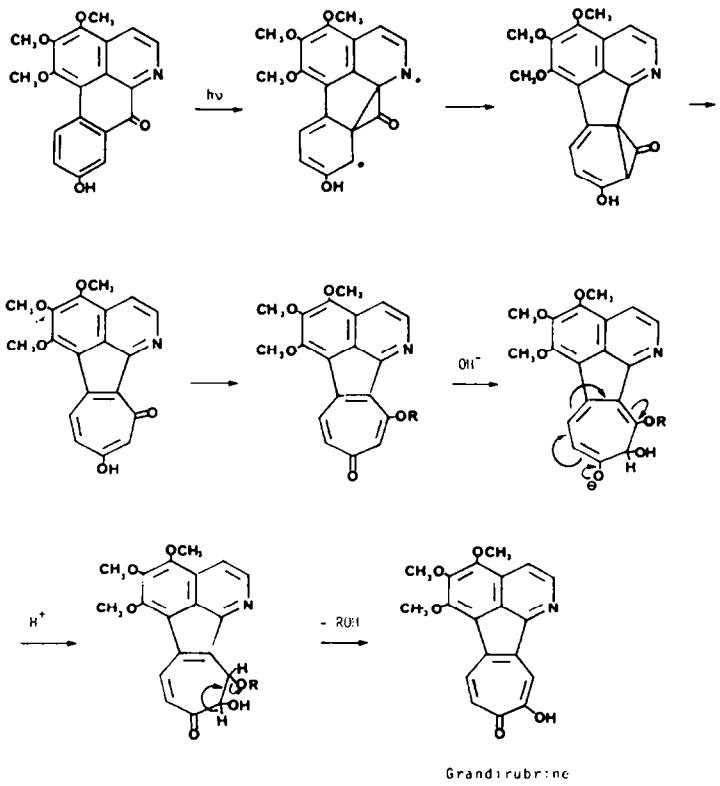
aporphine to its oxoaporphine analog may thus take place simply upon prolonged contact with air, and may not always be enzyme mediated.[43]



It is possible that oxoaporphines, once formed, may sometime undergo a net decarbonylation. Such a transformation can best explain the biogenesis of rufescine, an interesting alkaloid isolated by Cava *et al.*[44] from *Abuta imene* (Menispermaceae). It should be cautioned, however, that to date the decarbonylation of an oxoaporphine, possibly by a photochemical process, has never been accomplished in the laboratory.

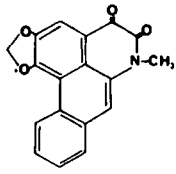


Besides producing rufescine and rufescine analogs, plants of the genus *Abuta* have also been found to generate tropolonoisoquinolines such as grandirubrine. The biogenesis of grandirubrine may proceed via a cyclopropanone intermediate closely related to that involved in the production of

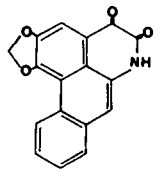


rufescine. In this instance, however, a carbon monoxide unit is not lost from the starting material. Rather, this unit is inserted into the bottom ring, resulting in ring expansion and formation of the tropolone system.

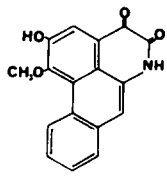
In some plants, it is found that an aporphine has been converted through oxidation not only to its corresponding oxoaporphine, but also to its 4,5-dioxoaporphine (or more exactly 4,5-dioxodehydroaporphine) analog.[3] A few 4,5-dioxoaporphine structures are presented below.



Cepharadione A



Tuberosinone

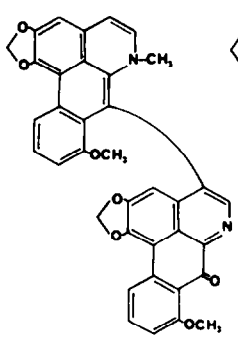


4,5-Dioxodehydro-asimilobine

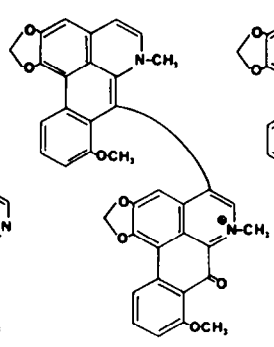
It is likely that the intermediates involved in the formation of the 4,5-dioxoaporphines are again the corresponding dehydro- and didehydroaporphines, so that the latter could proceed either to oxoaporphines or to 4,5-dioxoaporphines.

12. THE DIMERIC OXIDIZED APORPHINES

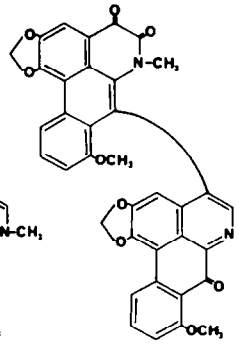
Lately, an interesting series of colored dimeric oxidized aporphines has come to light as a result of work carried out in the Cavé–Leboeuf laboratories on the paleotropical plant *Polyalthia cauliflora* var. *beccarii* (Annonaceae). Three of the alkaloids that are relevant to our discussion are beccapoline, the beccapolinium cation, and beccapolydione.[45,46]



Beccapoline



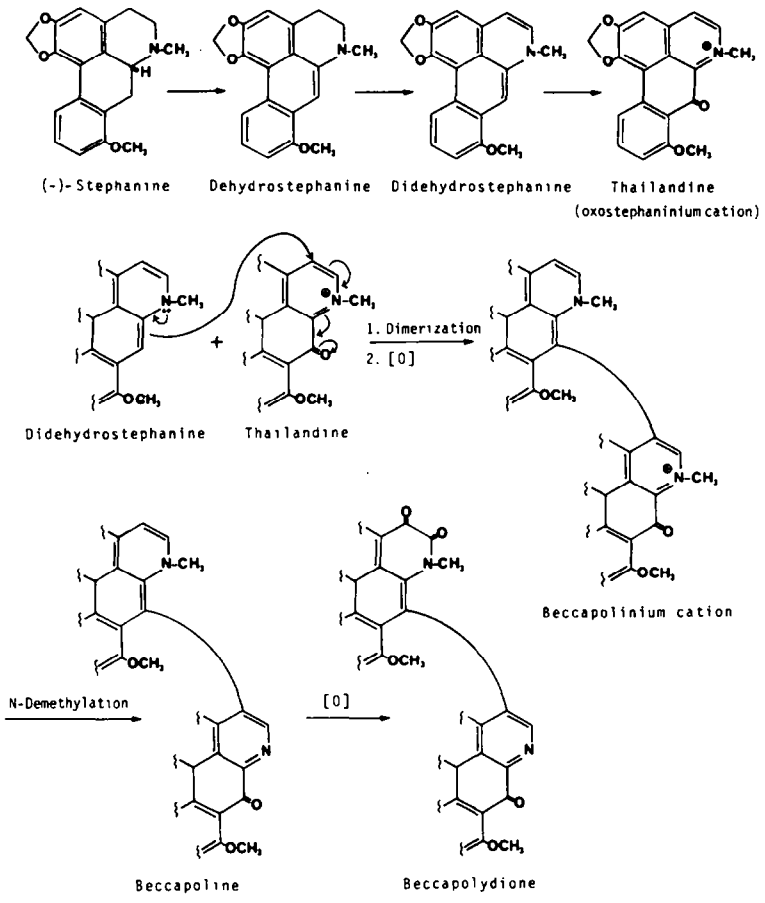
Beccapolinium cation



Beccapolydione

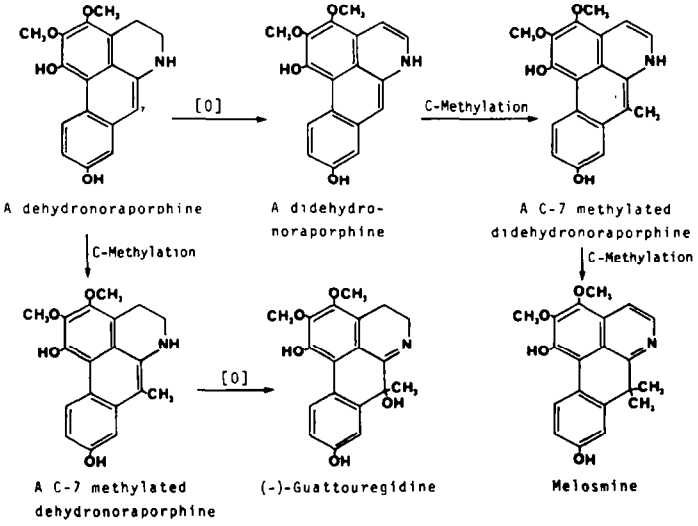
The biogenetic sequence involved in the dimerization probably originates with the known aporphine (−)-stephanine which is oxidized to its dehydro and then to its didehydro analogs. The latter may be further oxidized to the oxoaporphinium cation—in the present case thailandine. It is at this stage that dimerization must occur, with didehydrostephanine acting as the electron donor, and the thailandine cation as the electron acceptor to produce, following facile oxidation, the beccapolinium cation. This charged species can readily undergo N-demethylation. The resulting beccapoline, which

incorporates a didehydroaporphine moiety, can finally suffer further oxidation to supply beccapolydione.



13. ALKYLATION AT C-7 OR C-11

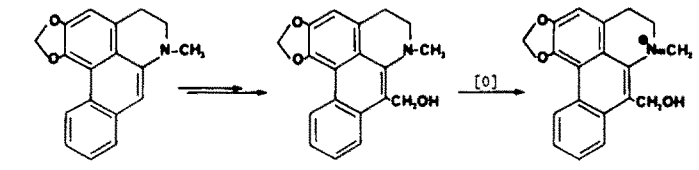
Melosmine is an interesting aporphine originally obtained from a *Guatteria* species (Annonaceae) by Schiff *et al.*[47] Its biogenesis is more than likely through a didehydronoraporphine which is methylated twice at C-7 using the natural methylating agent *S*-adenosylmethionine. No dehydroaporphines or dehydronoraporphines monomethylated at C-7 are presently known, but it is likely that they will be found in the future. This is especially apparent if one considers the structure of the



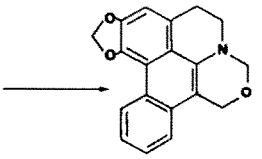
new alkaloid (−)-guattouregidine, also found in a *Guatteria* species.[48] Obviously in this case, a C-7 methylated dehydronoraporphine has undergone oxidation with concomittant transformation of the enamine into an imine.

Formation of an extra ring on the aporphine nucleus

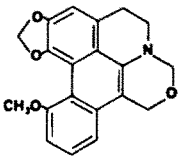
Work recently published as a result of studies on a *Duguetia* species (Annonaceae) describes two new aporphines incorporating an extra heterocyclic ring system. These aporphines are duguenaine and duguecalyne.[49] Their genesis could possibly proceed through stepwise conversion of a dehydroaporphine to its 7-hydroxymethyl analog. Subsequent oxidation to the iminium cation stage, followed by cyclization, would result in formation of the required new ring.



A dehydroaporphine

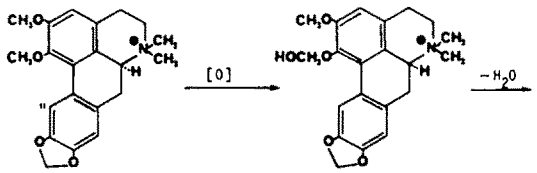


Duguenaine

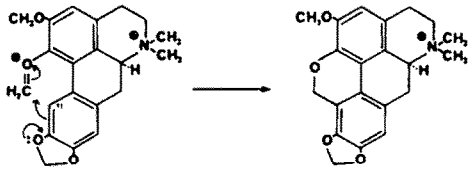


Duguecalyne

The genus *Thalictrum* (Ranunculaceae) can form an extra heterocyclic ring fused to the aporphine nucleus as in the alkaloid (+)-thalphenine which is present in *T. polygamum*. Enzymatic oxidation of the common aporphine (+)-nantenine N-metho salt found in the same plant could provide an oxonium ion which could cyclize at C-11 to add the extra ring to the aporphine.[50,51]



(+)-Nantenine
N-metho salt

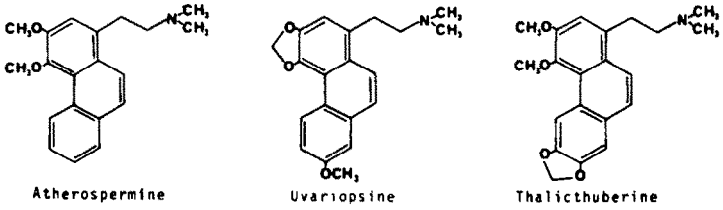


(+)-Thalphenine

14. CATABOLISM OF APORPHINES THROUGH CLEAVAGE OF RING B

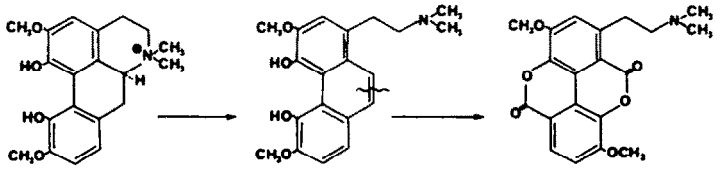
Some eighteen alkaloids are known which incorporate a phenanthrene nucleus bonded to an N,N-dimethylaminoethyl side chain.[3] These phenanthrene alkaloids are clearly formed from *in vivo* Hofmann elimination of N-methoaporphinium salts, and can be considered the first stage in the further breakdown of aporphines. Since the aporphines are widely distributed in nature, being found in several

plant families, the phenanthrene alkaloids are also of widespread occurrence. Three of these alkaloids are represented here.



15. CATABOLISM OF APORPHINES THROUGH CLEAVAGE OF RING B, FOLLOWED BY OXIDATIVE CLEAVAGE OF RING C

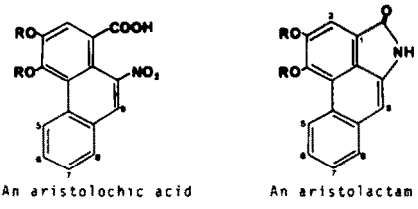
The optically inactive dilactonic base taspine is the only known alkaloid formed by cleavage of ring B followed by oxidative cleavage of ring C of the original aporphine skeleton, as described below. A parallel sequence, also starting from magnoflorine, has been achieved in the laboratory.[52]



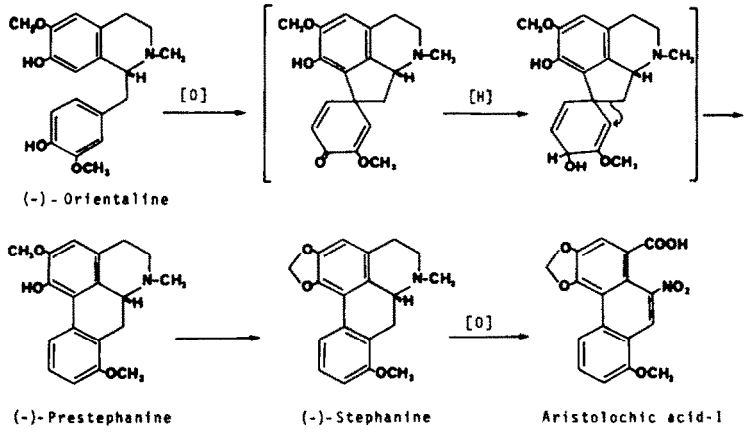
16. OXIDATIVE CLEAVAGE OF RING B OF APORPHINES

The aristolochic acids and aristolactams—Biogenesis of aporphines substituted at C-8, C-9, *or* C-8,9—*Photolysis of proaporphines*

Fourteen aristolochic acids and twelve aristolactams are known. They possess the skeletons delineated below, and they are found mainly among plants belonging to the family Aristolochiaceae.[53]

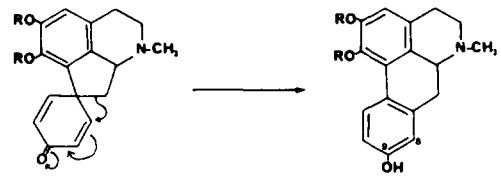


An *in vivo* experiment by Kapil, Bhakuni *et al.*, where doubly labelled (−)-orientaline was fed to *Aristolochia bracteata* (Aristolochiaceae), resulted in incorporation of labelled material into aristolochic acid. This result implied that the aporphine prestephanine was an intermediate in the biosynthesis. Subsequent experiments using labeled prestephanine and stephanine showed their incorporation into aristolochic acid. The following biogenetic sequence was, therefore, presented in which a dienol–benzene rearrangement takes place.[54]



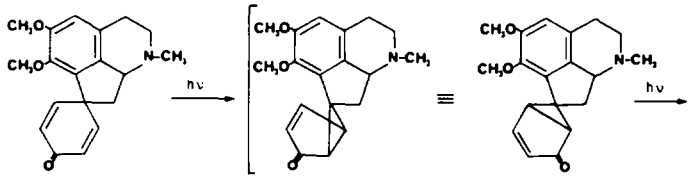
The *in vitro* dienol–benzene rearrangement in the proaporphinol series is known to follow the same rules as the dienone–phenol rearrangement, i.e. it is always the aryl ring A which migrates, and the migration is predominantly to that terminus of the dienol system which lies *syn* to H-6a (see Section 9 (i) above).[28] The aforementioned biogenetic scheme, however, clearly relies on an alkyl migration to obtain prestephanine. The question that needs to be answered, therefore, is: Do enzymes exist which will specifically induce alkyl over aryl migration during the dienone–phenol rearrangements? In other words, can the *in vitro* and *in vivo* dienone–phenol and dienol–benzene rearrangements follow different pathways?

If such enzymes do exist, then one can readily explain the biogenesis of C-8 oxygenated aporphines in nature, as well as that of the C-8,9 substituted analogs. They would both originate from orientaline or one of its close analogs, and in each rearrangement alkyl migration would occur. Similarly, 9-substituted aporphines of the *R* configuration would be formed through alkyl migration of a proaporphine derived from N-methylcoclaurine, as indicated. (For 9-oxygenated aporphines of the *S* configuration, see Section 5.)

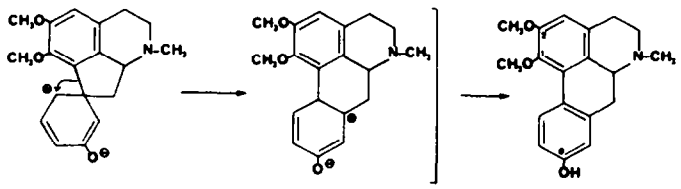


A proaporphine derived from N-methylcoclaurine

Supposing, however, that alkyl migration does not take place under any circumstances, how then can one explain the formation in nature of aporphines substituted at C-8 and C-9? A possible avenue for solving this dilemma was afforded by studies on the photolysis of proaporphines. Sunlight irradiation of pronuciferine produced 1,2-dimethoxy-9-hydroxyaporphine in good yield. Although again it would be tempting, *prima facie*, to postulate an alkyl migration, this transformation actually involves two light catalyzed rearrangements as shown, so that it is an aryl migration that applies.[55] It is, therefore, a plausible thesis that sunlight could be responsible for the transformation of some proaporphines into aporphines oxygenated at C-9. Two qualifying statements must be made at this stage. In the first place, no *in vivo* studies with labeled precursors have yet been carried out to support this possibility. Secondly, even if such *in vivo* studies were carried out and the results shown to be positive, it does not necessarily follow that all C-9 oxygenated aporphines are formed by such a route.

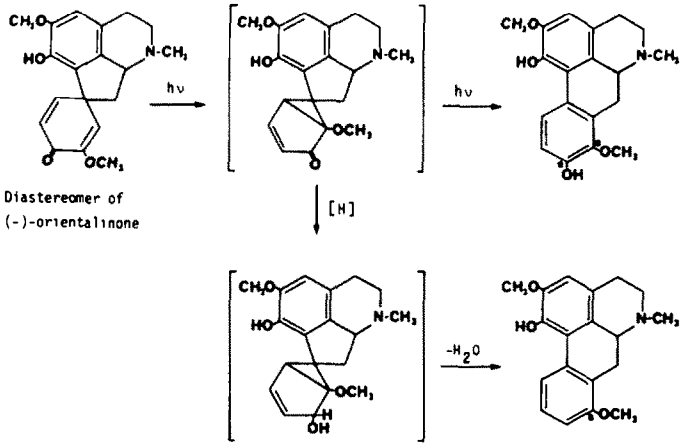


Pronuciferine

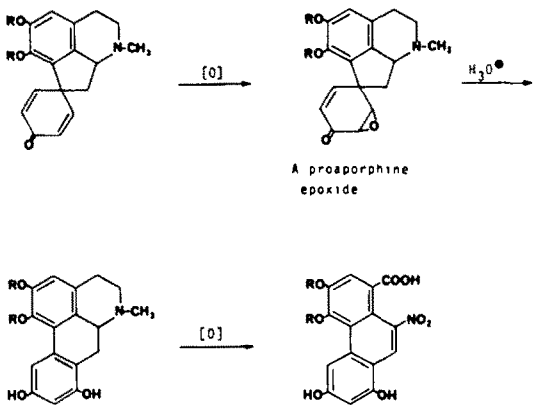


1,2-Dimethoxy-9-hydroxyaporphine

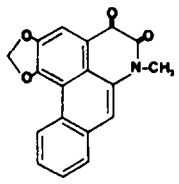
Modifications of the above sequence could then serve to explain the formation of C-8 and C-8,9 substituted aporphines. Although the photolysis of orientalinone has never been attempted, it is conceivable that either this alkaloid or much more probably its so far unknown diastereomer would furnish an 8,9-substituted aporphine. Reduction of the ketone at an appropriate stage, with elimination of water, would generate a C-8 oxygenated aporphine.[55]



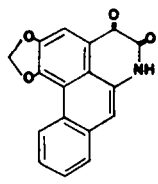
A special feature of aristolochic acids and aristolactams is that they sometimes possess oxygenated substituents in a *meta* relationship at C-6 and C-8. The biogenesis of such species is not readily understood. It just could be that a proaporphine epoxide is involved as an intermediate as shown, but there is presently no firm supporting evidence. Alternatively, the *meta* substitution pattern of the bottom ring could be due to a tetrahydrobenzylisoquinoline precursor trioxygenated in ring C. Phenolic oxidative coupling to the pentaoxygenated proaporphine, followed by reduction and dienol–benzene rearrangement, would then be the biogenetic pathway.



At this point, it is necessary to try to clarify whether it is the aristolochic acids or the aristolactams which are formed first in nature. Again, conclusive evidence is lacking. Two routes are possible. In the first, a 4,5-dioxoaporphine such as tuberosinone could suffer decarbonylation to generate an aristolactam which then through lactam hydrolysis and oxidation would supply the corresponding aristolochic acid. In the second route, a 4,5-dioxoaporphine such as cepharadione-A or tuberosinone would be oxidized directly to the aristolochic acid whose reduction and dehydration would give rise to the aristolactam. An available clue is that the aristolactams presently known possess an NH function rather than an N-methyl group. Additionally, cepharadione-A, which is N-methylated, has been found in an *Aristolochia* species.[53] It follows that it is the second, i.e. the direct oxidative route to the aristolochic acids which probably applies, since overall decarbonylation of cepharadione-A would have supplied an N-methylaristolactam.



Cepharadione A

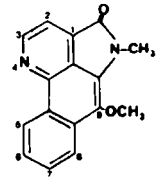


Tuberosinone

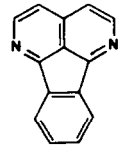
17. OXIDATIVE CLEAVAGE OF RINGS A AND B OF APORPHINES

Formation of a pyridine ring

The botanical family Eupomatiaceae is a small group of shrubs or small trees found mostly in New Guinea and eastern Australia. The alkaloid eupoloramine, isolated from one of the Australian species,[56] is an unusual alkaloid whose biogenesis can only be surmised. Eupoloramine could be derived from an aporphine whose ring A is cleaved between C-1 and C-2. Such fission would be followed by decarboxylation and loss of C-1 of the original aporphine. This transformation is then complemented by capture of nitrogen as ammonia, and recyclization to form the pyridine ring of eupoloramine. These events are either preceded or succeeded by oxidation of ring B of the aporphine. It will be noted that the lactam nitrogen of eupoloramine bears a Me substituent, which is never the case with the aristolactams. Additionally, C-9 in eupoloramine bears an oxygenated substituent—a feature not encountered among the aristolactams. (For more on the biogenesis of eupoloramine, see Section 19.)



Eupoloramine

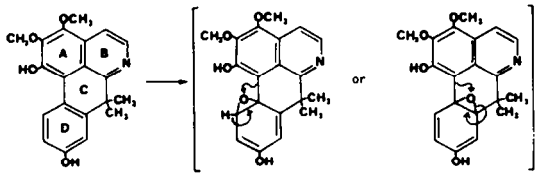


Eupolauridine

A related base found in the same Eupomatiaceae plant,[57] as well as in a member of the Annonaceae,[58] is the symmetrical eupolauridine. A net decarbonylation must have taken place in this instance.

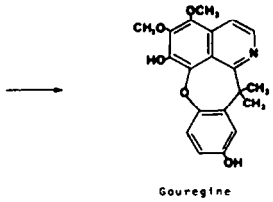
18. OXIDATIVE EXPANSION OF RING C OF APORPHINES

We have seen in Section 13 above how melosmine is an unusual alkaloid of the Annonaceae, probably derived by C-7 dimethylation of a didehydronoraporphine. It has been correctly recognized by Cavé and Leboeuf that the unique alkaloid gouregine, obtained by them from the same plant, *Guatteria ouregou*, must be an oxidation product of melosmine. In an *in vitro* experiment that followed, and which emulated the natural process, treatment of melosmine with Fenton's reagent ($FeCl_2 + H_2O_2$) was found to generate gouregine in good yield through the probable intermediacy of an epoxide.[59]



Melosmine

An epoxide



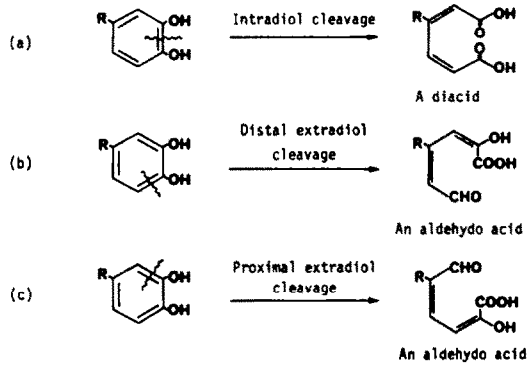
Gouregine

Gouregine may be formally classified as a cularine alkaloid. In reality, it is the product of the oxidation of ring D of an aporphine, resulting interestingly enough, in net expansion of ring C. It differs fundamentally from the classical type cularine alkaloids all of which are disubstituted in the bottom ring, and are formed by oxidative coupling of C-7,8,11,12 tetraoxygenated tetrahydrobenzylisoquinolines.

Since the aporphine melosmine cannot undergo quaternization and Hofmann elimination to give rise to a phenanthrene alkaloid, and also cannot be oxidized to an oxoaporphine, it is interesting to observe how nature handles the catabolism problem in this instance.

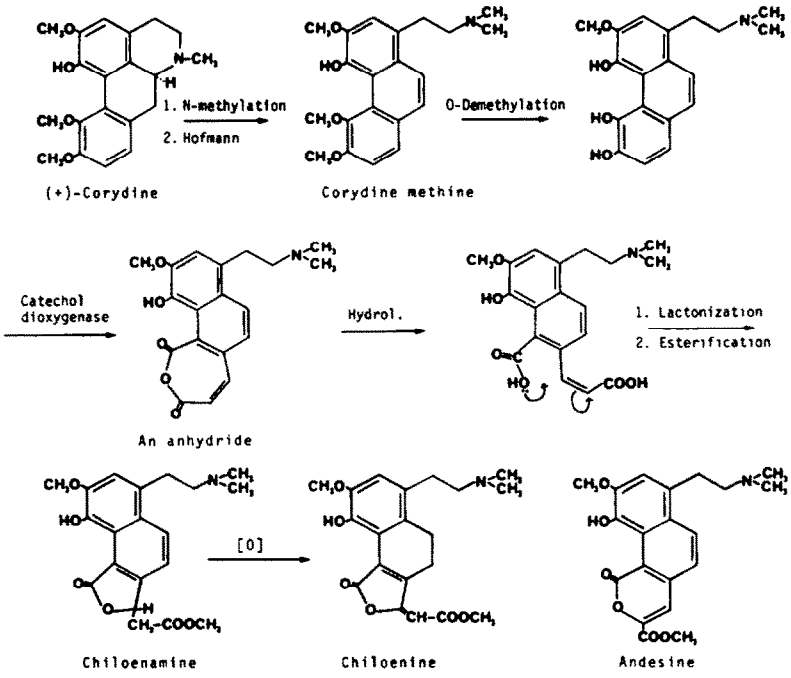
19. OXIDATION USING CATECHOL DIOXYGENASES

Dioxygenases are oxidizing enzymes which catalyze reactions in which both atoms of molecular oxygen are incorporated into the substrate. Several catechol dioxygenase enzymes are known, and they can achieve the cleavage of aromatic rings in any of three ways, as exemplified by the sequences below.[59a]

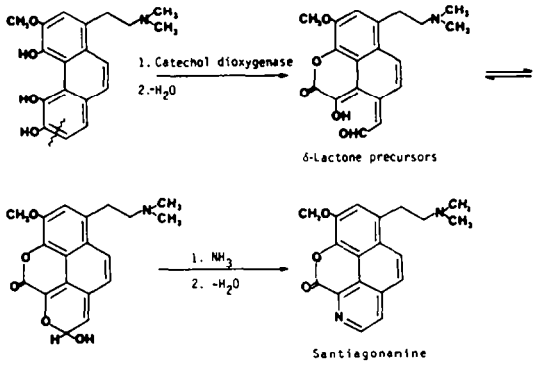


Usually, catechol dioxygenases that catalyze intradiol cleavage contain Fe(III) as cofactor, whereas those that induce extradiol fission have Fe(II) as sole cofactor.[59b]

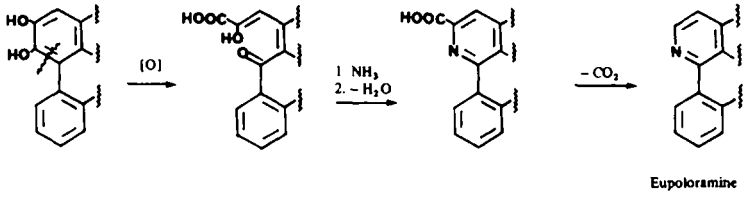
Known catechol dioxygenases are of microbial or mammalian origin, but they also occur in plants. An alkaloid recently found in a Chilean *Berberis* species is (±)-chiloenamine. Since the aporphine (+)-corydine was also found in the plant, the following reaction sequence, involving intradiol cleavage, may apply *in vivo*. Chiloenamine is also accompanied by chiloenine which is a further oxidation product.[60] A related *Berberis* alkaloid is andesine, shown below, whose lactonization must have occurred alpha rather than beta to the COOH (or $COOCH_3$) function.[60a]



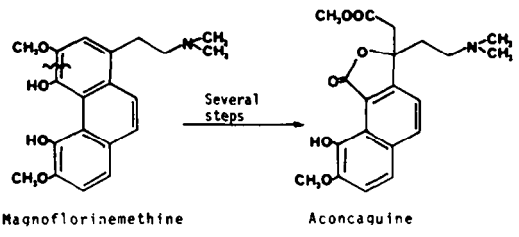
Even more recently, the novel alkaloid santiagonamine has also been obtained from a Chilean barberry.[60b] Santiagonamine is the first phenanthridine alkaloid known, and it is in all probability formed by distal extradiol cleavage of a catechol, followed by ammonia capture.



The biogenesis of eupoloramine, an alkaloid referred to earlier in Section 17, may now be understood as proceeding by proximal extradiol cleavage of ring A of an aporphine derivative. Subsequent ammonia capture, dehydration, and decarboxylation would generate this interesting pyridine derivative.



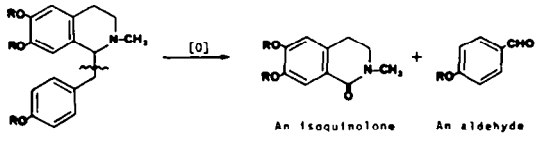
Another instance of ring A oxidative cleavage is presented by the *Berberis* base aconcaguine which is most probably derived from intradiol oxidative cleavage of magnoflorinemethine.[60c]



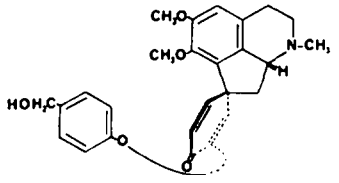
20. CATABOLISM OF PROAPORPHINE- AND APORPHINE-BENZYLISOQUINOLINES

Oxidative cleavage at a benzylic bond

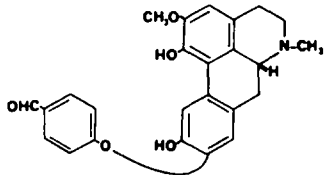
Isoquinoline alkaloid bearing plants usually possess an enzyme which we may conveniently label here as the "killer enzyme". This killer enzyme can oxidize a tetrahydrobenzylisoquinoline and cleave it into an isoquinolone and a substituted benzaldehyde as shown. Several monomeric isoquinolone alkaloids are in fact known, many of them no doubt formed by the route shown.[61] The accompanying aldehyde may sometimes be reduced to the alcohol stage, or alternatively it may be oxidized to the acid which can then be esterified.



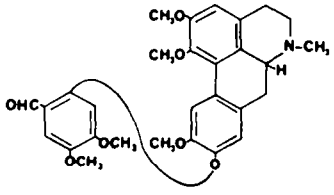
The identical process can also occur with the proaporphine– and aporphine–benzylisoquinoline dimers. (+)-Coyhaiquine, found in a Chilean barberry, is obviously formed by oxidative cleavage of a proaporphine–benzylisoquinoline, followed by reduction of the side chain aldehyde.[62] The alkaloid (−)-natalinine, also obtained from a Chilean barberry,[63] is formed by oxidation of an aporphine–benzylisoquinoline dimer, although it could also be the result of a dienone–phenol rearrangement of a coyhaiquine analog. Both of these alkaloids belong to the coclaurine series, but several are also known in the reticuline series, as for example (+)-hernandaline, obtained from a member of the Hernandiaceae. Hernandaline is very probably a catabolic product of (+)-thalicarpine.[64]



(+)- Coyhaiquine

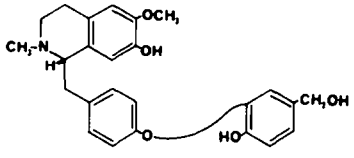


(-)- Natalinine

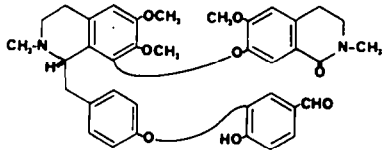


(+)- Hernandaline

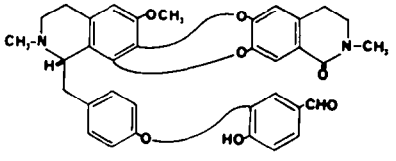
One should even add here that parallel oxidation in the bisbenzylisoquinoline series results in the formation of such seco alkaloids as the recently characterized (+)-karakoramine,[65] (−)-baluchistanamine[66] and (−)-punjabine.[67] These species are formed from the oxidation of



(+)-Karakoramine



(-)- Baluchistanamine



(-)-Punjabine

bisbenzylisoquinoline dimers possessing one, two or three diaryl ether linkages, respectively. It follows that any alkaloid incorporating a tetrahydrobenzylisoquinoline residue can have this portion of the molecule cleaved at the benzylic bond, regardless of the state or nature of the other half of the molecule.

21. CONCLUSIONS

There is such a plethora of avenues by which aporphines can be constructed in nature, that the same aporphine may be biosynthesized by different pathways in different plants. In like fashion, the same alkaloid may be metabolized by separate routes in different botanical families or genera.

Clearly, much remains to be understood concerning the biosynthesis of the aporphinoids. But as new alkaloids are isolated and characterized, and as more studies with labeled precursors are carried out, our knowledge of alkaloid transformations will continue to expand. Some of the views enunciated in this paper will, therefore, undoubtedly need to be refined, modified or expanded. Nevertheless, the aporphinoids are the first group of alkaloids whose biogenesis as well as catabolism (degradation) are fairly well understood.

It is the special charm of natural products chemistry that there presently appears to be no end in sight as to the number and variety of new alkaloidal types that can be discovered. What we are witnessing when we consider the aporphinoids in their totality is a natural, almost Shiva-like, dance involving cycles of creation and destruction, with oxidation processes acting both as creator (especially through phenolic oxidative coupling) and as destroyer.

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[1] Permanent address: Faculté de Médecine et de Pharmacie, Université de Limoges, 87032 Limoges Cedex, France; and E.R.A. 317, U.E.R. de Chimie Thérapeutique, Centre d'Etudes Pharmaceutiques, 92290 Chatenay-Malabry, France.

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