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Potential Utilization of Brazilian Wood Extractives

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Attention is called to the potentialities of Brazilian trees in offering compounds of biological interest. The chemical knowledge which has been acquired about phenolics (arylpyrones, benzophenones, neolignans, xanthones, coumarins, isocoumarins, flavonoids), polyketides, terpenoids (sesqui-, di-, triterpenoids, prenylnaphthoquinones), and alkaloids is reviewed, provided a group of biogenetically related compounds has been isolated and biodynamic activity can be pointed out.

A conservative estimate situates the number of plant species native to Brazil close to 120000. An ever increasing number of Brazil's wood-producing species is constantly being absorbed into the mainstream of international commerce. Their utilization for uses other than construction and carpentry, charcoal, and cellulose manufacture constitutes a challenge which chemists and pharmacologists have only recently started to meet. It is true that interest in the natural wealth of the country reaches back to the time of its discovery by Portuguese seafarers in the year 1500. The first orderly description of plants used for medicinal purposes by the inhabitants was undertaken by a scientific mission brought to the northeastern part of the country by Maurice of Nassau during the time of its occupation by the Dutch (1630–1654). It was Willem Pies, a physician, who described the most important indigenous drugs, among which were jaborandi, ipecac, and tobacco.

One hundred and seventy years later, another mission played a decisive role in the beginnings of scientific activity in Brazil. Brought to the recently independent monarchy by princess Leopoldina of Austria, the bride of Pedro I, the country's first emperor, its most famous members, Johann Baptist von Spix, zoologist, and Karl Friedrich Phillip von Martius, botanist, exhaustively documented their thorough observations on the country's natural wealth. It was upon Martius' encouragement that Theodor Peckolt, an obscure pharmacist from Silesia, arrived in Brazil in 1847. With admirable drive and enthusiasm Peckolt analyzed by methods available to him at the time over 6000 plants, publishing the results of his studies in more than 150 papers. Although his analyses were necessarily crude by present-day standards, he nevertheless described a number of chemical entities which have withstood the rigor of modern scrutiny. Thus, Peckolt (1870) was probably the first to isolate, describe, and name an iridoid. He extracted the bitter principle of agoniada bark (*Plumeria lancifolia* Mart., Apocynaceae) and accordingly called it agoniadin. Twenty-five years later Boorsma (1894) isolated the same substance from *P. acutifolia* Poir. and, unaware of Peckolt's work, named it plumierid. Shortly afterward Franchimont (1899, 1900) recognized the identity of the two compounds. The name plumierid or plumieride has been maintained in the literature, but precedence actually belongs to agoniadin. The structure (Figure 1, **1**) was elucidated, 88 years after isolation, by Halpern and Schmid (1958).

The properties of specific pure iridoids have been investigated only in a few cases (Sticher, 1977). Plumieride exhibits a weak activity against fungi, while several nonglucosidic iridoids from *Plumeria* species were shown to possess antimicrobial properties (Jewers et al., 1975).

Iridoids, both nonglucosidic and in the form of glucosides, have also been found in another Brazilian tree, the genipapo (*Genipa americana* L., Rubiaceae). Genipic acid and genipinic acid (Figure 1, **2**) are also antimicrobial (Tallent, 1964), whereas the glucosides geniposide and geniposidic acid (Figure 1, **3**) exhibit purgative activity (Yamaguchi et al., 1974, 1976; Inouye et al., 1974).

These and investigations on many other natural compounds have been sparked by indigenous use of their plant hosts, a topic which we brought recently into historical focus with respect to Amazonian species (Gottlieb and Mors, 1978). The best known outcomes of such studies concern emetine from ipecac, pilocarpine from jaborandi, and curarizing alkaloids from several Loganiaceae and Menispermaceae, classical drugs originally introduced from Brazil and supplied from the mentioned plant sources to this day (Mors and Rizzini, 1966; Valle, 1978).

In more recent times, particularly during the last 20 years, considerable activity in the field of phytochemistry has been going on in Brazil. Hundreds of compounds have been isolated from plants and their structures have been established. Brazilian pharmacologists have, nevertheless, only very recently begun to undertake a purposeful study of plant products, concentrating to this day on the so-called etiotropic properties, i.e., activity against organisms which are the causative agents of diseases. Outstanding among these are schistosomiasis and Chagas' disease, nonexistent in the more developed countries of Europe and North America. The systematic study of organotropic properties, i.e., those manifest on higher animals and man, is just now being initiated. It is to be expected that many of these investigations will lead to interesting practical applications.

We shall now endeavor to convey, in a number of charts, the chemical knowledge which has been acquired about

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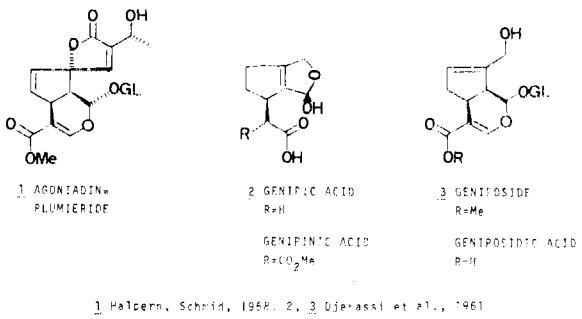


Figure 1. Iridoids from Brazilian Apocynaceae and Rubiaceae.

the constituents of Brazilian trees, provided (1) not just one or two, but a group of biogenetically related compounds has been isolated, and (2) some kind of biodynamic activity can be pointed out, relative to at least one or the other of its members.

PHENOLICS

Arylpyrones and Benzophenones. Modern phytochemical research in Brazil began in the 1950's, dealing with the arylpyrones of the genus *Aniba* (Lauraceae). This class of compounds had been known since Borsche's work on the constituents of kawa root (*Piper methysticum* Forst., Piperaceae) (Mors et al., 1962). Kawa was used in Polynesia for centuries to prepare an intoxicating beverage and in Europe before World War I for the treatment of cystitis, gonorrhoea, and gout (Israili and Smissman, 1976). It is now known that the arylpyrones are CNS depressant, which explains the sedative and soporific properties of the drug. In addition, the pyrones possess analgetic, antiarrhythmic, antiedemic, antimycotic, antiphlogistic, local anesthetic, smooth muscle relaxant, and spasmolytic activity, besides potentiating barbiturate narcosis and protecting against chemo- and electroshock. A structure–activity investigation on this class of compounds was conducted comparing the effect of structural differences on the anticonvulsant and local anesthetic activity of the four types of pyrones known at the time (Figure 2, 2–4). The degree of hydrogenation of the molecule has a marked influence on the effectiveness. In particular, the compounds with conjugated double bonds have the lowest activity (Meyer and Kretzschmar, 1969). The remaining, more recently discovered types (Figure 2, 5–8), deserve no doubt to be investigated, particularly since most of these structures are nowadays accessible through synthesis (Figure 3).

4-Methoxyphenylcoumalin (Figure 4, 1), the simplest of the pyrones, remarkably has a nitrogenous analogue in anibine (Figure 4, 2), where the phenyl substituent is replaced by β-pyridyl (Mors et al., 1957). Anibine itself was shown to have analeptic properties (Gonçalves et al., 1958) and its camphosulfonate has been patented for use as an antispasmodic agent in the treatment of heart and respiratory failure, as well as in comatose conditions induced by morphine and barbiturates (Boissier and Combes, 1964).

The same kind of relationship exists between cotoin (Figure 4, 3) and duckein (Figure 4, 4), both compounds also isolated from *Aniba* species. Cotoin, a benzophenone, was once used as an antiseptic and adstringent in the treatment of intestinal ailments and as a sudorific (Messner, 1926). Nothing is known about the pharmacology of duckein.

Neolignans. The genus *Aniba* revealed itself additionally a rich source of a biogenetic group of compounds designated neolignans.

Investigations concerning the pharmacologic activity of neolignans (Gottlieb, 1974, 1978a,b) should derive motivation by their structural relation to the lignans which attained some importance as antitumor and cytotoxic agents (Cordell and Farnsworth, 1974, 1976). Most of the neolignans with known biodynamic properties, such as otobain, nordihydroguaiaretic acid and schizandrin, are 8.8′ (= β,β′) linked phenylpropanes (Gottlieb, 1977b). Among the ca. 100 neolignans isolated from Brazilian Lauraceae and Myristicaceae during the past few years, however, only a few belong to this tail-to-tail linked type. The vast majority of these natural oxidative dimers show head-to-head (Figure 5) and tail-to-head (Figures 6, 8–10) links. As little as is known about their biological properties will now be reviewed.

The bark of *Magnolia officinalis* Red. et Wills. (Mag-

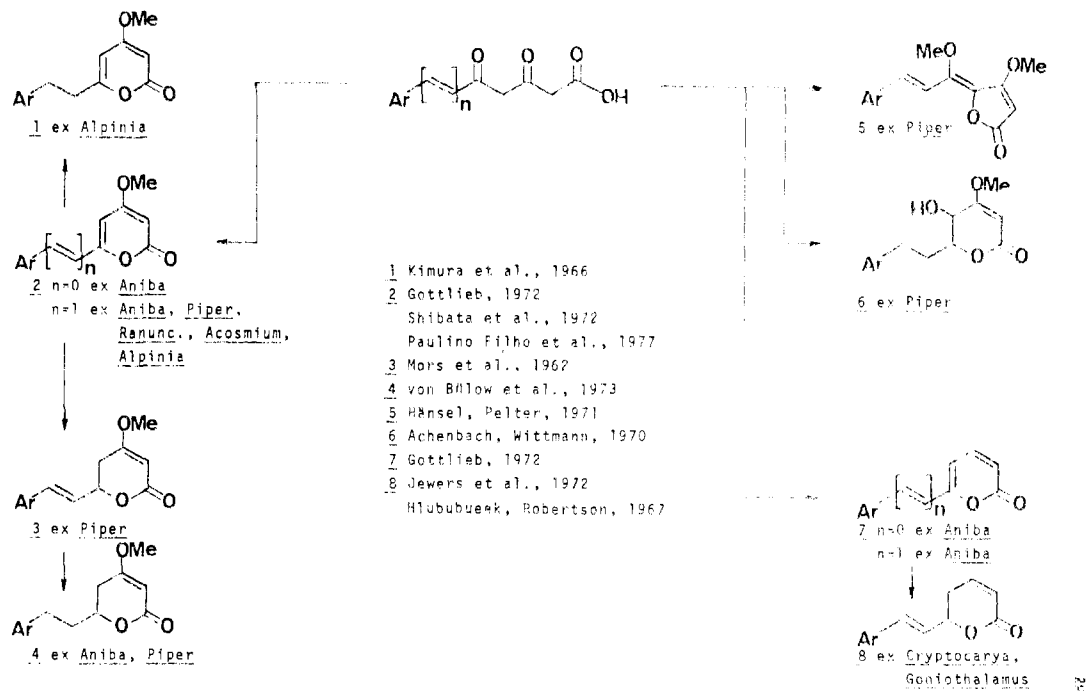


Figure 2. Biogenetic relation of arylpyrones in Brazilian *Aniba* species.

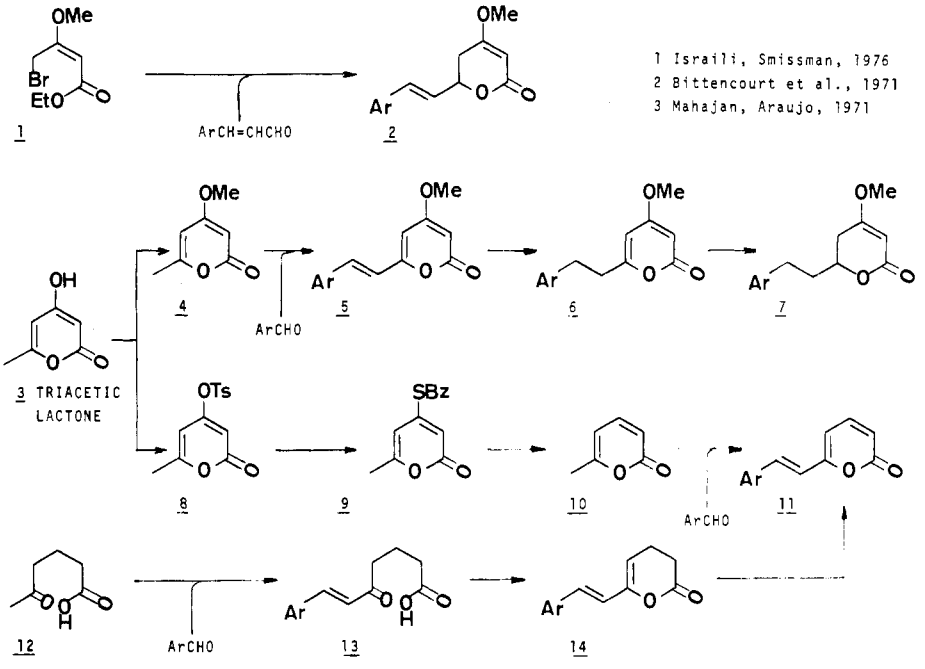


Figure 3. Syntheses of styryl- and arylethylpyrones.

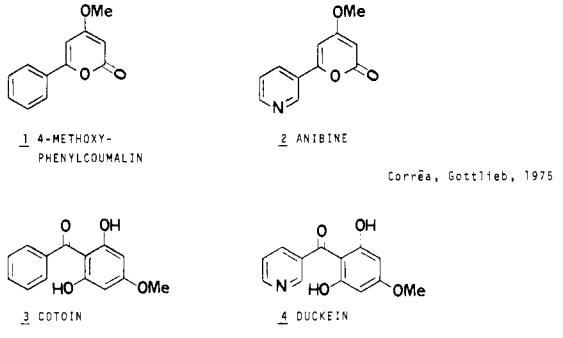


Figure 4. Arylpyrone–diaryl ketone pairs from Brazilian Lauraceae.

noliaceae) has been used in Chinese and Japanese traditional medicine against anxiety or muscle stiffness, including Parkinsonism. The CNS-depressing effects of the drug were recently attributed to magnolol (Figure 5, 1, R = H) (Watanabe et al., 1976). The bark of *Magnolia acuminata* L., at one time an official north American drug used in the treatment of malaria and rheumatism, contains three 8.8′,7.0.7′-neolignans, besides acuminatin (Figure 5, 4). The common spices nutmeg and mace, from the Asian tree *Myristica fragrans* Houtt. (Myristicaceae), have been used in folk medicine for many years for their alleged abortifacient, narcotic, and therapeutic action. Although we ignore any direct experimental proof, these properties may be due to the presence of compounds 1 and 2 in Figure 6.

In contradistinction we know that compounds of type 3 (Figure 6), ex *Virola surinamensis* (Rol.) Warb. (Myristicaceae) from the mouth of the Amazon, are active against cercariae of *Schistosoma mansoni* Sambon. The ketone 3 in Figure 7 prepared as an intermediary product during a synthesis of surinamensin (Figure 6, 3, Ar = tri-*O*-methylpyrogallyl) proved cytotoxic (Oliveira, 1979), as did megaphone, megaphone acetate, and megaphyllone acetate (Figure 8, 1). In preliminary tests (Oliveira, 1979) burchellin (Figure 8, 4) also showed this type of activity, while piperenone (Figure 9, 4) is an insect antifeeding constituent of *Piper futokadzura* Sieb. et Zucc. (Piperaceae) active against larvae of *Spodoptera litura*.

While nothing is yet known about the biodynamic properties of the bicyclo[3.2.1]octanoid types (Figure 10), biological testing of neolignans will surely gain impetus in

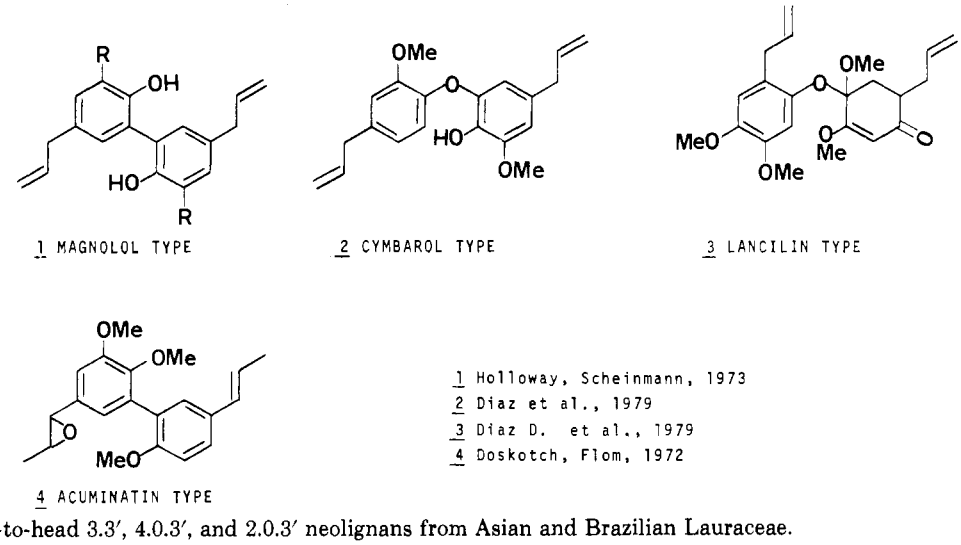
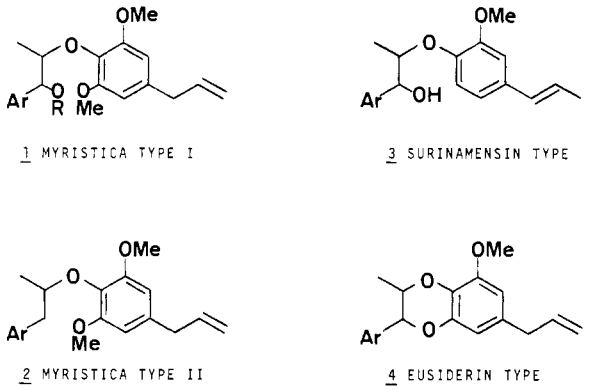


Figure 5. Head-to-head 3.3′, 4.0.3′, and 2.0.3′ neolignans from Asian and Brazilian Lauraceae.



1, 2 Forrest et al., 1974
3 Barata et al., 1978
4 Braz Filho et al., 1976

Figure 6. Tail-to-head 8.0.4′ and 8.0.4′,7.0.3′ neolignans from African and Brazilian Myristicaceae and Lauraceae.

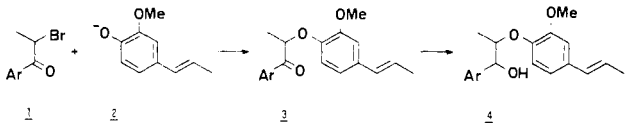
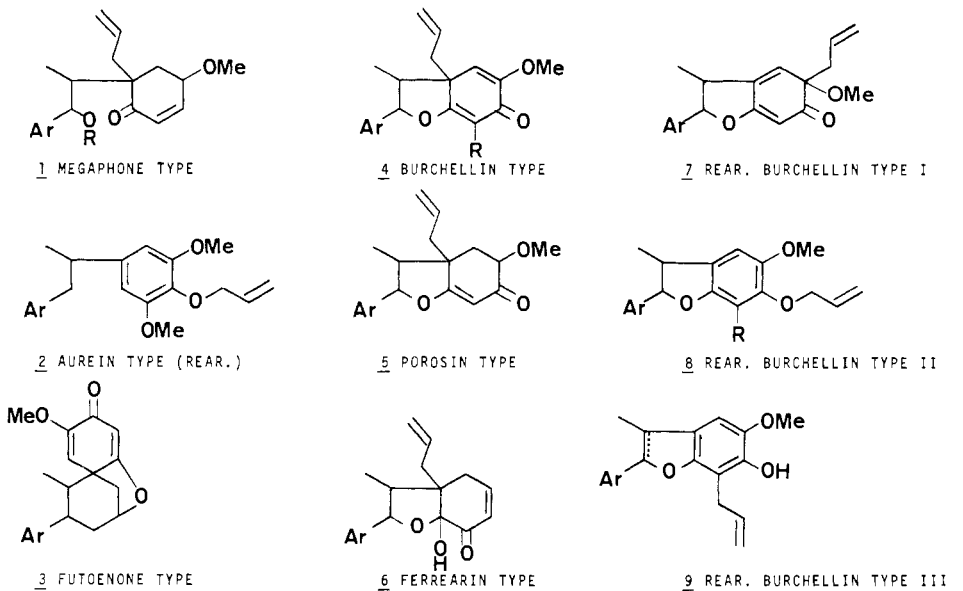


Figure 7. Synthesis of surinamensin.

the near future. Indeed, many representatives are, since recent times, not only interconvertible by preparatively useful rearrangements (Figures 11 and 12), but also accessible by total synthesis (Figure 13).

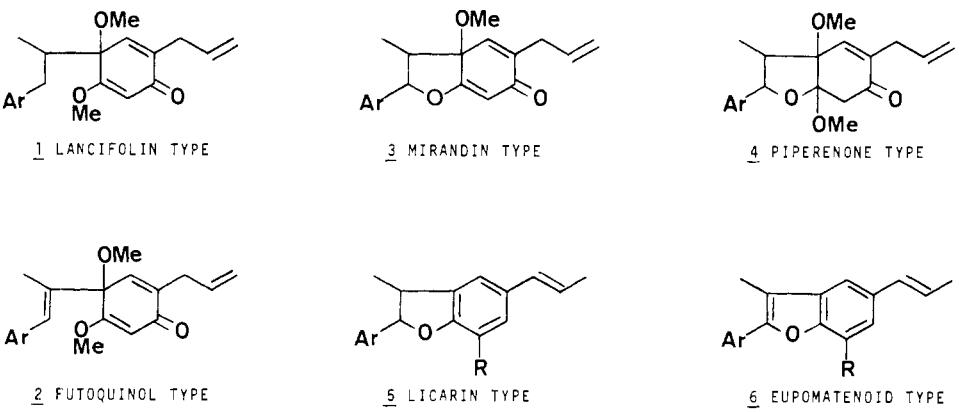
Xanthones. Arylpropanoids not only form oxidative dimers such as lignans and neolignans, but occur also as structural units in other phenolics, mostly contributing to the formation of benzodioxans.

Benzodioxans are useful pharmacons (Merck, 1968), and, indeed, a substantial body of evidence has accumulated in the past decade that the flavonolignoids, e.g., silybin



1 Kupchan et al., 1978. 3 Ogiso et al., 1970. 6 Andrade et al., 1979. 2, 5, 7-9 Gottlieb, 1978

Figure 8. Tail-to-head 8.1′, 8.1′,7.9′, and 8.1′,7.0.2′ neolignans from Asian Piperaceae and Brazilian Lauraceae.



1 Diaz D. et al., 1979. 2 Takahashi, Ogiso, 1970. 4 Matsui, Munakata, 1975. 6 Picker et al., 1973. 2-6 Gottlieb, 1978

Figure 9. Tail-to-head 8.3′ and 8.3′,7.0.4′ neolignans from Asian, Australian, and Brazilian Lauraceae and Piperaceae.

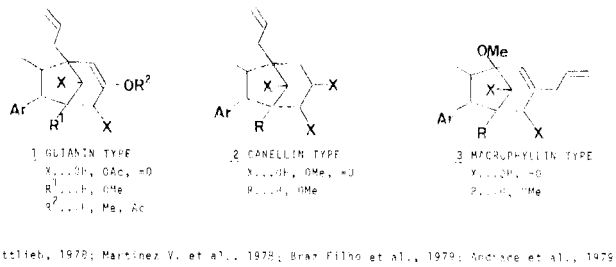


Figure 10. Tail-to-head 8.1′, 7.3′ and 8.5′,7.3′ neolignans from Brazilian Lauraceae.

(Figure 14, 1) of the European milk thistle *Silybum marianum* Gaertn., exert an almost specific influence on the liver parenchyma (Vogel, 1977). A drug (Legalon), based on an extract of this Compositae species was patented (by Madaus). In view of this fact it would be of interest to examine the benzodioxan neolignans 3 (Figure 14) from the Brazilian genera *Aniba*, *Licaria* (Lauraceae) (Gottlieb, 1978a) and *Virola* (Myristicaceae) (Fernandes et al., 1979), and the African *Eusideroxylon* (Lauraceae) (Hobbs, King, 1960), as well as the xanthonolignoids (Figure 14, 2) from the Brazilian genera *Kielmeyera* and *Caraipa* (Castelão et al., 1977). Eusiderin (Figure 14, 3, Ar = tri-*O*-methylpyrogallyl) is also available by synthesis (Figure 14) and kielcorin (Figure 14, 2, Ar = guaiacyl) was recently found in the cosmopolitan Guttiferae genus *Hypericum* (Nielsen and Arends, 1978).

A chemical survey of Brazilian Guttiferae revealed the presence of about 50 xanthones, 25% of the known xanthones from any natural source. This finding is relevant since natural and synthetic xanthones have been reported, inclusively in many patents (Oliveira, 1976), to be adrenergic blocking, amoebicidal, analeptic, analgesic, antiallergic, antiasmatic, antidepressive, antifilaria, antihelmintic, antiinflammatory, antileukemic, antinematode, antiparkinson, antipyretic, antirheumatic, antiviral, bactericidal, CNS-depressing, CNS-stimulating, fungicidal, immunostimulating, immunosupressive, insecticidal,

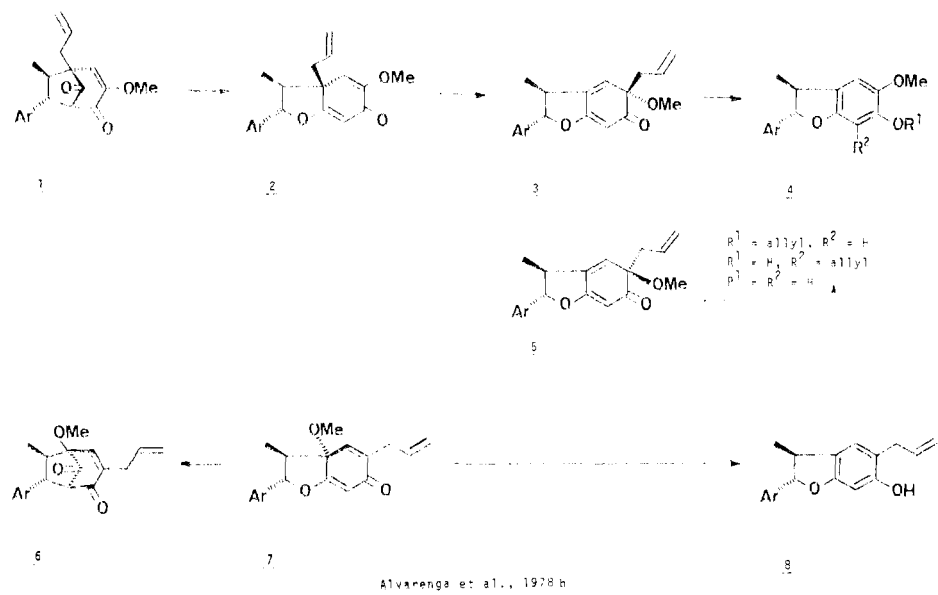


Figure 11. Bicyclo[3.2.1]octanoid-hydrobenzofuranoid 7,8-*trans*-neolignan rearrangements.

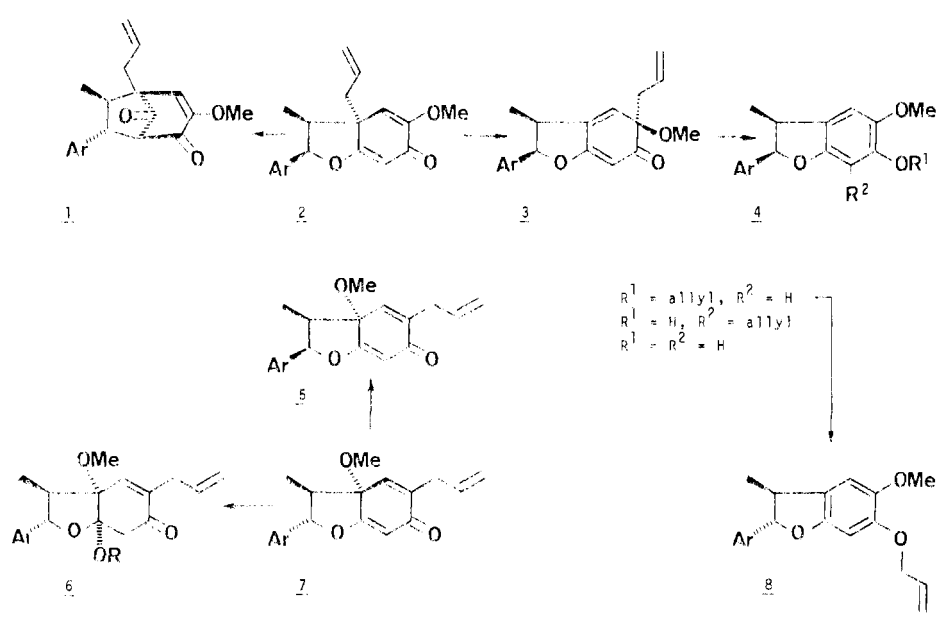


Figure 12. Bicyclo[3.2.1]octanoid-hydrobenzofuranoid 7,8-*cis*-neolignan rearrangements.

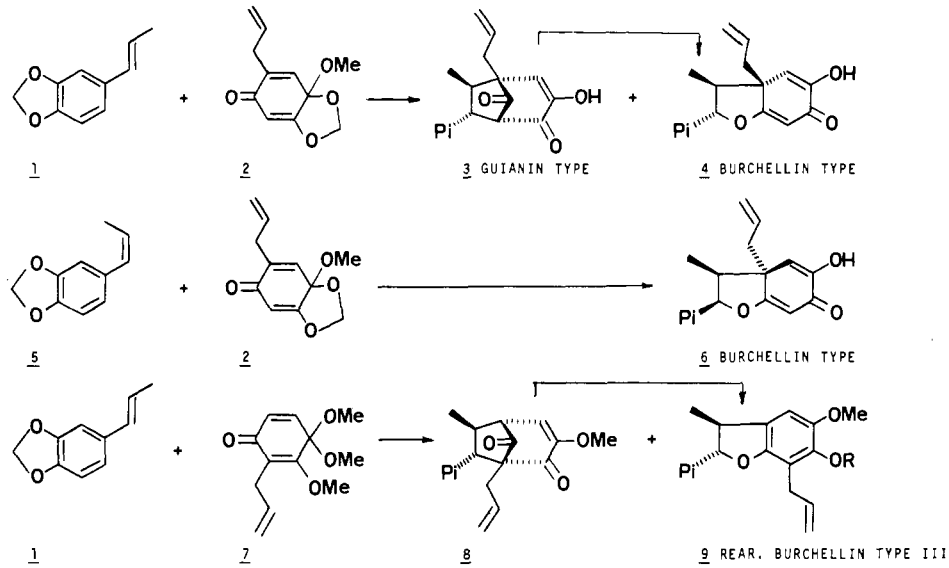


Figure 13. Synthesis of tail-to-head 8.1′ neolignans.

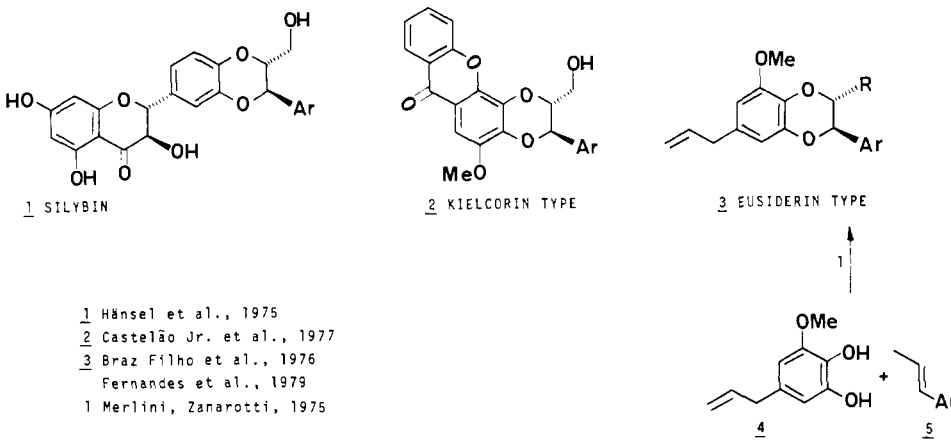


Figure 14. Benzodioxans from European Compositae and Brazilian Guttiferae, Lauraceae, and Myristicaceae.

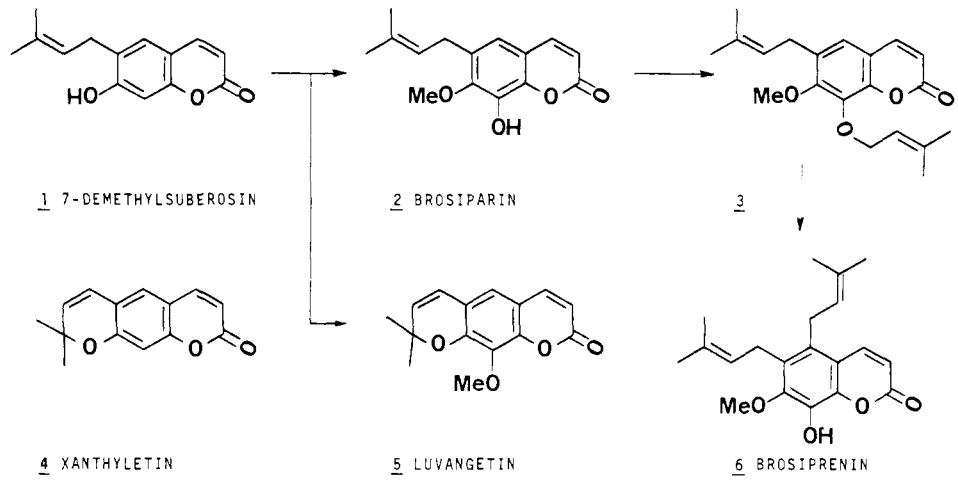


Figure 15. Biogenetic relations of coumarins from Brazilian Moraceae.

muscle relaxant, psychoactive, schistosomicidal, sedative, strongyloidicidal, termite repellent, trichomonicidal, tuberculostatic, and tumor inhibiting.

In connection particularly with compounds from Brazilian plants, 1,7-dihydroxy-6′,6′-dimethylpyrano-[2′,3′:2,3]xanthone, and 1,7-dihydroxy-8-methoxyxanthone from *Kielmeyera ferruginea* A. P. Duarte (Gottlieb et al., 1969) are cercaricidal and molluscicidal, respectively (Gilbert, 1976).

Coumarins and Isocoumarins. Coumarins constitute another class of compounds where many of its members have been shown to possess some kind of biological activity.

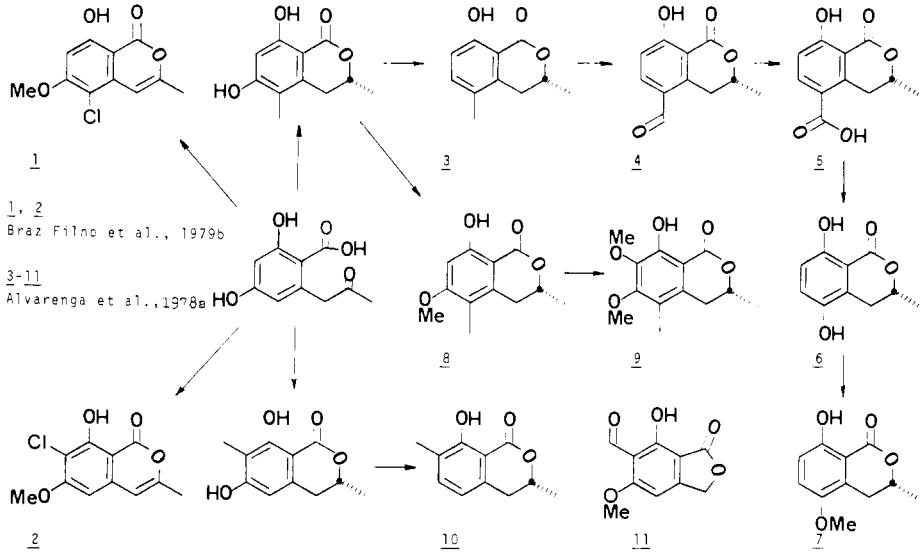


Figure 16. Biogenetic relations between iso- and dihydroisocoumarins from Brazilian wood samples infested by fungi.

Those from *Mammea americana* L. (Guttiferae) are known for their insecticidal properties (Finnegan and Mueller, 1965). Xanthyletin (Figure 15, 4) is present in high proportion (several percent) in the heartwood of *Brosimum rubescens* Taub. (Moraceae), being accompanied by at least four minor constituents. Figure 15 shows their structures as well as hypothetical biogenetic relationship. Conversion of **2** to **6** (Figure 15), via the O-prenylated intermediate **3** (Figure 15), has been accomplished in the laboratory (Braz Filho et al., 1972).

Furocoumarins have since long been known as stimulants of skin pigmentation, being still the only substances to offer a cure for vitiligo. Bergapten extracted from the root bark of another species of the same genus, *B. gaudichaudii* Trêc., is the active ingredient of a remedy produced in Brazil for this purpose (Lima and Ribeiro, 1967).

Isocoumarins and dihydroisocoumarins have recently been found in many Brazilian wood samples of diverse botanical origin. The compounds shown in Figure 16 were isolated from species belonging to seven plant families. Several such substances were known as typical fungal metabolites and, indeed, microscopic examination of the wood samples in question revealed the presence of fungal infection. In freshly cut samples of the same species, such polyketides, or fungi, could not be detected. Thus, the fungal invasion must have taken place during the drying and storage period between collection and extraction. This conclusion shows the peril of unsuspected contamination in phytochemical work.

Flavonoids. To conclude the section on phenolics, some comments on flavonoids. These are usually classified into three constitutional types, flavonoids proper, isoflavonoids, and neoflavonoids (Eyton et al., 1965a), all richly represented in Brazilian trees.

African ayan wood (*Distemonanthus benthamianus* Baill.) causes dermatitis due to the presence of oxyayanins A (Figure 17, **3**) and B (Figure 17, **4**) (Morgan and Thomson, 1967), possibly via quinones (Hausen, 1973). Seen under this light, ayanin (Figure 17, 1, R = H), a further constituent should be inactive. Ayanin and the oxyayanins co-occur in the Brazilian tree *Apuleia leiocarpa* (Vog.) Macbr. with seven other flavonols most of which show additional oxygenation at C-6, 2′, or 6′ required for quinone formation.

Flavonols are among the most numerous and widespread natural products (Gottlieb, 1975). The special characteristic of the representatives from the African and South

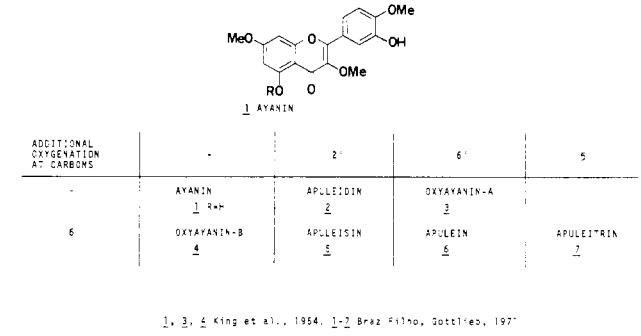


Figure 17. Flavonols from Brazilian and African Leguminosae.

American timbers under consideration is the 3′-OH,4′-OMe substitution which determines the biosynthesis of unusual 2′,4′,5′- and 2′,3′,4′-trioxygenation patterns (Braz Filho and Gottlieb, 1971). Both species have more in common than three constituents: They belong to monotypic genera of the Leguminosae–Caesalpinioideae.

The moderately cytotoxic eupatin (Kupchan et al., 1969) and centaureidin (Kupchan and Bauerschmidt, 1971) are of the oxyayanin-B (Figure 17, **4**) type.

Peltogynoids (Figure 18), which again occur in related Brazilian and African Leguminosae–Caesalpinioideae, are flavonoidal analogues of the much better known isoflavonoidal rotenoids and would thus be potentially interesting targets for biological testing.

Some bark resins derived from myristicaceous species are used in the Amazon region as hallucinogens and arrow poisons, effects attributed to tryptamines and carbolines (Agurell et al., 1969). Others find popular use against skin ailments, and here the activity is tentatively ascribed to neolignans and pterocarpans (Figure 19, **2**). Peculiar is the existence, in the bark of these trees, of flavans (Figure 19, **7**). These compounds can be seen as precursors of diarylpropanes (Figure 19, **8**), so far located only in Brazilian Myristicaceae, and these in turn of spirans (Figure 19, **4**). Spiroelliptin (Figure 19, **4**) from *Iryanthera elliptica* Ducke rearranges upon methylation to a dibenzocycloheptane. Flavans have also been proposed, through oxidative dimers, to be responsible for the intense red pigmentation of some of the bark resins (Gottlieb, 1979).

Species of the genus *Derris* (=*Lonchocarpus*; Leguminosae–Papilionoideae) were originally used as fish poisons by aborigines in several parts of the world. These plants attained prominence shortly before World War II, when

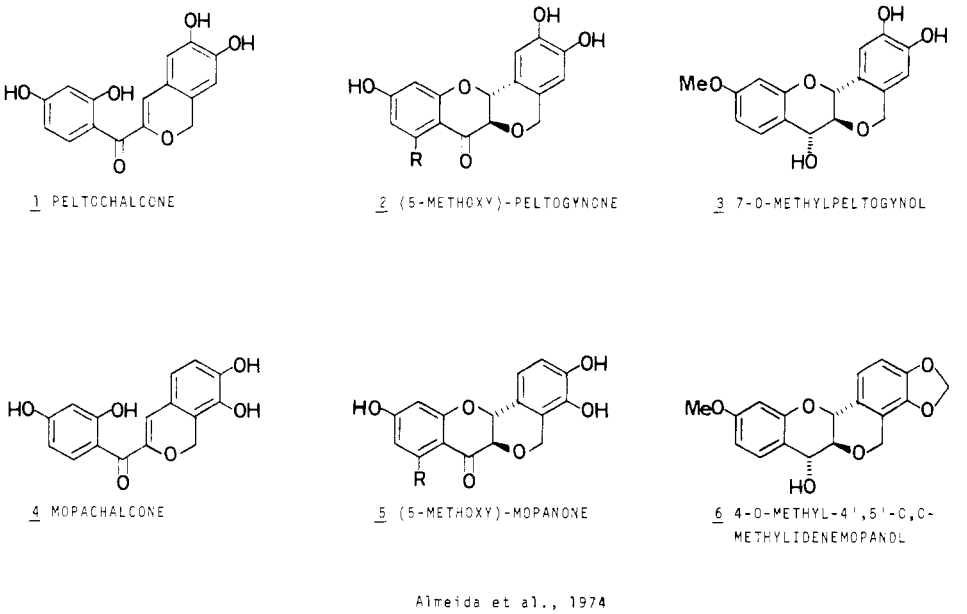


Figure 18. Peltogynoids from Brazilian Leguminosae.

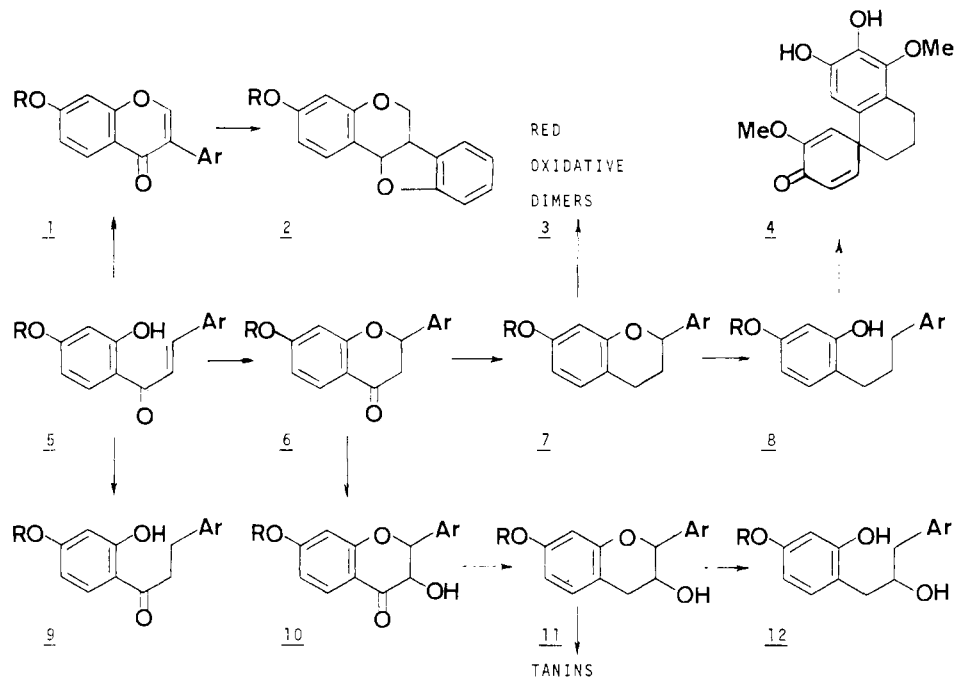


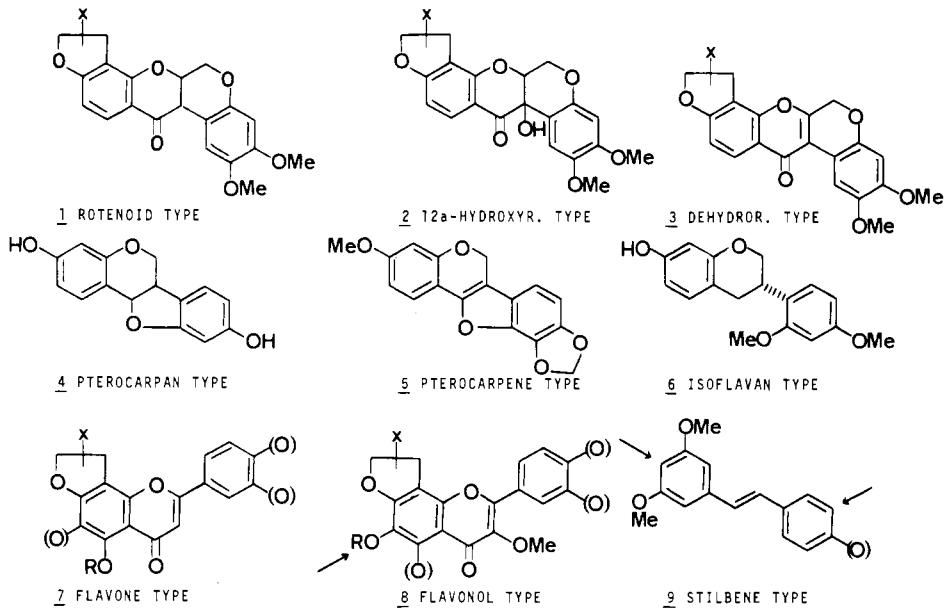
Figure 19. Biogenetic relation of flavonoids in Brazilian Myristicaceae.

their insecticidal properties were discovered and put to general use. The isolation of the active principles, the rotenoids, fell into the 1930's. Rotenone itself proved to be the most active of all compounds found in *Derris* species, both against fish and against insects. Its action exerts itself by disrupting the sequence of reactions in the respiratory chain through inhibition of oxidative phosphorylation. Although its use as an insecticide was discontinued with the general introduction of synthetics, the present caution regarding the use of nondegradable poisons and the outward prohibition of some of them in many countries allows one to predict a comeback of some of the naturals, with rotenone outstanding among them. If this should occur, Brazil will be no doubt one of the major producers.

But it is not only against insects that *Derris* is being employed. The ancient native habit of killing fish with these plants has been curiously revived in the last decades. Brazilian authorities have employed *Derris* powder in checking the proliferation of the dreaded piranhas in rivers and dams. Applied to the water in the proportion of 3 ppm, *Derris* powder has shown to kill all the piranhas and their eggs within 15 min, while causing only minor damage to other species present. By this method, piranhas have been exterminated in ten dams, comprising a river basin covering 48 000 sq km (Fontenelle, 1963).

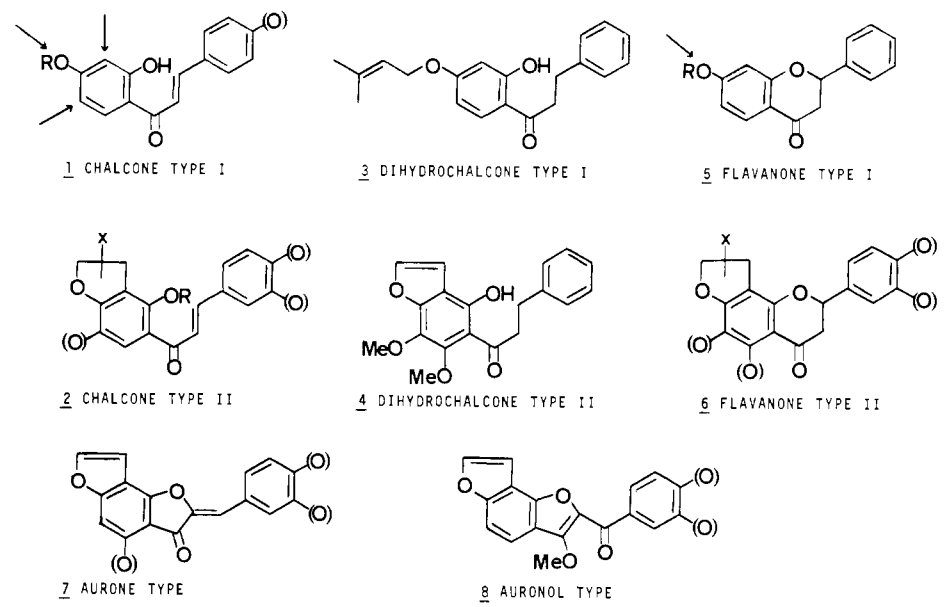
Identical utilization has been introduced in the United States, where so-called trash fish have been exterminated on a grand scale with the aid of *Derris* extracts (Leonard, 1939).

In accordance with this exposition, one could be tempted to assume that rotenoids (Figure 20, 1–3) are widespread within the genus. In reality, however, their occurrence is quite restricted, having been found so far in only two of



1-6, 9 Braz Filho et al., 1975a,b. 7-9 Nascimento, Mors, 1979

Figure 20. Isoflavonoids and other metabolites from Brazilian *Derris* species.



1, 2, 5 Braz Filho et al., 1975a,b, 1, 2, 4, 6-8 Nascimento, Mors, 1972; 1979; Nascimento et al., 1976. 1-3, 5 Lima et al., 1973; Delle Monache et al., 1974; 1978

Figure 21. Chalcones and related metabolites from Brazilian *Derris* species.

the about 30 Brazilian species. Even isoflavonoids in general (Figure 20, 4–6), as widespread as they are in the Leguminosae–Papilionoideae (Cagnin, Gottlieb, 1978), are apparently rare. The same seems to be true of flavones (Figure 20, 7) and flavonols (Figure 20, 8). The majority of flavonoids in this genus have not evolved very far, if at all, beyond the primitive chalcone–flavanone type. The result is a host of chalcones (Figure 21, 1 and 2), flavanones (Figure 21, 5 and 6), dihydrochalcones (Figure 21, 3 and 4), aurones (Figure 21, 7), and auronols (Figure 21, 8). The structural diversity in these products is surprising, in view of the simplicity of substitution usually associated with such metabolites. One could assume the existence of a blockage of the metabolic pathway which in other Leguminosae leads to the more evolved stages of flavonoid biosynthesis.

It was recently proposed to replace the constitutional subdivision of the flavonoids (Eyton et al., 1965a) by a biogenetic criterion (Gottlieb, 1977a) whereby the neoflavonoids encompass not only dalbergiquinols (Figure 22, 4), dalbergiones (Figure 22, 5), neoflavenes (Figure 22, 6), and dalbergins (Figure 22, 7), but also cinnamylphenols (Figure 22, 1 and 2), styryl-*p*-quinonemethides (Figure 22, 3) and, in case they are not artifacts of isolation, 2-aryl-3-methyl-2,3-dihydrobenzofurans (Figure 22, 8).

Indeed, since its inception this point of view (Figure 18) proved helpful, and together with preliminary accounts on the occurrence in Brazilian and Central American *Dalbergia* and *Machaerium* species (Leguminosae–Papilionoideae) of cinnamylphenols (Figure 22, 1 and 2) (Gregson et al., 1968a) and a styryl-*p*-quinonemethide (Figure 22, 3) (Gregson et al., 1968b) inspired a notable series of papers on their biogenesis (Larkin et al., 1970), synthesis (Jurd, 1969; Cardillo et al., 1969), and astoundingly varied potential uses. While obtusastyrene (type 1, Figure 22) (Gregson et al., 1978b) and a series of synthetic cinna-

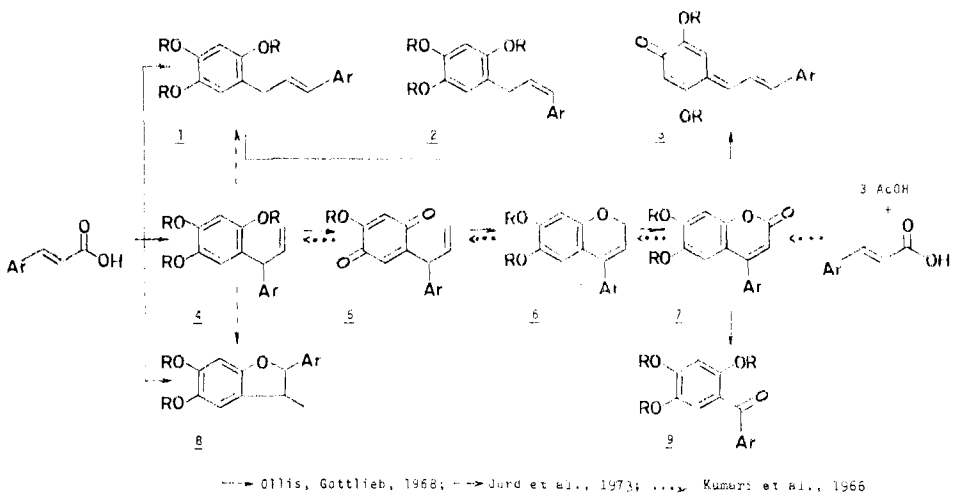
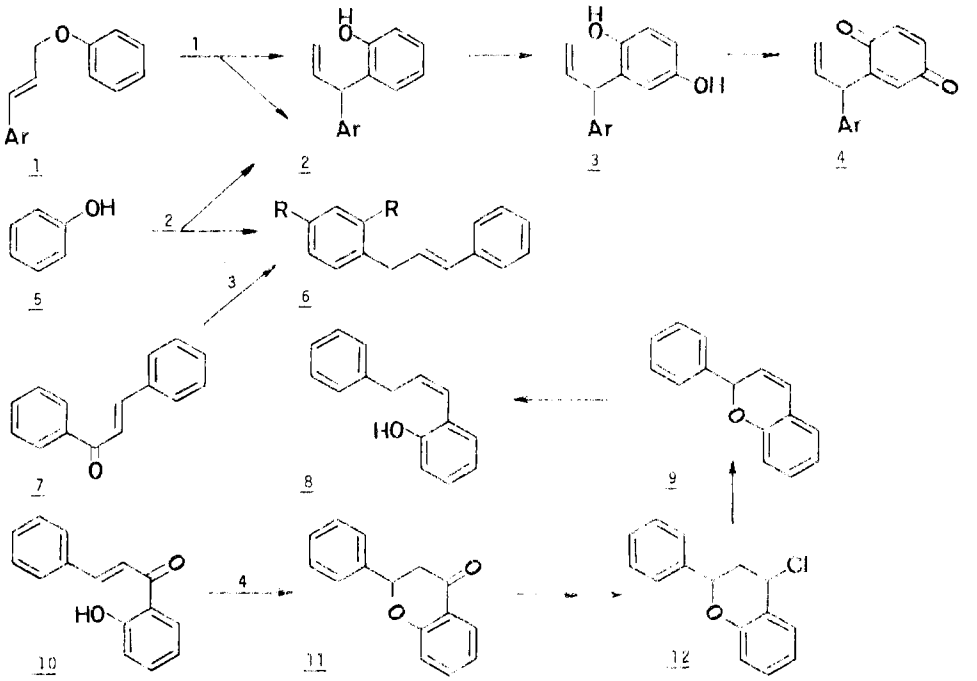


Figure 22. Biogenetic derivation of neoflavonoids in Brazilian Leguminosae.



1 Barnes et al., 1965; Gregson et al., 1978a. 2 Nageswaran et al., 1969; Jurd, 1969; 1976; Cardillo et al., 1969. 3 Gregson et al., 1978a; Kurosawa et al., 1976a. 4 Kurosawa et al., 1978a

Figure 23. Synthetic methods for dalbergiquinols, dalbergiones, *E*- and *Z*-cinnamylphenols.

mylated phenols are sterilants of female flies (Jurd, 1977), growth inhibitors of malaria mosquito larvae (Jurd, 1976/1977), algicides (Chan and Jurd, 1973), and microbicides (Jurd et al., 1971a,b; King et al., 1972; Lewis and Jurd, 1972), obtusaquinone (type **3**, Figure 22) (Gregson et al., 1978b), and synthetic styryl-*p*-quinonemethides are highly ichthyotoxic (Jurd et al., 1972) and effective in marine borer attack (Bultman et al., 1977; Jurd and Bultman, 1977).

One last word on the biodynamic properties of cinnamylphenols. It has been observed (Donnelly, 1975) that they are more causative of dermatitis than the isomeric dalbergiones (Figure 22, **5**) with which they frequently co-occur. This is an enlightening observation in view of the fact that usually dalbergiones, and specially *R*-3,4-dimethoxydalbergione (and its quinol) of *Machaerium scleroxylon* Tul. (Eyton et al., 1965b) are held responsible for the sensitizing effect (Morgan et al., 1968; Hausen, 1973). Other dalbergione containing jacarandá timber was reported to be inocuous (Bastos and Mattos Filho, 1960). The antibiotic activity of *Dalbergia nigra* Fr. Allem. extracts was ascribed to *R* 4 methoxydalbergione (Lima et al., 1961). More recent reports have shown, however, that while this compound is generally inactive against bacteria and fungi, it inhibits the growth of *Candida tropicalis* and a number of other yeasts (Jurd et al., 1971b). The structures of 4-methoxydalbergione and papaverine are somewhat similar and, indeed, also the former compound possesses antispasmodic activity at high dilution (Gábor and Magyarlaki, 1970).

The neoflavonoids of *Dalbergia* and *Machaerium* thus hold considerable promise, and it is fortunate that they are easily accessible by synthesis (Figure 23).

Structural development of neoflavonoids (Figure 22) is replaced in some Brazilian *Dalbergia* and *Machaerium* species by elaboration of the isoflavonoid theme (Oliveira et al., 1971). This fact led to the discovery of isoflavans (Figure 24, **5**) (Kurosawa et al., 1978b) and isoflavanquinones (Figure 24, **6**) as constituents of healthy wood of Leguminosae (Oliveira et al., 1975). Eleven isoflavans have since been recognized as phytoalexins of herbaceous legumes (Grisebach and Ebel, 1978). Increasing fungi-

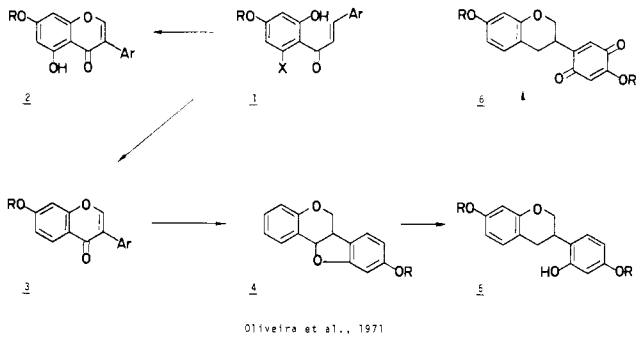


Figure 24. Biogenetic derivation of isoflavonoids in Brazilian Leguminosae.

toxicity of the isoflavonoids along the biosynthetic pathway (Figure 24) was linked to evolutionary advancement (Harborne, 1977). Measurement of fungitoxicity, applied to analogously substituted representatives of the neoflavonoid pathway (Figure 22), may thus clarify the so far controversial direction of its evolution.

Since the discovery of the biological activity of flavonoids (Rusznyak and Szent-Györgyi, 1936), this topic has been extensively covered in the general as well as in the patent literature. It was stated already in 1954 (Schreiber and Elvehjem, 1954) that in studies with experimental animals and in clinical use beneficial effects of flavonoids have been claimed in the treatment of capillary fragility and retinal hemorrhage in hypertension, diabetic retinophathy, purpura, rheumatic fever, arthritis, radiation disease, habitual abortion, frostbite, histamine and anaphylactic shock, experimental cancer, and in the prevention of chromodacryorrhea produced by dietary and environmental stress. Well studied are the estrogenic properties of isoflavonoids, such as genistein, responsible for the so-called "clover disease" or infertility syndrome in sheep (Bradbury and White, 1951), and the even more potent coumestrol (Bickoff et al., 1957). More modern evidence, such as effect on connecting tissue, skeletal muscle, liver, prostaglandin activity, biogenic amine liberation, fluidity of blood, metabolism of vitamin C, fungi, and viruses can be traced through a collection of papers on bioflavonoids (Farkás et al., 1977). More recently still, simple flavonols and their glycosides have been shown to be effective inhibitors of lens aldose reductase: quercitrin, administrated orally, delays the onset of cataract in diabetic animals (Varma et al., 1977). Some flavones, including apigenin, and isoflavones, including caviunin, are reported to inhibit enzymes responsible for the biooxidation of polycyclic hydrocarbons into carcinogenic and cytotoxic derivatives (Silva and Brentani, 1979). Among the members of chalcones and related substances from the Brazilian *Derris* species, derricidin, injected into immature female rats, inhibits the development of the uterus (Pereira et al., 1976); and the same effect has been observed quite recently with derriobtusone (Pereira, 1979). Considerable effort is also being devoted at present to the introduction of dihydrochalcones as sweeteners (Horowitz and Gentili, 1963; Bognár and Rákosi, 1977). The impetus of investigation is thus far from ebbing and a promising future seems to be in store for the exploration of bioflavonoids.

POLYKETIDES

Let us now pass from phenolics to polyketides such as the cytotoxic obtusilactone. Compounds of this type (Figure 25, **3**, x = 9 and 11; Niwa et al., 1975) and the related litsenolides (Figure 25, **4**, x = 9 and 11, Takeda et al., 1972) occur in Japanese Lauraceae. In the light of a number of compounds recently isolated from Brazilian Lauraceae, they are now recognized as belonging to a group of biosynthetically related metabolites (Figure 25). If the biosynthesis of the ethenyl and ethynyl (and consequently also of the ethyl) terminals involves decarboxylation as has been postulated, the uneven number of C atoms of **1**–**5** (Figure 25) requires all carbons to derive from polyketide, ramification of **3**–**5** (Figure 25) being due to rearrangement (Gottlieb, 1972). The formation of these terminals cannot involve decarboxylation if, as generally assumed since 1971 (Bohlmann and Grenz), the oxygenated ends of such molecules stem from pyruvic acid without rearrangement. Analogous doubts concerning the origin of **6** and **7** (Figure 25) suggest their inclusion in the same biogenetic group, in spite of intervention of a cinnamate unit. The relationship of these compound types becomes all the more obvious if the morphological affinity of Lauraceae and Myristicaceae is considered.

An extension of the biological evaluation of these substances beyond that of obtusilactone would most probably lead to interesting results. Indeed, injection into rats of an equimolecular mixture of rubrenolide and rubrynolide (Figure 25, **5**) from the trunk wood of the Amazonian *Nectandra rubra* (Mez) Allen resulted in catalepsy, followed by agressiveness (Zyngier et al., 1978).

TERPENOIDS

Sesquiterpenoids. Brazil is a traditional exporter of essential oils. Although most are produced from intro-

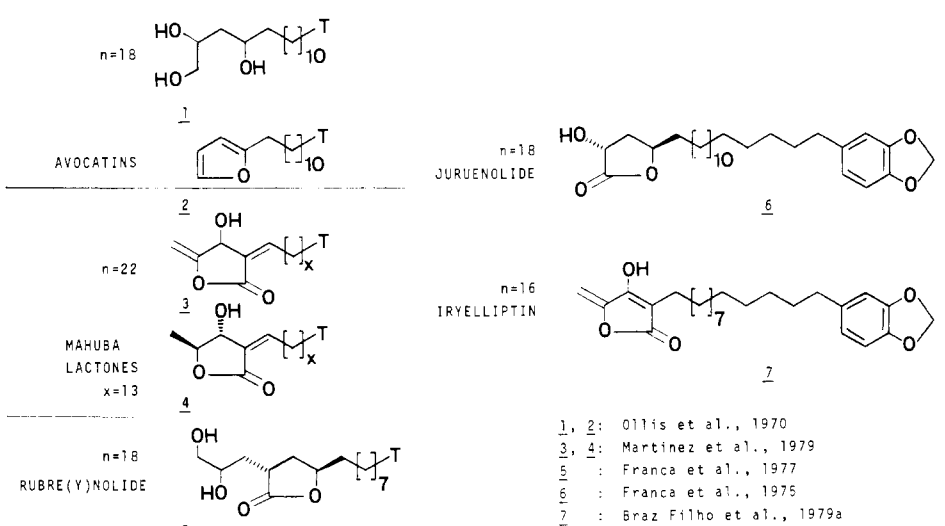


Figure 25. Polyketides from Brazilian Lauraceae and Myristicaceae.

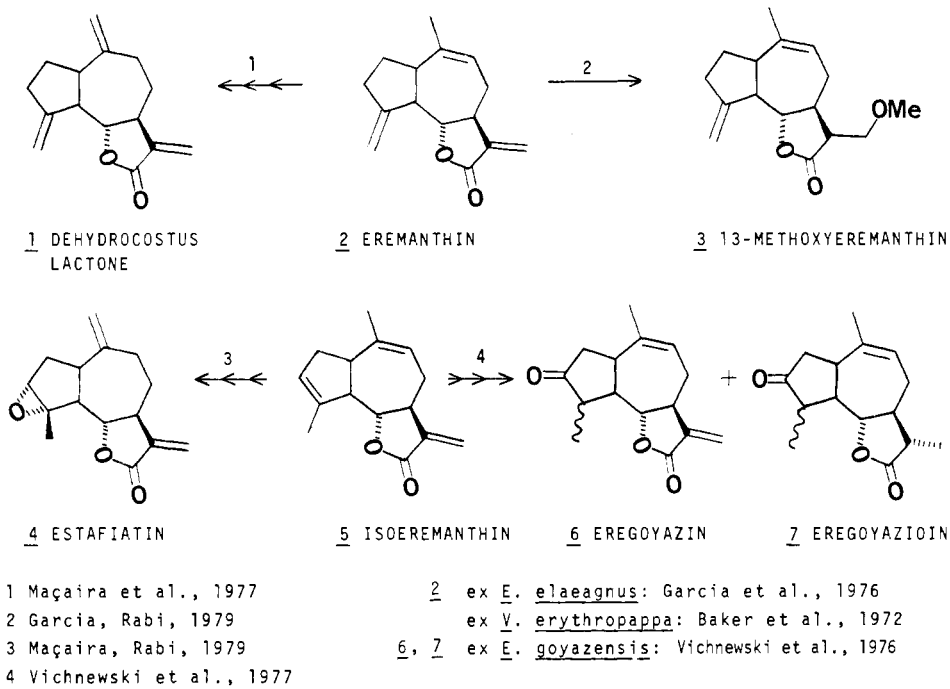


Figure 26. Sesquiterpene lactones from Brazilian Compositae.

duced plants, the oils of sassafras, rosewood, and cabreuva come from native trees, respectively *Ocotea pretiosa* (Nees) Mez, *Aniba duckei* Kosterm. (Lauraceae), and *Myroxylon balsamum* (L.) Harms. (Leguminosae–Papilionoideae). The major constituent of the former is the arylpropanoid safrol, while the latter two contain terpenoids, respectively, linalool and nerolidol.

Less volatile terpenoids are currently being investigated. Chiefly sesquiterpene lactones have attracted much attention due to their interesting chemistry and variety of biological activities. Found in many species throughout the plant kingdom, they are, however, most particular to the Compositae. The great majority of producers of this class of compounds are herbs. Well studied, for example, are species of *Artemisia*, *Ambrosia*, and *Eupatorium*. The Brazilian flora, however, possesses also a number of arboreous species of Compositae, where sesquiterpene lactones occur in the wood and bark. Rather well studied so far are species of the genera *Vanillosmopsis*, *Eremanthus* and *Moquinia*.

Biological activity of sesquiterpene lactones is extremely diverse (Rodriguez et al., 1976). Many have been shown to inhibit tumor growth. Others are bacteriostatic and fungistatic. Others, still, are plant growth inhibitors and insect antifeedants. Many are responsible for accidental poisoning in cattle and man.

In Brazil, interest in these compounds is mainly linked to prophylaxis against schistosomiasis. This disease affects one-tenth of the country's population and is spreading. It is caused by a fluke, *Schistosoma mansoni* Sambon, which localizes itself in the liver and intestine. The females continually produce hundreds of eggs which, by clogging capillaries in the liver, spleen, and intestines, cause severe malfunction of these organs and, consequently, physical disability of the host.

In order to complete its larval cycle, the parasite depends upon an intermediate host, an aquatic snail (*Biomphalaria glabrata* Say). Eggs of the fluke are carried from feces of the affected humans into the waterways in the vicinity of their housing. From these eggs, the first larval forms are hatched, myracidia, which infect the snails. Inside the snail the parasite multiplies in the form of sporocyst, with the production of thousands of cercariae, the larvae which eventually will again invade humans by penetration of the skin.

The problem is being attacked from every possible angle: education, hygienic measures, elimination of snails, search for a cure, and others, but progress in combatting the disease has been extremely slow. The discovery of chemical agents which inhibit cercarial skin penetration has called attention to a possible new approach. Compounds which are thus active are in their majority sesqui- and diterpenes (Gilbert et al., 1970) with sesquiterpene lactones prominent among them (Baker et al., 1972). In practice, topical application of the active compounds onto the skin constitutes the only possible prophylactic measure. It has, however, been demonstrated in mice that 14,15-epoxygeranylgeraniol is also systemically active, albeit in much higher concentration. This compound from the fruits of the leguminous species *Pterodon pubescens* Benth. (Mors et al., 1967), was actually the first recognized to inhibit skin penetration by cercariae. A number of cyclic diterpenes with the same property have subsequently been isolated from the same as well as other *Pterodon* species (Mahajan, Monteiro, 1973; Fascio et al., 1976). None, however, exhibits the high activity of the acyclic parent compound.

Figures 26 and 27 show the main sesquiterpene lactones from Brazilian trees which have been studied, their biogenetic interrelations, and chemical transformations. Such transformations can also be rewarding with regard to biological activity. Thus, isoeremanthin (Figure 26, **5**) is more active against cercariae than eremanthin (Figure 26, **2**), its natural isomer. 13-Methoxyeremanthin (Figure 26, **3**) is peculiar in that, without being cercaricidal, it inhibits cercarial movements in vitro.

The two trees which contain eremanthin (Figure 26, **2**), *Eremanthus elaeagnus* Schlt.-Bip. and *Vanillosmopsis erythropappa* (DC.) Schlt.-Bip., produce the sesquiterpene alcohol (−)-α-bisabolol as the major component of their essential oils (Gottlieb and Magalhães, 1958), considerable quantities of which have been exported from Brazil to Germany for years. Together with chamazulene, this compound occurs in camomile oil, both of them being responsible for its antiinflammatory activity. Bisabolol

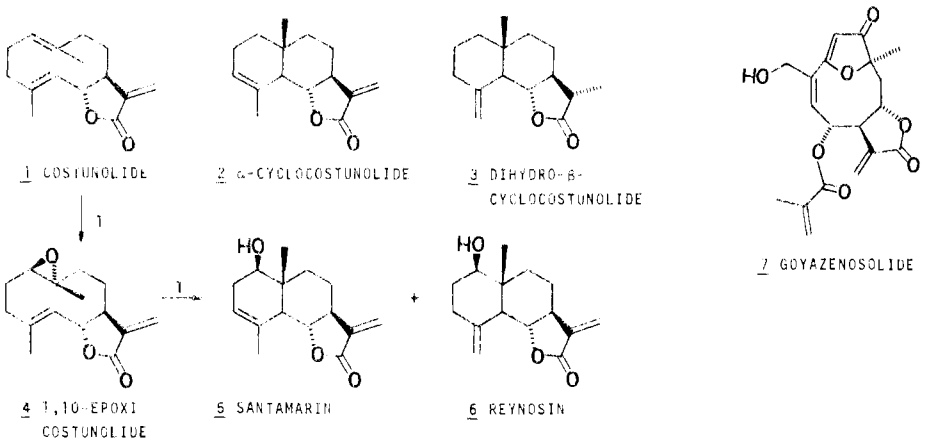


Figure 27. Sesquiterpene lactones from Brazilian Compositae.

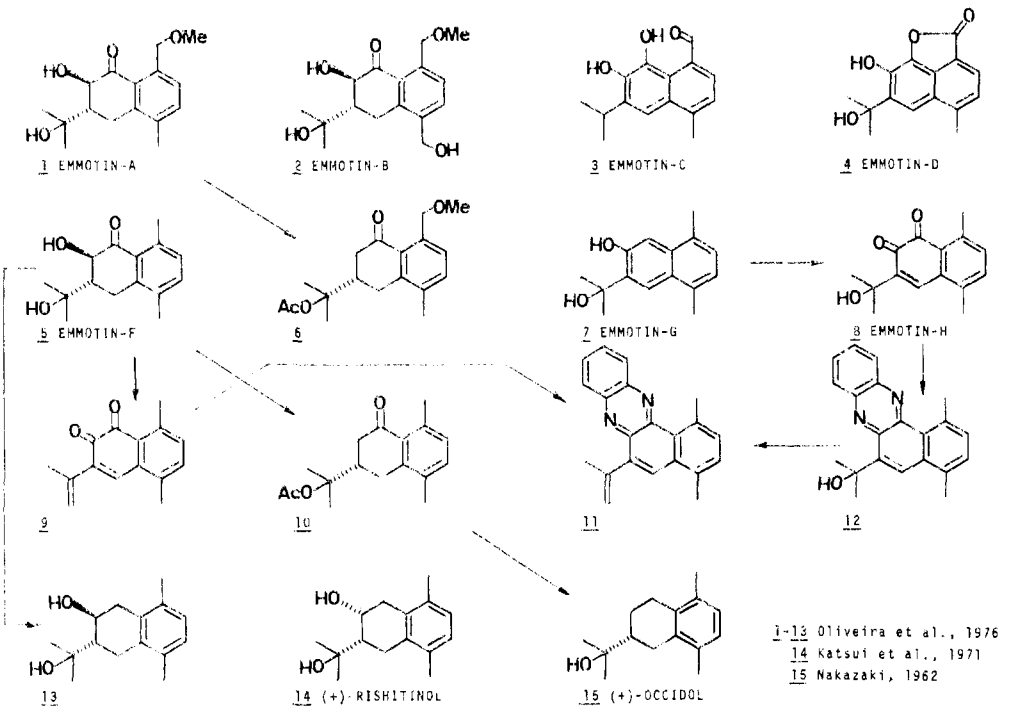


Figure 28. Emmotins from Brazilian Icacinaceae. Correlation with other rearranged eudesmane sesquiterpenes.

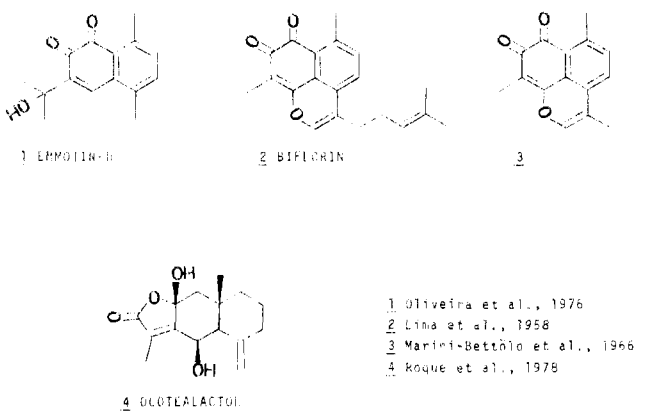


Figure 29. 1,2-Naphthoquinones from Brazilian Icacinaceae and Scrophulariaceae, and African Sterculiaceae species. Eudesmane sesquiterpene from a Brazilian Lauraceae.

has been reported to be less toxic than the azulenes, besides showing spasmolytic activity (Isaac et al., 1968).

Products of such transformations in many cases are by themselves naturally occurring compounds. Geissman (1973) considers 1,10-epoxicostunolide (Figure 27, **4**) to be the possible biogenetic precursor of eudesmanolides, and, in fact, this substance converts itself spontaneously to the known santamarin (Figure 27, **5**) and reynosin (Figure 27, **6**) (Rodrigues et al., 1978).

Very striking in their structures are the rearranged eudesmane type sesquiterpenes with tetralin or naphthalene skeletons isolated from the wood of Icacinaceae. All kinds of dehydrogenations and oxidations have occurred in their biosynthesis. This can be seen in Figure 28, which illustrates their correlation with (+)-rishitinol, a phytoalexin isolated from diseased potato tubers, and (+)-occidol.

There is, no doubt, a resemblance between these compounds (e.g., Figure 29, 1) and several biologically very active quinones found in the wood of an African *Mansonia* (Sterculiaceae) species (Figure 29, **3**). Clearly related to this, again, is biflorin (Figure 29, **2**), an antibiotic from the Brazilian *Capraria biflora* (Scrophulariaceae, herbaceous).

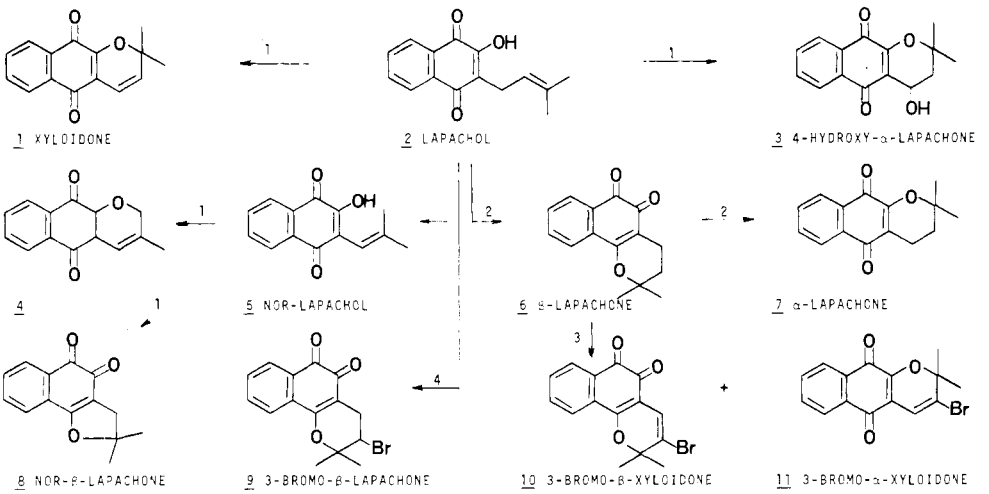


Figure 30. 1,2- and 1,4-Naphthoquinones from Brazilian Bignoniaceae.

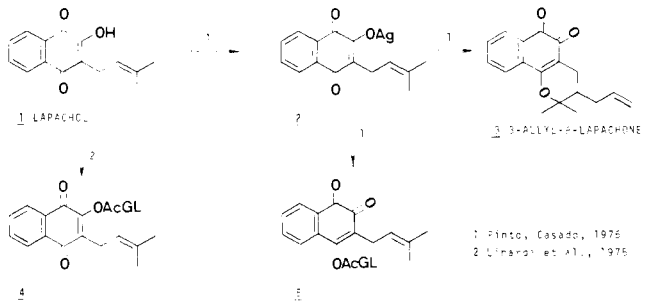


Figure 31. 1,4-Naphthoquinone from Brazilian Bignoniaceae.

A nonrearranged eudesmanolide, ocotealactol (Figure 29, 4) occurs in *Ocotea guianensis* Aubl. (Lauraceae).

Prenylnaphthoquinones. Another class of naphthalene derivatives are the prenylnaphthoquinone lapachol and several of its transformation products (Figures 30 and 31). Lapachol occurs, sometimes in astoundingly high proportion (over 5%), in the heartwood of a number of tropical trees, the majority belonging to the Bignoniaceae, in particular to the genus *Tabebuia* (*Tecoma*). It has also been found, however, in several species belonging to other families. The compound was originally isolated almost a hundred years ago (Paternò, 1882). Its chemistry and structure were exhaustively studied at the end of the 19th century, and again in the years 1915–1935 (Hooker, 1892, 1896, 1936). Synthesis was accomplished in 1927 (Fieser, 1927).

Evidence, however, that lapachol and several of its derivatives are toxic to termites (Thomson, 1971), cytostatic, cercaricidal, and antimicrobial has been forthcoming only recently.

The cytostatic properties of lapachol against a number of tumors (Figure 32; Driscoll et al., 1974), most significantly against Walker 256 carcinoma (Rao et al., 1968) and Yoshida sarcoma in mice (Lima et al., 1971), were first reported in 1968 and led to the issuing of a patent (Rao et al., 1969). Lapachol is produced by a laboratory (LAFEPE) in the state of Pernambuco for oral administration as an adjuvant to other drugs in cancer therapy; and indeed, in view of its low general toxicity, has been approved by the CCNSC for human clinical trials. The artificially prepared lapachol glucoside tetraacetate extends the activity of lapachol derivatives to the mouse lymphocytic leukemia P-388, a tumor which is almost unaffected by lapachol itself or its nonacetylated glucoside (Linardi et al., 1975).

Lapachol, along with the already mentioned 14,15-epoxygeranylgeraniol, is among the most active compounds

ACTIVITY	1,4-NAPHTHOQUINONES						1,2-NAPHTHOQUINONES					
AGAINST	30.2	30.1	30.3	30.7	30.11	31.4	30.6	30.8	30.9	30.10	31.3	31.5
TUMORS	W-256 CA-755 S-180	W-256 L-1210	-	W-256 S-180	-	P-388	-	-	-	-	-	-
CERCARIAE	*	-	+	+	-		+	*	+	-	-	-
BACTERIAE	Ba Br	Br										
FUNGI	Ca		Ca	Ep Mi Tr	Ep Mi Tr		Ep Mi Tr	Ep Mi Tr	Ep Mi Tr	Ep Tr		
Trypanosoma cruzi	+	-	-	-	•		*	-	+	+	* Δ	-

Ba...Bacillus, Br...Brucella, Ca...Candida, Ep...Epidenophyton, Mi...Microsporum, Tr...Tricophyton
Activity: *...outstanding, +...regular, -...absent, no sign...not tested, Δ...in chagasic blood

Figure 32. Biological activity of lapachol and derivatives.

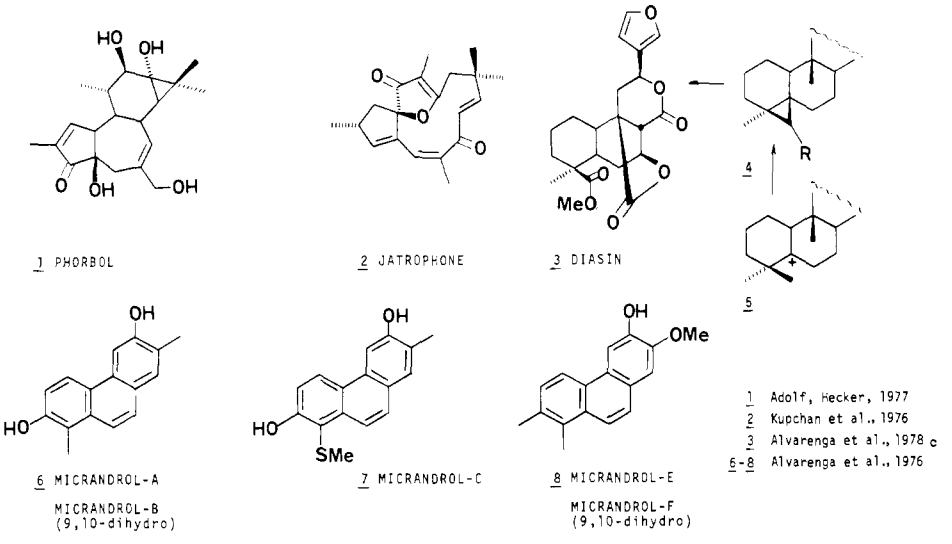


Figure 33. Diterpenes from Brazilian Euphorbiaceae.

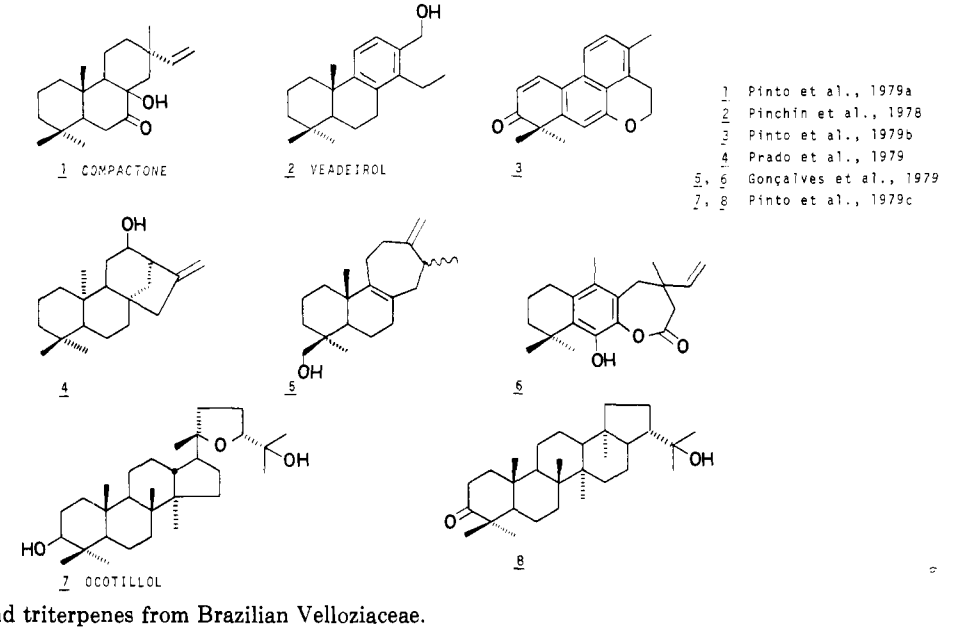


Figure 34. Di- and triterpenes from Brazilian Velloziaceae.

which inhibit skin penetration by cercariae of *Schistosoma mansoni*. Several of its derivatives are also active (Figure 32; Pinto et al., 1977).

While, furthermore, the bacteriostatic (Lima et al., 1956; 1962) and fungistatic (Gilbert et al., 1978) activity of lapachol and of several derivatives have been described, most important are the recent studies which place this class of compounds in the foreground among possible weapons against Chagas' disease. Not only do some of these substances [Figure 32, cf. **6** (Figure 30) and **3** (Figure 31)] show marked in vitro inhibitory activity against *Trypanosoma cruzi*, the protozoon which is the causative agent, but 3-allyl-β-lapachone (Figure 31, **3**) has been shown to be the most effective in treating blood intended for transfusions, which is often the vehicle by which the disease is transmitted (Lopes et al., 1978). Hopes to find an actual cure for this trypanosomiasis are increasing with the progress of this research.

Di- and Triterpenoids. The Euphorbiaceae include some of the most poisonous plants of tropical America. Their action was often traced to diterpenes, such as the vesicant and cocarcinogenic esters of phorbol (Figure 33, **1**), ingenol, resiniferonol etc. and the cytotoxic jatrophone (Figure 33, **2**). The roots of *Jatropha elliptica* (Pohl.) Muell. Arg. from Mato Grosso contain not less than 1% of the latter compound (Cavalcante et al., 1979), reported to inhibit tumor growth.

AB cis diterpenoids, such as diasin (Figure 33, **3**) from the Amazonian tree *Croton diasii* Pires, seem to be rare in nature. This configuration was rationalized considering the rearranged labdanic cation **5** (Figure 33) and the derived cyclopropane (Figure 33, **4**, R = H) and cyclopropanol (Figure 33, **4**, R = OH) as biogenetic intermediates. Opening of cyclopropanols with inversion of configuration is known to occur in vitro, and, suggestively, phorbol (Figure 33, **1**) derivatives incorporate cyclopropanol moieties.

The most singular constituents of Brazilian Euphorbiaceae so far are the micrandrols (**6–8**, Figure 33) from the Amazonian trees *Micrandropsis scleroxylon* W. Rodr. and *Sagotia racemosa* Bail. All known natural nitrogen-free phenanthrenes and 9,10-dihydrophenanthrenes bear only oxy substituents and at such positions that their biosynthetic derivation either by the shikimate or the shikimate–acetate routes seems assured. The nature and position of the substituents on the micrandrol ring system, however, suggest a mevalonate origin. The direct bonding of an S atom to an aromatic ring is a strange feature for

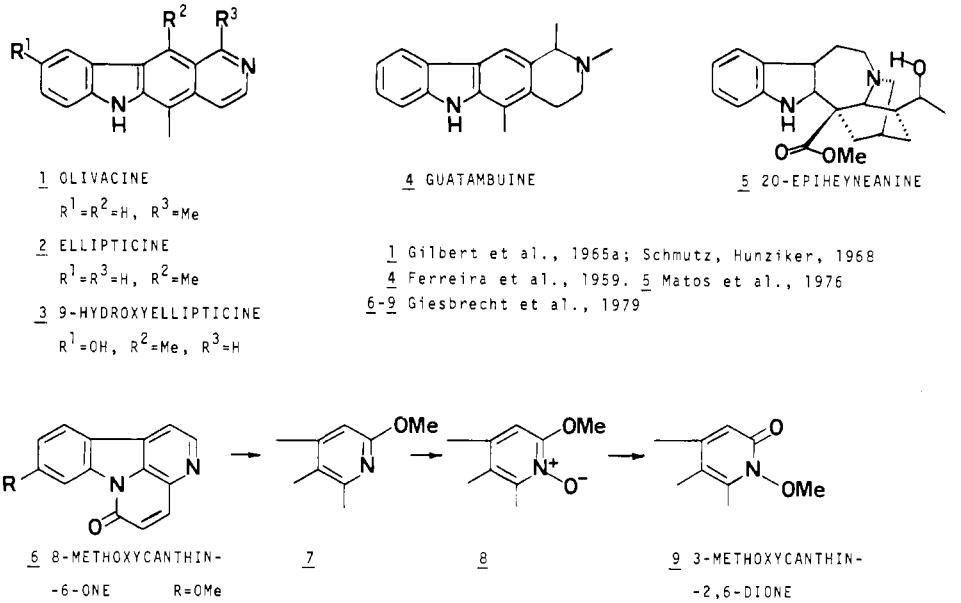


Figure 35. Indole alkaloids from Brazilian Apocynaceae and Simaroubaceae.

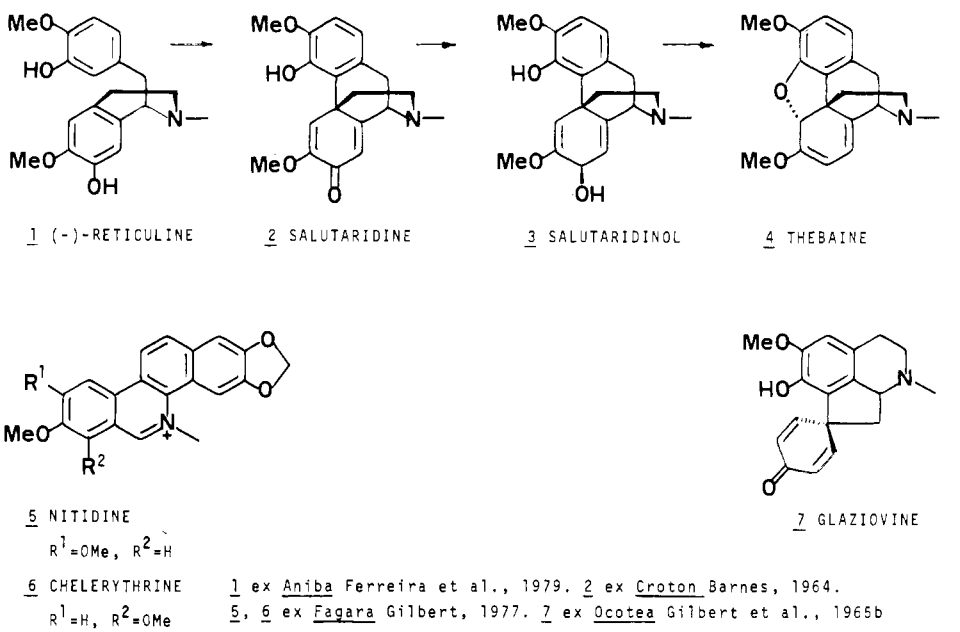


Figure 36. Benzylisoquinoline alkaloids from Brazilian Euphorbiaceae, Rutaceae, and Lauraceae.

a natural product and would require explanation.

Quite conspicuous is the diterpenic skeleton in some naphthalenic norditerpenes present in Velloziaceae. This family of the monocots is abundantly represented in the forests of south-central Brazil. Crude extracts of the stems have been found to have molluscicidal, cercaricidal, and fungicidal activity, in several instances also shown by some of more than twenty diterpenes isolated and described so far. The main types of these compounds are depicted in Figure 34. Other representatives show a clear interrelationship with those shown through oxidation and dehydrogenation.

The same plants also produce a number of triterpenes belonging to the lupane, dammarane (ocotillol 7, Figure 34) and hopane (Figure 34, 8) types. Ocotillol and other dammaranes were also described from Brazilian Meliaceae, *Cabralea polytricha* Jusss. (Cascon and Brown, 1972) and *C. eichleriana* DC. (Rao et al., 1975).

ALKALOIDS

In Brazil, pharmacological research has been slow in keeping pace with the chemical investigations. It suffices to remember the intense chemical work which, in the 1960's, has been done on the alkaloids of the Apocynaceae. Well over a hundered compounds were then isolated from numerous species of the genus *Aspidosperma* and had their structures determined. The majority can be classified among the indole and dihydroindole bases, being subdivided into a series of structural groups (Gilbert, 1965, 1968). Very little pharmacological work has been done with these compounds. Olivacine (Figure 35, 1) is an exception. Known for its DNA intercalating capability (Festy et al., 1971), it is also antileukemic in mice (Sampaio et al., 1974) and inhibits the growth, in culture, of the protozoa *Crithidia fasciculata* and *Trypanosoma cruzi*. Olivacine is, in fact, more active against these flagellates than ellipticine (2, Figure 35) and 9-hydroxyellipticine (3, Figure 35) (Gilbert, 1977). Other compounds which have been investigated to some extent include guatambuine (4, Figure 35) from *Aspidosperma longipetiolatum* Kuhlm., which served as a model in the synthesis of antitumor agents (Hartwell, 1969), and 20-epiheyneanine (5, Figure

35) from *Peschiera affinis* (M. Arg.) Miers, a common shrub of the Brazilian northeast, which possesses antispasmodic activity (Fonteles et al., 1974).

Plant extracts containing canthinones were shown to be active against various microorganisms; later, this activity was attributed to canthin-6-one itself (Mitscher, 1972). The bark of *Simaba cuspidata* Spruce, a simaroubaceous tree from the Amazon, yielded besides 8-methoxycanthin-6-one (Figure 35, **6**, R = OMe) 3-methoxycanthin-2,6-one (Figure 35, **9**, R = H). The rearrangement **8** → **9** (Figure 35) is a facile laboratory reaction, and by present evidence one cannot be certain if **9** (Figure 35) exists as such in the plant or is formed during the isolation procedure.

(−)-Reticuline (Figure 36, **1**), a benzylisoquinoline alkaloid originally isolated from *Annona reticulata* L. (Annonaceae) (Gopinath et al., 1959) is widespread in Brazilian *Aniba* species (Lauraceae). It is also a precursor in the biosynthesis of thebaine (Figure 36, **4**) and morphine. The predictive power of the originally suggested pathway (Barton et al., 1965) has been underlined by the discovery of the key intermediate salutaridine (Figure 36, **2**) (cf. Geissman and Crout, 1969) which occurs in the leaves of the Brazilian tree *Croton salutaris* Casar (Barnes and Gilbert, 1960) if only in minute amounts (Barnes, 1979). The compound is unfortunately also not freely available by synthesis, conversion of reticuline proceeding in very low yield, and thebaine can thus not be produced in significant quantities by this route.

The benzylisoquinoline biogenetic group includes furthermore phenanthridine alkaloids, such as the tumor inhibiting nitidine (Figure 36, **5**) and chelerythrine (Figure 36, **6**) described from *Fagara* species (Rubiaceae), and also found in some Brazilian species of that genus.

Even though with the increasing exploration of Brazilian forest reserves many extractives from wood, bark, and other plant material could be made available in significant amounts, we do not necessarily advocate the use of the natural substances. In many instances the trees themselves are rare, or the active principles occur in low concentration or are but minor constituents. Research, however, is well justified if we look at all these as model compounds the activity of which would warrant their synthesis or that of their analogues.

An extreme case is that of glaziovine (Figure 36, **7**), a proaporphine alkaloid from the bark of *Ocotea glaziovii* Mez, a Brazilian Lauraceae species. Glaziovine was later found also in *Annona purpurea* L., an African Annonacea (Sonnet and Jacobsen, 1971). *Ocotea glaziovii* is very rare, only two trees being known to the authors. (±)-Glaziovine, however, is an anxiolytic compound devoid of depressant, muscle relaxant or anticonvulsant effects. It has been shown to counteract experimentally induced gastric ulcers in the rat (Casagrande, 1974; Marzo et al., 1978). Therapeutic use of the drug has been patented (Siphar, 1971; Ferrari and Casagrande, 1975) and prompted several syntheses (Kametani et al., 1971), two of which (Casagrande and Canonica, 1975; Casagrande et al., 1975) were also protected by patents (respectively Casagrande and Canonica, 1974, 1975, 1976; and 1974) all over the world.

This final example, in addition to all those reported in this review, clearly shows how abundantly work on the chemistry of Brazilian plants will bear fruit once it is taken up with vigor and purpose by biologists, pharmacologists, and the pharmaceutical industry; and this in spite of the fact that since the time of Peckolt we have come to know only some of the constituents of 470 plants (Gomes and Gottlieb, 1977). In other words: with respect to number of species, we know nothing about the chemistry of 99.6% of the Brazilian flora.

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