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Review Paper

CHEMICAL STUDIES ON MEDICINAL MYRISTICACEAE FROM AMAZONIA*

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Summary

Drugs from Myristicaceae species are used in the Amazon region as hallucinogens and arrow poisons, as well as for the healing of infected wounds. The former effects were attributed by Schultes and Holmstedt to tryptamines and carbolines. The latter activity is now tentatively ascribed to pterocarpans and neolignans. This, and a proposal that the red colour of the bark resins may be due to oxidative dimers of flavans, are based on a review of the chemistry of Amazonian Myristicaceae.

Introduction

Ethnopharmacological interest in Myristicaceae was first evidenced in 1954 with Schultes' discovery that several species, *Virola calophylla* Warburg, *V. calophylloides* Markgraf and possibly *V. elongata* (Benth.) Warburg, represent the source of yakee-snuff, a potently hallucinogenic narcotic of the Amazon basin of Colombia (Schultes, 1954). Subsequent field research by the same author (Schultes, 1969) has indicated that the Waikà Indians of northwestern-most Brazil and adjacent Venezuela prepare their hallucinogenic epéna- or nyakwána-snuff basically from the resin of another species, *V. theiodora* (Spr. ex Benth.) Warburg, and has uncovered an interesting method of employing myristicaceous resin orally as a psychotomimetic agent. Finally, in a subsequent report, Schultes and Holmstedt (1971) indicated that the leaves, bark and resin of certain species of *Virola* and related genera are employed by unrelated groups of Indians for the preparation of washes believed to cleanse infected wounds or hasten their healing, and of plasters for the treatment of skin troubles. Three tribes of the Vauapés area of

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Colombia were stated to use two species of *Compsoneura* for treating what may be considered "mental conditions". Furthermore, the paper contains a fascinating report on the alternative use, made by Indian tribes of the upper Orinoco, of an identical alkaline preparation of bark-resin from *V. theiodora* as hallucinogenic snuff and as arrow poison.

A resumé of the work of Schultes and Holmstedt (1971), with some additional data from Le Cointe (1947), appears in Table 1 as an inspiring guide to pharmacological studies on the Amazonian Myristicaceae species. So far only the hallucinogenic properties of these plants have been traced to the presence of constituents of clearly defined structures. In the following exposé this and additional pertinent chemical knowledge are reviewed. It is hoped that the consequent hypotheses on further activity–structure correlations will stimulate work in this domain.

TABLE 1

Indigenous uses of Myristicaceae in Amazonia

Part	Preparation	Genus	Use	Treatment of:
Leaves	Tea	*Compsoneura*		Craziness, shaking
		Virola	Substitute for tea	Colic dyspepsias
	Plaster	*Iryanthera*		Infected wounds
		Virola		Fungal infection, itching of skin
Bark	Decoction	*Compsoneura*		Infected wounds
		Iryanthera		Ulcers, wounds
Bark	Plaster	*Virola*		Fungal skin infection, erysipelas, skin discoloration, toothache
	Decoction plus ash	*Virola*	Hallucinogenic snuff Hallucinogenic pellets Arrow poison	
Inner bark		*Virola*	Hallucinogenic smoke	
Kino		*Virola*	Brain stimulant	Bleeding, colic, ulcerating wounds
Sap		*Virola*		Haemorrhoids
Latex		*Iryanthera*		Stomach poisoning
Fruit		*Iryanthera*	Fish bait	
Seed	Fat	*Dialyanthera*		Skin infections of domestic animals, parasites
		Virola		Skin diseases, erysipelas, haemorrhoids, intestinal worms, rheumatism, asthma, tumours of joints, bad breath

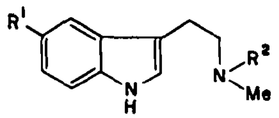
Bases

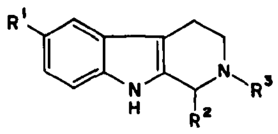
Anadenanthera peregrina (L.) Speg. (Leguminosae–Mimosoideae), the most widely recognized source of hallucinogenic snuffs made by South American Indian tribes, owes its biological activity chiefly to 5-methoxy-*N,N*-dimethyltryptamine (1.1d), accompanied by other tryptamines and 6-methoxy-β-carbolines (*e.g.* 1.2c). Agurell *et al.* (1969) were able to show that the same is true for epéna and nyakwána. One nyakwána preparation proved to be extraordinarily high in base content (11%). This may explain why the resin of *Virola theiodora* is also used as an arrow poison.

Considerable differences in the base composition of different parts of single plants (Agurell *et al.*, 1969), different species (Table 2) and even for analyses of different specimens (Cassady *et al.*, 1971) were encountered. When examining the data of Table 2 with respect to uses, it must be kept in mind that the preparation of snuffs, pellets and poison involves concentration of the resinous bark exsudate to a thick syrup which is subsequently dried, powdered or rolled into pellets which are then coated with leachings from ash. Such treatment would be expected to alter the original base composition. For example, 1.2c would suffer oxidation to 1.2d and the fully aromatic 1.2e (Cassady *et al.*, 1971). The latter compound, with its known monoamine oxidase inhibitory activity, may potentiate the hallucinogenic effect of the other bases (Schultes, 1969; Cassady *et al.*, 1971).

Fatty acid derivatives

"Ucuhuba" fats are produced industrially from *Virola sebifera* Aublet, *V. surinamensis* (Rol.) Warburg and other species. Their value is due to the high trimyristin (29 - 38 mol %) and laurodimyristin (30 - 39 mol %) content (Steger and van Loon, 1935; Culp *et al.*, 1965). Soaps of myristic acid





	R¹	R²
1.1a	H	H
1.1b	H	Me
1.1c	OMe	H
1.1d	OMe	Me

	R¹	R²	R³	Δ
1.2a	H	H	Me	
1.2b	OMe	H	Me	
1.2c	OMe	Me	Me	
1.2d	OMe	Me	H	1, 2
1.2e	OMe	Me	H	1, 2, 3, 4

Chart 1. Bases.

TABLE 2

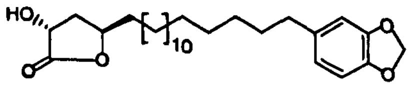
Occurrence of bases in *Virola* species (% = bases in g/100 g of dry part, *major component)

Species	Part	%	1.1a	1.1b	1.1c	1.1d	1.2a	1.2b	1.2c	1.2d	1.2e	Ref.
V. theiodora	Bark	0.250	+	*		*		+				[1]
	Root	0.017		+	+	*						
	Leaves	0.044		*		+	+					
V. calophylla	Bark	0.009		*		+						
	Root	0.001		*		+						
	Leaves	0.155	+	*								
V. rufula	Bark	0.200		+	+	*		+				
	Root	0.144		+	+	*		+				
	Leaves	0.098	+	*								
V. multinervia	Bark	0.001		*								
	Root	0.001		*		*						
	Leaves											
V. venosa	Bark											
	Root	0.001				+						
	Leaves	0.001			+	+						
V. sebifera	Bark			+								[2]
V. cuspidata	Leaves								*	+	+	[3]

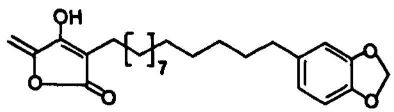
[1] Agurell *et al.*, 1969; [2] Corothie and Nakano, 1969; [3] Cassady *et al.*, 1971.

($C_{13}H_{27}\cdot CO_2H$) are reputed for the mildness of action on the skin and the creamy texture of their lather.

The biogenesis of juruenolide (2.1) and of 2-ω-piperonyltridecyl-4-methylidenetetronic acid (2.2), constituents of *Iryanthera juruensis* Warburg (Franca *et al.*, 1975) and *I. elliptica* Ducke (Braz Filho *et al.*, 1979a), respectively, may involve condensation of cinnamate with either C_{18} and C_{16} fatty acids, respectively, or with C_{14} and C_{12} fatty acids, respectively. Concurrent phenomena would include in the first case decarboxylation and oxidation of the aliphatic terminals, and in the second case condensation with pyruvate. Analogous doubts concern the origin of the avocatins (Alves *et al.*, 1970),



2.1



2.2

Chart 2. Fatty acid derivatives.

the obtusilactones, litsenolides and mahuba lactones (Martinez *et al.*, 1979), as well as rubrenolide and rubrynolide (Franca *et al.*, 1977) from Lauraceae species (Gottlieb, 1972). All these compounds should thus belong to the same biogenetic group, a hypothesis which becomes more plausible if the morphological affinity of Lauraceae and Myristicaceae is considered.

Neolignans

The fungistatic or fungicidal activity of the seed fat from *Dialyanthera otoba* (H. et S.) Warburg was ascribed to the presence of (—)-otobain (3.2a). Several structurally similar neolignans (3.1, 3.2) were subsequently isolated as minor constituents of the same material and from *Virola* species (Table 3). These include (+)-guaiacin (3.1c), an active principle of *Guaiacum officinale* L. (Zygophyllaceae) (Gottlieb, 1978).

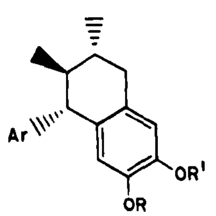
In connection with a project designed to provide naturally occurring compounds active against the penetration of cercariae of *Schistosoma mansoni* Sambon into the human body, about fifty plant species were collected at the mouth of the Amazon and submitted to biological testing. A hexane extract of the leaves of *V. surinamensis* showed the strongest activity. The extract contained elemicin and four neolignans (Table 3). Its biological activity, however, was due solely to virolin (3.4a) and surinamensin (3.4b) which belong to a novel natural product type. The ketone 4.1, prepared as

TABLE 3

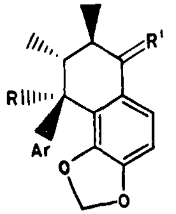
Occurrence of neolignans in Amazonian Myristicaceae

Species	Part	Compound	Ref.
Dialyanthera otoba	Seed	(+)-Otobaphenol (3.1a)	[1]
		(+)-Isogalcatin (3.1b)	
		(—)-Otobain (3.2a)	
		(—)-Hydroxyotobain (3.2b)	
Virola carinata	Bark	(+)-Guaiacin (3.1c)	[2]
		(—)-Isootobaphenol (3.1d)	
		(—)-Galcatin (3.1e)	
	Wood	(—)-Galcatin (3.1e)	
V. cuspidata	Bark	(—)-Hydroxyotobain (3.2b)	[3]
V. sebifera	Seed	Hydroxyoxootobain (3.2c)	[4]
V. surinamensis	Leaves	Galbacin (3.3a)	[5]
		(+)-Veraguensin (3.3b)	
		Virolin (3.4a)	
		Surinamensin (3.4b)	
V. guggenheimii	Wood	Eusiderin (3.5a)	[6]
V. pavonis	Bark	Eusiderin C (3.5c)	
		Eusiderin D (3.5d)	

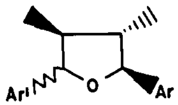
[1] Gottlieb, 1977; [2] Gottlieb *et al.*, 1976; [3] Blair *et al.*, 1969; [4] Lopes *et al.*, 1979; [5] Barata *et al.*, 1978; [6] Fernandes *et al.*, 1979.



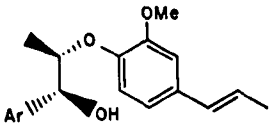
	Ar	R	R[1]
3.1a	Pi	H	Me
3.1b	Pi	Me	Me
3.1c	Gu	H	Me
3.1d	Gu	$-CH_2-$	
3.1e	Ve	$-CH_2-$	



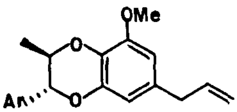
	Ar	R	R[1]
3.2a	Pi	H	2H
3.2b	Pi	OH	2H
3.2c	Pi	OH	O



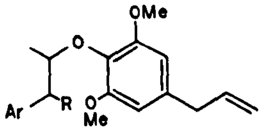
	Ar	Ar[1]
3.3a	α-Pi	Pi
3.3b	β-Ve	Ve



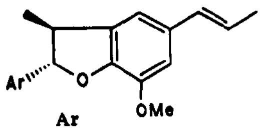
	Ar
3.4a	Ve
3.4b	Tp



	Ar
3.5a	α-Tp
3.5b	α-Pi
3.5c	β-Tp
3.5d	β-Ve



	Ar	R
3.6a	Pi	OH
3.6b	Tp	OH
3.6c	Gu	OH
3.6d	Pi	OAc
3.6e	Hd	OH
3.6f	Tp	H

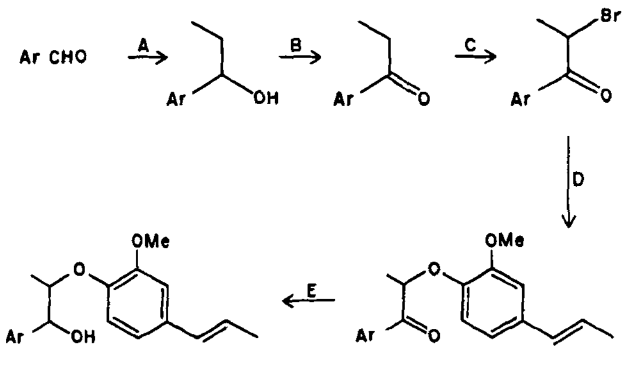


	Ar
3.7a	Gu
3.7b	Sy

Chart 3. Neolignans.
Symbols for aryl groups used in formulae:

Ca	Catechyl (3,4-dihydroxyphenyl)
Pi	Piperonyl (3,4-methylenedioxyphenyl)
Gu	Guaiacyl (4-hydroxy-3-methoxyphenyl)
Ve	Veratryl (3,4-dimethoxyphenyl)
Tp	Tri-*O*-methylpyrogallyl (3,4,5-trimethoxyphenyl)
Sy	Syringyl (4-hydroxy-3,5-dimethoxyphenyl)
Hd	3-Hydroxy-4,5-dimethoxyphenyl

an intermediary product during the synthesis of surinamensin 4.2 (=3.4b) (Barata *et al.*, 1978), proved cytotoxic (de Oliveira, 1979), as did natural neolignans such as megaphone from Lauraceae (Kupchan *et al.*, 1978) and



4.2 4.1

A ≡ (1) EtMgBr, Et_2O; (2) dry ice, H_2O. B ≡ CrO_3, H_2SO_4. C ≡ Br_2, $CHCl_3$, 0 °C. D ≡ sodium salt of *E*-isoeugenol, DMF. E ≡ $NaBH_4$, EtOH.

Chart 4. Preparation of virolin (4.2, Ar ≡ Ve) and surinamensin (4.2, Ar ≡ Tp).

nordihydroguaiaretic acid from Zygophyllaceae, which has even been implicated in cancer therapy (Oliveto, 1972).

Virolin (3.4a) and surinamensin (3.4b) are close biosynthetic relatives of eusiderin (3.5a) and eusiderin B (3.5b) from Lauraceae (Braz Filho *et al.*, 1976b). Indeed, as was consequently to be expected, eusiderin (3.5a), as well as two further neolignans of the benzodioxane type, eusiderins C (3.5c) and D (3.5d), occur in *Virola* species (Table 3).

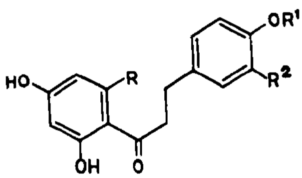
Although derived from the Malaysian *Myristica fragrans* Houtt., brief reference is also in order here to the common spices nutmeg and mace, which are the seed and aril of the fruit of the tree, and have been used in folk medicine for their alleged abortifacient, narcotic and therapeutic properties. These materials again contain neolignans (3.6, 3.7) (Forrest *et al.*, 1974), which are structurally closely akin to 3.4. The proven occurrence of neolignans in three genera and in several parts of Myristicaceae (Table 3) clearly justifies the expectation that this class of phenylpropanoids will be recognized as a general feature of the family.

A last look at the neolignan structures from Myristicaceae is in connection with a report according to which the kino of *Virola bicuhyba* (Schott) Warburg is a "brain stimulant", reviving the memory and the intelligence (Table 1). Similar properties were recently ascribed to the schizandrin-type neolignans, extracted from *Schizandra chinensis* Bail., long used in the orient as a stimulant (Gottlieb, 1978). The Schizandraceae family, by the way, belongs to the plant order Magnoliales, precisely as do the Myristicaceae.

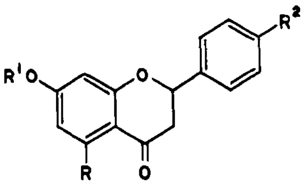
Thus, for several reasons, the lead into the neolignan chemistry of the Myristicaceae would seem well worth following.

Flavonoids

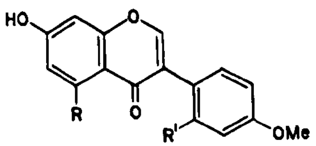
Biosynthetic derivatives of cinnamate + triacetate of the Amazonian Myristicaceae include dihydrochalcones (5.1a) from *Iryanthera laevis* (Braz



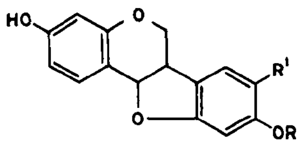
	R	R¹	R²
5.1a	OMe	Me	H
5.1b	H	H	OMe



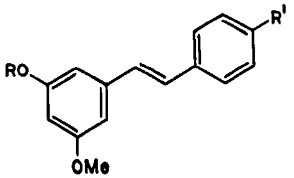
	R	R¹	R²
5.2a	H	Me	OMe
5.2b	OH	H	H



	R	R¹
5.3a	H	H
5.3b	H	OH
5.3c	OH	H
5.3d	OH	OH
5.3e	OH	OMe



	R	R¹
5.4a	Me	H
5.4b	CH_2O	



	R	R¹
5.5a	H	H
5.5b	Me	OMe

Chart 5. Flavonoids, isoflavonoids and stilbenes.

Filho *et al.*, 1979b) and from *I. polyneura* Ducke (Almeida *et al.*, 1979), flavanones (5.2a) from *Virola carinata* (Benth.) Warburg (Gottlieb *et al.*, 1976) and (5.2b) from *I. polyneura* (Almeida *et al.*, 1979), flavans (6.2), 1,3-diarylpropanes (6.4), 1,3-diaryl-2-hydroxypropanes (6.8), isoflavones (6.9), pterocarpans (6.10) and stilbenes (5.5). A unified biogenetic scheme accounts satisfactorily for the formation of all flavonoids (Chart 6) (Gottlieb 1977).

Flavans

Known plant sources for flavans include, in addition to the Myristicaceae only Liliopsida (Table 4), where they appear in coloured resins, such as "dragon's blood" (ex *Daemonorops draco* Blume), jointly with their oxidativ dimers (*e.g.* the biflavonoid dracorubin) (Whalley, 1961; Merlini and Nasini, 1976). It is tempting to consider a similar composition for the blood-red resins of *Virola* and related genera, noted by Schultes (1969). Pharmacologi-

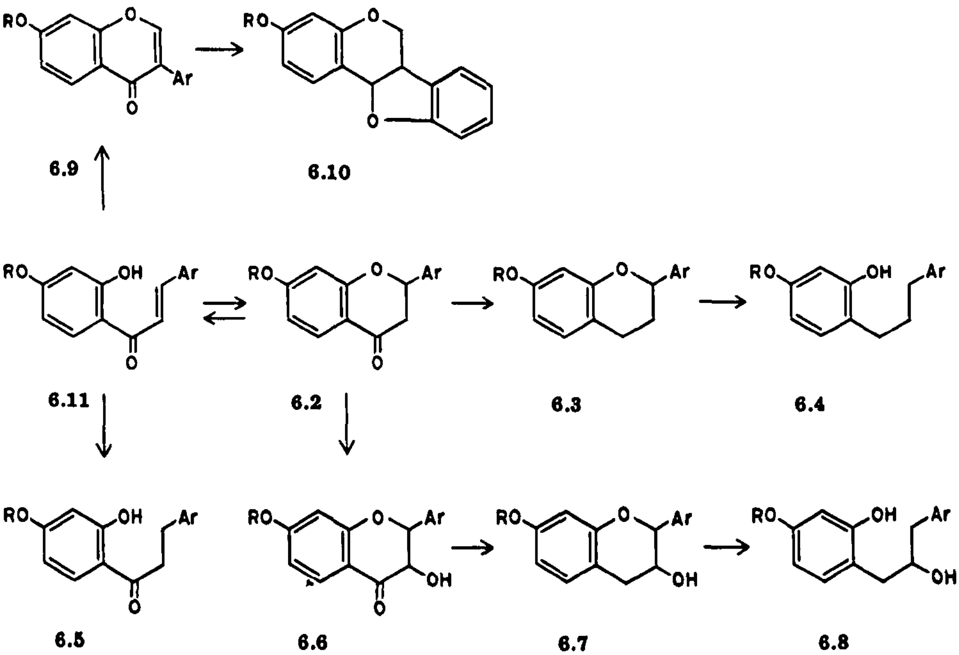


Chart 6. Biogenesis of flavonoids.

cal activity of biflavonoids has been reported (Marini-Bettòlo and Delle Monache, 1972; Schwarting, 1977) with respect to the inhibition of tumour growth *in vivo* (de Oliveira *et al.*, 1972).

Syntheses of flavans, effected in support of structural proposals, are summarized in Chart 7. Reduction of flavans with sodium in liquid ammonia, which can be used for the same purpose, gives 1,3-diarylpropanes (Birch and Salhuddin, 1964).

1,3-Diarylpropanes

1,3-Diarylpropanes have so far been located only in Amazonian Myristicaceae (Table 5). The structural proposals for virolane (8.2) and virolanol (8.4) were substantiated by the syntheses represented in Chart 7.

1,3-Diarylpropanes were available by the reduction of chalcones long before their discovery in nature. Several synthetic derivatives led to the corresponding dienones by oxidative coupling (Chart 9) (Tobinaga, 1975). The consequent expectation that spiro-derivatives should also occur in nature was recently fulfilled with the isolation of spiroelliptin (10.1) from *Iryanthera elliptica* Ducke (Braz Filho *et al.*, 1979a). On the other hand, 1,3-diaryl-2-propanols were available by the hydrogenolysis of catechols (6.7).

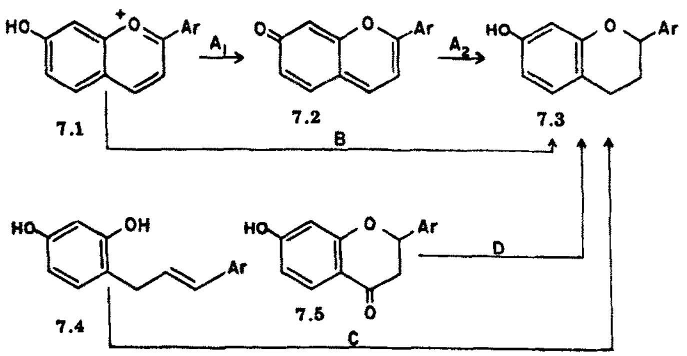
1,3-Diarylpropanes can be prepared, furthermore, by the direct cinnamylation of phenols and catalytic hydrogenation of the resulting cinnamyl phenols (7.4). Products obtained in this way recently appeared in the patent literature (Jurd, 1976) and are stated to prevent and/or retard the growth of malaria mosquito larvae.

TABLE 4

Occurrence and synthesis of flavans

Source and method of synthesis (*cf.* Chart 7)	Substituents at C-							Config. at C-2	Ref.
	5	6	7	8	2′	4′	5′[a]		
Daemonorops draco	OMe		OH					S	[1]
7.1 → 7.3 via A									
D. draco	OMe	Me	OH					S	[1]
7.1 → 7.3 via A									
Buckleya lanceolata	OX		OH			OH		S	[2]
7.5 → 7.3 via D									
Xanthorrhoea preissii[b]	OMe		OMe			OMe		R,S	[3]
Stypandra grandis			OMe			OH		S	[4]
7.1 → 7.3 via B									
Dianella tasmanica			OH			OH			[4]
7.1 → 7.3 via B									
D. revoluta			OMe	Me		OH		S	[4]
7.1 → 7.3 via B									
Iryanthera coriacea	OMe		OMe			OH	OH	R,S	[5]
I. juruensis			OMe		OH	OCH_2O		R,S	[5]
I. elliptica			OH			OH	OMe	R,S	[6]
I. laevis		Me	OH	Me	OH	OCH_2O			[7]
	OMe		OH	Me	OH	OCH_2O			[7]
	OH	Me	OMe	Me	OH	OCH_2O			[7]

[a] In absence of substitution at C-2′, more properly designated 3′.
[b] Isolated from the methylated resin.
X D-Xylose.
[1] Cardillo *et al.*, 1971; [2] Sashida *et al.*, 1976; [3] Birch and Salhuddin, 1964; [4] Cooke and Down, 1971; [5] Franca *et al.*, 1974; [6] Braz Filho *et al.*, 1979a; [7] Braz Filho *et al.*, 1979b.



$A_1 \equiv Na_2CO_3$; $A_2 \equiv NaBH_4$. $B \equiv H_2$/cat. $C \equiv$ acid. $D \equiv NaBH_4$, EtOH or Zn/Hg, HCl.

Chart 7. Methods of synthesis of flavans.

Isoflavonoids

According to recent findings (Braz Filho *et al.*, 1976c; 1977), isoflavonoids seem to constitute a general characteristic of Amazonian Myristicaceae.

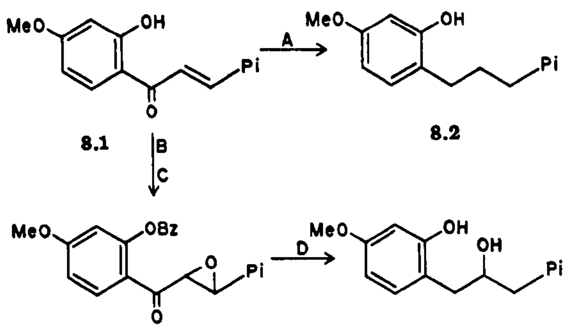
TABLE 5

Occurrence and synthesis of 1,3-diarylpropanes (structural types 6.4 and 6.8) from *Iryanthera* and *Virola* species

Source and method of synthesis (*cf.* Chart 8)	Trivial name of compound	Substituents at C- 2	2′	3′	4′	5′	2″	4″	5″[a]	Ref.
V. multinervia	Virolane		OH		OMe			OCH_2O		[1]
V. caducifolia										[2]
V. divergens										[3]
V. flexuosa										[2]
V. guggenheimii										[3]
V. melinonii										[4]
V. pavonis										[4]
V. surinamensis										[4]
V. venosa										[4]
V. coriacea										[5]
I. polyneura										[6]
8.1 → 8.2										[7]
I. coriacea					OMe		OH	OCH_2O		[5]
I. coriacea			OH		OH			OCH_2O		[5]
I. polyneura										[6]
I. paraensis										[8]
I. tricornis										[9]
V. multinervia			OMe		OH			OMe	OH	[10]
I. coriacea			OMe		OH			OH	OMe	[5]
I. elliptica										[11]
I. paraensis										[8]
I. tricornis										[9]
I. coriacea			OH		OH		OMe	OCH_2O		[5]
I. laevis										[12]
I. paraensis										[8]
I. tricornis										[9]
I. polyneura			OH	Me	OH		OMe	OCH_2O		[6]
I. laevis										[12]
I. paraensis										[8]
I. coriacea			OH	Me	OH	Me	OH	OCH_2O		[5]
I. laevis										[12]
I. laevis			OH		OMe	Me	OMe	OCH_2O		[12]
										[12]
In all virolane-containing *V.* spp.	Virolanol	OH	OH		OMe			OCH_2O		[1-4]
8.1 → 8.4										[7]

[1] Braz Filho *et al.*, 1973; [2] Braz Filho *et al.*, 1977; [3] Fernandes *et al.*, 1979; [4] Gottlieb *et al.*, 1973; [5] Lima *et al.*, 1975; [6] Almeida *et al.*, 1979; [7] de Oliveira *et al.*, 1973; [8] Silva *et al.*, 1979; [9] Vieira *et al.*, 1979; [10] Braz Filho *et al.*, 1976a; [11] Braz Filho *et al.*, 1979a; [12] Braz Filho *et al.*, 1979b.

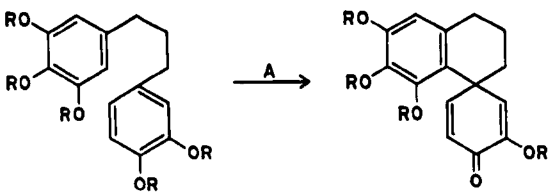
Specifically, it was reported that in the trunk wood of *Virola caducifolia* W. Rodr. formononetin (5.3a) and biochanin-A (5.3c), two relatively widespread isoflavones, are accompanied by the respective 2′-hydroxy- (5.3b, 5.3d) and 2′-methoxy- (5.3e) derivatives. With the exception of biochanin-A, all these



8.1 8.2 8.3 8.4

A ≡ H_2, Pd/C, AcOH. B ≡ BzCl, C_5H_5N. C ≡ H_2O_2/NaOH. D ≡ H_2, Pd/C, AcOH.

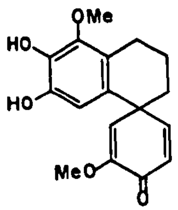
Chart 8. Methods of synthesis of 1,3-diarylpropanes.



9.1 9.2

A ≡ [Fe(DMF)$_3$Cl$_2$]·[FeCl$_4$].

Chart 9. Transformation of flavans into spiro-dienones.



10.1

Chart 10. Spiroelliptin.

isoflavones were also isolated from the wood of *Virola multinervia* Ducke. The presence of 5.3c in this species is, nevertheless, highly probable, since it should function as a precursor of the 2′-hydroxyisoflavone 5.3. 2′-Hydroxyisoflavones are precursors of pterocarpanoids, and, indeed, two compounds of this class, (±)-medicarpin (5.4a) and (±)-maackiain (5.4b) were isolated, together with kaur-16-en-19-oic acid, from the wood of *Osteophleum platyspermum* (DC.) Warburg.

Stilbenes

In the Lotoideae, the subfamily of the Leguminosae to which isoflavonoids, and specially pterocarpans, were thought to be largely confined (Wong

1975), such metabolites are frequently accompanied by stilbenes. It is, therefore, biosynthetically significant that the wood of *Virola venosa* (Benth.) Warburg contains 3-hydroxy-5-methoxy-*E*-stilbene (5.5a) (Braz Filho *et al.*, 1977) and the bark of *Virola cuspidata* (Benth.) Warburg contains 3,5,4'-trimethoxy-*E*-stilbene (5.5b) (Blair *et al.*, 1969).

Conclusion

Recent chemical investigations on Amazonian Myristicaceae suggest the widespread occurrence of neolignans, isoflavones, flavans and 1,3-diarylpropanes in this family, and lead to the hypotheses that the alleged usefulness of plasters made from leaves or bark resin in the treatment of skin infections may be due to the fungitoxic or fungistatic activity of pterocarpans (Harborne, 1977) and possibly neolignans, and that the red colour of the bark resins may be due to oxidative dimers of flavans. Both proposals await testing.

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