

Alkaloid Chemosystematics, Chemotaxonomy and Biogenesis in the Atherospermataceae

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The Monimiaceae *sensu lato* are an almost entirely tropical family of trees, shrubs, and rarely climbers, a few of which extend into southern extratropical regions. As defined in Money, Bailey and Swamy's 1950 monograph (1), followed by Hegnauer in his "Chemotaxonomie der Pflanzen" (2), this family consists of about 35 genera and 450 species combining primitive and advanced features.

In spite of the exclusion of *Austrobaileya*, *Amborella*, and the Trimeniaceae from the Monimiaceae (1), this taxon is still quite heterogeneous. It had previously been suggested that the Amborellaceae and Atherospermataceae be segregated (3), and familial status has also been proposed for the Siparunaceae (4). In this regard, Schodde maintains that the characters of the Atherospermataceae and Siparunaceae are equivalent to those delimiting other Lauralean families (5), while Thorne calls this "an exercise in taxonomic inflation that would seem to serve no useful purpose" (6). As the latest revision (in preparation) of the *Atherosperma* group treats it as a family (7), this position is adhered to in the present discussion.

The systematic position of the Monimiaceae alliance, based on morphological, anatomical, palynological, embryological, and cytological studies (1, 8, 9, 10, 11), is generally admitted to be close to the Lauraceae but, on the whole, less specialized than the more advanced Lauraceous taxa. Cronquist (12) places the Monimiaceae in the order Magnoliales, forming a group with the Amborellaceae, Trimeniaceae, Lauraceae, Gomortegaceae and Hernandiaceae. Other authors recognize similar affinities within their circumscriptions of the orders Annonales (6) or Laurales (8, 9). For the sake of convenience, Takhtajan's system (9) is followed in this review.

Similarities have been observed which support the idea that the Monimiaceae *sensu lato* are not a "natural" family. The relatively primitive genus *Hortonia* and the clearly more specialized Monimioideae have been said to be closer to the Hernandiaceae *sensu stricto* than the *Atherosperma* and *Siparuna* groups, which supposedly form a natural alliance with the Gyrocarpaceae, Lauraceae and Gomortegaceae (10). Cytological evidence appears to contradict this (11), but the issue seems far from being settled. Chemical data which could help to clarify the situation are still quite insufficient.

The Atherospermataceae, as circumscribed by Schodde (7), coincide with the sum of the tribes Laurelieae and Atherospermeae described in the Pax monograph (13) and with the subfamily Atherospermoideae *sensu* Money et al. (1). Schodde's classification is summarized as follows:

ATHEROSPERMATACEAE

Atherospermataeae
Atherosperma
Laureliopsis
 Laurelieae
Dryadodaphne
Nemuaron
Laurelia
Doryphora
Daphnandra

In this scheme, the tribe Laurelieae differs slightly from the traditional con-

cept with the inclusion of *Doryphora* and the recently created *Dryadodaphne*. The Atherospermateae (including *Laureliopsis*, created by segregation of *Laurelia philippiana* Looser from the rest of the genus) must not be confused with Pax (13) and Hutchinson's (8) Atherospermeae (*Atherosperma* and *Doryphora*). As will be shown later, neither of the tribal separations proposed is reflected in the chemistry of these plants.

The Atherospermateaceae are the southernmost members of the Monimiaceae *sensu lato*. This predominantly arboreal family (only *Nemuaron* spp. are shrubs), grows in New Guinea (*Dryadodaphne*), New Caledonia (*Nemuaron*), East Australia (*Daphnandra*, *Doryphora*, and *Atherosperma*), Tasmania (*Atherosperma*), New Zealand (*Laurelia*), and southern Chile (*Laurelia* and *Laureliopsis*).

Many species are used by man in one way or another. *Atherosperma moschatum*, *Doryphora sassafras*, and *Daphnandra micrantha* are cut for timber in Australia, and *Laurelia sempervirens* and *Laureliopsis philippiana* are used likewise in Chile. The barks of *Atherosperma* and *Doryphora* are reported by Hutchinson (8) to be used in medicinal or refreshing teas, and the leaves of *Laurelia sempervirens* have been used as folk remedies in the treatment of headache, skin, and venereal diseases (14). The branches of this species, together with those of *Drimys winteri*, were used in Araucanian religious ceremonies and as emblems of glory and victory.

CHEMISTRY

The chemical work published on the Monimiaceae *sensu lato* is singularly devoid of chemosystematic or chemotaxonomic comments. Regarding the related families, the Lauraceae have been studied quite intensively (15), although the mere size of this taxon makes any coverage seem inadequate. Some Hernandiaceae have been studied, and so have a couple of Gyrocarpaceae; but the other Lauralean families are still practically intact from the chemist's point of view.

The Atherospermateaceae occupy a privileged position in that, being a group of only seven genera and about fifteen species, nearly all its members have been analyzed for essential oils and/or alkaloids. The major alkaloids of all these genera are known, and every species but *Dryadodaphne celastroides* and *Nemuaron humboldtii* has been examined for these metabolites. Essential oils of all the genera except *Dryadodaphne* have also been analyzed.

The leaves and trunk bark of the Atherospermateaceae are usually fragrant. In spite of Hegnauer's assertion that "all real Monimiaceae possess large oil cells" (2), these organs are quite devoid of essential oils in *Laurelia novaezelandiae*. We are unaware of any recent studies on these components in the family, but Hegnauer's review of the literature up to 1965, which includes data on *Atherosperma*, two *Daphnandra* species, *Doryphora*, the Chilean species of *Laurelia* (including *Laureliopsis*), and *Nemuaron humboldtii*, shows that all these plants resemble each other closely in this respect. Phenylpropene derivatives predominate in most cases accompanied by terpenes, a combination commonly found in the Lauraceae.

More recently, it was shown that the stem bark of *Laurelia sempervirens* contains *E*-3-(3,4-methylenedioxyphenyl)prop-2-en-1-ol, an arylpropanoid which had not been isolated previously from a natural source (16). No lignans or neolignans have been reported as being present in any of the Atherospermateaceae, and the same is true regarding flavonoids.

The alkaloid chemistry of this family is much better known now than it was at the time of Hegnauer's review (2), and some conclusions may be drawn from a simple analysis of the distribution of different structural types in the Atherospermateaceae and in more or less distantly related taxa. Consideration of the

more likely biogenetic routes to these compounds is also a profitable approach to the search for possible inter- and intrafamilial relationships and differences.

All the alkaloids found in this group of plants are isoquinoline derivatives, and most of them belong to the large category of biogenetically related bases derived from the 1-benzyl-1,2,3,4-tetrahydroisoquinoline skeleton. The specific structural types present are: simple tetrahydroisoquinolines, isoquinolones, benzyltetrahydroisoquinolines, proaporphines, morphinandienones, aporphines, oxoaporphines, 1-(dimethylaminoethyl)phenanthrenes, and bisbenzylisoquinolines (specifically, biscoclaurines). The probable biogenetic relationships between these metabolites are illustrated in figure 1.

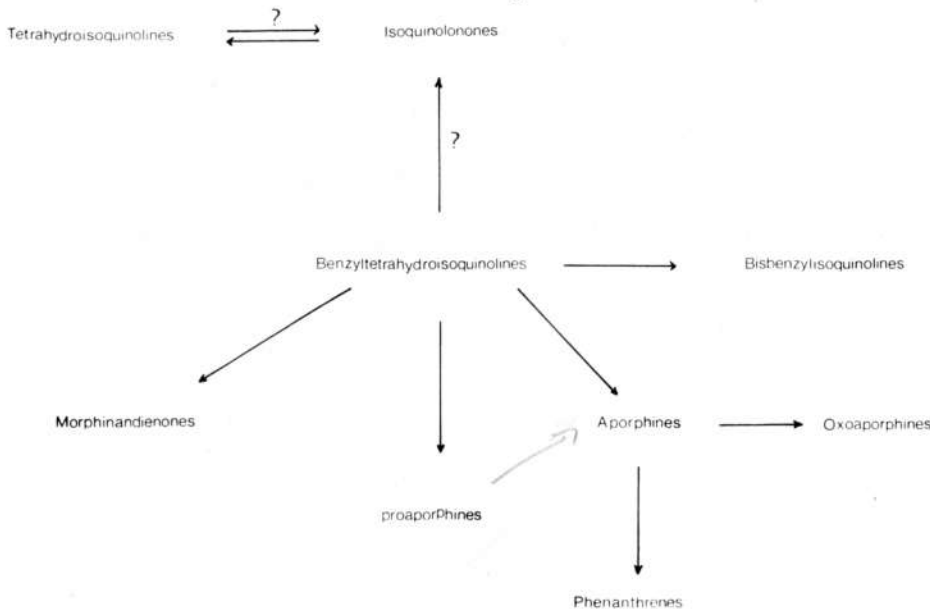


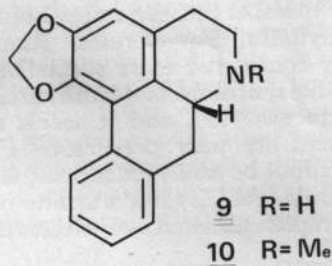
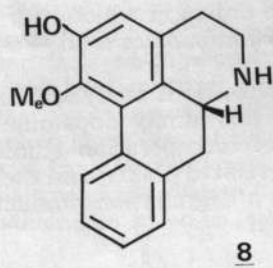
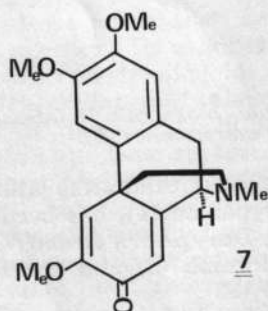
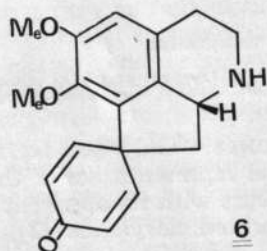
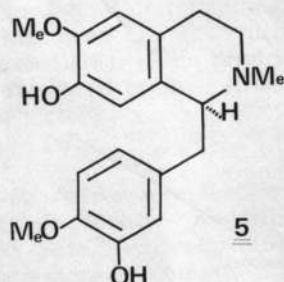
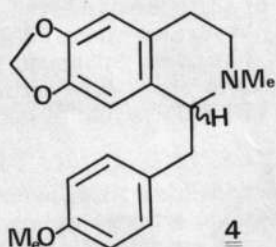
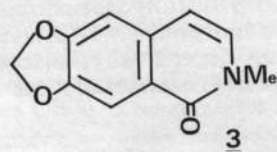
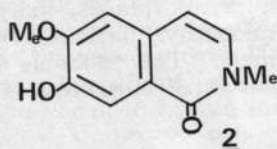
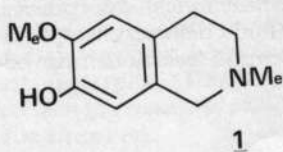
FIG. 1. Probable biogenetic relationship between *Atherospermataceous* alkaloids (based on reference 28).

TETRAHYDROISOQUINOLINES AND ISOQUINOLONES.—Only one tetrahydroisoquinoline, corypalline (1), has been found in one representative of the *Atherospermataceae*, *Doryphora sassafras*. It co-occurs with its apparent oxidation product doryfornine (2) and the further elaborated doryanine (3), both isoquinolones (17, 18).

Simple tetrahydroisoquinolines abound in the *Cactaceae* and are found occasionally in the closely related *Chenopodiaceae*, in the more distant *Fumariaceae*, *Papaveraceae*, *Ranunculaceae* and *Nelumbonaceae*, and in the deeply diverging *Fabaceae*. None of these families can be considered close relatives of the *Atherospermataceae*. No simple tetrahydroisoquinolines have ever been found in other members of the order *Laurales*, and the orders in which they do occur, *Caryophyllales*, *Papaverales*, *Ranunculales*, *Nelumbonales* and *Fabales*, are generally considered more specialized.

The biosynthesis of tetrahydroisoquinolines has been fairly well studied in the *Cactaceae* (19), and it seems clear that in this family dopamine and glyoxylic acid are near precursors. The results of incorporation studies in one family cannot be safely extrapolated to other, less related plants; and the proposal, for example, that hydrocotarnine in *Papaver* is a degradation product of some more complex alkaloid (20) deserves consideration.

The discoverers of doryanine, the first isoquinoline to be found in a plant, suggested that it might be formed by oxidation of a benzyltetrahydroisoquinoline (17) such as doryafranine (4), also present in *Doryphora*. This kind of reaction would explain the origin of the isoquinolones found in *Thalictrum* spp. (21, 22, 23) and in *Hernandia ovigera*, where an isoquinolone is found together with the more complex hernandaline presumably arising from the same oxidation



(24). A similar origin is postulated for baluchistanamine, from *Berberis baluchistanica* (25). Such an unusual degradation would merit no further comment if it were restricted to closely related families such as the Atherospermataceae and Hernandiaceae (order Laurales) or the Ranunculaceae and Berberidaceae. Its occurrence in both alliances, however, may be more than coincidental in view of other indications of parallel evolution exemplified by Hutchinson (8): "The opposite leaves and the plumose styles of *Doryphora* seem to indicate a development parallel with that in the Ranalean group of families as exhibited by *Clematis*." According to this view, the presence of corypalline in this plant could be explained as a reduction product of doryfornine.

A biogenetically plausible alternative could be the oxidation of corypalline to doryfornine, whose logical conclusion would be the cyclization of doryfornine to doryanine. This would suggest, however, that *Doryphora* possesses a metabolic pathway leading directly to simple isoquinolines. The need of biosynthetic experiments to decide the issue one way or the other in *Doryphora*, in *Hernandia*, and in the Ranalean alliance is evident.

BENZYLtetrahydroisoquinoline DERIVATIVES.—The benzyltetrahydroisoquinolines and their biogenetic derivatives are found in about eighteen orders, according to Takhtajan's system (9). Their distribution in flowering plants is illustrated superimposed on Takhtajan's dendrogram showing probable relationships between the different orders. The Caryophyllales, Theales, and Orchidales are included as exponents of isoquinoline-synthesizing plants (figure 2).

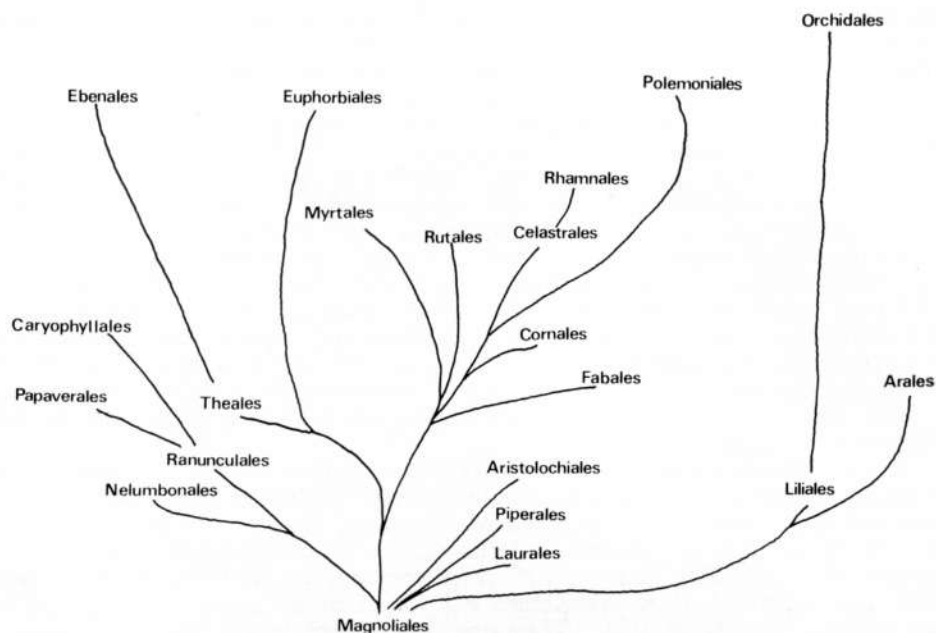


FIG. 2. Probable phylogenetic relationships between isoquinoline-synthesizing plant orders (based on reference 9).

The genera in which benzyltetrahydroisoquinoline derivatives occur most frequently are clustered in and around the Magnoliales, generally accepted as the most primitive angiosperms, in the class Magnoliatae or Dicotyledones. Within Takhtajan's Magnoliales, these compounds have been found in the families Magnoliaceae, Eupomatiaceae, and Annonaceae. In the Laurales, they are

widely distributed in the Lauraceae and Atherospermataceae and are also present in the Monimiaceae *sensu stricto*, Siparunaceae and Hernandiaceae (including Gyrocarpaceae). In the Aristolochiales, this type of alkaloid appears in the genus *Aristolochia*. A similar situation obtains in the Nelumbonales (*Nelumbo*). The Ranunculalean Menispermaceae, Ranunculaceae (including Hydrastidaceae) and Berberidaceae (including Nandinaceae) often synthesize these bases; their presence seems to be universal in all three Papaveralean families, Papaveraceae, Hypecoaceae and Fumariaceae.

The occurrence of benzyltetrahydroisoquinoline derivatives in other orders is quite isolated. They have been found in the Piperales, Ebenales, Euphorbiales and Myrtales. In the Rutales, the supposedly more primitive species of the *Zanthoxylum/Fagara* complex, *Evodia*, and *Phellodendron* (Rutaceae), produce a range of benzyltetrahydroisoquinoline metabolites which are seemingly replaced by anthranilic acid-derived alkaloids as specialization increases (26). In the Rhamnales, some Rhamnaceae produce benzyltetrahydroisoquinolines and aporphines which tend to be replaced in a few genera by styrylamine cyclopeptide alkaloids. Finally, isolated findings of these alkaloids have been reported in the Cornales (27) and Polemoniales (20, 28).

The class Liliatae or Monocotyledones is poor in taxa synthesizing benzyltetrahydroisoquinoline derivatives, which are restricted to the Liliales and Arales. More specialized isoquinoline alkaloids originating in different biogenetic pathways are fairly widely distributed, however, in the Liliales and Orchidales.

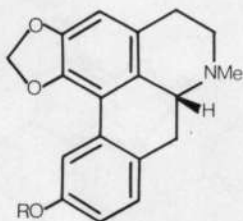
The widespread occurrence of benzyltetrahydroisoquinoline metabolites in the Atherospermataceae is a reflection of their Lauralean alliance and of their not-too-distant relationship with the other orders in which these compounds are frequent. It also lends support to the idea that benzyltetrahydroisoquinoline synthesis is a primitive chemical character (26).

Of the various types of benzyltetrahydroisoquinoline alkaloids found in the Atherospermataceae, aporphines, oxoaporphines and bisocclaurines are particularly common. Doryafranine (4) and S(+)-reticuline (5) are the only unelaborated benzyltetrahydroisoquinolines isolated so far from representatives of this group (*Laureliopsis* and *Doryphora*, respectively). Only one proaporphine, R(+)-stepharine (6) (in *Laurelia novae-zelandiae*) and one morphinandienone, R(-)-O-methylflavinantine (7) (in *Nemuaron vieillardii*) have been shown to be present. The accumulation of reticuline, doryafranine and stepharine, likely precursors of aporphines and oxoaporphines which are also synthesized by *Laureliopsis*, *Doryphora* and *Laurelia*, is probably of no taxonomic significance. The synthesis of O-methylflavinantine by *Nemuaron*, on the contrary, seems to be a rather isolated biosynthetic process in the Atherospermataceae.

The aporphines are the most widespread class of alkaloids and have been found in about twenty Dicotyledonous families as well as in the Monocotyledonous Liliaceae and Araceae. Their presence, therefore, seems to be devoid of any systematic significance beyond underlining the relationships known to exist between these families and the Atherospermataceae. With the apparent exception of *Daphnandra*, aporphines are found in all genera of this family and in every species studied. They are also present in the few Monimiaceae *sensu stricto* which have been examined for alkaloids. The classification of these bases on biogenetic grounds is discussed later.

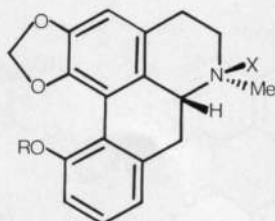
Oxoaporphines are presumably oxidation products of the corresponding aporphines (28) or nor-aporphines and are found in many of the families which contain their putative precursors. They are present in all the Atherospermataceae examined but *Daphnandra*; and, in view of this distribution, some comment on their occurrence in other species of the Monimiaceae alliance seems warranted in spite of the paucity of chemical data. In the Monimiaceae *sensu*

stricto, three species of *Palmeria* (29) and the monotype *Peumus boldus* (30, 31, 32) have been studied without any oxoaporphines being reported. A careful search for these weak bases in our laboratory gave no indication of their presence in the leaves and stem bark of the latter species. In the Siparunaceae, on the other hand, *Siparuna guianensis* has recently been shown to contain liriodenine (26) and the 3-methoxylated oxoaporphine cassamedine (33). We



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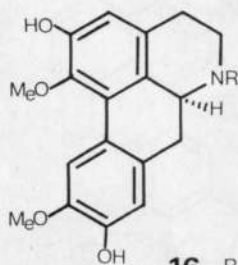
12 R = Me



13 R = H ; X = O

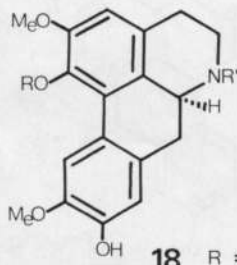
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15 R = H ; X = O



16 R = H

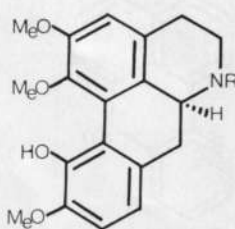
17 R = Me



18 R = H ; R' = Me

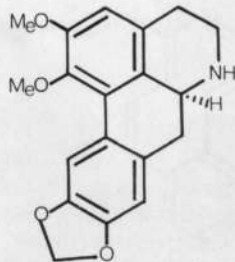
19 R = Me ; R' = H

20 R = R' = Me

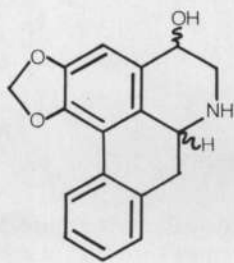


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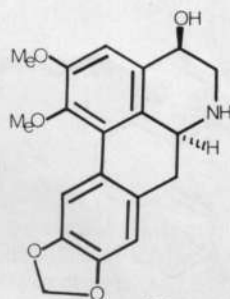
22 R = Me



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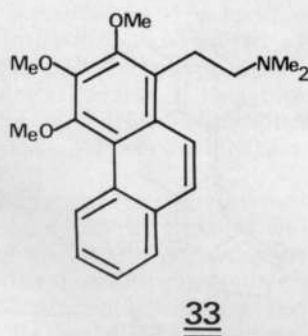
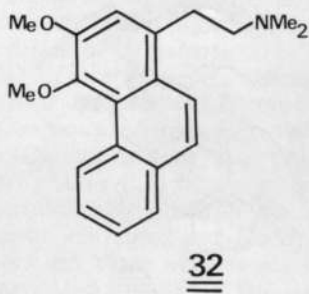
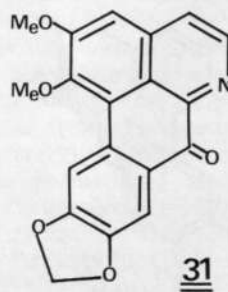
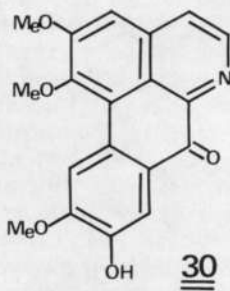
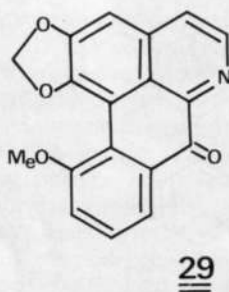
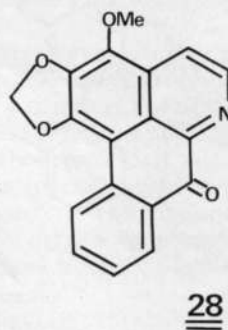
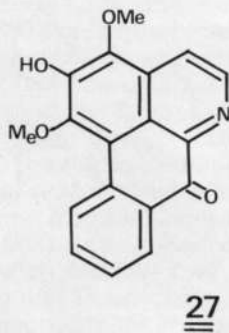
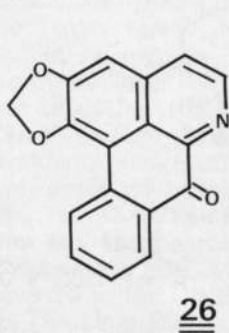
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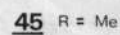
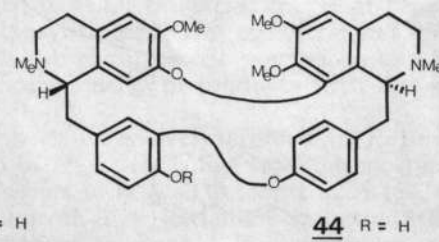
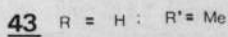
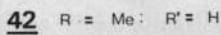
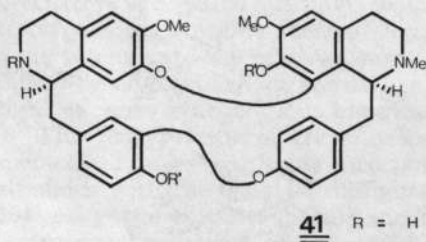
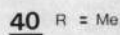
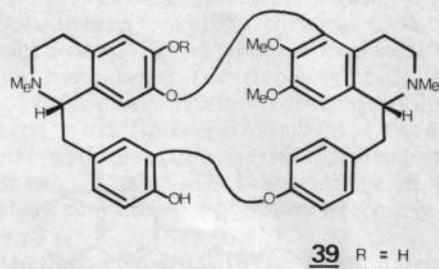
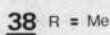
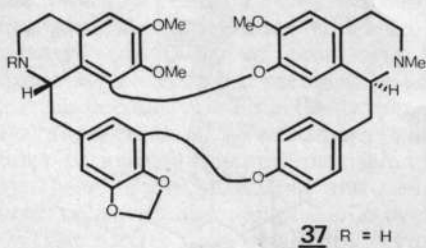
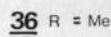
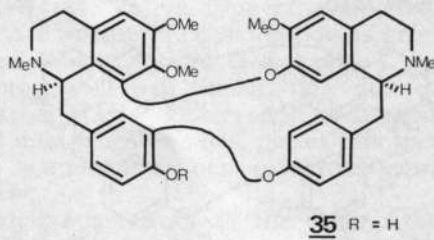
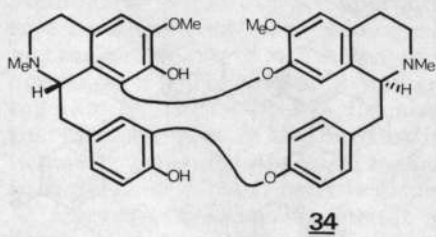
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feel that special attention must be paid to the possible accumulation of oxoaporphines in future alkaloid studies in the Monimiaceae alliance, as their presence or absence may be highly significant from the taxonomic viewpoint.

The bisbenzylisoquinolines are also a very widespread class of alkaloids. All the bases isolated from the Atherospermataceae and belonging to this group are, strictly speaking, biscoclaurines and are not as widely distributed in the family

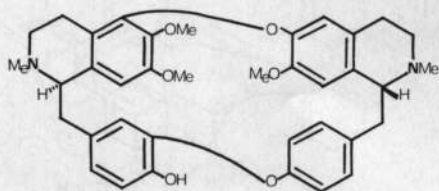
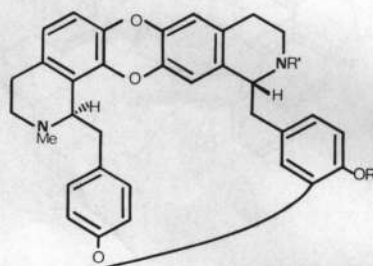
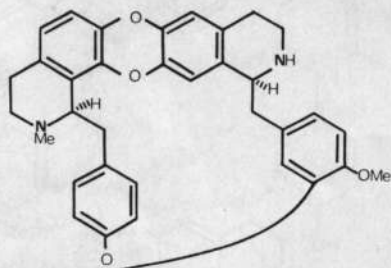
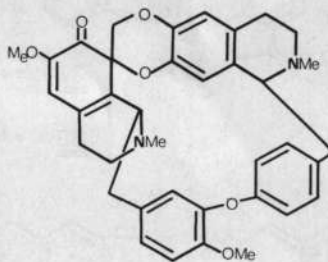
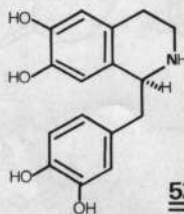
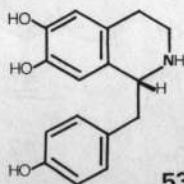


as the aporphines and oxoaporphines. They are the only type of alkaloid found in all the species of *Daphnandra* and are also present in the monotypic *Atherosperma moschatum* and in *Dryadodaphne novoguineensis*, *Nemuaron vieillardii*, and *Laurelia sempervirens*. However, they seem to be absent from *L. novaezelandiae*, *Laureliopsis philippiana*, and *Doryphora sassafras*.



From the foregoing it seems that *Daphnandra* occupies a unique position within the family, being the only genus apparently incapable of cyclizing benzyl-tetrahydroisoquinolines to morphinandienones, proaporphines or aporphines. On the other hand, this genus is characterized by an unusually large variety of bisocclaurines, some belonging to structural types which have rarely, if ever,

been found elsewhere (37, 38, 41-45, 47-51). The distinctiveness of the alkaloid chemistry of this genus seems to conflict with its affinities as based on its more traditional characters, according to which it is included by Pax (13), Hutchinson (8) and Schodde (7) in their respective definitions of the tribe Laurelieae. It should be remembered, however, that Pichon (3) singles out *Daphnandra* because of its orthotopous ovule, which is not found elsewhere in the Monimiaceae *sensu lato*.

4647 R = R' = H48 R = Me; R' = H49 R = R' = Me50515253

Atherosperma moschatum seems to diverge from the rest of the family in two chemical respects: it contains 1-(2-dimethylaminoethyl)phenanthrenes [atherosperminine (32) and its 2-methoxy-derivative (33)] that are presumably Hofmann elimination products of aporphine metho salts; and it also contains aporphine derivatives with an extra methoxy group at C-3 in the oxoaporphines, moschatoline (27) and atherospermidine (28) and at the corresponding C-2 in

methoxyatherosperminine (33)). No quaternary bases have been isolated from the Atherospermataceae, but their presence in appreciable amounts in plants which have already been examined for chloroform-extractable alkaloids is certainly a possibility. This poses the question whether the phenanthrenes are biosynthetic products or artifacts.

Laureliopsis philippiana is the only member of this family shown to accumulate 4-hydroxy-nor-aporphines (34) (24, 25), a type of compound as rare as the phenanthrene alkaloids but more worthy of consideration as genuine metabolites. The introduction of oxygen substituents at C-3 and C-4 would appear to be biogenetically unrelated processes, even though they are found together in *Abuta imene* (Menispermaceae) (35). However, it is suggestive that Schodde (7), on the basis mainly of anatomical studies, places this species (formerly *Laurelia philippiana* Looser) as a monotype next to *Atherosperma moschatum* in his tribe Atherospermateae.

Doryphora sassafras stands somewhat apart from all the other Atherospermataceae in its synthesis of corypalline (1) and the isoquinolones (2, 3), whatever their origin may be. Finally, *Nemuaron vieillardii* is distinguished by its capability of synthesizing a morphinandienone (7).

On the basis of alkaloid chemistry alone, *Atherosperma*, *Laureliopsis*, *Laurelia* and *Dryadodaphne* appear to be closely related. *Laureliopsis* oxidizes aporphines at C-4, whereas *Atherosperma* oxidizes them at C-3 and quaternizes or degrades them to phenanthrenes. *Doryphora* possesses the unusual capability of producing the non-benzylated (or debenzylated) isoquinoline skeleton but seems to be unable to couple benzyltetrahydroisoquinolines intramolecularly. This limitation is shared with *Laureliopsis* and *Laurelia novaezelandiae*. *Nemuaron vieillardii* cyclizes benzyltetrahydroisoquinolines to aporphines and morphinandienones. *Daphnandra* specializes in the synthesis of biscoclaurines and seems to lack the enzyme systems necessary to achieve intramolecular phenolic cyclization.

The distribution of alkaloid types in the Atherospermataceae is summarized in table 1.

Biogenetic considerations.—To the best of our knowledge, no biosynthetic work has been carried out in the Atherospermataceae or, for that matter, in the Monimiaceae *sensu lato*. Experiments in allied families using labelled precursors are many but have seldom shed light on the steric course of benzyltetrahydroisoquinoline-derived alkaloid biosynthesis. Far too little has been done to evaluate the relative incorporations of enantiomeric precursors, and the difficulty of establishing stereochemical homogeneity of products with low isotopic excesses is an obvious handicap.

The biosynthesis of these bases has been extensively studied in *Papaver* species. The stereospecific incorporation of *R*(-)-reticuline into the morphine alkaloids with the usual *R* configuration seems to be well demonstrated (64, 65, 66), as is the equally specific incorporation of *S*(+)-reticuline into the tetrahydroprotoberberines and derived metabolites in several Ranunculacean and Papaveralean genera (67, 68, 69, 70).

Regarding the aporphines, the utilization of *S*(+)-orientaline in the synthesis of *S*(+)-isothebaine by *Papaver orientale* was demonstrated in the early 1960's by Battersby's group (71, 72). Shortly thereafter, Barton's team showed that *S*(+)-*N*-methylcoclaurine is incorporated into *S*(+)-roemerine in *Papaver dubium*, but the *R*(-)-isomer is not (73, 74). The stereospecific pathway from *R*(+)-coclaurine to the proaporphine *R*-crotonisine in *Croton* (Euphorbiaceae) was also explored (75), with some confusion arising from the apparent inversion at C-6a in the reported transformation of *S*-linearisine into *R*-crotonisine (76). Feeding experiments with labelled *R*(-)-reticuline in *Litsea glutinosa* (Lauraceae) led to the isolation of *S*(+)-boldine with 0.01% of the label, which may well be meaningless (77).

TABLE 1. Occurrence of isoquinoline alkaloid types in the *Atherospermataceae*.

	simple isoquinolines	isoquinolones	benzylisoquinolines	proaporphines	aporphines	oxaporphines	phenanthrenes	morphinandienones	bisocclaurines	Formulae nos.	References
<i>Atherosperma moschatum</i>					++	++	+		+	22, 26-28, 30, 32-36	36-42
<i>Laureliopsis philippiana</i>			+		++	++			+	5, 8-9, 19, 21, 23-26, 30-31	16, 34
<i>Laurelia sempervirens</i>			+		++	++			+	19, 23, 26, 30-31, 36	16, 34, 43
<i>Laurelia novae-zelandiae</i>					++	++				6, 10-18, 26, 29	44-48
<i>Doryphora sasafra</i>					++	++				1-5, 9, 22, 26	17-18
<i>Dryadophne novoguineensis</i>		+			++	++				19, 26, 30, 39-40	49
<i>Nemuaron vieillardii</i>					++	++		+		7, 19-21, 30, 46	50-51
<i>Daphnandra repandula</i>					++	++				38, 44-45	52, 55, 58-59
<i>Daphnandra aromatica</i>					++	++				41-42	53, 57
<i>Daphnandra micrantha</i>					++	++				41, 43, 47	54, 56, 60
<i>Daphnandra tenuipes</i>					++	++				37-38, 42	56
<i>Daphnandra dieisii</i>					++	++				38, 44-45	56
<i>Daphnandra sp.</i>					++	++				48-50	62
<i>Daphnandra sp.</i>					++	++				51	63

Assuming that the chirality of C-1 in benzyltetrahydroisoquinolines is conserved in the course of biosynthetic elaboration, it is possible to make some generalizations.

As in other taxa, the biscoclaurine alkaloids found in the Atherospermataceae incorporate units derived from both *R*- and *S*-coclanoline without following any obvious pattern. The aporphines, on the other hand, can be assigned in most cases to two series with different biosynthetic precursors. With extension of Shamma's stereochemical rule (28), it can be said that the ring D-unsubstituted aporphines and those bearing a single oxygen atom on this ring at C-10, with the notable exception of the Papaveraceae, in which *R*- and *S*-reticuline are interconverted (64, 66), are derived from *R*-coclanoline (53) and have the *R* configuration. However aporphines with ring D monosubstituted at other positions and those bearing two oxygen atoms on this ring are usually derived from *S*-norlaudanoline (52) and have the *S* configuration.

In the Atherospermataceae, this biogenetic rule is illustrated by the *R*-coclanoline-derived *R*(-)-asimilobine (8); *R*(-)-anonaine (9); *R*(-)-roemerine (10); *R*(-)-mecambroline (11) and its methyl ether *R*(-)-laureline (12); the proaporphine *R*(-)-stepharine (6); probably 4-hydroxy-anonaine (24); and by the *S*-norlaudanoline-derived *S*(+)-laurolitsine (16); *S*(+)-boldine (17); *S*(+)-isoboldine (18); *S*(+)-laurotetanine (19) and its *N*-methyl derivative (20); *S*(+)-nor-isocorydine (21); *S*(+)-isocorydine (22); *S*(+)-nornantenine (23); 6a*S*,4*S*-hydroxy-nornantenine (25); and *S*(+)-reticuline (5), the likely precursor of some of these bases.

In this context, the presence of *R*(-)-pukateine (13), its methyl ether (14), and its *N*-oxide laurepukine (15) in *Laurelia novae-zelandiae* is a striking exception, as biogenetic theory would require these alkaloids to be synthesized from *R*-norlaudanoline (enantiomer of 52). The synthesis of *R*(-)-*O*-methylflavinantine (7) by *Nemuaron vieillardii* is the only other known instance in which a member of this family apparently utilizes *R*-norlaudanoline. If biosynthetic studies should indicate that this is actually the case and that in these species the enantiomers of some benzyltetrahydroisoquinoline are interconverted, the apparent stereochemical peculiarity of the Papaveraceae would be severely challenged. A careful examination of stereochemical assignments in putative norlaudanoline metabolites of other families may also be a rich source of stereochemical anomalies and should receive attention.

Conclusion.—According to the published data regarding the alkaloid chemistry of the Atherospermataceae, this family appears to be divisible into two chemical "tribes", one containing aporphines and further elaborated metabolites of these abundant bases and another coinciding with the genus *Daphnandra*, in which these alkaloids have not been found and seem to be replaced by biscoclaurines. This division cuts across the tribal classifications of Pax (13), Hutchinson (8) and Schodde (7) and suggests a possible rearrangement of the Atherospermataceous genera taking into consideration chemical evidence as well as, for example, embryological characters (3) which may have been underestimated in previous work. Benzyloquinoline dimers have been found in *Atherosperma*, *Laurelia*, *Dryadodaphne* and *Nemuaron*, but in these genera they appear as one more type of alkaloid derived from coclanoline, whereas in *Daphnandra* they are the only basic metabolites isolated so far. Further chemical studies on unexamined parts of these plants should clarify the position of this seemingly distinctive genus.

Aporphines occur frequently in the Magnoliaceae and Annonaceae, which are generally placed near the bottom of Angiospermous phylogenetic trees. The phenolic cyclizations leading to proaporphines and aporphines thus seem to be ancient processes which have been preserved in the course of evolution, surviving in some isolated genera of such specialized orders as the Euphorbiales and Arales.

The bisbenzylisoquinolines, on the contrary, are rare in the Magnoliaceae and Annonaceae and also in more advanced aporphine-synthesizing families like Hernandiaceae *sensu lato*, Lauraceae and Aristolochiaceae. The capability of effecting phenolic oxidative coupling between two benzylisoquinoline moieties is developed into an important metabolic route in the phyletic sequence Menispermaceae-Ranunculaceae-Berberidaceae. The synthesis of pilocereine by several Cactaceae (Caryophyllales) may be a vestige of the same ability inherited from some possibly Protoranunculalean ancestor. It is interesting that in the Laurales the Atherospermataceae should be the only family in which bisbenzylisoquinolines are fairly common, thus appearing to be a taxon in which alkaloid synthesis is evolving in a direction similar to that taken in the Menispermaceae-Ranunculaceae-Berberidaceae. The isolated occurrence of isoquinolones and corypalline in *Doryphora* points the same way.

If bisbenzylisoquinoline synthesis is regarded as an advanced process over phenolic cyclization to proaporphines and aporphines, it can be speculated that the Atherospermataceae which have retained the capability of synthesizing aporphines are more primitive chemically than *Daphnandra*, which has apparently lost it. Nevertheless, the aporphine C-3 and C-4 oxidations in *Atherosperma* and *Laureliopsis* should not be overlooked as possible signs of specialization along another phylogenetic branch.

The oxidation of aporphines at C-7 to hydroxy- and oxoaporphines is most frequent in the Magnoliaceae and Annonaceae and can also be considered as a primitive character in this context. It is found somewhat less often in the more advanced Hernandiaceae and Atherospermataceae and is rather rare in the Menispermaceae-Ranunculaceae-Papaveraceae and quite unknown in the Berberidaceae. We believe that a quantitative approach to the evolution of benzylisoquinoline chemistry in plants is now becoming possible with the rapid accumulation of reliable data, and we intend to attempt such an analysis in the near future.

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