(43) In Table XIII, the chemical composition of yucca oil is presented from which it can be observed the high level of insaturation.
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Wood Extractives as Models for the Development of New Types of Pest Control Agents

Leonard Jurd* and Gary D. Manners

Molecular modification of obtusastyrene, a cinnamylphenol microbicide, and obtusaquinone, a *p*-quinone methide fish poison and marine borer larvicide, both of which occur in the durable timber, *Dalbergia retusa*, has led to the recognition of new structural types of insect control agents. A number of cinnamyl and benzyl derivatives of alkylphenols and 1,3-benzodioxoles have now been shown to be promising, highly effective sterilants for different fly species, mosquito growth inhibitors, beetle repellents, preservatives for wood in the marine environment, and, in some cases, toxicants for other insect pests. The most active benzylphenols are nonmutagenic in the Ames' test. Sterilant activity may be due to in vivo oxidation to reactive quinone methides.

Pesticide research in the agricultural industry generally continues to emphasize studies on the development and use of synthetic, broadly toxic compounds. However, health and environmental problems, and increasing insect resistance to many of these pesticides, clearly indicate that basic research must be directed to the discovery of new, safer types of pest control agents in order to insure high production and preservation of plant and animal agricultural products. Ideally, these new types of pest control agents should be active against a limited number of species, including specific target organisms, be biodegradable to nontoxic products, and be suitable for use in programs of integrated pest management.

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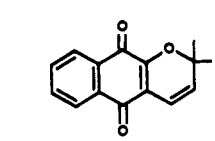
With a few exceptions, notably pyrethrums and rotenones, plant constituents are usually insufficiently active against insect and microbial pests to be of practical use. Thus, with the introduction of highly toxic, synthetic pesticides early in this century, research on plant sources of potentially useful insecticides has largely been neglected. However, a program was recently initiated at the Western Regional Research Center to determine, in cooperation with a number of USDA entomology laboratories, whether molecular modification of biologically active constituents of durable woods could lead to the recognition and development of new classes of possibly safer pest control agents. This approach to new pest control substances has been developed chiefly from initial chemical studies on constituents of *Dalbergia retusa*, a Panamanian hardwood which is very resistant (Southwell and Bultman, 1971) to attack by fungi and marine organisms. It should be noted, however, that other unrelated woods have also given a variety of unusual compounds which may be worthy of similar chemical modification and biological evaluation (Manners et al., 1975; Jurd and Manners, 1977; Stevens and Jurd, 1976; Manners and Jurd, 1977; Roitman and Jurd, 1978), e.g., *Tabebuia guayacan* yields derivatives 1–3



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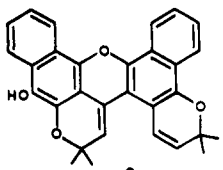

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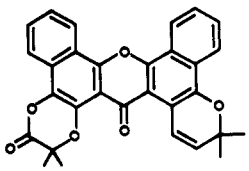

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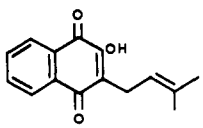

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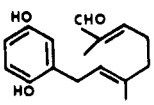

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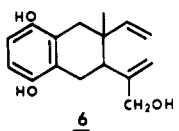

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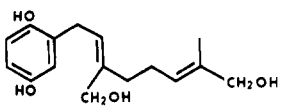

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of lapachol 4, a naphthaquinone which is toxic to termites (Thomson, 1971) and possesses antitumor properties worthy of clinical testing (Rao et al., 1968); *Cordia alliodora* contains a long series of phenolic terpenoids, e.g., 5–7, which structurally resemble some antibiotics of fungal origin, such as grifolin (Isobe and Goto, 1968) and siccanin (Suzuki and Nozoe, 1971).

Extensive chemical studies on the *Dalbergia*, and closely related *Machaerium*, genus by Ollis, Gottlieb, and others since about 1965 have shown that species of these genera contain a unique group of cinnamylphenols, neoflavanoids, and quinonoid compounds which have not yet been detected in any other genus (for recent summary, see Gottlieb, 1977). *Dalbergia retusa* yields, in addition to 4-methoxydalbergione, obtusaquinol, and isoflavones (Jurd et al., 1972a), a cinnamylphenol, obtusastyrene 8, a *p*-

Scheme I

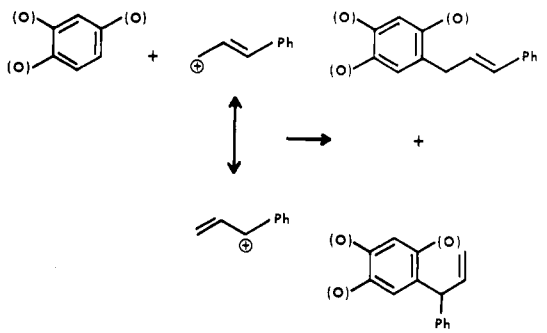
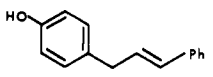


Table I. Toxicity of Obtusaquinone to Fish at 12 °C[a] Concentration (ppm) and Percent Mortality at

species	3 h		24 h	
	0.2	2.0	0.2	2.0
rainbow trout	0	100	100	100
carp	0	0	100	100
white sucker	0	0	90	100
blue gill	0	100	100	100
channel catfish	0	60	100	100

[a] Bioassay by L. M. Marking, U.S. Department of the Interior, Bureau of Sport Fisheries and Wildlife.



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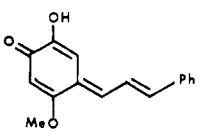

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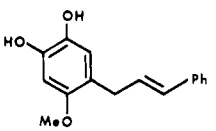

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quinone methide, obtusaquinone 9, and the corresponding cinnamyl catechol 10 (Gregson et al., 1968; Jurd et al., 1972b; Manners et al., 1974; Gregson et al., 1978). These compounds are biologically active and, like other cinnamyl derivatives, may be synthesized readily via aqueous acid catalyzed condensation of cinnamyl alcohol (Jurd, 1969) with appropriate phenols (Scheme I).

Obtusaquinone 9 is a potent fish poison (Table I) and an effective marine borer larvicide (Bultman et al., 1977), causing abnormal shell formation and interrupting larval metamorphosis (Waite, 1976). It proved to be inactive against a representative group of bacteria and fungi. Obtusastyrene 8 also inhibits larval metamorphosis of marine organisms. In contrast to obtusaquinone, however, obtusastyrene (and isomeric 2-cinnamylphenol) is an effective microbicide (Table II) and algicide with activities superior to some of the synthetic food preservatives in current use (Jurd et al., 1971a,b; Chan and Jurd, 1973). At low concentrations, it inhibits bacterial and yeast growth in wine and its dihydro derivative inhibits fungal rot of citrus fruits. Although relatively few compounds are known which induce sporostasis of bacterial spores, obtusastyrene prevents germination and outgrowth of *Bacillus megaterium* spores at concentrations (10–32 ppm) well below those of most known sporostats (Lewis and

Table II. Minimal Inhibitory Concentrations (Micrograms/Milliliter) of Phenols against Bacteria and Fungi

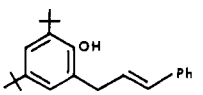
microorganisms	obtusa-styrene	2-cinnamyl-phenol	*O*-phenyl-phenol	heptyl-paraben	propyl-paraben
Bacillus cereus 2006	25	12	100	12	400
Staphylococcus aureus SG3A	25	25	200	12	400
Streptococcus lactis	25	25	100-200	12	400
Alcaligenes faecalis B170	50	100	100	*a*	400
Escerichia coli ML30	50	100	100-200	*a*	400
Pseudomonas aeruginosa 111	*a*	*a*	*a*	*a*	*a*
Salmonella typhimurium Tml	*a*	*a*	200	*a*	*a*
Serratia marcescens	*a*	*a*	*a*	*a*	*a*
Zygosaccharomyces japonicus C124	12	12	100-200	12-25	200
Candida tropicalis C147	12	12-25	100	12-25	150
Pichia chodati C238	25	50	100	*a*	400
Hansenula anomala	50	50	200	*a*	400
Saccharomyces cerevisiae Y44	25	25	100-200	100	200
Torula utilis NRRL Y660	50	50	200	25	200
A. niger A-7705	50	100	100	*a*	200
Penicillium chrysogenum 52	50	25-50	50	*a*	200
Rhizopus senti NRRL 2868	6	50	100	25	200
Botrytis cinerea NRRL 3492	25-50	12-25	12-25	50-100	100
Byssochlamys fulva NRRL 3493	25	25	50	*a*	200
Alternaria sp	25	25	50	50-100	100

[a] No growth inhibition with 500 μg/mL.

Jurd, 1972). This observation may have an application against heat resistant, spore-forming food spoilage bacteria.

Early tests on a limited number of organisms indicated that both obtusaquinone and obtusastyrene are essentially ineffective against insects. However, the feasibility of structurally modifying the nucleus of these microbicidal and/or marine borer larvicidal compounds to produce substances with promising, practical potential as highly active insect growth regulators, sterilants, toxicants, or repellents has now been unequivocally demonstrated. This is illustrated by some examples taken from entomological evaluations in progress in cooperating USDA laboratories. Up to this time, different mosquito, fly, and beetle species have chiefly been used as test organisms.

The introduction of alkyl groups onto the cinnamylphenol nucleus gives compounds which are mosquito larvicides, the larvicidal effect increasing with size of the alkyl group. As indicated in Table III, the di-*tert*-butyl derivatives **11** and **12** of 2-cinnamylphenol and obtusastyrene



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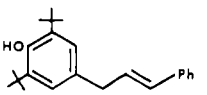

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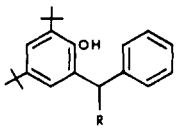
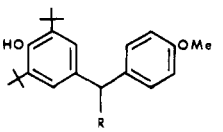


13 a R = H
b R = Me



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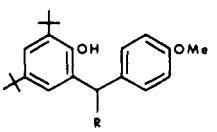

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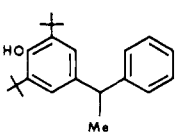
b R = Me



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are active mosquito development inhibitors with LC_{90} values of 0.15 and 0.16 ppm, respectively. Replacement of the cinnamyl group in these molecules by 1-phenylethyl and 4-methoxybenzyl groups to give compounds **13b** and **14a** greatly increases this activity, the LC_{90} of these two compounds being only 0.04 ppm. Because of their high activity, **13b** and **14a** are now undergoing full field investigation at the Insects Affecting Man Laboratory (Florida) as potential mosquito control agents. Insect growth regulators with LC_{90} value of 0.02–0.1 ppm are classified as Class III, i.e., effective enough to warrant full investigation. Compounds with LC_{90} of 0.02 ppm are exceptional (Class IV).

Table III. Growth Inhibitory Activity against the Malaria Mosquito (*Anopheles quadrimaculatus*)[a]

compd	lethal concn[b] LC_{90}, ppm
11	0.15
12	0.16
13a	1.37
13b	0.04
14a	0.04
15a	0.22
17c	0.04
18b	0.35
18c	0.04
19b	0.025

[a] Bioassay by D. D. Dame, Insects Affecting Man Laboratory, Gainsville, Fl. [b] Late 3rd-4th larval stage in water containing ground hog supplement for larval food. Data based on percentages of treated insects that fail to complete development to the free-flying adult stage.

Although tepa [tris(1-aziridinyl)phosphine oxide] is an effective insect sterilant, the suspected mutagenic and toxic properties of aziridines and similar alkylating agents have virtually excluded the use of chemosterilants as agents for insect control. However, the search for new types of sterilants which are nonmutagenic, have low mammalian toxicity, and may be used safely under field conditions has continued (Chang et al., 1964). In feeding experiments with mixed sexes of adult houseflies (*Musca domestica* L.), it has now been shown that cinnamyl and benzyl analogues of obtusastyrene are effective sterilants (Jurd et al., 1979). The aziridine sterilant, tepa, routinely used as a standard in housefly feeding tests, gives 100% sterilization of mixed sexes without significant mortality at a minimum concentration of 0.25% in the diet. As indicated in Table IV, the mosquito growth inhibitor **11** is nontoxic but completely sterilizes the flies at a concentration of 0.25%. The isomeric 4-cinnamylphenol **12** does not sterilize at the highest concentration (1%) tested. Benzyl and 1-

Table IV. Sterilizing Effects of Compounds in the Diet of Mixed Sexes of Houseflies[a] (*Musca domestica* L.)

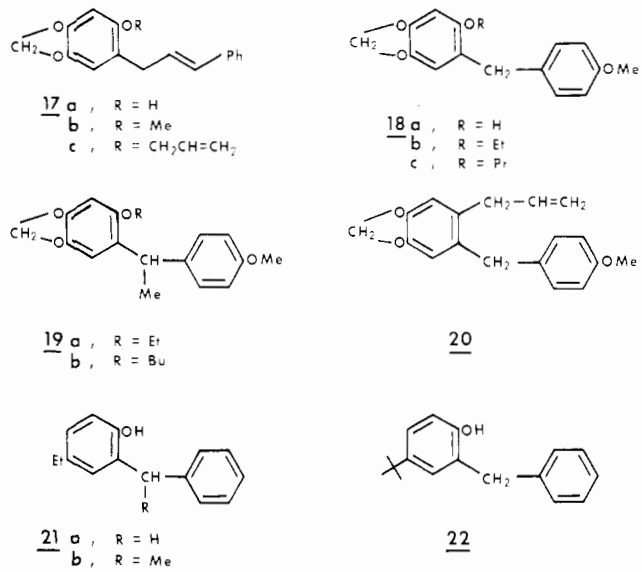
compd	concn, %	mortality, %	hatch, %
11	0.25	0	0
12	1.0	0	normal
13a	0.1	0	0
13b	0.1	0	0
14a	1.0	0	normal
15a	0.025	0	0
15b	0.5	0	0
23	0.25	0	0
17b	0.25	80	0
18b	0.025	0	0
	0.01	0	19
19a	0.5	0	NO[b]
19b	0.25	0	0
20	0.025	0	0

[a] Bioassay by R. L. Frye and J. Morgan, Insect Affects Man Laboratory, Florida. [b] NO, no oviposition.

phenylethyl analogues of 11, viz., **13a**, **13b**, **15a**, are even more effective, the most active sterilant being the 4-methoxybenzyl compound **15a**, which produces 100% sterilization of the mixed sexes without mortality at concentrations of only 0.025%. These sterilants are chiefly active against female flies. As with **12**, *p*-(4-methoxybenzyl)phenol (**14a**), isomeric with **15a**, is devoid of sterilant properties.

Most importantly, the sterilants **15a** and **13a** are nonmutagenic in standard Ames' bacterial tests with three *Salmonella typhimurium* strains and have high oral LD_{50}'s (3550 and 3430 mg/kg, respectively) with mice. **13b** is slightly more toxic (LD_{50} = 2510 mg/kg) and the Ames' test indicates that it *may* be an extremely weak mutagen with one of the bacterial strains. If the low mammalian toxicity and nonmutagenicity of these benzylphenols are confirmed in additional tests, they may provide a cheap, efficient, and safe chemosterilant for a number of important fly pests. In this connection, it is noteworthy that these compounds are currently being considered for possible inclusion in a planned program to eradicate or suppress the screwworm fly, a pest which causes severe stock losses and occasional human diseases in southwestern areas of the U.S. and Mexico. Extensive work (Rawlins, 1979) has established that these compounds are highly effective against the screwworm; female flies can be completely sterilized by a single feeding of compound **15a** in dried blood and also by tarsal contact with surfaces coated with the sterilant.

A number of natural and synthetic methylenedioxybenzene derivatives (1,3-benzodioxoles), e.g., sesamin, piperonyl butoxide, are widely used as insecticide synergists and some have been shown to have juvenile hormone activity (Bowers, 1968). We were particulary interested, therefore, in determining whether methylenedioxy analogues of obtusastyrene and related benzylphenols are biologically active. As indicated in Table IV, 2-cinnamylsesamol (**17a**) does not sterilize flies; however, ethers, e.g., **17b**, **17c**, of this compound, prepared by alkylation of the phenolic OH, are active. Similarly, 2-(4-methoxybenzyl)sesamol **18a** is inactive, whereas its ethers are very effective fly sterilants. The most active sterilants in this series of compounds are the ethyl ether **18b**, which completely sterilizes mixed sexes of flies at a concentration of 0.025%, the propyl ether **18c**, which sterilizes female flies at 0.1%, and **19a** which sterilizes females at 0.05%. Interestingly, simple cinnamyl and benzyl derivatives of safrole, a constituent of plant essential oils, are also highly effective female fly sterilants, **20** producing 100% sterilization of females at concentrations of 0.025%. In addition to their ability to sterilize houseflies, some of the methylenedioxy compounds mentioned above are potent mosquito growth inhibitors (Table III), e.g., both **17c** and **18c** have a LC_{90} value of 0.04 ppm with the malaria mosquito, while the butyl ether **19b** borders on the exceptional, with a LC_{90} of only 0.025 ppm.



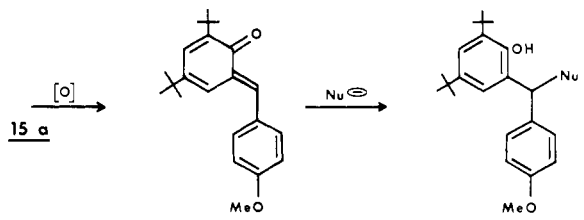
As a final example of the range of biological activity of these types of compounds, the insect repellency of some benzylphenols is particularly noteworthy. For a number of years the Stored Products Insect Research and Development Laboratory (Georgia) has been searching for repellents that are safe, more effective, more persistent, and more economical than synergized pyrethrins, which are currently used for protecting packaged foods and cereal grains against infestation by the confused flour beetle (*Tribolium confusum*). In repellency tests, which involve exposing beetles to laminated paper strips coated with candidate compounds (McDonald et al., 1970), the standard repellent—pyrethrin synergized with piperonyl butoxide—is rated as a Class III repellent, i.e., it repels 40–60% of the insects. A number of simple monoalkylbenzylphenols, e.g., **21a**, **21b**, **22**, which do not show sterilant or growth inhibitory properties with mosquitoes and flies, are exceptional beetle repellents (highest Class V), repelling 80–90% of the insects over a 2-month test period (Gillenwater et al., 1979). Preliminary studies have indicated that these inexpensive benzylphenols may be repellent to a variety of beetle pests, including the black carpet beetle (Bry et al., 1978), as well as the Japanese beetle (Ladd, 1978) and the cucumber beetle, which attack vegetable crops. Compound **22** appears especially promising against the cucumber beetle (Reed, 1979), although problems with phytotoxicity must be solved before these phenols could be used on growing crops.

The range and species specificity of biological action of the sterilants and growth inhibitors have only been partially explored at this time. Studies in progress, however, indicate that the fly sterilant **18b** is toxic at low concentrations to some important crop pests, including the pink bollworm (Flint, 1979) and the cotton boll weevil (Wright, 1978). Furthermore, the benzylphenols **13a** and **13b** are excellent preservatives for wood against marine teredos and pholads (Jurd and Bultman, 1977) and are fairly toxic to the Indian Meal Moth (Brower, 1979).

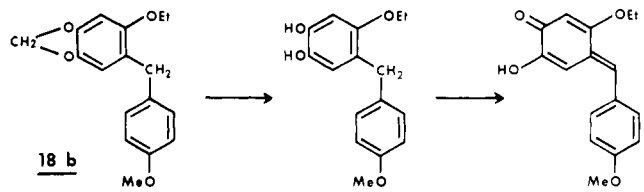
STRUCTURAL BASIS FOR STERILANT ACTION

Since benzyl and cinnamyl derivatives of di-*tert*-butylphenols and nonphenolic 1,3-benzodioxoles differ

Scheme II



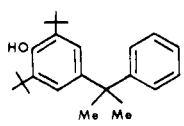
Scheme III



markedly in structure, it may not be apparent how structure and sterilant activity of these compounds can be correlated. However, sterilant activities can be rationalized by assuming that, after translocation in the insect to the site of action, they undergo microsomal oxidation to bioreactive quinone methides. In addition to structural features necessary for translocation to the action site, we propose that two principal factors determine the ability of benzylphenols and 1,3-benzodioxoles to sterilize, viz., (1) to be effective sterilants the compounds must possess structural groupings which allow facile formation of quinone methide intermediates, and (2) the quinone methide which is formed must be sufficiently reactive to undergo nucleophilic attack by a cell constituent(s) which is significant in the reproductive process.

It has recently been suggested that quinone methide intermediates are responsible for the antineoplastic properties of some antitumor drugs (Moore, 1977). *o*-Quinone methides are highly unstable and until recently they have not been isolated because of the ease with which they undergo nucleophilic attack (Turner, 1964; Jurd, 1977). *p*-Quinone methides, however, are generally more stable and a number of wood, e.g., obtusaquinone, and insect pigments with this structural unit have been isolated (Brown and Baker, 1971; Edwards, 1972).

In accord with these observations, the most active phenolic sterilants are the *o*-benzyl and cinnamylphenols, **11**, **13a,b**, **15a,b**, all of which can give rise to highly reactive *o*-quinone methides on oxidation (Scheme II). Oxidation of the *p*-cinnamylphenol **12** and the *p*-(4-methoxybenzyl)phenols **14a** and **14b** yields *p*-quinone methides which are stable and can readily be crystallized. These phenols are inactive as sterilants. It is apparent that quinone methide formation requires the presence of at least one hydrogen in the benzylic position ortho or para to the phenolic OH. Thus, in contrast to the sterilant activity of **16**, which forms an unstable *p*-quinone methide, the related α,α-dimethyl compound **23** is inactive. Since

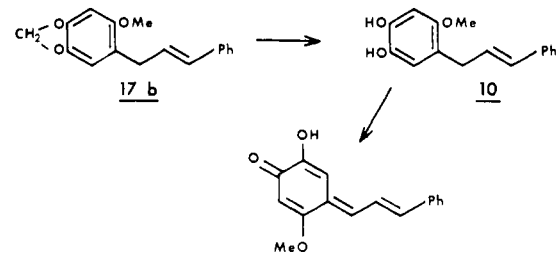


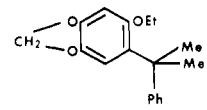
23

23 does not have a benzylic hydrogen, it could form a quinone methide only by an oxidative demethylation.

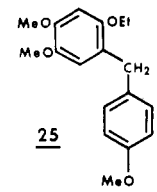
The sterilant activity of 1,3-benzodioxoles (Table IV) can be accounted for by a similar theory of in vivo oxidation to reactive quinone methides. Thus, it has previously been shown that the synergistic activity of methylenedioxybenzenes is due to oxidative demethylation to yield catechols which inhibit enzymic degradation of the insecticide (Hennessy, 1965). If the sterilant 1,3-benzodioxoles are similarly metabolized, the initially formed catechols would be expected, because of the benzyl substituents, to undergo further oxidation to reactive quinone methides (Scheme III). In accord with this theory, closely related ethers of α,α-dimethylbenzylsesamol, e.g., **24**, are

Scheme IV





24



25

devoid of sterilant activity. Furthermore, the importance of the easily removable methylenedioxy group has been confirmed by the complete absence of sterilant activity with ethers such as **25**, in which the methylenedioxy group was replaced by stable methoxy groups.

Finally, it is interesting to note that the proposed quinone methide theory of sterilant action suggests that the sterilant activity of the cinnamylsesamol methyl ether **17b** is due to its absorption, translocation, and oxidation in the fly to obtusaquinone **9**, the fish poison and marine borer larvicide originally isolated from *Dalbergia retusa* (Scheme IV).

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Chemistry and Utilization of Phenylpropanoids Including Flavonoids, Coumarins, and Lignans

Tom J. Mabry* and A. Ulubelen

Phenylpropanoids are perhaps the most widespread types of natural products occurring in nature. In this account of the chemistry and utilization of phenylpropanoids we emphasize a few of the useful physiological, pharmacological, and chemical properties of flavonoids, lignans, and coumarins which are three of the major classes of compounds containing the C_6–C_3 phenylpropanoid moiety.

FLAVONOIDS

With the exception of most algae[1] flavonoids are found throughout the plant kingdom, and within individual plants they may occur in every organ but are usually concentrated in leaves and flower parts. Except for the well-known pollinator-attracting red and blue anthocyanins and yellow aurones and chalcones, most flavonoids absorb light between 240–370 nm, an ultraviolet spectral region also visible to many pollinators.

Many flavonoids including those which are phytoalexins[2,3] provide plants with a defense against viral infections.[4-7] Others exhibit antitumor[8-11] and general antiinflammatory[12,13] activity. The estrogenic action of many isoflavones is well known,[14] and mixtures of flavonoids are commonly used commercially to reduce capillary fragility.[15]

Since most flavonoids are isolated in only small amounts, their structures are primarily determined by spectral methods, especially UV,[16-18] ^1H[16,17] and ^{13}C[19-23] NMR, and MS.[24-26]

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Flavonoids are biogenetically formed from a malonate-derived C_6 unit and a shikimic acid-derived C_6–C_3 phenylpropanoid moiety to give initially the chalcones. The chalcone–flavanone isomeric pair then undergoes further transformations (see Figure 1) including oxidations, rearrangements, alkylations, acylations, and glycosylations all of which give structural diversity to the thousands of distinct flavonoids known at the present time.

Isolation of Flavonoids. Flavonoid isolation remains the most time-consuming aspect of research in this field. Most isolations involve extracting air-dried ground plant material with methanol–water (80:20) and then partitioning the material obtained from this extract between water and a series of organic solvents: hexane, methylene dichloride, and ethyl acetate. The hexane and methylene dichloride layers yield mostly aglycons, especially highly methoxylated types, while the ethyl acetate yields some aglycons but mostly mono- and diglycosides. The remaining water layer contains glycosides, especially di-, tri-, and tetraglycosides, as well as sulfated flavonoids.

Flavonoids may be obtained in large quantities by column chromatography using such supports as polyamide, cellulose, Sephadex, and silica gel and by preparative high-pressure liquid–liquid chromatography.[27-30] Flavo-

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