THE NATURALLY OCCURRING LIGNANS

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I. Introduction

The term lignan was originated by Haworth (124) to describe the group of naturally occurring compounds which, at least formally, would seem to be formed by joining certain derivatives of *n*-propylbenzene at the β-carbon atoms of the side chains. The aromatic rings of the known lignans are all oxygenated and bear hydroxyl, methoxyl, or methylenedioxy groups. The side chains within this broad group of compounds exist in varying degrees of oxidation and in some cases are further modified by cyclization to tetrahydrofuran or tetrahydronaphthalene derivatives.

In relationship to other non-carbohydrate plant constituents the lignans would represent a dimer stage intermediate between monomeric propylphenol units and lignin. Naturally occurring trimers and tetramers have not been reported.

The lignans are of wide occurrence and in different instances have been obtained from roots, heartwood, foliage, fruits, or resinous exudates of plants. The presence of a given lignan is sometimes characteristic of a certain botanical group and therefore of taxonomic interest (83).

The literature on lignans has been partially covered by older reviews (84, 124, 125, 126, 302). The present review includes only naturally occurring lignans. Dimers, such as dehydrodiisoeugenol, syringaresinol, and dehydrodiconiferyl alcohol, which are produced chemically or enzymatically but which are optically inactive are omitted.

II. Classification and Nomenclature of Lignans

All of the lignans contain one or more asymmetric carbon atoms and are optically active. Since the stereochemistry of many of them has not yet been established, they are almost always designated by trivial names.

The lignans may be classified into five principal groups on the basis of the structure formed by the side chains of the two combining units of propylbenzene. The classification used in table 1 is essentially that of Haworth (125). In the table the skeletal structure common to each group is given, along with the numbering system used in this review. The known basic members of each class are listed with their distinguishing functional groups other than glucosyl or acetyl groups, which are noted in the body of the text.

TABLE 1

Classification of the lignans

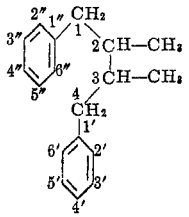
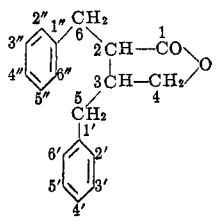
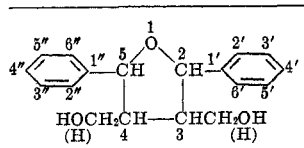
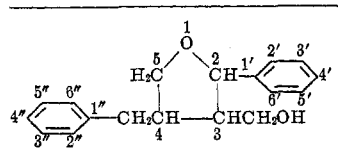
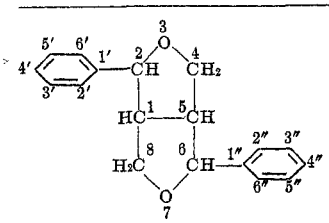
Skeletal structure	Known examples	
	Trivial name	Systematic Name
A. 1,4-Diarylbutane derivatives		
	Dihydroguaiaretic acid	1,4-Bis(4-hydroxy-3-methoxyphenyl)-butane
	Guaiaretic acid	1,4-Bis(4-hydroxy-3-methoxyphenyl)-1-butene
	Nordihydroguaiaretic acid	1,4-Bis(3,4-dihydroxyphenyl)butane
B. 2,3-Dibenzylbutyrolactone derivatives		
	Hinokinin (cubebinolide)	2,3-Bis(3,4-methylenedioxybenzyl)-butyrolactone
	Savinin	2,3-Bis(3,4-methylenedioxybenzyl)-$\Delta^{2,6}$-butyrolactone
	Matairesinol	2,3-Bis(4-hydroxy-3-methoxybenzyl)-butyrolactone
	Arctigenin	2-(4-Hydroxy-3-methoxybenzyl)-3-(3,4-dimethoxybenzyl)butyrolactone
	Cubebin	2,3-Bis(3,4-methylenedioxybenzyl)-butyrolactol (CHOH at carbon No. 1 instead of carbonyl)
C. Tetrahydrofuran derivatives. 1. 2,5-Diaryltetrahydrofurans		
	Olivil	2,5-Bis(4-hydroxy-3-methoxyphenyl)-3,4-bis(hydroxymethyl)tetrahydrofuran
	Galbacin	3,4-Dimethyl-2,5-bis(3,4-methylenedioxyphenyl)tetrahydrofuran
	Galgravin	3,4-Dimethyl-2,5-bis(3,4-dimethoxyphenyl)tetrahydrofuran
C. Tetrahydrofuran derivatives. 2. 2-Aryl-4-benzyltetrahydrofurans		
	Lariciresinol	4-(4-Hydroxy-3-methoxybenzyl)-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyltetrahydrofuran
D. Tetrahydrofurofuran derivatives. 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octanes		
	Pinoresinol	2,6-Bis(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane
	Phillygenol (forsythigenol)	2-(4-Hydroxy-3-methoxyphenyl)-6-(3,4-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane
	Eudesmin	2,6-Bis(3,4-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane
	Sesamin	2,6-Bis(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane
	Asarinin	2,6-Bis(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane
	Gmelinol	1-Hydroxy-2,6-bis(3,4-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane
	Symplocosigenin	2,6-Bis(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane

TABLE 1—*Continued*

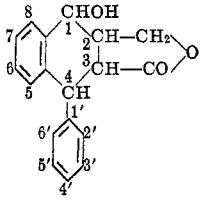
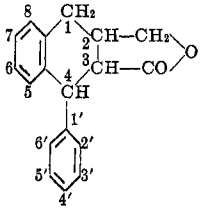
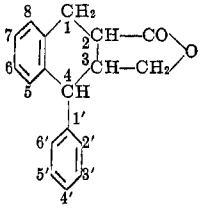
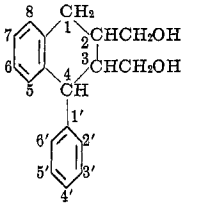
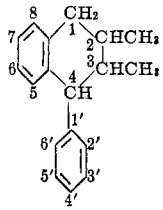
Skeletal structure	Known examples	
	Trivial name	Systematic Name
E. 4-Aryltetrahydronaphthalene derivatives. 1. 1-Hydroxy-2-hydroxymethyl-3-carboxylic acid lactones		
	Podophyllotoxin	1-Hydroxy-2-hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactone
	Demethylpodophyllotoxin	1-Hydroxy-2-hydroxymethyl-4-(4-hydroxy-3,5-dimethoxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactone
	Sikkimotoxin	1-Hydroxy-2-hydroxymethyl-6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactone
E. 4-Aryltetrahydronaphthalene derivatives. 2. 2-Hydroxymethyl-3-carboxylic acid lactones		
	Desoxypodophyllotoxin	2-Hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactone
	α-Peltatin	8-Hydroxy-2-hydroxymethyl-6,7-methylenedioxy-4-(4-hydroxy-3,5-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactone
	β-Peltatin	8-Hydroxy-2-hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactone
E. 4-Aryltetrahydronaphthalene derivatives. 3. 3-Hydroxymethyl-2-carboxylic acid lactones		
	Conidendrin	6-Hydroxy-3-hydroxymethyl-7-methoxy-4-(4-hydroxy-3-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid lactone
E. 4-Aryltetrahydronaphthalene derivatives. 4. 2,3-Bis(hydroxymethyl) derivatives		
	Isoölivil	2,3-Bis(hydroxymethyl)-1,6-dihydroxy-7-methoxy-4-(4-hydroxy-3-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene
	Isotaxiresinol	2,3-Bis(hydroxymethyl)-6-hydroxy-7-methoxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydronaphthalene

TABLE 1—*Continued*

Skeletal structure	Known examples	
	Trivial name	Systematic Name
E. 4-Aryltetrahydronaphthalene derivatives. 5. 2,3-Dimethyl derivatives		
	Galbulin	6,7-Dimethoxy-2,3-dimethyl-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene
	Galcatin	2,3-Dimethyl-6,7-methylenedioxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene

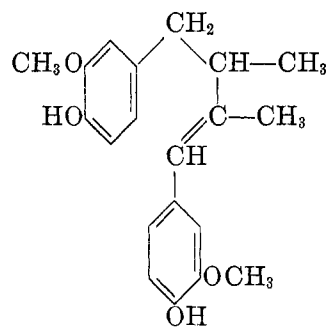
III. Occurrence, Isolation, Proof of Structure, and Chemistry of Individual Lignans

A. 1,4-Diarylbutane derivatives

1. Guaiaretic acid and the dihydroguaiaretic acids

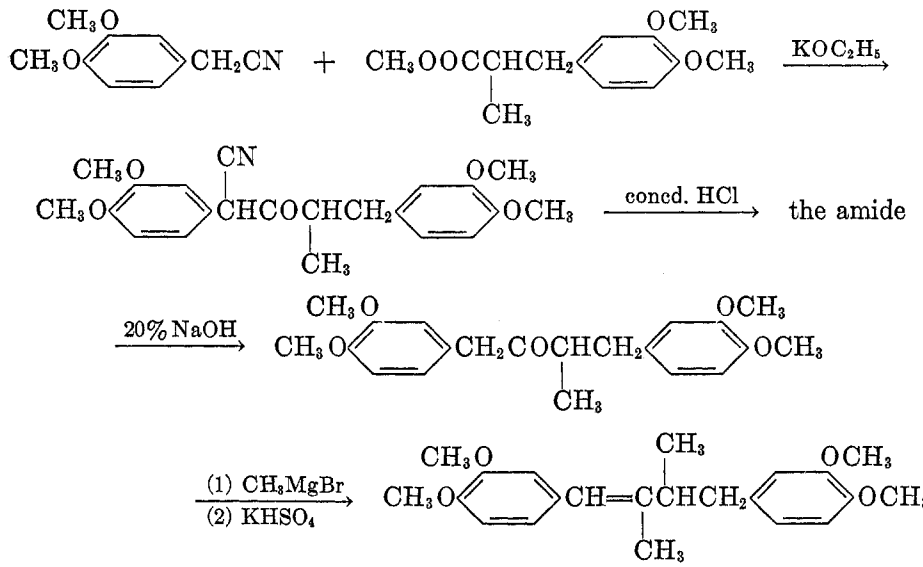
Guaiaretic acid and the dihydroguaiaretic acids occur together in the resin of *Guaiacum officinale* L. or *G. sanctum* L. They constitute 10–12 per cent of the resin and are obtained as the sparingly soluble potassium salts when alcoholic potassium hydroxide is added to an alcohol extract of the resin (43a, 66, 155, 162, 163, 164).

The accepted structure of guaiaretic acid, which was proposed in 1918 by Schroeter, Lichtenstadt, and Irineu (272), is that of a dimer in which two isoeugenol units are coupled at the carbon atoms beta to the rings:



Guaiaretic acid

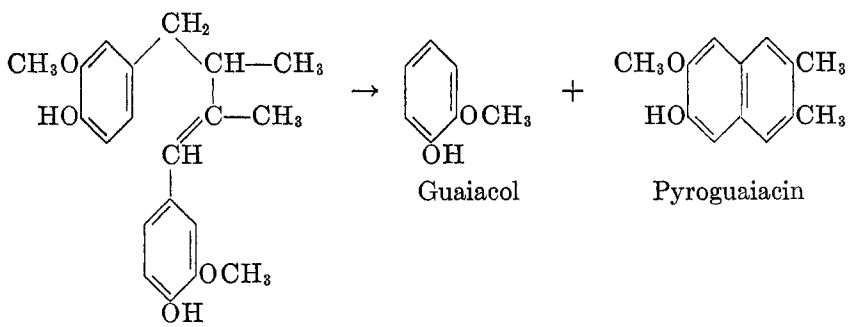
This structure has been verified by synthesis of the racemic dimethyl and diethyl ethers of guaiaretic and dihydroguaiaretic acids (135, 136). The reaction sequence used by Haworth, Mavin, and Sheldrick (135) is as follows:



Analogous reactions were used for the synthesis of the 4′,4″-diethyl ether of guaiaretic acid.

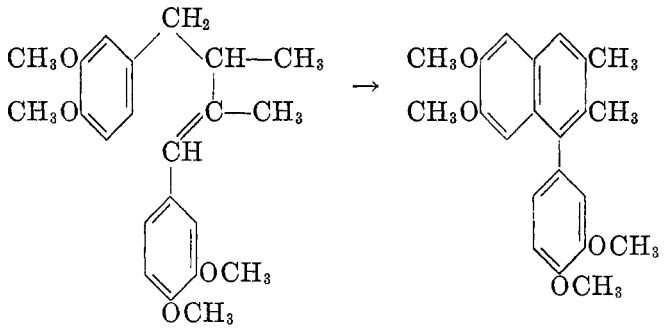
The functional groups of guaiaretic acid react quite as expected. The phenolic hydroxyls are readily acylated or alkylated (156, 157, 158, 272). The aliphatic double bond has been reduced with sodium in alcohol and also catalytically over nickel or palladium–carbon to give dihydroguaiaretic acid (135, 272). Although the aromatic rings of dihydroguaiaretic acid react to give dibromo and dinitro derivatives (136, 272), the positions of the groups introduced have not been reported. Heating dihydroguaiaretic acid or its ethers with concentrated hydriodic acid cleaved the methoxyl groups, forming nordihydroguaiaretic acid (157, 158, 272).

Thermal decompositions of guaiaretic acid are accompanied by cyclization. Thus, distillation with zinc dust removes the oxygen atoms and one of the aromatic rings to give guaiaene, which was shown by synthesis to be 2,3-dimethylnaphthalene (31, 158, 272, 311). Dry distillation similarly cleaved one of the rings, forming guaiacol and pyroguaiacin (66, 158, 254, 272):



The structure of pyroguaiacin was proposed from analytical data, from its conversion to guaiaene by distillation with zinc dust, and from its oxidation to the corresponding naphthoquinone (158, 272, 312). It was later synthesized from 4-(3,4-dimethoxyphenyl)-2,3-dimethylbutanoic acid (134).

Guaiaretic acid would be expected to cyclize readily to a tetrahydronaphthalene. This reaction has not yet been reported, although cyclizations of guaiaretic acid dimethyl ether under oxidizing conditions have been found to yield the naphthalene derivative, dehydroguaiaretic acid. The cyclodehydrogenation was effected in 45 per cent yield by Hübl's reagent (iodine and mercuric chloride) (272).



Dehydroguaiaretic acid

Dehydroguaiaretic acid dimethyl ether is obtainable from several lignans by dehydrogenation with selenium (5). Thus the dimethyl ethers of olivil, isoölivil, lariciresinol, and isolariciresinol gave it in about 8 per cent yields (5). Dehydroguaiaretic acid has also been obtained from the dehydrogenation of isoeugenol by means of ferric chloride (206a).

TABLE 2

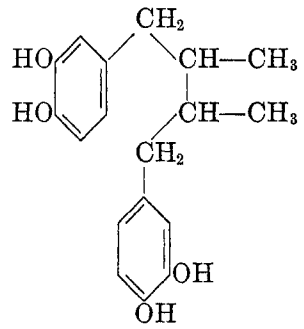
Derivatives of guaiaretic acid and dihydroguaiaretic acid

Compound	Melting Point	Optical Rotation	References
	°C.		
Guaiaretic acid	99–100.5	$[\alpha]_D = -94°$ (alcohol)	(272)
Diacetylguaiaretic acid	108–110		(156, 157)
Dibenzoylguaiaretic acid	132–135		(157)
Dimethylguaiaretic acid	94–94.5	$[\alpha]_D = -92°$ (alcohol)	(272)
Dimethylguaiaretic acid (racemic)	112–113		(135)
Diethylguaiaretic acid	100–102		(158)
Diethylguaiaretic acid (racemic)	98–99		(136)
Dimethyldehydroguaiaretic acid	179		(125, 272)
Dimethyldihydroguaiaretic acid	86–87	$[\alpha]_D = -27°$ (alcohol)	(135, 272)
Dinitrodihydroguaiaretic acid	123	$[\alpha]_D = -49.5°$	(135, 272)
Dibromodihydroguaiaretic acid	122	$[\alpha]_D = -42°$	(135, 272)
Dimethyldihydroguaiaretic acid	101–102		(135, 272)
Dibromodihydroguaiaretic acid	131–132		(135, 272)
Dinitrodihydroguaiaretic acid	151–152		(135, 272)
Nordihydroguaiaretic acid	184–185		(135, 272)
Diacetyldihydroguaiaretic acid	112		(43b)

The melting points and optical rotations of guaiaretic acid, dihydroguaiaretic acid, and derivatives are given in table 2. In the case of dihydroguaiaretic acid the derivatives may be of either the levo or the *meso* form; hence two sets of physical constants are given.

2. Nordihydroguaiaretic acid

The only naturally occurring lignan reported to date containing neither alkoxyl nor methylenedioxy groups is nordihydroguaiaretic acid. This lignan has found



Nordihydroguaiaretic acid

wide commercial use as an antioxidant (159, 209), particularly in foods, because of its lack of toxicity. It has become known commonly under the abbreviation NDGA, which will be used here for simplicity.

NDGA occurs in the resinous exudates of many plants (225, 260); however, the North American creosote bush (*Larrea divaricata* Cav. or *Corillea tridentata*) is the richest source. The leaves and stems of this perennial shrub contain up to 12 per cent NDGA (30). This maximum is reached in old bushes only.

The first isolation of NDGA was reported by Waller and Gisvold (308), who obtained it by an alkaline extraction in the presence of sodium hydrosulfite to minimize oxidation (96, 97). Subsequently, Gisvold (98, 99, 100) patented improved methods for its extraction with organic solvents. Adams (1) also described a process of extraction using a water-miscible organic solvent, while Page (244) used a water-immiscible solvent. Undoubtedly the extraction of creosote bush with a solvent followed by suitable purification is the best means for obtaining NDGA.

Preparation of a "synthetic" NDGA was carried out (272) many years before it was isolated as a naturally occurring material by demethylating the hydrogenated dimethyl ether of guaiaretic acid (see Section III,A,1). Proof of the structure of NDGA (as well as of guaiaretic acid) was obtained through synthesis (135, 136) (see Section III,A,1).

Since the structure of NDGA was already known when the substance was first isolated in nature, it was only necessary to compare its melting point and that of its derivatives (308) with those of the synthetic materials.

The optical rotation of naturally occurring NDGA has not been reported. It is probably the *meso* form however, since its melting point and that of its tetramethyl ether (308) agree with those for Schroeter's optically inactive NDGA

and tetramethyl ether obtained by the hydrogenation of guaiaretic acid (272) (see table 3).

NDGA has also been synthesized by Lieberman, Mueller, and Stiller (204), who have patented their process (231). Their process involves the following reactions:

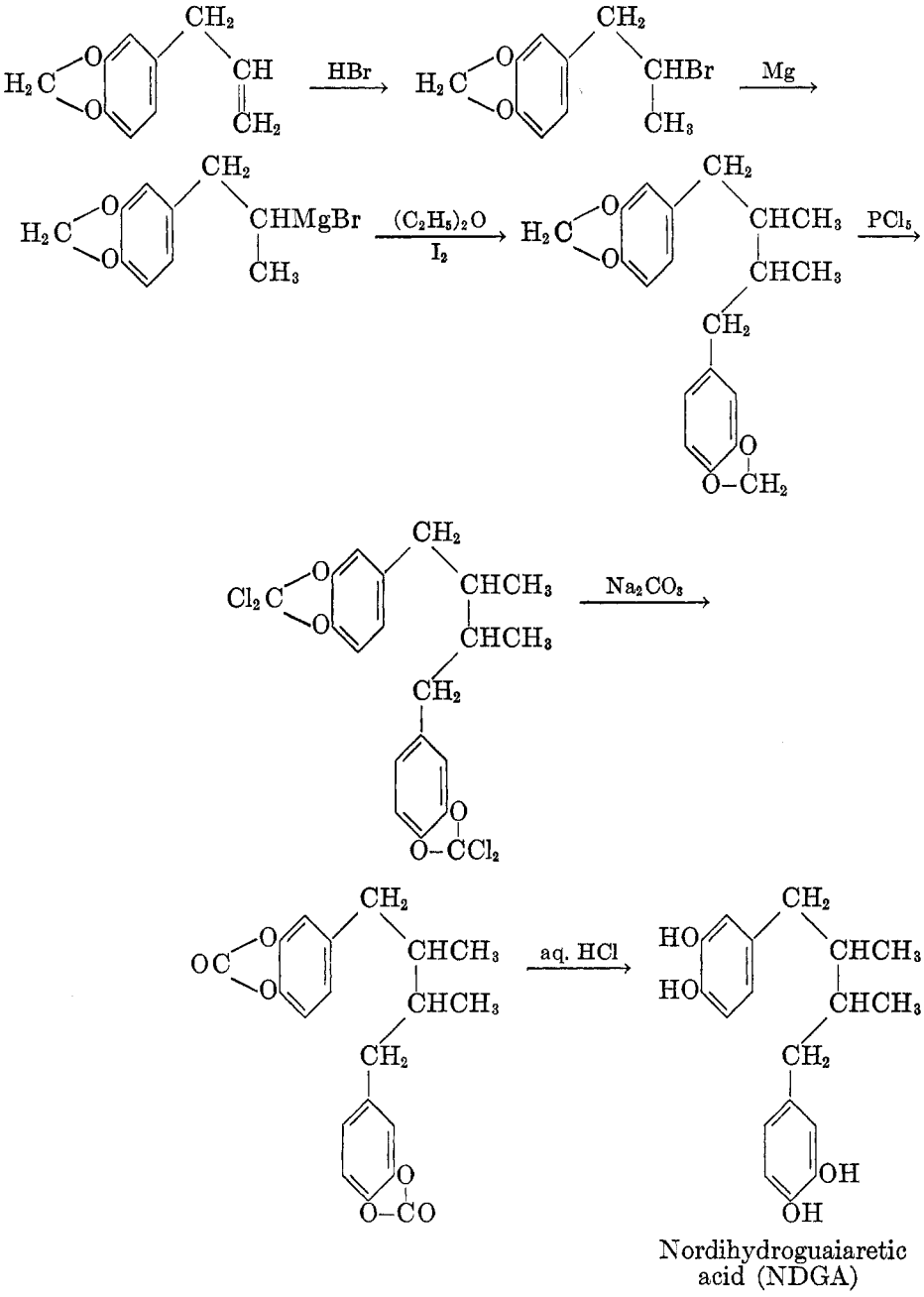


TABLE 3

Nordihydroguaiaretic acid (NDGA) and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
NDGA (from guaiaretic acid)	184–185	$[\alpha]_D = 0°$	(272)
NDGA (from creosote bush)	184–185	$[\alpha]_D = 0°$	(308)
NDGA (from safrole)	185–186		(204)
Tetramethyl NDGA (optically active)	86–87	$[\alpha]_D = -27°$ (alcohol)	(272)
Tetramethyl NDGA (*meso*)	100–101	$[\alpha]_D = 0°$	(272)
Tetramethyl NDGA	102–103		(308)
Tetraacetyl NDGA	102–103		(308)
Tetraethyl NDGA	89–91		(308)

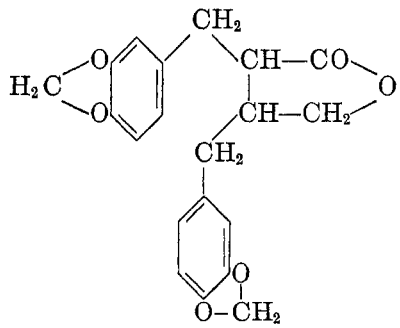
B. 2,3-DIBENZYLBUTYROLACTONE DERIVATIVES

1. Hinokinin (cubebinolide)

Hinokinin occurs in the resin from *Chamaecyparis obtusa* Sieb. et Zucc. and is separated from the wood by extraction with ether. The other materials in the extract are removed by steam distillation, followed by extraction with benzene and 1 per cent sodium hydroxide. The residue, which is largely hinokinin, is then dissolved in hot 10 per cent sodium hydroxide and precipitated by acidification (293).

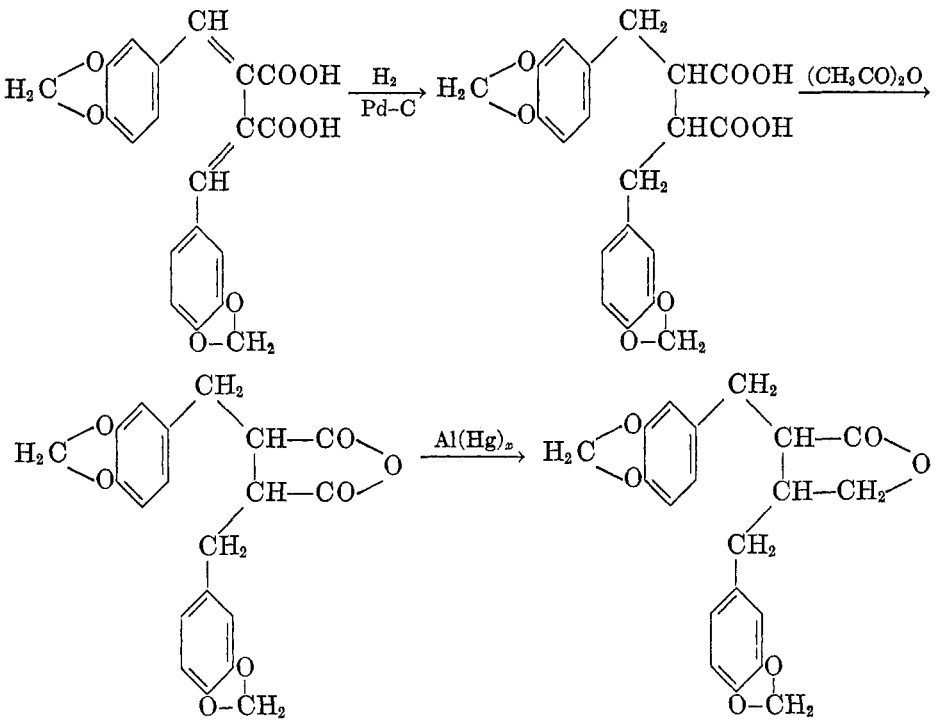
Hinokinin also results in good yield from the oxidation of cubebin with alkaline hypobromite (217, 218) and was, in fact, first obtained by this method (220, 293).

The analytical data and reactions showed hinokinin to be a lactone containing two methylenedioxyphenyl groups for each twenty carbon atoms and led to the following formulation (185, 293):



Hinokinin

The racemate having this structure was synthesized from dipiperonylidene-succinic acid by the following sequence of reactions (183, 185):



The dibasic acid resulting from the first step consisted almost entirely of the higher-melting *meso* form but contained also some of the lower-melting racemic form (146). The same anhydride (racemic) resulted from either the *meso* or the racemic acid, although hydrolysis of the anhydride gave only the racemic dibasic acid.

By resolving the racemic dibasic acid and completing the synthetic sequence with the *d*- and *l*-forms, Haworth and Woodcock (146) synthesized both (−)- and (+)-hinokinin. It is interesting that each step in the sequence caused a change in the direction of rotation. Thus, the (−)-dibasic acid gave a (+)-anhydride which was reduced to (−)-hinokinin (146).

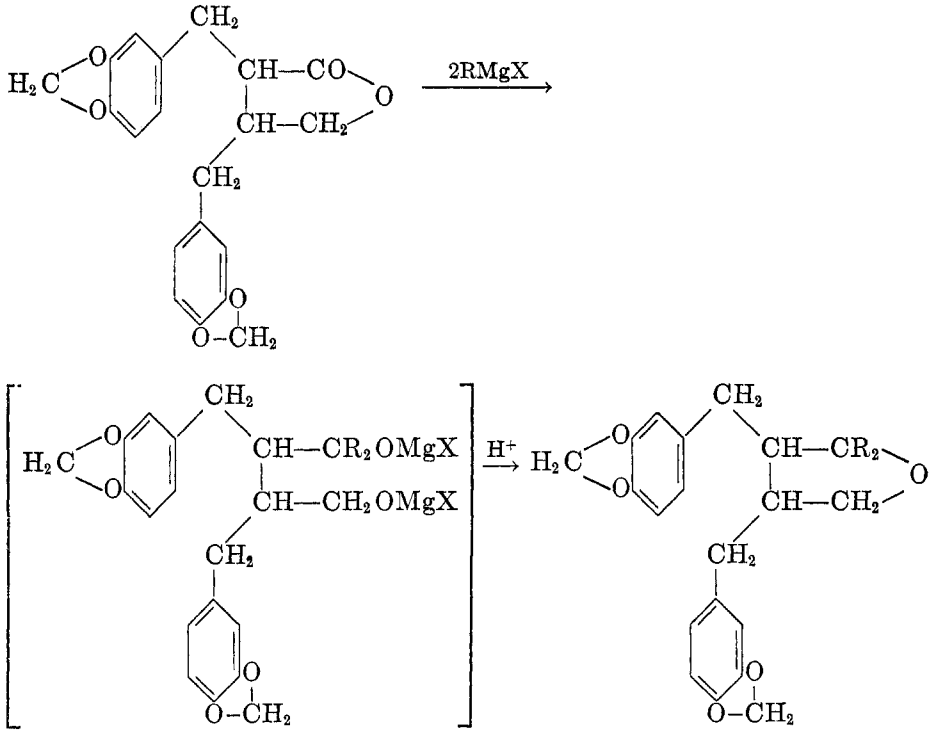
The identity of the synthetic and natural compounds was shown by the optical rotation and mixed melting points of the compounds and their dibromo and dinitro derivatives, and by the correspondence of the rates of lactonization and hydrolysis (146). The detailed comparison was required in this case since an earlier synthesis (127), which was at first thought to have produced racemic hinokinin, gave instead the isomeric compound, 2,4-bis(3,4-methylenedioxybenzyl)butyrolactone. This compound was similar to hinokinin in all the above respects except that its rate of lactonization was much slower.

The reactions of hinokinin are mainly those of the aromatic and lactone rings. The aromatic rings are brominated with bromine in chloroform to give a dibromo derivative (218, 293). Nitration in glacial acetic gives an almost quantitative yield of dinitrohinokinin (205, 218), which crystallizes as dimorphic forms

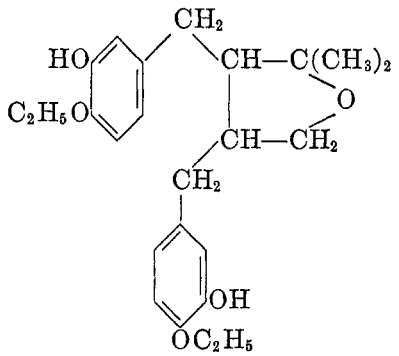
melting at either 162°C. or 184°C. (146). The nitro groups are in the 6′- and 6″-positions, since oxidation gave 6-nitropiperonylic acid (218). Reduction of the dinitro compound with tin and hydrochloric acid gave the unstable diamino derivative, which was obtained in crystalline form as its dihydrochloride (293).

The lactone ring of hinokinin is opened by heating with warm aqueous alkali to form the metal salt of the hydroxy acid (217). Upon acidification the lactone ring again closes. The lactone ring of either hinokinin or its dibromo derivative is also opened by hot alcoholic ammonia, forming the hydroxy amide, which reverts back to hinokinin upon heating or upon attempted Hofmann degradation (218). Methanolic hydrogen chloride also opens the lactone ring, giving an almost quantitative yield of the chloro ester (217, 293). Dissolution of the ester in alkali, followed by acidification, regenerates hinokinin.

The addition of Grignard reagents under usual conditions follows the expected course, with the intermediate glycol spontaneously undergoing dehydration to give the tetrahydrofuran:



Thus methylmagnesium iodide gave the dimethyltetrahydrofuran (182, 184) and phenylmagnesium bromide gave the diphenyl analog (217). When hinokinin was heated in toluene with 6 moles of methylmagnesium iodide the above reaction was accompanied by opening of the methylenedioxy groups (183) to yield the following compound:



The positions of the ethoxyl and hydroxyl groups were demonstrated by methylation and oxidation, which gave 4-ethoxy-3-methoxybenzoic acid (183).

TABLE 4

Hinokinin and derivatives

Compound	Melting point	Optical Rotation	References
	°C.		
Hinokinin	64–65	$[\alpha]_D^{17} = -34.0°$ (*c* 0.981, $CHCl_3$)	(146, 182, 220, 293)
Dinitrohinokinin	184–185 159–160	$[\alpha]_D^{18} = -90.60°$ (acetone); $[\alpha]_D^{17} = -146°$ (*c* 1.603, $CHCl_3$)	(146, 182, 218, 293)
Dibromohinokinin	136	$[\alpha]_D^{15} = -32.4°$ (*c* 1.302, $CHCl_3$)	(146, 182, 218, 293)
Diaminohinokinin	310		(293)
Hinokinin hydroxy acid sodium salt	205	$[\alpha]_D^{15} = -7.65°$ (H_2O)	(217, 293)
Hinokinin hydroxy acid amide	129–130		(218)
Dibromohinokinin hydroxy acid amide	164–167		(218)
Hinokinin chloromethyl ester	95	$[\alpha]_D = +13.89°$ ($CHCl_3$)	(217, 293)
Isohinokinin	116–117	$[\alpha]_D^{22} = +106.14°$	(185)
Dibromoisohinokinin	160–161	$[\alpha]_D^{22} = +41.32°$	(183)
Dinitroisohinokinin	202–203	$[\alpha]_D^{20} = +50.31°$	(183)

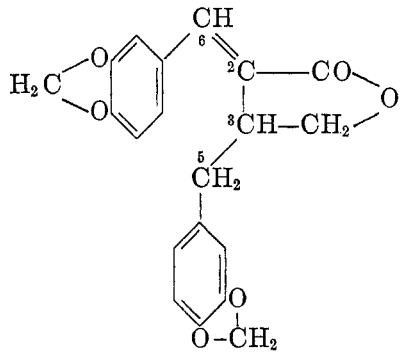
The methylenedioxy groups have also been cleaved by heating with alcoholic potassium hydroxide at 180°C., followed by hydrolysis of the intermediate methoxymethyl ethers (184). This reaction was used to remove the methylenedioxy groups in the conversion of hinokinin to matairesinol dimethyl ether (184).

(−)-Hinokinin is partially isomerized by treatment with alkali to a dextrorotatory compound, (+)-isohinokinin (183, 185). The isomerization probably involves an inversion about the asymmetric carbon adjacent to the carbonyl group (183). Haworth and Woodcock, however, report that synthetic (−)-hinokinin is stable to alkalies (146). This apparent contradiction may reflect the different conditions of treatment, as shown in the case of matairesinol (127).

2. Savinin

While searching for the components of various conifer needles which had been found to be active in damaging Sarcoma 37 in mice, Hartwell, Johnson, Fitzgerald, and Belkin (115) isolated a compound from the needles of *Juniperus*

sabina which they called savinin. The active compound in the needles of this tree was found to be podophyllotoxin, while savinin was inactive. (The *Juniperus sabina* needles actually used were a commercial preparation called savin.)



Savinin

Savinin was isolated (115) by extraction of savin with acetone, yielding 17 per cent solubles. The addition of ligroin precipitated 47 per cent of the material, which was dissolved in absolute ethanol and chromatographed on activated alumina. The low fractions of the chromatograph were combined and crystallized from benzene and then from absolute ethanol to give essentially pure savinin. Further chromatographing of this product and recrystallization (270) gave a pure material.

TABLE 5

Savinin and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
Savinin	146.2-147.3	$[\alpha]_D^{22} = -88°$ (*c* 1.00, $CHCl_3$)	(270)
Savinic acid	108	$[\alpha]_D^{23} = +64°$ (*c* 0.18, ethanol)	(270)
Dihydrosavinin (isohinokinin)	116.3-116.7	$[\alpha]_D^{21} = +107°$ (*c* 1.03, $CHCl_3$)	(270)

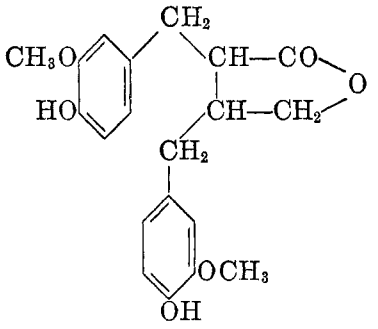
Analyses of savinin gave the empirical formula $C_{20}H_{16}O_6$ (270). Catalytic hydrogenation afforded dihydrosavinin, $C_{20}H_{18}O_6$, which was found to be identical with isohinokinin by optical rotation and melting point. Ultraviolet and infrared spectra showed that the double bond was between carbon atoms 2 and 6 in the alicyclic ring. The configuration around the asymmetric carbon atom (No. 3) must be the same as in hinokinin, since hydrogenation would not affect its configuration.

3. Matairesinol

Matairesinol occurs along with conidendrin in the partly crystalline, yellowish-white resin that deposits in the heartwood cracks of the New Zealand *matai* (*Podocarpus spicatus*) (71, 140). It constitutes about 50 per cent of the resin and is obtained by methanol extraction of either the wood or the separated resin, followed by concentration and cooling to facilitate crystallization (71, 137).

Matairesinol is a butyrolactone lignan. The two phenolic hydroxyl groups

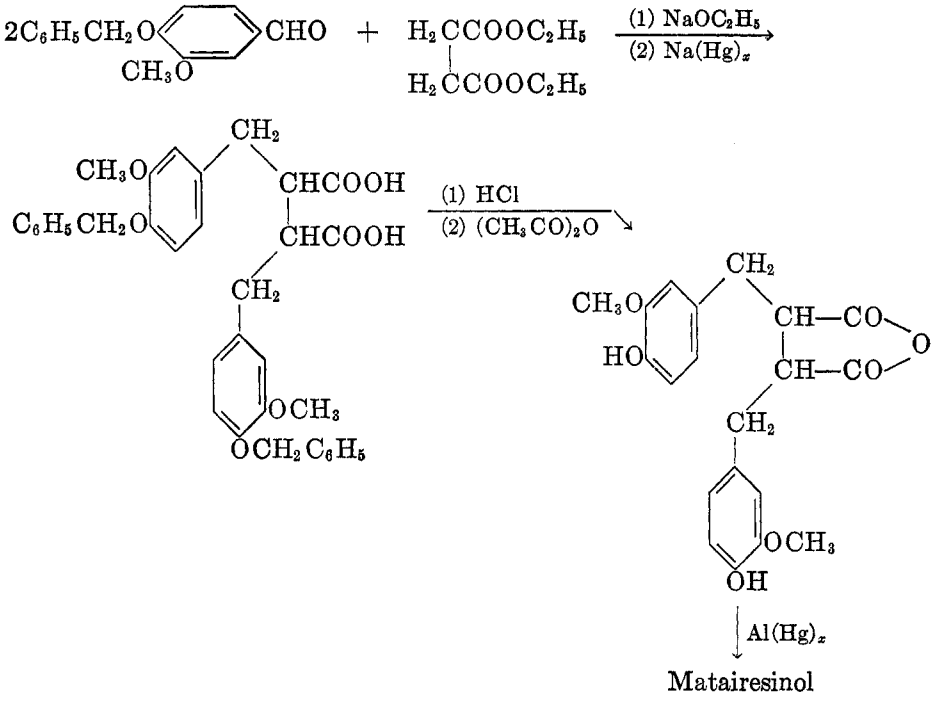
readily form ethers and esters, and the lactone ring is opened by heating with dilute alkali (36, 71). Acidification of the alkaline solution usually regenerates matairesinol, although the crystalline hydroxy acid (matairesinolic acid) has been obtained by cautious acidification with acetic acid (36).



Matairesinol

The above structural formula was verified by the synthesis of (−)-, (+)-, and (±)-matairesinol dimethyl ether (147). The syntheses started with 2,3-diveratrylidenesuccinic acid and paralleled the reaction sequence given above for hinokinin. The isomeric lactone, 2,4-bis(3,4-dimethoxybenzyl)butyrolactone, was also synthesized and was found to differ considerably from matairesinol dimethyl ether in its rate of lactonization and behavior towards lead tetra-acetate (127, 132).

Matairesinol itself was synthesized from *O*-benzylvanillin as follows (142):



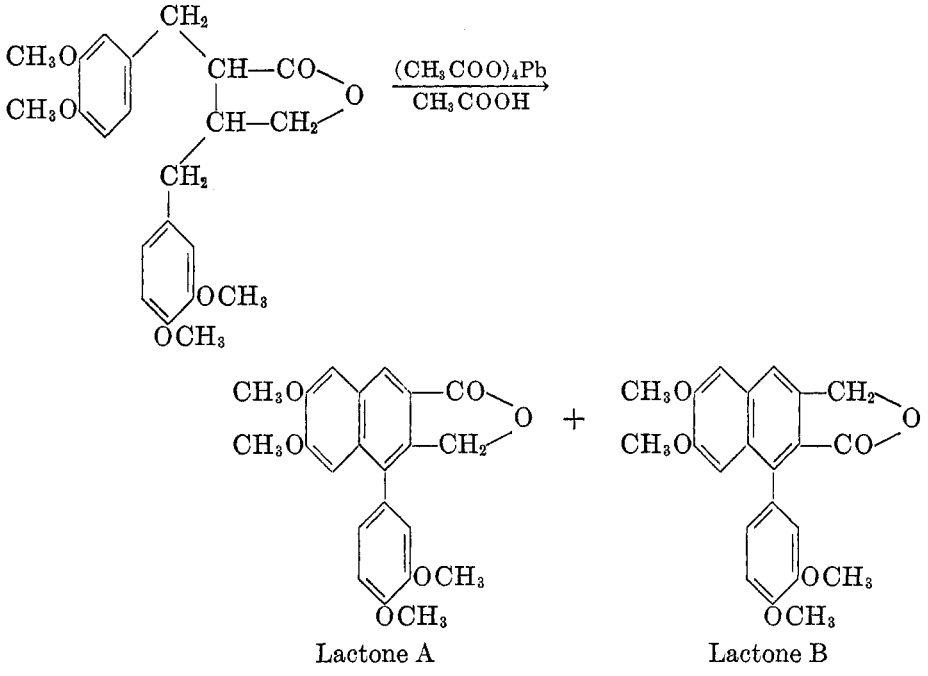
Matairesinol

The acid resulting from the first step above was largely the *meso* form. After cleavage of the benzyloxy linkage the acid was converted to the racemic anhydride. Hydrolysis of this anhydride gave the racemic dibasic acid. After resolution by means of the strychnine salts, the (−)-acid was converted to the anhydride and reduced to obtain (−)-matairesinol (142).

The aromatic rings of matairesinol react readily. The dimethyl ether is brominated in acetic acid to give 80 per cent of the dibromo derivative and slowly forms a tetrabromide with excess bromine in chloroform (36, 137). The ether is also nitrated almost quantitatively in acetic acid to a dinitro derivative and with cold fuming nitric acid forms a tetranitro derivative (137). The positions of the groups in these compounds have not been demonstrated.

Oxidation after protection of the phenolic hydroxyl groups by etherification cleaves the aliphatic portion. Thus, oxidation of the dimethyl ether with alkaline aqueous-methanolic potassium permanganate gave a 55 per cent yield of veratric acid, while the diethyl ether gave a 60 per cent yield of 4-ethoxy-3-methoxybenzoic acid (36, 137). These oxidations served to demonstrate the presence of two veratryl nuclei and to show the position of the free hydroxyl groups.

Oxidation of dimethylmatairesinol with lead tetraacetate in acetic acid proceeds by cyclodehydrogenation and yields 10–15 per cent of a mixture of the two naphthalene lactones shown below (137).



Lactone A Lactone B

The mixture results because either of the two aromatic nuclei may be involved in the ring closure. The naphthoic acid lactones differed only by transposition of

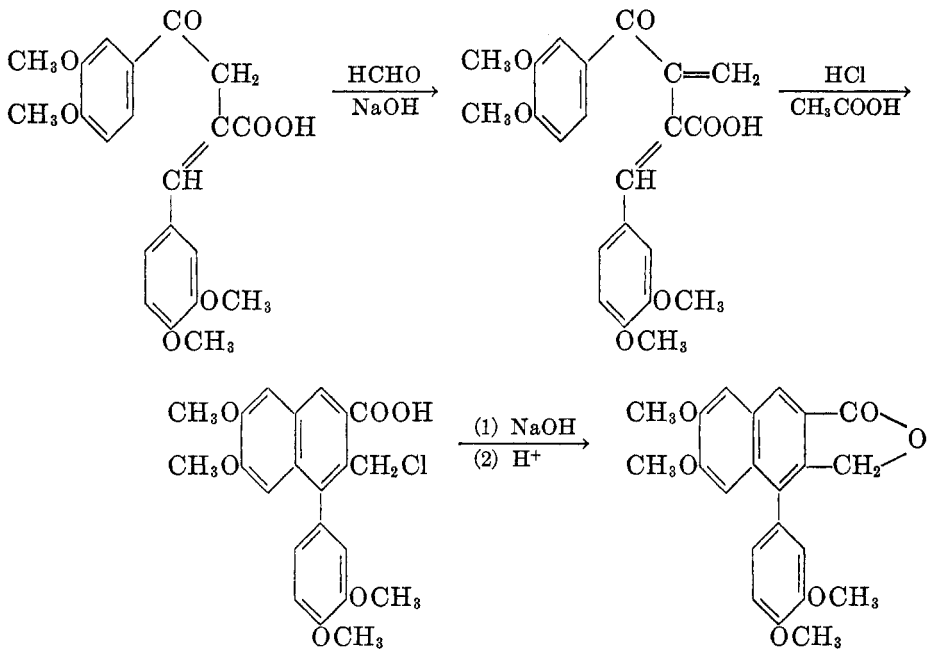
TABLE 6

Matairesinol and derivatives

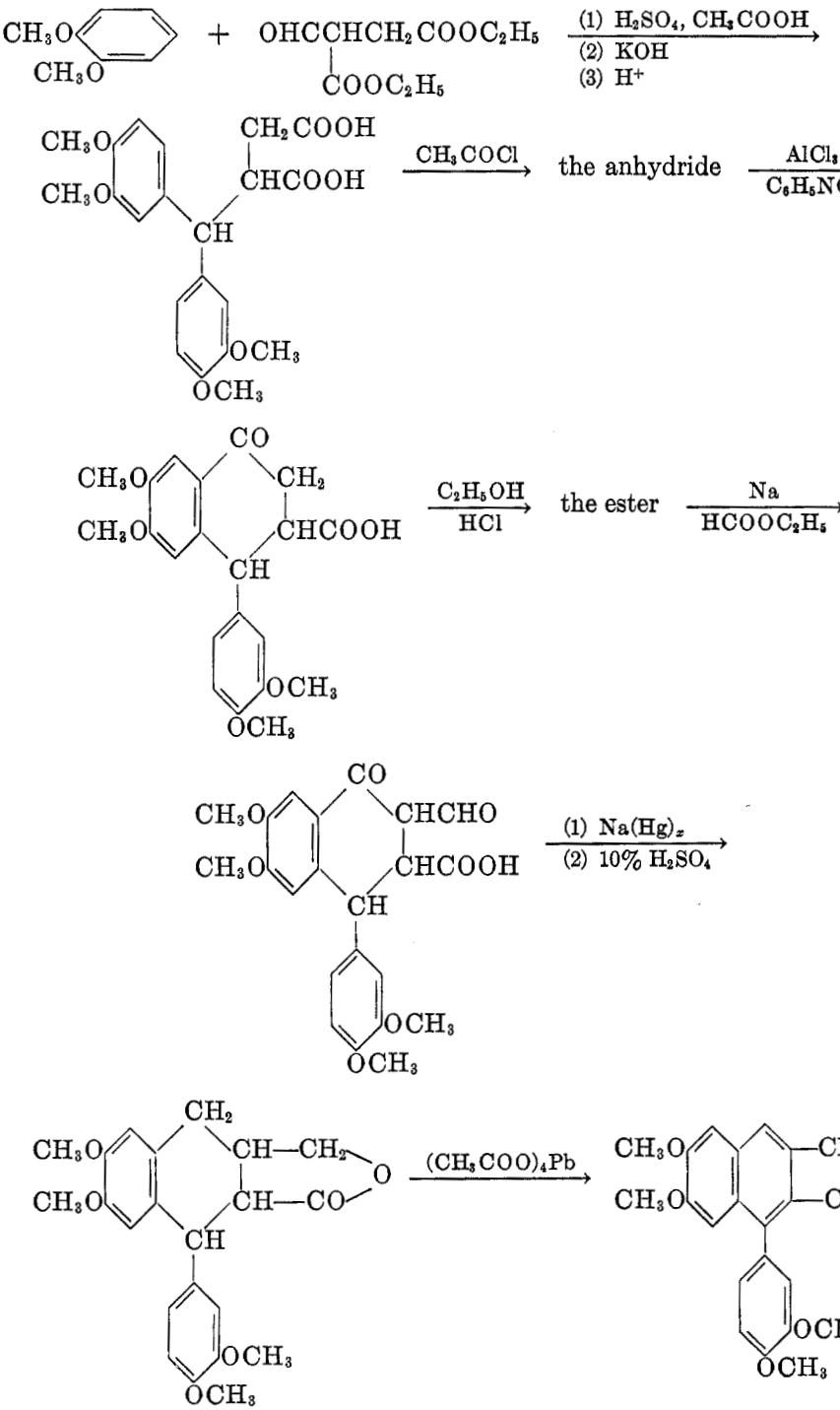
Compound	Melting Point	Optical Rotation	References
	°C.		
Matairesinol	119	$[\alpha]_D^{18} = -48.6°$ (*c* 2.41, acetone)	(137)
Dibenzoylmatairesinol	134.5		(36, 71)
Diacetylmatairesinol	110		(36, 71)
Bis(*p*-nitrobenzoyl)matairesinol	157–158	$[\alpha]_D^{18} = +90°$ (*c* 1.0, $CHCl_3$)	(142)
Dimethylmatairesinol	127–128	$[\alpha]_D^{19} = -35.6°$ (*c* 3.74, $CHCl_3$)	(137)
Diethylmatairesinol	97–98		(36, 137)
Dibromodimethylmatairesinol	126–127	$[\alpha]_D^{18} = -38.4°$ (*c* 3.54, $CHCl_3$)	(137, 240, 241)
Dinitrodimethylmatairesinol	179–180	$[\alpha]_D^{18} = -126.6°$ (*c* 3.61, $CHCl_3$)	(137, 240, 241)
Tetranitrodimethylmatairesinol	202–203	$[\alpha]_D^{19} = -161.6°$ (*c* 0.526, acetone)	(137, 241, 274)
Matairesinolic acid	80 (d.)	$[\alpha]_D^{20} = -3.04°$ (acetone)	(36, 71)
Dimethylmatairesinolic acid	80–84 (d.)		(36)
Dimethylisomatairesinol	111–112	$[\alpha]_D^{19} = +78°$ (*c* 4.01, $CHCl_3$)	(127, 243)
Dibromodimethyliso matairesinol	144	$[\alpha]_D^{20} = +18.8°$ (*c* 1.15, $CHCl_3$)	(127)
Dinitrodimethylisomatairesinol	161–162	$[\alpha]_D^{20} = +105.5°$ (*c* 1.20, $CHCl_3$)	(127)

the carboxyl and hydroxymethyl groups, since both gave the same dibasic acid upon oxidation with hypobromite (137). Lactone A was identical with the one obtained by dehydrogenating conidendrin dimethyl ether (77, 140). The structure of each of the lactones was confirmed by synthesis, as shown below (139, 140).

Synthesis of lactone A (139):

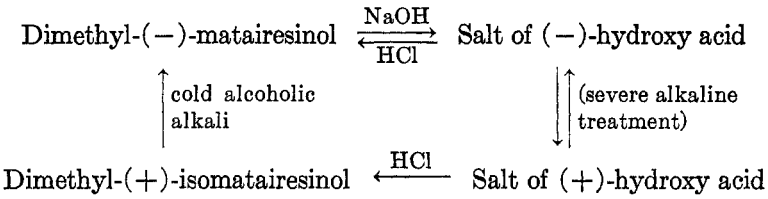


Synthesis of lactone B (140):



Dimethylmatairesinol is isomerized by severe alkaline treatment such as boiling 50 per cent potassium hydroxide to an equilibrium mixture containing the salts of the hydroxy acids of dimethylmatairesinol and an isomeric structure, dimethylisomatairesinol (127, 240, 243). However, under mild alkaline conditions a different result is obtained. Dimethylmatairesinol is stable toward reagents such as cold alcoholic potassium hydroxide, whereas dimethylisomatairesinol is isomerized to dimethylmatairesinol (127).

The transformation may be summarized as follows:

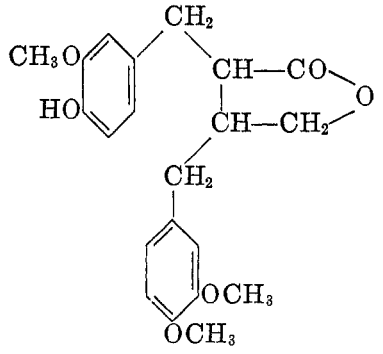


Haworth and Atkinson (127) suggest that the isomerization consists of inversion about the asymmetric carbon atom adjacent to the carbonyl group and that inversion occurs without opening of the lactone ring under the mild conditions. The two isomers are quite similar and both are dehydrogenated similarly with lead tetraacetate. The lactone rings of both hydrolyze at the same rate, but the rate of lactonization of dimethyl-(−)-matairesinol is enough greater than that of the iso form to permit separation of the two on this basis (127). The tertiary hydrogen atoms on the lactone ring are *trans* in matairesinol and *cis* in isomatairesinol, since reduction gave the levorotatory and *meso* diols, respectively (144).

4. Arctiin and arctigenin

Arctiin was the first lignan found naturally as a glycoside. It occurs in the seeds of burdock (*Arctium lappa* L.) along with its aglycone, arctigenin (274). Extracting the seeds with ether removes arctigenin, and the residue, after washing with alcohol, is extracted with water to remove arctiin (274).

Arctiin, $C_{27}H_{34}O_{11}$, is hydrolyzed by aqueous alcoholic sulfuric acid to give 64 per cent of arctigenin and glucose (240, 274). No further work seems to have been done on the glucoside.



Arctigenin

TABLE 7

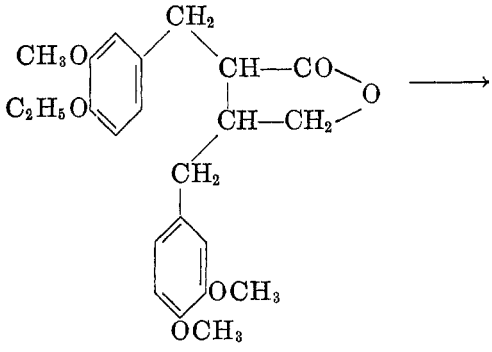
Arctiin and arctigenin and derivatives

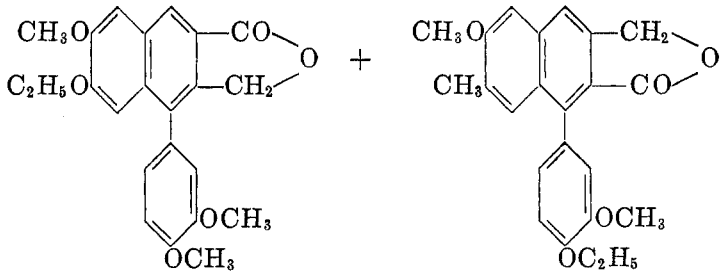
Compound	Melting Point	Optical Rotation	References
	°C.		
Arctiin	112	$[\alpha]_D^{18} = -38.8°$	(274)
Arctigenin	102	$[\alpha]_D^{19} = -28.69°$	(240, 274)
Arctigenin hydroxy acid	117–118		(274)
Acetylarctigenin	52–60		(274)
Tribromoarctigenin	194–195		(274)
Tribromomethylarctigenin	131–132	$[\alpha]_D^{19} = -25.17°$	(240)
Tribromomethylarctigenin	127	$[\alpha]_D^{15} = -36.2°$	(241, 274)
Dibromoethylarctigenin	128–129		(129)
Dinitroethylarctigenin	166–167		(129)
Cycloarctigenin	239–240	$[\alpha]_D^{17} = -78.6°$ ($CHCl_3$)	(242)
Methylcycloarctigenin (dimethyl-α-conidendrin)	179–180	$[\alpha]_D^{17} = -99.5°$ ($CHCl_3$)	(242)
Ethylcycloarctigenin	183–184	$[\alpha]_D^{17} = -132.0°$ ($CHCl_3$)	(242)
Ethylcycloarctigenin hydroxy acid	170–172		(243)
Isoarctigenin	92	$[\alpha]_D^{19} = +83.6°$	(240, 243)
Isoarctigenin hydroxy acid	82	$[\alpha]_D^{19} = +30.95°$	(240, 243)
Isocycloarctigenin	229–230	$[\alpha]_D = 0°$	(243)
Methylisocycloarctigenin	145–146	$[\alpha]_D = 0°$	(243)
Methylisocycloarctigenin hydroxy acid	155	$[\alpha]_D^{15} = +49.85°$	(243)
Ethylisocycloarctigenin	160–161	$[\alpha]_D = 0°$	(243)
Ethylisocycloarctigenin hydroxy acid	165–166	$[\alpha]_D^{15} = +51.72°$	(243)

The gross structural features of arctigenin were established when Omaki (241) demonstrated the identity of methylarctigenin and dimethylmatairesinol. The phenolic hydroxyl is readily etherified by the use of diazoalkanes or dialkyl sulfates and alkali (129, 240, 241, 273, 274) and is readily acylated. Bromination in glacial acetic acid yields a tribromide which contains one bromine atom in the veratryl nucleus, since oxidation gave 6-bromoveratric acid (274). Reduction of the tribromide with a zinc–copper couple regenerated arctigenin (274).

Arctigenin has not yet been synthesized, and assignment of the position of the free hydroxyl group is based on degradation and cyclization studies. The hydroxyl group is para to the point of attachment of the ring, since oxidation of the ethyl ether gave veratric acid and 4-ethoxy-3-methoxybenzoic acid (273).

Since the two aromatic rings are not symmetrically situated, it was necessary to determine which one contained the free hydroxyl group. This was shown by cyclization studies. Lead tetraacetate in acetic acid cyclodehydrogenated ethylarctigenin to give a mixture of two naphthalenic lactones (127, 129); this parallels the analogous reaction of dimethylmatairesinol.

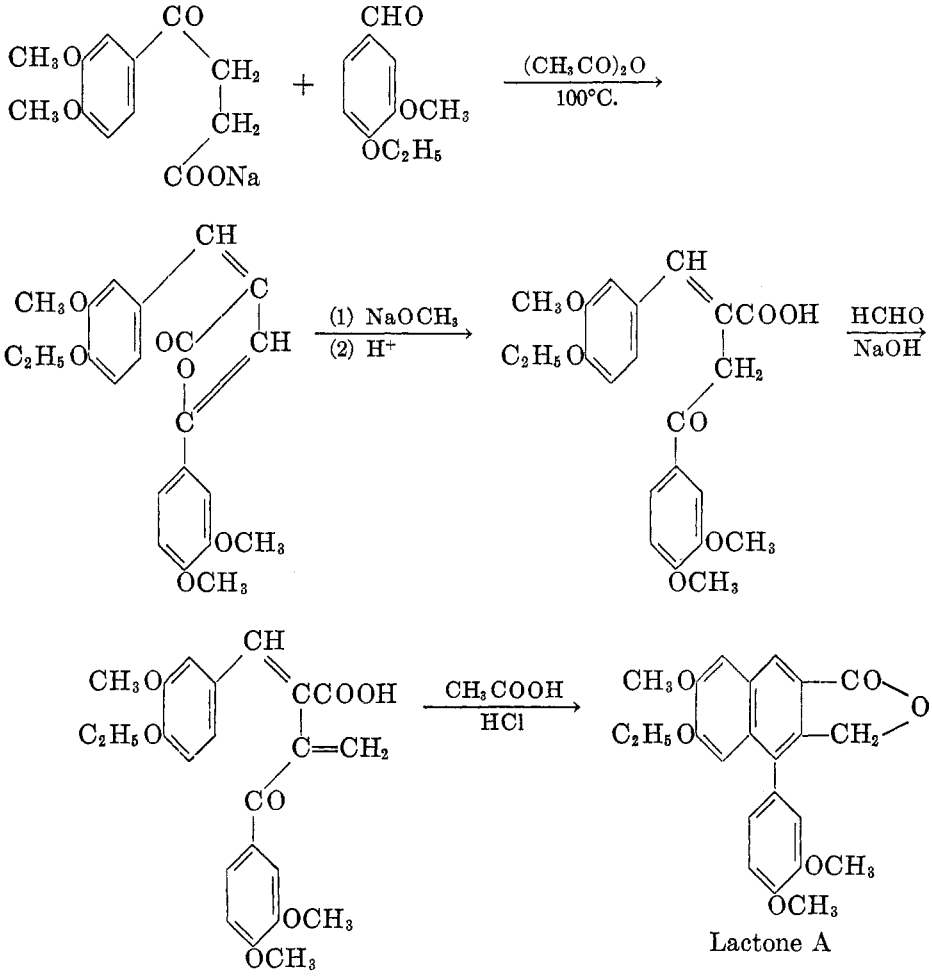




Lactone A Lactone B

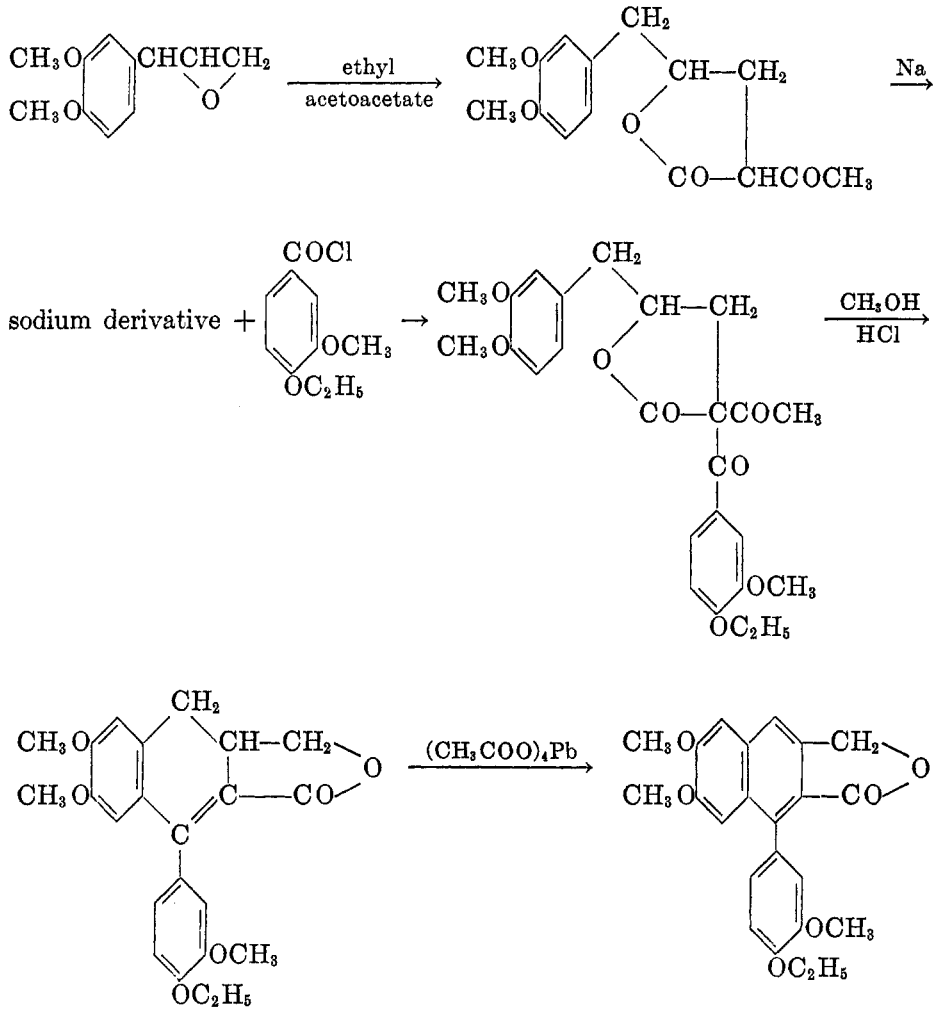
Haworth and Kelly (129) demonstrated the structures of the two lactones by synthesis, using the following reaction paths:

Synthesis of lactone A (129):



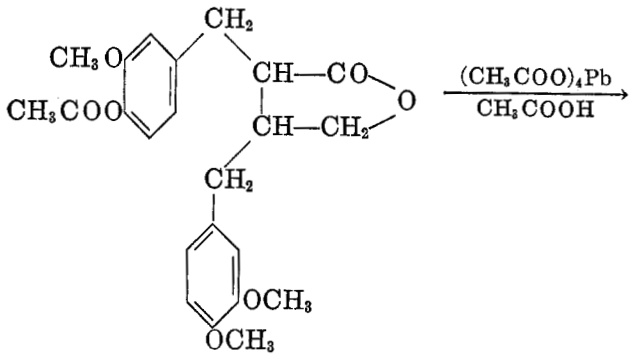
Lactone A

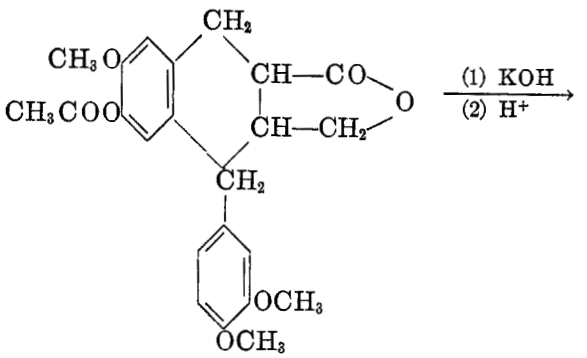
Synthesis of lactone B (127, 129):

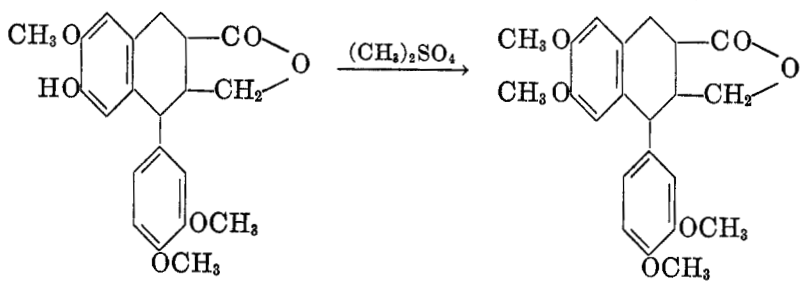


Lactone B

In contrast to its reaction with the arctigenin ethers, lead tetraacetate did not dehydrogenate acetylarctigenin completely to the naphthalenic lactone. Instead it removed only two hydrogen atoms, forming a single tetrahydronaphthalenic lactone named cycloarctigenin (242). This cyclization is stereospecific, since methylation of cycloarctigenin gave dimethyl-α-conidendrin (242). The sequence is as follows:

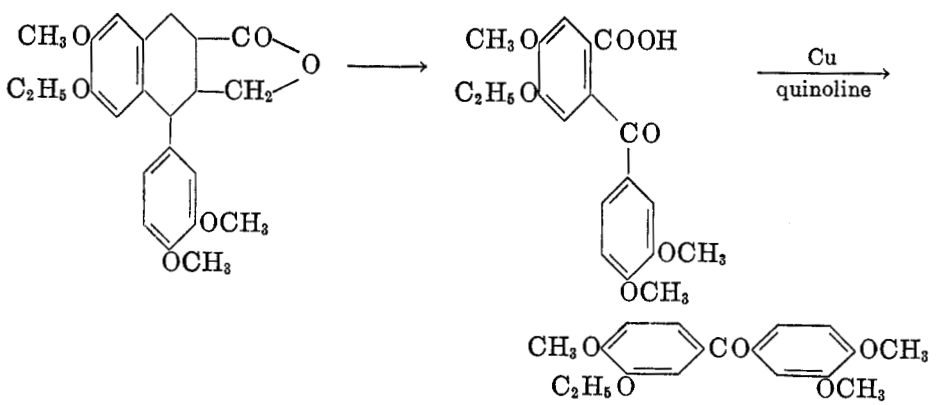






Cycloarctigenin Dimethyl-α-conidendrin

The position of the free hydroxyl group in cycloarctigenin, and hence also in arctigenin, was shown by ethylation and oxidation (242):



The final phenone was identical with the one synthesized from veratrole and 3-ethoxy-4-methoxybenzoic acid (243). Had the ethoxyl group been on the other aromatic ring, the phenone would have been 4-ethoxy-3,3′,4′-trimethoxybenzophenone.

The type of reaction occurring when the butyrolactone lignans react with lead tetraacetate is markedly affected by the groups attached to the phenolic oxygens. Thus, dimethylmatairesinol and the arctigenin ethers give naphthalenic lactones, while acetylated arctigenin gives the tetrahydronaphthalenic lactone and hinokinin does not react (128).

Arctigenin is labile toward alkaline agents and its isomerization is similar to that of dimethylmatairesinol (which is methylarctigenin). Thus, prolonged heating with 50 per cent potassium hydroxide produced a dextrorotatory isomer named isoarctigenin (240, 243). Isoarctigenin, on the other hand, was isomerized to arctigenin by mild treatment (243). The methyl ether of isoarctigenin apparently is dimethylisomatairesinol (127, 243).

Cycloarctigenin is similarly isomerized by heating with alcoholic sodium ethoxide, giving an optically inactive lactone named isocycloarctigenin (243). This isomerization is probably analogous to the isomerization of α-conidendrin to β-conidendrin, since the methyl ether of isocycloarctigenin appears to be identical with dimethyl-β-conidendrin. The lack of optical activity in isocycloarctigenin and its ethers is not due to racemization, since the corresponding hydroxy acids are dextrorotatory. Isocycloarctigenin and its ethers are not isomerized by acids or alkalies (243).

5. Cubebin

Cubebin is obtained from the unripe fruit of cubeb (*Piper cubeba*), which has been used pharmaceutically since the Middle Ages. It was one of the first lignans to be examined (3, 40, 41, 44, 45, 46, 90, 227, 228, 229, 250, 262, 285, 309). The berries are extracted with alcohol, and the extract is steam-distilled to remove volatile oils. The non-volatile residue is made alkaline, and the cubebin is removed from the alkaline mass by ether extraction (213). The yield is 1–5 per cent of the dry fruit (213).

Cubebin, which has not yet been synthesized, is a hydroxy aldehyde existing in equilibrium with the lactal ring (172).

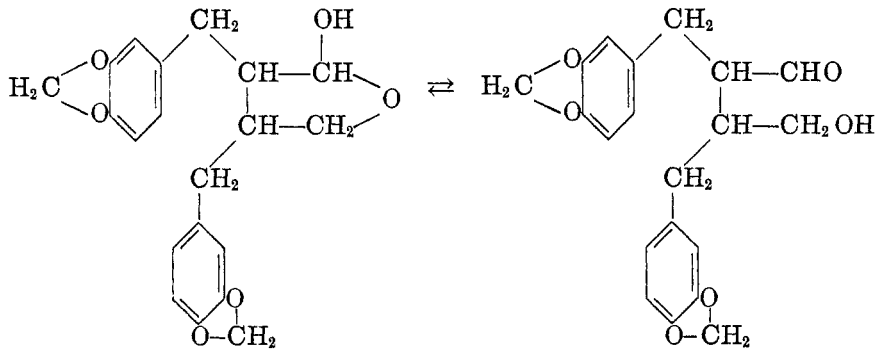


TABLE 8

Cubebin and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Cubebin	128	$[\alpha]_D = -45.7°$ ($CHCl_3$)	(41, 213, 214)
Cubebin semicarbazone	144		(130, 172)
Dihydrocubebin	104	$[\alpha]_D^{18} = -30.6°$ ($CHCl_3$)	(37)
Dinitrocubebin methylcycloacetal	136–137		(172)
Cubebinic ether	78	$[\alpha]_D = +23.3°$ ($CHCl_3$)	(214)
Cubebinic ether	70.5	$[\alpha]_D^{13} = +23.78°$ ($CHCl_3$)	(172)
Dihydrocubebinic ether	131–132	$[\alpha]_D^{19} = -58.70°$ ($CHCl_3$)	(172)
Cubebinol	92	$[\alpha]_D = +34.81°$ ($CHCl_3$)	(215)
Acetylcubebinol	71	$[\alpha]_D = +23.12°$ ($CHCl_3$)	(215)
Benzoylcubebinol	155	$[\alpha]_D = -21.68°$ ($CHCl_3$)	(215)
Phenylcarbamylcubebinol	155		(215)
Isocubebinic ether	157	$[\alpha]_D = +20.02°$ (benzene)	(216)

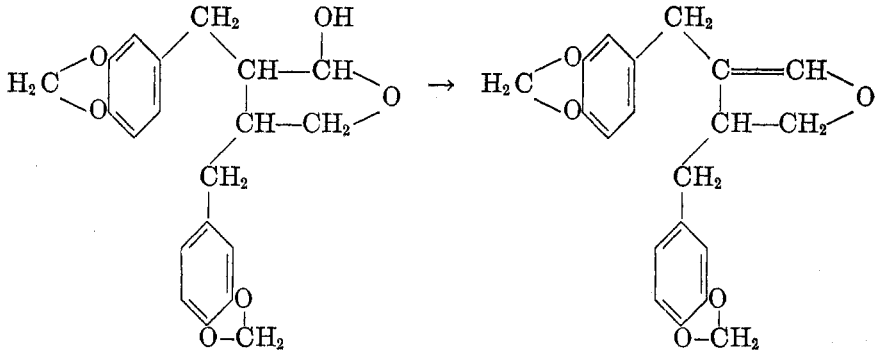
The presence of two catechol nuclei was shown by alkali fusion, which produced 50–70 per cent yields of protocatechuic acid (310). The phenolic hydroxyl groups were not free, since the compound was insoluble in alkali; the presence of the methylenedioxy groups was shown by oxidation with alkaline permanganate to give piperonylic acid (249).

The presence of the hydroxyl group on the lactal ring was shown by analysis for active hydrogen (95, 130), by the formation of a monobenzoate (249), and by the formation of the methyl cycloacetal from the reaction of cubebin with methanolic hydrogen chloride (172). The aldehyde group reacted normally, forming a semicarbazone (130, 172), and was easily oxidized without loss of carbon to the hydroxy acid which lactonized to give hinokinin (217, 220).

Nitration of cubebin is accompanied by oxidation, giving an 85 per cent yield of dinitrohinokinin (218, 246). Bromination has to be conducted in such a way as to remove the hydrogen bromide; otherwise dehydration occurs. Bromination in glacial acetic acid in the presence of calcium carbonate gave a mixture of dibromohinokinin and an unidentified higher-melting compound which was insoluble in boiling 10 per cent potassium hydroxide (218).

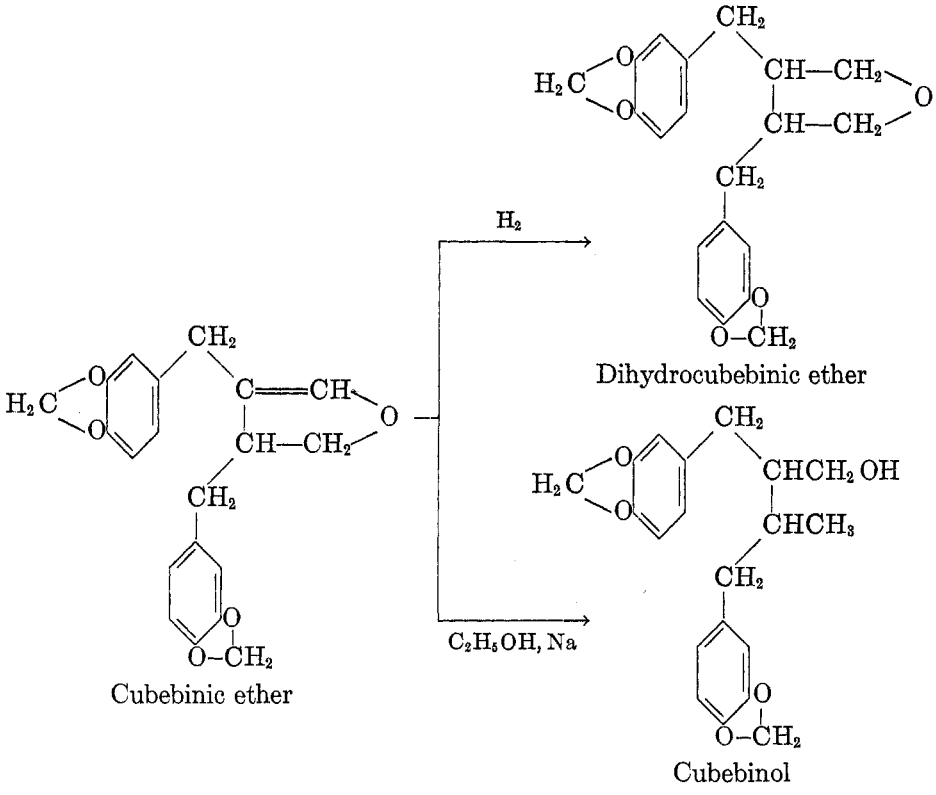
The aldehyde group of cubebin can be reduced with aluminum amalgam, forming the corresponding levorotatory diol (37). The reduction apparently is not readily achieved catalytically and an earlier claim to have achieved the reduction with hydrogen over platinum oxide (172) has been disputed (37).

Cubebin ordinarily is resinified by warming with acids. However, under suitable conditions it undergoes intramolecular dehydration, forming the corresponding dihydrofuran, cubebinic ether (172, 214, 219). The ether is formed upon attempted acetylation with acetyl chloride or acetic anhydride–sodium acetate (249) and the yield is almost quantitative with cold halogen acids, preferably hydriodic acid (214).



Cubebin Cubebinic ether

The double bond of cubebinic ether can be reduced catalytically over platinum oxide (172) to form dihydrocubebinic ether. Reduction with sodium in ethanol opens the ring to give the monohydroxy compound, cubebinol (172, 215).



Dihydrocubebinic ether

Cubebinic ether Cubebinol

When the dehydration of cubebin was achieved by the use of sulfuric acid in glacial acetic acid solution a higher-melting dextrorotatory compound named isocubebinic ether was obtained in good yield (216). Its structure has not been determined. It differs from cubebinic ether in being stable to sodium in boiling alcohol but is hydrolyzable by boiling for 15 min. in 15 per cent hydrochloric acid to give an 85 per cent yield of cubebinol (216).

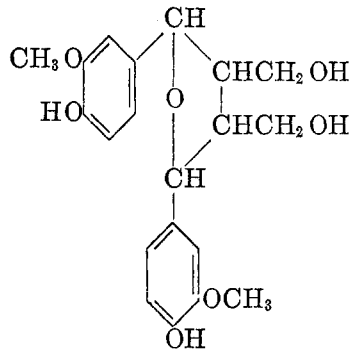
C. TETRAHYDROFURAN DERIVATIVES

1. 2,5-Diaryltetrahydrofurans

a. Olivil

Olivil is found in the resinous exudate of the olive tree (*Olea europaea*) and was first reported by Pelletier in 1816 (247). It is separated by extracting the resin with boiling ethanol and cooling the extract to precipitate the crystalline monoalcoholate of olivil (190). The yield varies greatly with the habitat of the tree and exceeds 50 per cent in the most favorable cases (298).

Olivil, $C_{20}H_{24}O_7$, contains two methoxyl groups, two hydroxyl groups that are readily etherified with alkyl iodides, and two additional acetylatable hydroxyl groups (191). Its structure is that of two coniferyl alcohol units joined at the β-carbon atoms and connected by an oxygen bridge at the α-carbon atoms:



Olivil

Oxidation of dimethylolivil with alkaline permanganate gave a 50 per cent yield of veratric acid along with veratroylformic acid and oxalic acid (191). The permanganate oxidation of olivil in boiling glacial acetic acid gave a high yield of acetylvanillic acid, showing the phenolic hydroxyls to be para to the point of attachment of the aliphatic portion.

The two aromatic rings of olivil are symmetrically situated, as shown by the fact that monomethylation followed by ethylation gave the same compound as monoethylation followed by methylation (191).

The bromination of dimethylolivil gave monobromo and dibromo derivatives in which the bromine atoms were meta to the side chain, as shown by oxidation to give 5-bromoveratric acid (191). Mercuration of dimethylolivil introduced two acetoxymercuri groups which were removable with ammonium sulfide (191).

The tetrahydrofuran ring of olivil is easily opened. Hydrogenation in acetic acid over palladium–carbon opened the ring to give a levorotatory triol (148). Such hydrogenolysis is characteristic of benzyl ether linkages and has proved a useful tool in investigations of the stereochemistry of lignans (148).

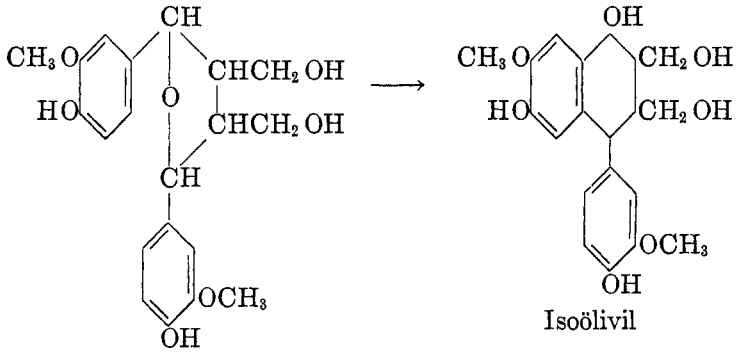
The tetrahydrofuran ring is also opened under mild acidic conditions accompanied by ring closure to give a tetrahydronaphthalene structure named isoölivil

TABLE 9

Olivil and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
Olivil	142.5	$[\alpha]_D^{12} = -127°$ (*c* 0.314, H_2O)	(191)
Dimethylolivil	156	$[\alpha]_D^{24} = +56.4°$ (alcohol)	(191)
Diethylolivil	182		(295)
Dipropylolivil	135.5		(295)
Dibenzylolivil	150		(295)
Monomethylolivil	218		(295)
Monoethylolivil	145		(295)
Methylethylolivil	169		(295)
Monobromodimethylolivil	128		(295)
Dibromodimethylolivil	132		(295)
Dihydrodimethylolivil	137–138	$[\alpha]_D^{17} = -14.7°$ (*c* 0.646, $CHCl_3$)	(148)

(189). Isoölivil, which occurs naturally, is discussed in a later section (Section III,E,4,a).



Isoölivil

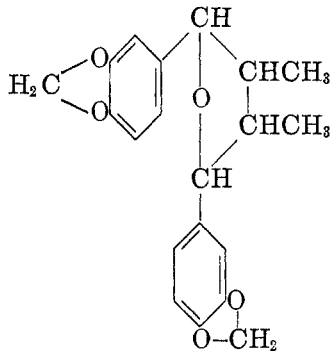
This conversion is effected in almost quantitative yield even by boiling aqueous acetic acid and is stereospecific, since only one compound results (295, 296, 304, 304a).

b. Galbacin

Galbacin was recently obtained by Hughes and Ritchie from the bark of *Himantandra baccata* Bail. (171). It occurs mixed with two tetrahydronaphthalene lignans and the three constitute about 0.1 per cent of the bark.

The milled bark was extracted exhaustively with cold methanol. After being freed from acidic materials and alkaloids, the three lignans were crystallized from ethanol and separated by means of the differences in their rates of solution upon warming.

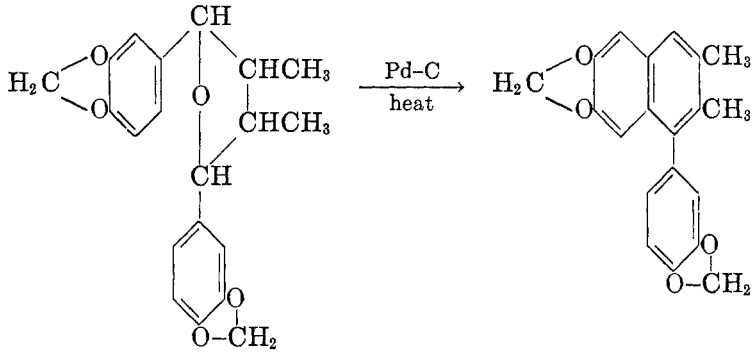
Galbacin has been assigned the following structure (171):



Galbacin

Galbacin gave an almost quantitative yield of a dinitro derivative with nitric acid in acetic acid solution. With fuming nitric acid cleavage occurred to give 4,5-dinitromethylenedioxybenzene.

The isomerization of galbacin to a tetrahydronaphthalene lignan does not occur readily. However, the isomerization was effected by using perchloric acid in acetic acid. The product was not crystalline, but was dehydrogenated when heated with palladized charcoal to give a naphthalene derivative.



Cleavage of the methylenedioxy groups of galbacin with sodium methoxide in methanol at 180°C. followed by methylation gave a levorotatory isomer of galgravin (171).

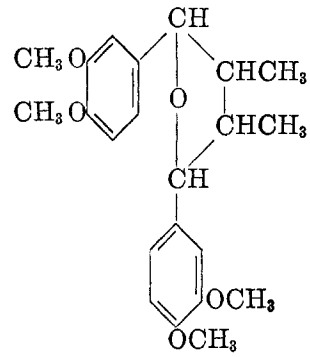
TABLE 10

Galbacin and galgravin and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
Galbacin	116	$[\alpha]_D^{20} = -114°$ (*c* 0.8, $CHCl_3$)	(171)
Dinitrogalbacin	145		(171)
Galgravin (inactive)	121	$[\alpha]_D^{20} = 0°$	(171)
Galgravin (from galbacin)	139–140	$[\alpha]_D^{20} = -102°$ (*c* 0.648, $CHCl_3$)	(171)
Dinitrogalgravin	161–162		(171)
Dihydrogalgravin	108		(21)
Cyclized dihydrogalgravin (racemic isogalbulin)	86	$[\alpha]_D = -2°$ (ethanol)	(20a)

c. Galgravin

The optically inactive lignan, galgravin, was recently obtained from the bark of *Himantandra belgraveana* F. Muell. by Hughes and Ritchie (171). The isolation procedure is the same as described in the preceding section for galbacin, and the yield was 0.6 per cent of the bark.

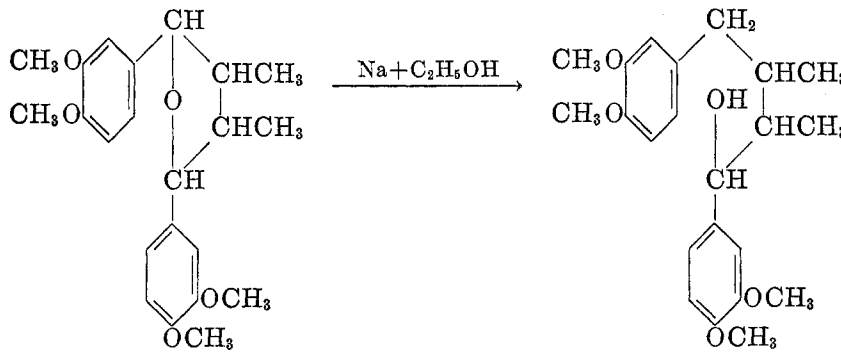


Galgravin

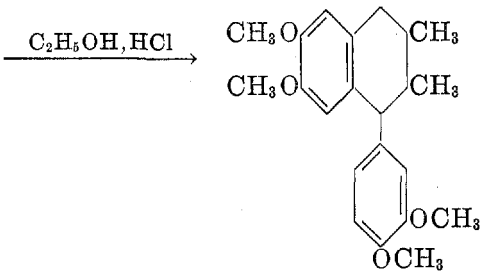
Like galbacin, it is nitrated in acetic acid solution to a dinitro derivative and is cleaved by fuming nitric acid to give 4,5-dinitroveratrole.

The isomerization and dehydrogenation of galgravin to form the corresponding naphthalene derivative was achieved in 40 per cent yield by simply heating at 200°C. with palladized charcoal in diphenyl ether. The product was dimethyldehydroguaiaretic acid.

The tetrahydrofuran ring was opened by reduction with sodium and ethanol in ammonia to give dihydrogalgravin which, with ethanol and hydrochloric acid (21), was cyclized to an optically inactive tetrahydronaphthalene. This isomer appears (269b) to be racemic isogalbulin, the optically active form of which is described in the section on galbulin.



Galgravin Dihydrogalgravin



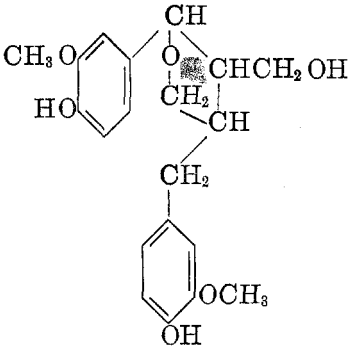
Isogalbulin

2. 2-Aryl-4-benzyltetrahydrofurans

a. Lariciresinol

Lariciresinol was first obtained by Bamberger (10) in 1897 from the resinous exudate of *Larix decidua*. The lignan was precipitated as its potassium salt by adding concentrated potassium hydroxide solution to an ethanol extract of the resin (130). Cautious acidification of the salt liberated lariciresinol.

Lariciresinol has the same empirical formula as coniferyl alcohol and is easily visualized as a coniferyl alcohol dimer:



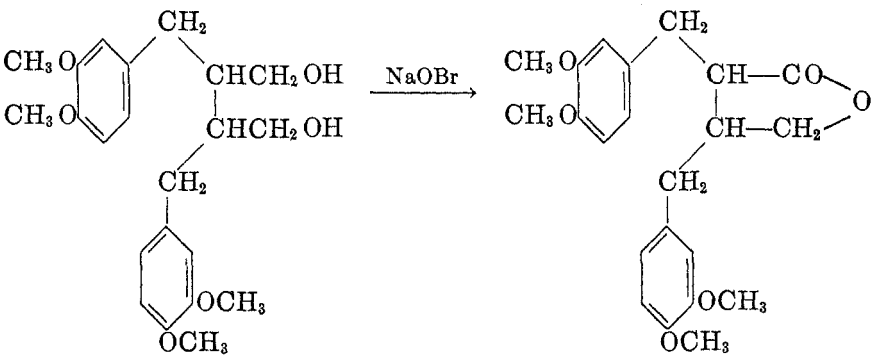
Lariciresinol

Under the usual etherification conditions, the phenolic hydroxyls react to give alkali-insoluble ethers. These still contain one hydroxyl group which reacts with phthalic anhydride or triphenylchloromethane (130).

In common with the other lignans containing benzyl ether linkages the dimethyl and diethyl ethers of lariciresinol are cleaved by concentrated nitric acid to give 40 per cent yields of 4,5-dinitroveratrole and 1-ethoxy-2-methoxy-4,5-dinitrobenzene (10, 130, 154), respectively.

The tetrahydrofuran ring of dimethyllariciresinol is opened by hydrogen over palladium–carbon to give a 70 per cent yield of a levorotatory diol (148). The structure of this diol was shown by alkaline hypobromite oxidation, which gave

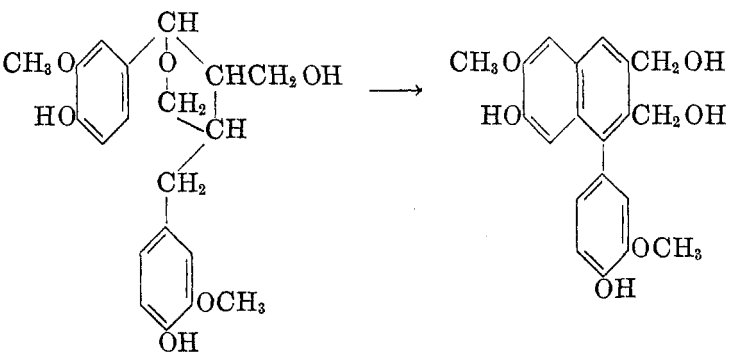
a 30 per cent yield of dimethylmatairesinol (148), and also by obtaining it when dimethylmatairesinol was reduced with lithium aluminum hydride (144).



Dimethylmatairesinol

The above levorotatory diol could be dehydrated to the levorotatory 3,4-dibenzyltetrahydrofuran in 80 per cent yield by heating at 180°C. with potassium bisulfate (148).

In contrast to its stability toward alkaline reagents lariciresinol is easily isomerized by acidic reagents to yield a dextrorotatory substance having a tetrahydronaphthalene structure and called isolariciresinol (130). Partial isomerization may occur even during isolation unless the excess acid used to liberate lariciresinol from its salt is quickly destroyed with bicarbonate (130). Most of the derivatives recorded in the early literature are derivatives of isolariciresinol rather than of lariciresinol (10, 11, 12, 130). The isomerization proceeds as follows:



Lariciresinol Isolariciresinol

The isomerization is effected in 80 per cent yield by refluxing for 30 min. in 20 per cent formic acid (130). One additional hydroxyl group is produced in the isomerization, as shown by the easy formation of isolariciresinol tetraacetate (12, 130). This tetraacetate is also produced when lariciresinol is refluxed with acetyl chloride (10, 130). The phenolic hydroxyl groups may be selectively alkylated, forming dialkyl ethers which are readily acetylated to diacetyl derivatives that are saponified to regenerate the ethers (130). The diacetate of iso-

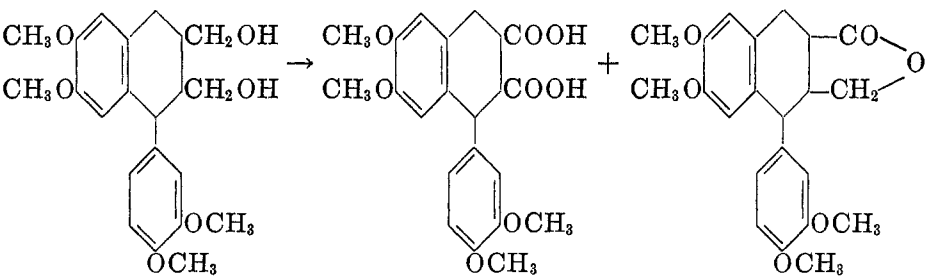
TABLE 11

Lariciresinol and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Lariciresinol	167–168	$[\alpha]_D^{14} = +19.7°$ (*c* 2.23, acetone)	(130)
Dimethyllariciresinol	79–80	$[\alpha]_D^{14} = +22°$ (*c* 2.05, acetone)	(130)
Diethyllariciresinol	103–104		(130)
Dimethylmonotrityllariciresinol	134–135		(131)
Triacetyllariciresinol	92		(11)
Isolariciresinol	112	$[\alpha]_D^{14} = +69.4°$ (*c* 3.42, acetone)	(130)
Tetraacetylisolariciresinol	162	$[\alpha]_D^{15} = +18.4°$ (*c* 2.28, acetone)	(12, 130)
Dimethylisolariciresinol	166–167	$[\alpha]_D^{14} = +20°$ (*c* 1.95, $CHCl_3$)	(130)
Diethylisolariciresinol	168		(11, 130)
Diacetyldiethylisolariciresinol	114–115	$[\alpha]_D^{15} = +21.7°$ (*c* 2.87, acetone)	(130)
Anhydroisolariciresinol	209–210	$[\alpha]_D^{14} = +7.9°$ (*c* 2.16, CH_3COOH)	(130, 154)
Dimethylanhydroisolariciresinol	146–147	$[\alpha]_D^{15} = -33.4°$ (*c* 2.90, acetone)	(130)
		$[\alpha]_D^{20} = -50°$ (*c* 1.51, $CHCl_3$)	(270a)
Diethylanhydroisolariciresinol	132–133		(130)
Dehydroanhydroisolariciresinol	201–202		(131)
Ditosyldimethylisolariciresinol	161.5–162.5	$[\alpha]_D^{20} = +2.2°$ (*c* 1.53, $CHCl_3$)	(43a, 270a)
Dimesyldimethylisolariciresinol	148–149.5	$[\alpha]_D^{20} = +7.0°$ (*c* 0.98, $CHCl_3$)	(270a)

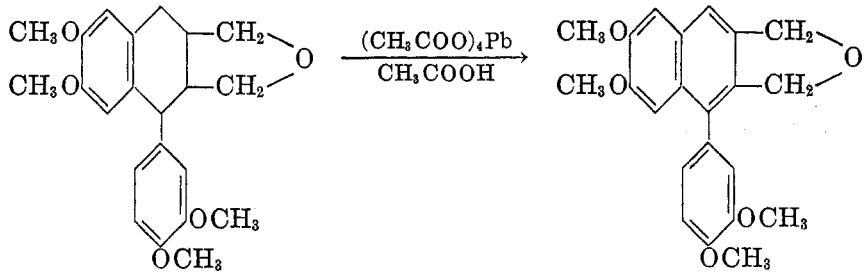
lariciresinol diethyl ether also results when lariciresinol diethyl ether is refluxed with acetyl chloride (130). The ready isomerization of this ether is in contrast with the behavior of galcatin, galgravin, and ethers of olivil.

The tetrahydronaphthalene structure assigned to isolariciresinol, which seemed likely by analogy with the olivil–isoölivil transformation, was confirmed by oxidation studies. Oxidation of isolariciresinol dimethyl and diethyl ethers by alkaline permanganate gave, respectively, *o*-veratroylveratric acid and 2-(4-ethoxy-3-methoxybenzoyl)-4-ethoxy-3-methoxybenzoic acid (130). Oxidation of isolariciresinol dimethyl ether by sodium hypobromite gave a mixture of products including *o*-veratroylveratric acid and the dimethyl ethers of conidendreic acid and conidendrin (130):



When lariciresinol is refluxed with saturated methanolic hydrogen chloride isomerization is effected; the intermediate isolariciresinol reacts further by dehydration to give a 60 per cent yield of a dextrorotatory compound called anhydroisolariciresinol (130, 154). Anhydroisolariciresinol readily gave a levorotatory dimethyl ether which is identical with the product resulting when the dimethyl ethers of either lariciresinol or isolariciresinol are heated at 180°C. with potassium bisulfate (130). Anhydroisolariciresinol dimethyl ether is de-

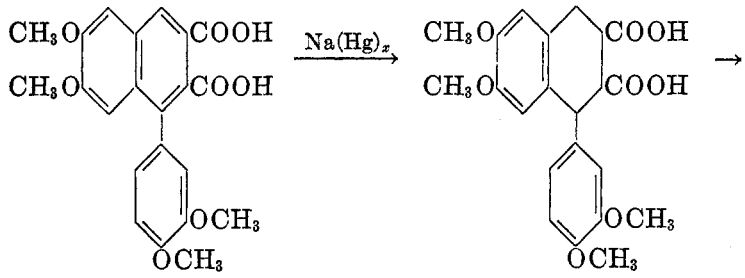
hydrogenated with lead tetraacetate in acetic acid to give a 33 per cent yield of the corresponding naphthalene derivative, which is called dehydroanhydroisolariciresinol dimethyl ether (131).



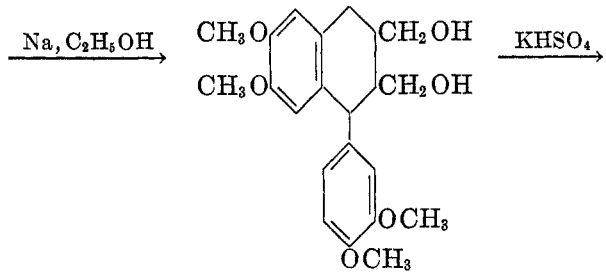
Anhydroisolariciresinol dimethyl ether

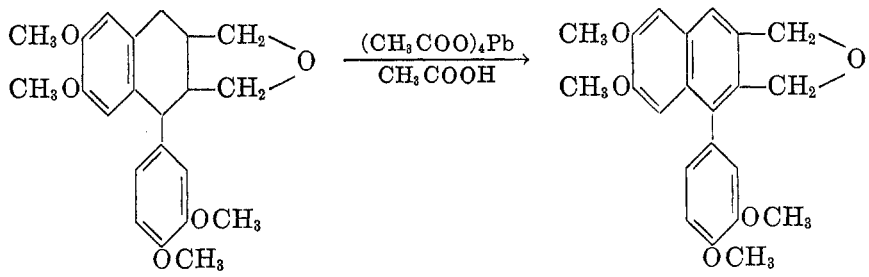
Dehydroanhydroisolariciresinol dimethyl ether

The dimethyl ether of dehydroanhydroisolariciresinol was synthesized by Haworth and Woodcock (149), using the following sequence:



the ethyl ester





Dehydroanhydroisolariciresinol dimethyl ether

The intermediate isolariciresinol structure was a partly crystalline mixture of diastereoisomers. Both the crystalline and the oily portions gave the same final product. The percentage yields of the steps were 90, 20, 45, 90, and 45, respectively (149).

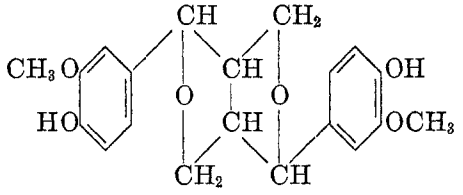
D. TETRAHYDROFUROFURAN DERIVATIVES

1. Pinoresinol

Pinoresinol was first isolated in 1894 by Bamberger (8) from the resinous exudate of *Pinus laricio*. It has since been obtained from the resin of several species of *Pinus* and *Picea* (226) and recently has been isolated from fir cambial sap (93a).

Pinoresinol is obtained from the crude resin by dissolution in alcohol followed by the addition of concentrated aqueous potassium hydroxide to precipitate the slightly soluble potassium salt of pinoresinol (8, 76). The yield of pinoresinol may be 20–25 per cent of the resin (76). Purification is rather difficult and has been achieved by reacting an aqueous solution of the potassium salt with benzoyl chloride followed by recrystallization (314) or by reacting the dry potassium salt with acetic anhydride and pyridine, followed by recrystallization (76, 93a). These procedures require several recrystallizations, and purification is better achieved by adsorbing the impurities in an alumina column (81).

Pinoresinol has the molecular formula $C_{20}H_{22}O_6$ (78, 314), which suggests that it is a dimer formed from coniferyl alcohol by the loss of two hydrogen atoms. Its structural formula is as follows (87):



Pinoresinol

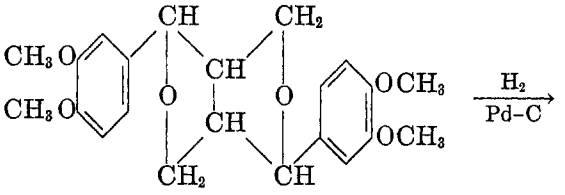
The two phenolic hydroxyl groups of pinoresinol are readily etherified and esterified. Monoethers can be obtained in low yield with care, and Erdtman (80) used these to demonstrate the presence of a rotating axis of symmetry, since the ethylated methyl ether and methylated ethyl ether were identical. The symmetry has also been demonstrated by showing the equivalence of nitrated bromodimethylpinoresinol and brominated nitrodimethylpinoresinol (103).

Pinoresinol dimethyl ether may be nitrated with a dilute solution of nitric acid in acetic acid, giving a 50 per cent yield of dinitropinoresinol dimethyl ether along with a 25 per cent yield of 4-nitroveratrole (78). With fuming nitric acid in the cold, oxidative cleavage occurs giving a 73 per cent yield of 4,5-dinitroveratrole; if the solution is warmed, the cleavage gives a 65 per cent yield of

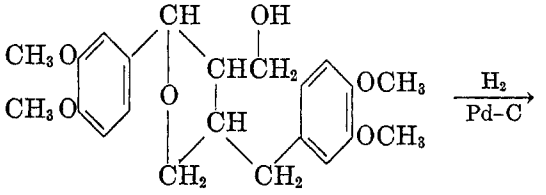
trinitroveratrole (78, 94). Nitration thus occurs ortho to the point of attachment of the aromatic rings.

Both the ethers and the esters of pinoresinol react readily with bromine, giving dibromo derivatives (78). The bromine atoms enter ortho to the point of attachment of the rings, as shown by the fact that the nitric acid cleavage of dibromopinoresinol diethyl ether gave an 83 per cent yield of 5-bromo-4-nitroguaiacol ethyl ether (82).

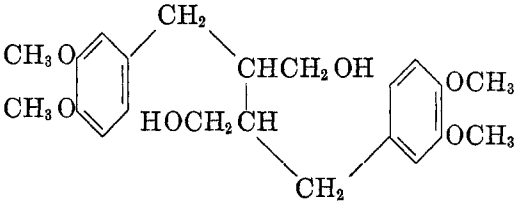
The tetrahydrofuran rings of pinoresinol dimethyl ether are opened by mild hydrogenolysis over palladium–carbon, leading first to (+)-lariciresinol dimethyl ether and, upon opening the second ring, to a levorotatory diol (148).



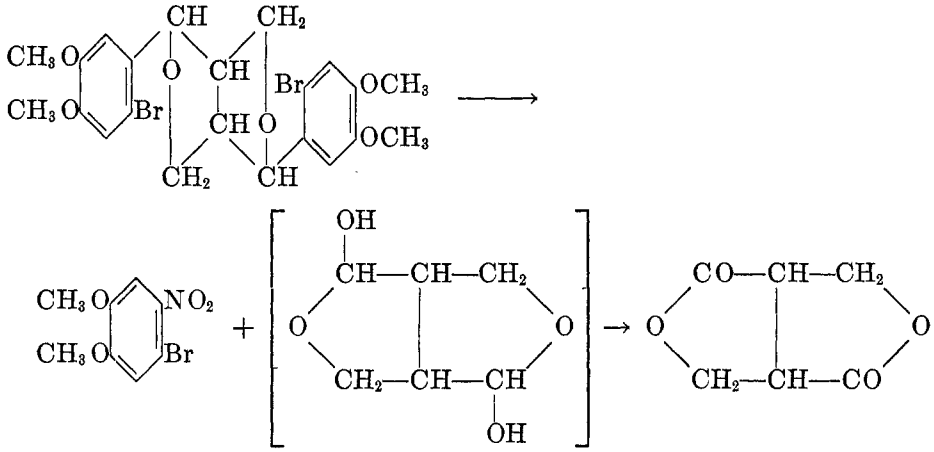
Pinoresinol dimethyl ether



(+)-Lariciresinol dimethyl ether



Conclusive evidence of the nature of the aliphatic portion of pinoresinol was obtained from the nitric acid cleavage of dibromopinoresinol dimethyl ether, which gave 5-bromo-4-nitroveratrole as above; upon neutralizing and evaporating the mother liquors there was obtained a 65 per cent yield of dextrorotatory bis(hydroxymethyl)succinic acid dilactone (87). The racemic dilactone was similarly obtained from racemic dimethylpinoresinol (an equimolecular mixture of dimethylpinoresinol and its antipode, eudesmin) (87). This inactive lactone was identical with a synthetic specimen (87). The reaction was represented as proceeding through an intermediate lactal, which was then oxidized by the nitric acid as follows:



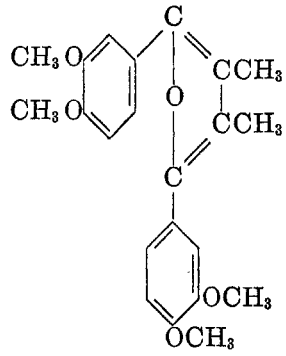
Pinoresinol can be partially isomerized by refluxing for 3 hr. with alcoholic hydrochloric acid; the resulting mixture is methylated to give a mixture containing dimethylpinoresinol and an isomer named dimethylepipinoresinol (83). The isomerization is reversible and hence not deep-seated (105, 179, 180, 199). Dimethylepipinoresinol gave two different mononitro derivatives and bromination of these gave two bromonitro derivatives (104). Thus epipinoresinol is not symmetrical and the isomerization most likely involves an inversion about one of the benzyl carbon atoms (104).

TABLE 12

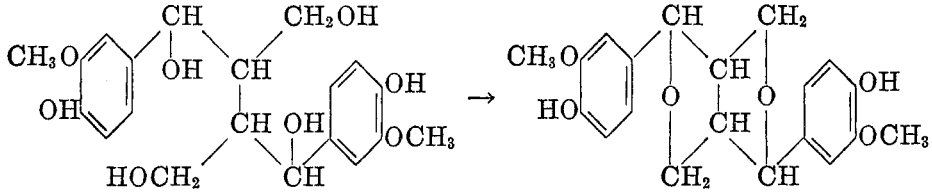
Pinoresinol and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Pinoresinol	120–121	$[\alpha]_D^{21}$ = +84.4° (acetone)	(78)
Diacetylpinoresinol	166–167.5	$[\alpha]_D^{20}$ = +49.1° ($CHCl_3$)	(8, 76, 78)
Dibenzoylpinoresinol	163–164	$[\alpha]_D^{20}$ = +46.9° ($CHCl_3$)	(76, 78, 314)
Dibromodibenzoylpinoresinol	177–178	$[\alpha]_D^{19}$ = +2.2° ($CHCl_3$)	(78)
Dibromodiacetylpinoresinol	169–170	$[\alpha]_D^{22}$ = −18.4° ($CHCl_3$)	(78)
Dimethylpinoresinol	107–108	$[\alpha]_D^{20}$ = +64.5° ($CHCl_3$)	(8, 76, 78)
Diethylpinoresinol	122–123	$[\alpha]_D^{21}$ = +62.0° ($CHCl_3$)	(10, 79)
Dinitrodimethylpinoresinol	212–213	$[\alpha]_D^{22}$ = −124.7° ($CHCl_3$)	(78)
Dibromodimethylpinoresinol	172–173	$[\alpha]_D^{21}$ = −69.1° ($CHCl_3$)	(78)
Dibromodiethylpinoresinol	143–144	$[\alpha]_D^{21}$ = −59.6° ($CHCl_3$)	(79)
Monomethylbenzoylpinoresinol	110–111		(80)
Monoethylbenzoylpinoresinol	121–122		(80)
Methylethylpinoresinol	75–76	$[\alpha]_D^{25}$ = +100° (benzene)	(80)
Dinitromethylethylpinoresinol	183–184	$[\alpha]_D^{25}$ = −122° ($CHCl_3$)	(80)
Monobromodimethylpinoresinol	121–122		(103)
Bromonitrodimethylpinoresinol	180–181	$[\alpha]_D^{23}$ = −180° ($CHCl_3$)	(83, 103)
Dimethylepipinoresinol	130–131	$[\alpha]_D^{18}$ = +141° (*c* 1.30, $CHCl_3$)	(104, 179)
α-Nitrodimethylepipinoresinol	141	$[\alpha]_D^{21}$ = +41° (*c* 1.01, $CHCl_3$)	(104)
β-Nitrodimethylepipinoresinol	129–130	$[\alpha]_D^{20}$ = +114° (*c* 1.00, $CHCl_3$)	(104)
Bromo-α-nitrodimethylepipinoresinol	157–157.5	$[\alpha]_D^{21}$ = +78° (*c* 0.98, $CHCl_3$)	(104)
Bromo-β-nitrodimethylepipinoresinol	181–182	$[\alpha]_D^{21}$ = +84° (*c* 1.15, $CHCl_3$)	(104)
α-Bromodimethylepipinoresinol	143–144	$[\alpha]_D^{21}$ = +51° (*c* 1.15, $CHCl_3$)	(104)
(±)-Pinoresinol	111	$[\alpha]_D$ = 0°	(94)
Dinitrodimethylepipinoresinol	160, 182		(83, 179)

Dehydrogenation by selenium of the dimethyl ethers of pinoresinol or epipinoresinol did not lead to a naphthalene but instead gave a furan derivative. The furan was identical with the one synthesized from 2-bromo-1-(3,4-dimethoxyphenyl)propanone and copper, followed by dehydrating the resulting 1,4-diketone (126):



Inactive pinoresinol has recently been obtained by a high-vacuum distillation of 2,3-bis(α-hydroxyvanillyl)-1,4-butanediol (94).

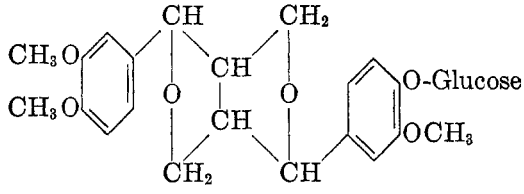


Pinoresinol

2. Phillyrin (forsythin) and phillygenol (forsythigenol)

Phillyrin, which was first reported by Carboncini (42) in 1836, has been obtained by alcohol extraction of the twigs, twig bark, or leaves of various species of *Forsythia* and *Phillyrea* (17, 89, 180, 192, 193, 194, 197, 280). Yields up to 1.6 per cent of the fresh bark of *P. latifolia* L. have been reported (193).

Phillyrin is a glucoside of a monomethyl ether of epipinoresinol (105, 180) and has the following structure:



Phillyrin

TABLE 13

Phillyrin and phillygenol and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Phillyrin	162 or 181	$[\alpha]_D$ = +46.71° (alcohol)	(193, 197)
Phillygenol	134–135	$[\alpha]_D$ = +121.7° (alcohol)	(193)
Monoethylphillygenol	124		(193)

The glucoside is dimorphic; the form melting at 162°C. was named phillyrin (192, 193, 194), while the form melting at 181°C. was named forsythin (197, 198, 199). The aglycone also was known as either phillygenol or forsythigenol.

Phillyrin is cleaved by acidic hydrolysis or alcoholysis, or by the action of emulsion or *Aspergillus niger* (17, 193, 280), but is stable toward yeast α-glucosidase (193).

The nature of the aglycone was largely established when its methyl ether was shown to be identical with dimethylepipinoresinol (104, 105, 180). However, the two aromatic rings of epipinoresinol are not equivalent as shown above, and it is not yet known which ring contains the hydroxyl group.

3. Eudesmin

Eudesmin was first obtained by Maiden and Smith (211) in 1895 from the kinos of Australian *Eucalyptus*. It is not found in all Eucalyptus species but only in the group that contains aromadendrin, catechol tannins, and cineole-pinene oils. Those species containing phellandrene, resorcinol, or phloroglucinol tannins, and pinene as the main oil, do not yield eudesmin (258).

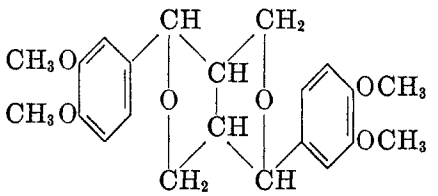
The kinos of *Eucalyptus hemiphloia*, which are sometimes as large as hens' eggs, contain about 10 per cent of eudesmin, which is separated by heating the kinos with sufficient water to form a paste and extracting with ether. Evaporation of the ether gives a crystalline mixture of eudesmin and aromadendrin; this mixture is separable, since eudesmin is dissolved by cold chloroform (258).

Eudesmin is levorotatory and has the molecular formula $C_{22}H_{26}O_6$ (258). It contains four methoxyl groups and the remaining two oxygens are inert and ethereal. The detailed structure of eudesmin was established when Erdtman (78) recognized it as the optical antipode of pinoresinol dimethyl ether.

TABLE 14

Eudesmin and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Eudesmin	107	$[\alpha]_D^{21}$ = −64.3° ($CHCl_3$)	(258)
Dinitroeudesmin	212–213	$[\alpha]_D$ = +124.0° ($CHCl_3$)	(78, 258)
(±)-Dinitroeudesmin	241–242		(78)
Dibromoeudesmin	172–173	$[\alpha]_D^{22}$ = +69.4° ($CHCl_3$)	(78, 258)
(±)-Dibromoeudesmin	177–178		(78)
Dichloroeudesmin	163		(258)



Eudesmin

Reduction with sodium and ethanol in ammonia cleaved the benzyl ether linkages, forming a dextrorotatory diol that is the enantiomer of the one obtained from dimethylpinoresinol (21).

4. (+)- and (−)-Sesamin

The oil of sesame seeds contains a number of materials, including about 1 per cent of (+)-sesamin (39). Saponification of the oil with alcoholic potassium hydroxide followed by dilution with water and extraction with ether removes (+)-sesamin, which is purified by recrystallization (2, 24, 25, 26, 153, 176, 307).

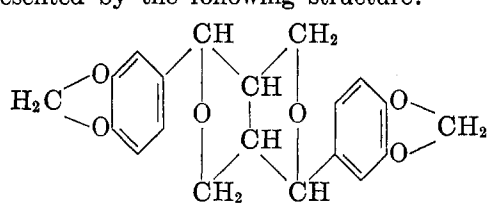
TABLE 15

(+)- and (−)-Sesamin and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
(+)-Sesamin	122–123	$[\alpha]_D^{21} = +68.1°$ (*c* 2.95, $CHCl_3$)	(26, 176)
(−)-Sesamin	123–124	$[\alpha]_D^{17} = -68.1°$ (*c* 1.34, $CHCl_3$)	(176, 178)
(+)-Dinitrosesamin	240–241	$[\alpha]_D^{16} = +35.1°$ (*c* 1.23, $CHCl_3$)	(26, 176, 307)
(−)-Dinitrosesamin	240–241	$[\alpha]_D^{19} = -34.5°$ (*c* 0.42, $CHCl_3$)	(176)
(+)-Dibromosesamin	182–183	$[\alpha]_D^{21} = +14.5°$ (*c* 1.31, $CHCl_3$)	(178)
(−)-Dibromosesamin	183–184	$[\alpha]_D^{21} = -13.8°$ (*c* 6.67, $CHCl_3$)	(57, 178)
Dichlorosesamin	191–192	$[\alpha]_D^{6.5} = +22.4°$ ($CHCl_3$)	(173)
(±)-Sesamin	129–130		(178)
(±)-Dinitrosesamin	223		(176)
(−)-Diaminosesamin hydrochloride		$[\alpha]_D = +60.0°$	(26)

(−)-Sesamin was obtained from the roots of *Asarum sieboldi*, where it occurs along with (−)-asarinin (178). The minced roots were extracted with alcohol and the extract steam-distilled. Ether extraction of the non-volatile portion removed the lignans, which were taken up in alcohol. After treatment with alcoholic lead acetate and hydrogen sulfide the mother liquor was concentrated; it yielded crystalline (−)-asarinin and (−)-sesamin upon standing (178). The two were separable, since (−)-asarinin is more soluble in ether (178).

Sesamin has the molecular formula $C_{20}H_{18}O_6$ (2, 26, 57) and is one of the stereoisomers represented by the following structure:



Sesamin

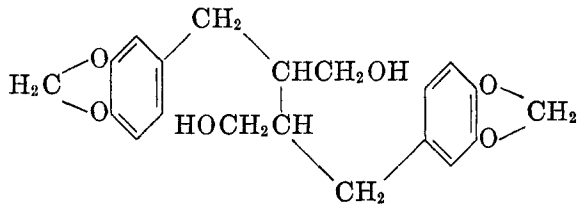
In accord with the above formula, the reactions of sesamin are those of the aromatic rings, benzyl hydrogen atoms, and ether groups. Sesamin is readily brominated in acetic acid to give an almost quantitative yield of the levorotatory dibromide, which in turn reacts with concentrated nitric acid to give an almost quantitative yield of 5-bromo-1,2-methylenedioxy-4-nitrobenzene (57). The dibromide thus was the 5′,5″-derivative and the presence of two methylenedioxyphenyl residues was established.

Sesamin is nitrated in acetic acid, giving a 58 per cent yield of dinitrosesamin along with some 4-nitromethylenedioxybenzene and a nitropiperonal (26, 307).

Chlorination of (+)-sesamin gave the 5′,5″-dichloro derivative (173). The dichloro derivative underwent oxidative cleavage when heated at 100°C. in a carbitol solution of hydrochloric acid and hydrogen peroxide to give a 15 per cent yield of 4,5-dichloro-1,2-methylenedioxybenzene (173). When acetic acid was the solvent instead of carbitol, a 15 per cent yield of 3,4,5-trichloro-1,2-methylenedioxybenzene resulted; if the reaction was continued until the evolution of chlorine ceased, a 20 per cent yield of 3,4,5,6-tetrachloro-1,2-methylenedioxybenzene resulted (173).

The tetrahydrofurofuran structure of the aliphatic portion of (+)-sesamin was shown by removing the methylenedioxy group with alcoholic potassium hydroxide at 170°C. and methylating the intermediate compound. The product was a mixture of the dimethyl ethers of pinoresinol and epipinoresinol (83, 179).

The tetrahydrofuran rings of (+)-sesamin are opened readily by hydrogenolysis over palladium–carbon in acetic acid to give a levorotatory diol that is identical with the one produced from cubebin (37).

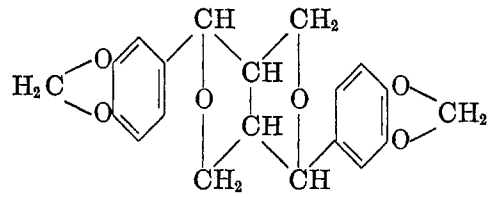


In common with the other tetrahydrofurofuran lignans (+)-sesamin is isomerized by heating in alcoholic hydrochloric acid to a compound which has a higher positive rotation and was recognized as (+)-asarinin (18, 176). The reverse transformation, the conversion of (−)-asarinin into (−)-sesamin, has also been realized (176). In both cases the racemic mixture was a compound melting higher than either antipode (176).

5. (+)- and (−)-Asarinin

(−)-Asarinin has been obtained in 0.2–0.5 per cent yield from a petroleum ether extract of the roots and rhizomes of *Asarum sieboldi* (54, 174, 175) and from a benzene extract of the bark of *Xanthoxylum carolinianum* (62, 63). (+)-Asarinin was only recently isolated from the leaves of *Acronychia muelleri* (60a).

Asarinin is stereoisomeric with sesamin and is one of the isomers represented by the following structure:



Asarinin

The ordinary chemical reactions of asarinin parallel those given above for sesamin (176).

Alkaline opening of the methylenedioxy rings, followed by methylation, gave a mixture of eudesmin and epieudesmin (83, 170, 179). Hydrogenolysis in acetic acid over palladium–carbon gave a dextrorotatory diol, which apparently is the antipode of the diol obtained from either cubebin or (+)-sesamin. The equimolecular mixture of the two diols melted unsharply about 10°C. below the melting point of either (37).

TABLE 16

Asarinin and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
(−)-Asarinin	122–123	$[\alpha]_D^{20} = -118.6°$ (*c* 3.94, $CHCl_3$)	(54, 170, 176)
(+)-Asarinin	122–123	$[\alpha]_D^{20} = +118.6°$ ($CHCl_3$)	(176)
(±)-Asarinin	135–136		(176)
(−)-Dinitroasarinin	220–221	$[\alpha]_D^{17} = -29.5°$ ($CHCl_3$)	(176)
(+)-Dinitroasarinin	220–221	$[\alpha]_D^{18} = +30.6°$ (*c* 0.80, $CHCl_3$)	(170, 176, 177)
(±)-Dinitroasarinin	196–197		(176)
Dibromoasarinin	63–65		(62)

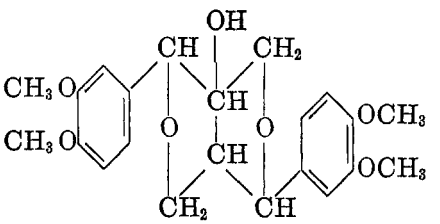
Asarinin was isomerized by heating with alcoholic hydrogen chloride into a mixture from which 40 per cent of asarinin and 10 per cent of (−)-sesamin were isolated (170). This isomerization is probably analogous to the interconversion of pinoresinol and epipinoresinol.

Although it has not been shown whether the sesamin or asarinin configuration is the symmetrical (pinoresinol) one, the change in specific rotation caused by nitration indicates that asarinin may have the symmetrical structure (81) and sesamin the unsymmetrical (epipinoresinol) structure.

6. Gmelinol

Gmelinol occurs crystalline in the white deposit in cracks and cell cavities of the Australian species *Gmelina leichhardtii* (278). It is obtained by leaching the wood shavings with hot water and cooling the extract, whereupon crystalline gmelinol separates (22, 110). The yield from selected wood specimens was 2.3 per cent (22).

Gmelinol is known to be one of the stereoisomers represented by the following formula (6, 21):



Gmelinol

Gmelinol is sufficiently stable to be distillable at 20 mm. pressure (330°C.) (22). Destructive distillation at atmospheric pressure produced traces of veratraldehyde and veratric acid along with a 10 per cent yield of homoveratrole (22). Fusion with potassium hydroxide gave protocatechuic acid (278). Veratric acid resulted from oxidation either with chromium trioxide in acetic acid or with alkaline permanganate (22, 278). The yield with the latter reagent was 63 per cent, a result which served to demonstrate the presence of the two veratryl groups.

TABLE 17

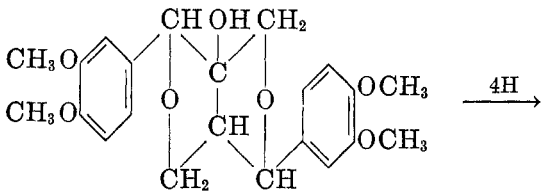
Gmelinol and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Gmelinol	124	$[\alpha]_D = +123.3°$ ($CHCl_3$)	(22, 278)
Acetylgmelinol	118		(110, 278)
Gmelinol phenylurethan	189		(110)
Dinitrogmelinol	190		(22)
Dibromogmelinol	145		(22)
Tetrahydrogmelinol	132	$[\alpha]_D = -3.2°$ (ethanol)	(21)
Isogmelinol	147	$[\alpha]_D = +30°$ (*c* 1, $CHCl_3$)	(278)
Dibromoisogmelinol	196		(22)
Dinitroisogmelinol	235		(22, 110)

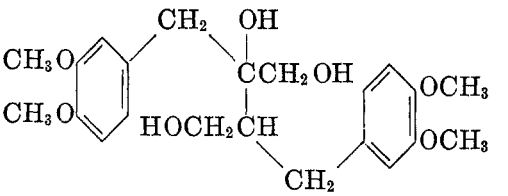
The hydroxyl group of gmelinol reacts to form an acetate or phenylurethan (110, 278). It behaves as a bridgehead hydroxyl in being otherwise inert. All attempts to replace it with halogen were unsuccessful (110), and it could not be oxidized to a carbonyl group (22, 110, 278). Reactions which should have led to dehydration produced isomerization or formation of tar (110).

Gmelinol is readily nitrated or brominated to dinitro or dibromo derivatives (22). In accord with its tetrahydrofurofuran structure either gmelinol or its dinitro derivative may be cleaved with concentrated nitric acid to give a 50 per cent yield of 4,5-dinitroveratrole (22). Similar cleavage of the dibromo derivative gave 5-bromo-4-nitroveratrole (22).

The benzyl ether linkages may also be opened by reduction with sodium and alcohol in ammonia, giving a triol (21):



Gmelinol



Tetrahydrogmelinol

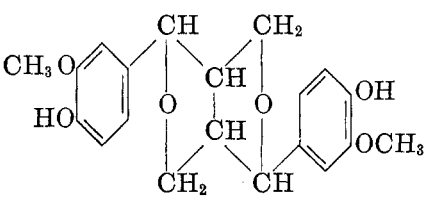
The production of the triol served to show that the aromatic rings were situated as shown, rather than as in olivil. The triol (tetrahydrogmelinol) was readily cleaved by lead tetraacetate, producing formaldehyde and an unstable hydroxy ketone (21). The original hydroxyl group of gmelinol must thus have been at the bridgehead as shown.

In common with eudesmin or pinoresinol, gmelinol may be isomerized by suitable acidic treatment to produce a dextrorotatory isomer named isogmelinol. The isomerization proceeds in 50 per cent yield by refluxing for 10 hr. in 20 per cent formic acid (22), and has also been achieved by other treatments (110). Dibromogmelinol, but not dinitrogmelinol, is isomerized by refluxing with alcoholic hydrochloric acid.

The isomerization seems similar to the pinoresinol–epipinoresinol transformation and probably consists in inversion at one of the benzyl carbon atoms. The nitration, bromination, and cleavage reactions of isogmelinol parallel those of gmelinol (110); reduction with sodium and alcohol in ammonia produced a triol identical with the one obtained directly from gmelinol (21).

7. Symplocosin and symplocosigenol

Nishida, Sumimoto, and Kondo (236) have reported the isolation from the bark of *Symplocos lucida* Sieb. et Zucc. of a glucoside which they have named symplocosin (237). On hydrolysis with emulsin (showing a β-linkage), symplocosin gave 1 mole of glucose and a phenol which they named symplocosigenol. The latter has been shown to be identical with the enantiomorph of dimethylphillygenol (or forsythigenol); hence it probably has the following structure (234):



Symplocosigenol

Elemental analysis showed symplocosin to have the structure $C_{26}H_{32}O_{11} \cdot 6H_2O$, and the aglycone $C_{20}H_{22}O_6 \cdot 2H_2O$. Two methoxyls were found by analysis and two phenolic hydroxyls by alkylation. No other active substituents could be located (237).

Oxidation (234) of symplocosigenol yielded no identifiable products, but the action of permanganate on its dimethyl ether gave veratric acid. Similarly, permanganate with the diethyl ether yielded ethylvanillic acid. Ethylation of symplocosin, followed by hydrolysis of the glucose residue and then methylation, gave a methylethylsymplocosigenol, which, on oxidation, gave a mixture of veratric acid and ethylvanillic acid.

TABLE 18

Symplocosin, symplocosigenol, and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
Symplocosin	171–171.5 ($6H_2O$)	$[\alpha]_D^{11} = -44.9°$	(237)
Symplocosigenol	141.5–142 ($2H_2O$)	$[\alpha]_D^{17} = -118.9°$	(237)
Symplocosin pentamethyl ether	115–116		(236)
Symplocosigenol monomethyl ether	132.5	$[\alpha]_D^{17} = -124.7°$	(236)
Symplocosigenol dimethyl ether	128–128.5	$[\alpha]_D^{19} = -114.6°$	(237)
Symplocosigenol methylethyl ether	124–124.5		(237)
Symplocosigenol diethyl ether	118.5–119.5		(237)
Symplocosigenol diacetate	148–150	$[\alpha]_D^{12} = -72.24°$	(237)
Dipotassium symplocosigenol	210 (d.)		(237)
Dinitrosymplocosigenol dimethyl ether	162–163.5	$[\alpha]_D^{15} = -71.5°$	(237)
Dibromosymplocosigenol dimethyl ether	171.5–172		(237)
Dinitroepisymplocosigenol dimethyl ether	178–179	$[\alpha]_D^{19} = -48.1°$	(234)

Dinitrosymplocosigenol dimethyl ether with mineral acid gave a diastereoisomer which was designated an epi form (234). This epi form after several recrystallizations apparently gave the original compound.

The above reactions led Nishida to suspect a pinoresinol structure for symplocosigenol. A comparison then of the physical constants of symplocosigenol derivatives and phillygenol derivatives (234) established the identity of the former as the enantiomorph of dimethylphillygenol. From this relationship it can be concluded that symplocosigenol dimethyl ether is identical with the enantiomorph of epipinoresinol dimethyl ether.

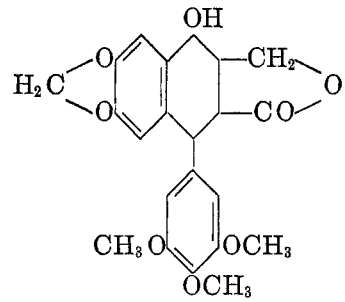
Nishida (235) further showed the relationship of symplocosigenol to the furofuran lignans by converting symplocosigenol dimethyl ether to eudesmin and epieudesmin by treatment with methanolic hydrochloric acid. Also, the dinitroepisymplocosigenol dimethyl ether mentioned above was found to have the same melting point as dinitrophillygenol dimethyl ether and the same optical rotation but with opposite sign, showing them to be enantiomorphs.

E. 4-ARYLTETRAHYDRONAPHTHALENE DERIVATIVES

1. 1-Hydroxy-2-hydroxymethyl-3-carboxylic acid lactones

a. Podophyllotoxin

Podophyllotoxin was first isolated by Podwyssotzki (248) in 1881 from podophyllin.[1] Kürsten (200) later purified it and carried out the first analysis, which, however, was incorrect.



Podophyllotoxin occurs as an extractive in the North American May apple (*Podophyllum peltatum*) and in a similar plant in India (*Podophyllum emodi*). Podophyllum also occurs in Russia and yields a resin equivalent to that from the American plant (294). Recently Hartwell, Johnson, Fitzgerald, and Belkin (115) have found podophyllotoxin in four species of juniper, the first occurrence of this material noted in a conifer.[2]

Podophyllotoxin has been isolated from podophyllin by extraction followed by laborious purification (27, 70, 200); however, Hartwell (113) recently has developed a much simpler technique based on chromatography.

The early analyses by Kürsten (200) showed podophyllotoxin to have the empirical formula $C_{23}H_{24}O \cdot 2H_2O$. Borsche and Niemann (27), however, established the correct formula, $C_{22}H_{22}O_8$, and showed that the substance not only formed a hydrate but could form mixed solvates with water, alcohol, acetone, and benzene depending on the solvent mixture used for crystallization. These solvates of crystallization are lost by drying at 100°C. (27, 116).

Proof of the structure of podophyllotoxin is intimately associated with that of picropodophyllin, an isomer obtained from the former by treatment with alkali. This isomerization was observed by Podwyssotzki (248) in 1881, when he "extracted" podophyllotoxin with ammonia, but subsequently the isomerization has been much more extensively studied (27, 116).

[1] Podophyllin is the resin extracted by alcohol from *Podophyllum peltatum* (the North American May apple) or from *Podophyllum emodi* ("Indian Podophyllin"). Considerable early work was performed on these resins (69, 165, 200) and the resins from each source were found to be identical (70), although recent work shows differences (186). For information on the occurrence and biology of the *Podophyllum* genus see the work of Chatterjee (47, 53) and of Hartwell (186). Podophyllin has long been used in medicine as a purgative.

[2] Podophyllotoxin acetate, as well as picropodophyllin acetate (see paragraph below), has been found by King (187) in *Hernandia sonora*.

TABLE 19

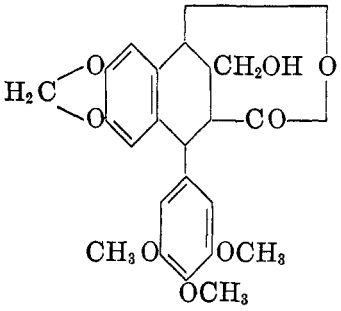
Podophyllotoxin and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Podophyllotoxin	183–184	$[\alpha]_D^{20} = -132°$ (c 1.0, $CHCl_3$)	(116)
Picropodophyllin	231.5–232.5	$[\alpha]_D^{20} = +9.4°$ ($CHCl_3$)	(116, 281)
Acetylpodophyllotoxin	209.5–210.5	$[\alpha]_D^{20} = -143°$ (c 1.0, $CHCl_3$)	(116)
Acetylpicropodophyllin	216.5–217	$[\alpha]_D^{20} = +19.4°$ (c 1.0, $CHCl_3$)	(116)
Picropodophyllin ethyl ether	227–229	$[\alpha]_D^{21} = +58°$ (c 0.5, $CHCl_3$)	(269)
Benzoylpodophyllotoxin	111–115	$[\alpha]_D^{20} = -116°$ (c 1.0, $CHCl_3$)	(116)
Benzoylpicropodophyllin	209.5–211	$[\alpha]_D^{20} = +16.3°$ (c 1.0, $CHCl_3$)	(116)
Podophyllotoxin chloride	179–180.5	$[\alpha]_D^{20} = -27.1°$ (c 1, C_2H_5OH-free $CHCl_3$)	(116)
Podophyllotoxin bromide	157.5–159	$[\alpha]_D^{21} = +15.8°$ (c 1, C_2H_5OH-free $CHCl_3$)	(116)
Epipodophyllotoxin	159.4–161.2	$[\alpha]_D^{20} = -75°$ (c 1, $CHCl_3$)	(116)
Epipicropodophyllin	158.3–158.6	$[\alpha]_D^{20} = +84°$ (c 1, $CHCl_3$)	(116)
Epipodophyllotoxin ethyl ether	194.8–195	$[\alpha]_D^{20} = -88°$ (c 1, $CHCl_3$)	(116)
Epipicropodophyllin ethyl ether	151.2–152.7	$[\alpha]_D^{21} = +45.2°$ (c 1, $CHCl_3$)	(116)
Acetylepipodophyllotoxin	174.4–175.4	$[\alpha]_D^{20} = -141°$ (c 1, $CHCl_3$)	(116)
Acetylepipicropodophyllin	157–157.4	$[\alpha]_D^{20} = +7.4°$ (c 1, $CHCl_3$)	(116)
Epipodophyllic acid	166–171	$[\alpha]_D^{20} = -43.9°$ (c 1, absolute ethanol)	(116)
Podophyllic acid	163–165	$[\alpha]_D^{16} = -102.8°$ (c 1.616, C_2H_5OH)	(27, 116)
α-Apopicropodophyllin	243–245	$[\alpha]_D^{20} = -18°$ (c 0.5, $CHCl_3$)	(257, 266)
Podophyllomeronic acid	236–237		(27)
Methyl podophyllomeronate	121–123		(27)
Monobromopodophyllomeronic acid	287–288		(27)
Dibromopodophyllomeronic acid	320		(28)
Dinitropodophyllomeronic acid			(27)
β-Apopicropodophyllin	220.5–220.9	$[\alpha]_D^{20} = +99°$ (c 0.5, $CHCl_3$)	(257, 266)
Methyldibromopodophyllomeronic acid	233–234		(28)
Podophyllomerol	129–129.5		(28)
Phyllomeronic acid	243–244		(28)
Methyl phyllomeronate	186–187		(28)
Methyl dimethylphyllomeronate	125–126		(28)
Dimethylphyllomeronic acid	223–225		(28)
Phyllomerol	161–162		(28)
Phyllomerol dimethyl ether	98–100		(28)
Podophyllic acid hydrazide	155–160		(28)
Dehydroanhydropicropodophyllin	270–271		(138, 266, 281)
α-Apopodophyllic acid	173–174	$[\alpha]_D^{20} = -163°$ (c 1, $CHCl_3$) $[\alpha]_{5461}^{21} = -279°$ (c 1, $CHCl_3$)	(27, 266)
Methyl α-apopodophyllate	172–173	$[\alpha]_D^{20} = -155°$ (c 1, $CHCl_3$)	(266)
γ-Apopodophyllic acid	249–250		(266)
γ-Apopicropodophyllin	252–253	$[\alpha]_D^{21} = +26.4°$ (c 0.5, $CHCl_3$)	(266)
6,7-Methylenedioxy-1-(3,4,5-trimethoxyphenyl)-3-hydroxymethylnaphthalene	148–148.6		(266)
Isodesoxypodophyllotoxin	251–252	$[\alpha]_D^{21} = +82°$ (c 0.52, $CHCl_3$)	(267)
Desoxypicropodophyllin	168–170	$[\alpha]_D^{19} = +39°$ (c 0.53, $CHCl_3$)	(267)

TABLE 19—*Continued*

Compound	Melting Point	Optical Rotation	References
	°C.		
6,7-Methylenedioxy-1-(3,4,5-trimethoxyphenyl)-3-methyl-1,2,3,4-tetrahydro-2-naphthoic acid	236–237.5	$[\alpha]_D^{20} = -144°$ (*c* 0.55, pyridine)	(267)
Isodesoxypicropodophyllin	202–202.5	$[\alpha]_D^{20} = -114°$ (*c* 0.51, $CHCl_3$)	(67, 267)
6,7-Methylenedioxy-1-(3,4,5-trimethoxyphenyl)-3-hydroxymethyl-5,6,7,8-tetrahydro-2-naphthoic acid lactone	177–178		(267)
Racemic isodesoxypicropodophyllin	203–203.8		(267)
Tetramethyl 3′,4′,5′-trimethoxybiphenyl-2,3,4,5,6-tetracarboxylate	168–172.5		(267)
Isodesoxypodophyllic acid	213, 250–252	$[\alpha]_D^{20} = -110°$ (*c* 0.53, pyridine)	(267)
Methyl isodesoxypodophyllate	200.7–201.6	$[\alpha]_D^{20} = -23°$ (*c* 0.62, $CHCl_3$)	(267)
Ethyl isodesoxypodophyllate	148.8–149.6	$[\alpha]_D^{21} = -22°$ (*c* 1.3, $CHCl_3$)	(267)
Podophyllyl alcohol	198–200	$[\alpha]_D^{25} = -0°$ (*c* 0.312, $CHCl_3$)	(67)
Podophyllyl alcohol tris-(*p*-nitrobenzoate)	130.6–134.6	$[\alpha]_D^{25} = -31°$ (*c* 0.629, $CHCl_3$)	(67)
Anhydropodophyllyl alcohol	256.3–257.3	$[\alpha]_D^{25} = +13°$ (*c* 0.489, $CHCl_3$)	(67)
Anhydropodophyllyl alcohol *p*-nitrobenzoate	194.7–196.1	$[\alpha]_D^{25} = -46°$ (*c* 0.474, $CHCl_3$)	(67)
Anhydropodophyllyl alcohol methyl ether	167.1–173.6	$[\alpha]_D^{25} = +3°$ (*c* 0.450, $CHCl_3$)	(67)
Anhydropodophyllyl alcohol benzoate	169.6–171.6	$[\alpha]_D^{25} = -27°$ (*c* 0.498, $CHCl_3$)	(67)
Picropodophyllyl alcohol	160.2–162.2	$[\alpha]_D^{25} = -67°$ (*c* 0.347, $CHCl_3$)	(67)
Picropodophyllyl alcohol tris(*p*-nitrobenzoate)	118.5–125.5	$[\alpha]_D^{25} = -29°$ (*c* 0.942, $CHCl_3$)	(67)
Anhydropicropodophyllyl alcohol		$[\alpha]_D^{25} = +73°$ (*c* 0.463, $CHCl_3$)	(67)
Anhydropicropodophyllyl alcohol *p*-nitrobenzoate		$[\alpha]_D^{25} = +66°$ (*c* 0.197, $CHCl_3$)	(67)
Isodesoxypicropodophyllyl alcohol		$[\alpha]_D^{25} = +120°$ (*c* 0.544, $CHCl_3$)	(67)
Isodesoxypicropodophyllyl alcohol bis(*p*-nitrobenzoate)	97–107	$[\alpha]_D^{25} = +59°$ (*c* 0.472, $CHCl_3$)	(67)
Anhydroisodesoxypicropodophyllyl alcohol	162.7–163.7	$[\alpha]_D^{25} = +64°$ (*c* 0.497, $CHCl_3$)	(67)
4′-Demethyl-β-apopicropodophyllin	272–282	$[\alpha]_D^{20} = +106°$ (*c* 0.31, $CHCl_3$)	(264)
4′-Ethyldemethyl-α-apopodophyllic acid	155–156	$[\alpha]_D^{21} = -159°$ (*c* 1.0, $CHCl_3$)	(264)
Podophyllotoxin chloroacetate	209–210	$[\alpha]_D^{22} = -140°$ (*c* 1.05, $CHCl_3$)	(265)
Podophyllotoxin bromoacetate	192	$[\alpha]_D^{22} = -133°$ (*c* 1.03, $CHCl_3$)	(265)
Podophyllotoxin iodoacetate	192 d.	$[\alpha]_D^{22} = -128°$ (*c* 1.01, $CHCl_3$)	(265)
Picropodophyllin chloroacetate	154–155, 178–191	$[\alpha]_D^{21} = +47°$ (*c* 1.01, $CHCl_3$)	(265)
Acetylpodophyllotoxin-ω-pyridinium chloride	158–159	$[\alpha]_D^{21} = -97°$ (*c* 0.54, CH_3OH)	(265)
Acetylpodophyllotoxin-ω-pyridinium iodide	156–157		(265)

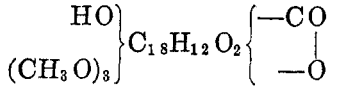
The early work also showed the presence of three methoxyl groups and a lactone in both podophyllotoxin and picropodophyllin (70, 248). In 1932, Borsche and Niemann in their laboratory and Späth, Wessely, and Nadler started working independently on the structure of podophyllotoxin. Their work led to the same formula, which was nearly correct.



Borsche and Niemann (27) confirmed the presence of three methoxyl groups in podophyllotoxin and picropodophyllin. They also reported two active hydrogens by Zerewitinov determination in both materials, but no ethylenic double bond, aldehyde group, or ketone group. Späth, Wessely, and Kornfeld (281) showed correctly, however, that there was only one active hydrogen present. The hydroxy acid formed by acidifying the solution of podophyllotoxin in alkali was called podophyllic acid. On treatment with boiling dilute acid it gave picropodophyllin.

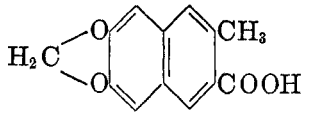
Neither podophyllotoxin nor picropodophyllin gave a color with ferric chloride, nor did they react with diazomethane; hence the active hydrogen was not phenolic (27). This hydroxyl group could be acetylated, however; podophyllotoxin with acetic anhydride alone gave a podophyllotoxin acetate but with acetic anhydride and sodium acetate gave a different acetate (116, 281), which was also formed by the acetylation of picropodophyllin and therefore was a picropodophyllin acetate.

The above information gave a partial formula as follows:



The picropodophyllin acetate, when treated with concentrated sulfuric acid in acetic anhydride, lost acetic acid and gave an unsaturated compound, $C_{22}H_{20}O_7$, apopicropodophyllin. (For the mechanism of this reaction see Schrecker and Hartwell (269).) This substance could be reduced to $C_{22}H_{22}O_7$, desoxypicropodophyllin.

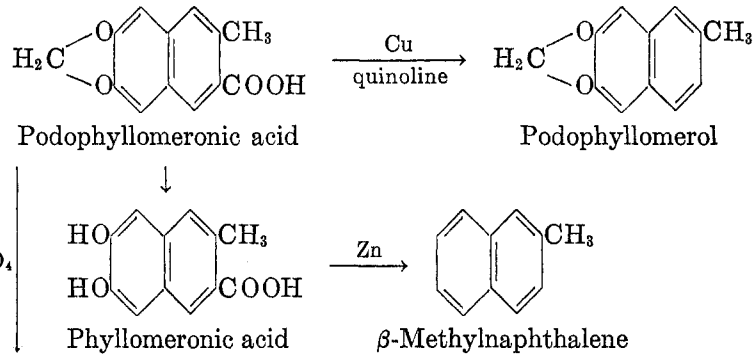
Podophyllotoxin when degraded with hydriodic acid in acetic acid gave podophyllomeronic acid, $C_{13}H_{10}O_4$ (27):



Podophyllomeronic acid

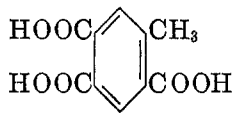
The structure of this compound was deduced from the following observations (28): (*1*) treatment with copper in quinoline removed the carboxyl group, giving

podophyllomerol; (2) heating with potassium hydroxide removed the methylenedioxy group, giving the dihydroxymethylnaphthalene acid (phyllomeronic acid), which could then be methylated; (3) phyllomeronic acid with zinc dust gave β-methylnaphthalene; (4) oxidation of podophyllomeronic acid with potassium permanganate gave toluene-2,4,5-tricarboxylic acid.



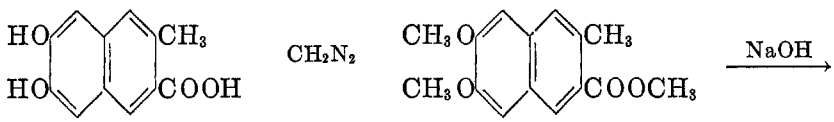
Podophyllomeronic acid — Podophyllomerol

Phyllomeronic acid — β-Methylnaphthalene

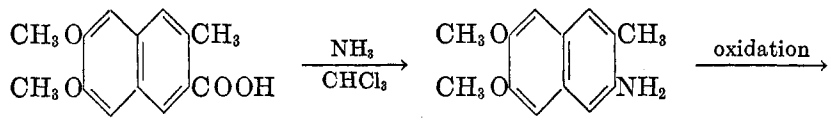


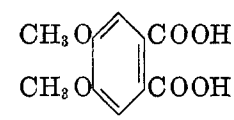
Toluene-2,4,5-tricarboxylic acid

Further evidence for the structure of podophyllomeronic acid was given by Späth (282), as follows: Phyllomeronic acid was methylated and the ester hydrolyzed; this dimethyl ether was treated with ammonia in chloroform to replace the carboxyl group with an amino group; this product was then oxidized to *m*-hemipinic acid.



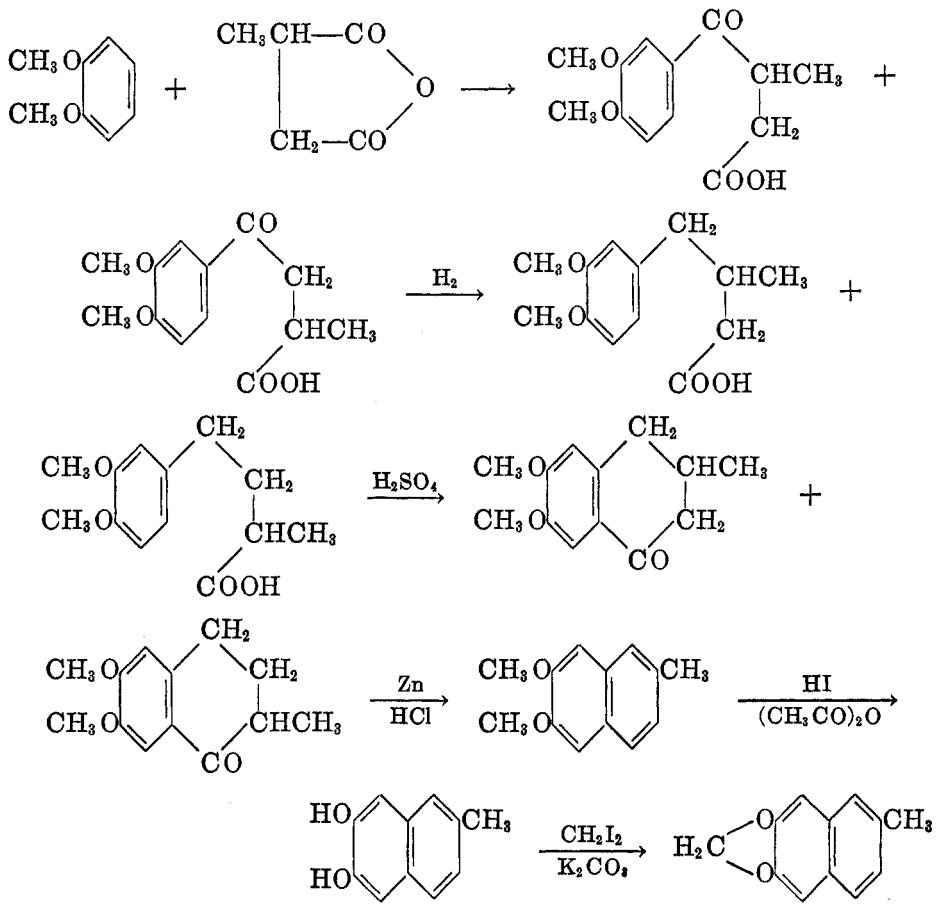
Phyllomeronic acid





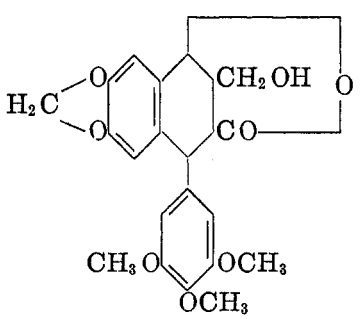
m-Hemipinic acid

Final proof of the structure of podophyllomeronic acid was provided when Robertson and Waters (257) synthesized podophyllomerol by the following reactions:

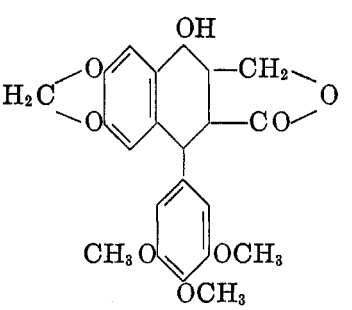


Podophyllomerol

By oxidation of picropodophyllin with potassium permanganate at 100°C., gallic acid trimethyl ether was formed (28). This evidence plus the structure of podophyllomeronic acid led Borsche and Niemann (28, 29) to postulate the following structures for podophyllotoxin and picropodophyllin:

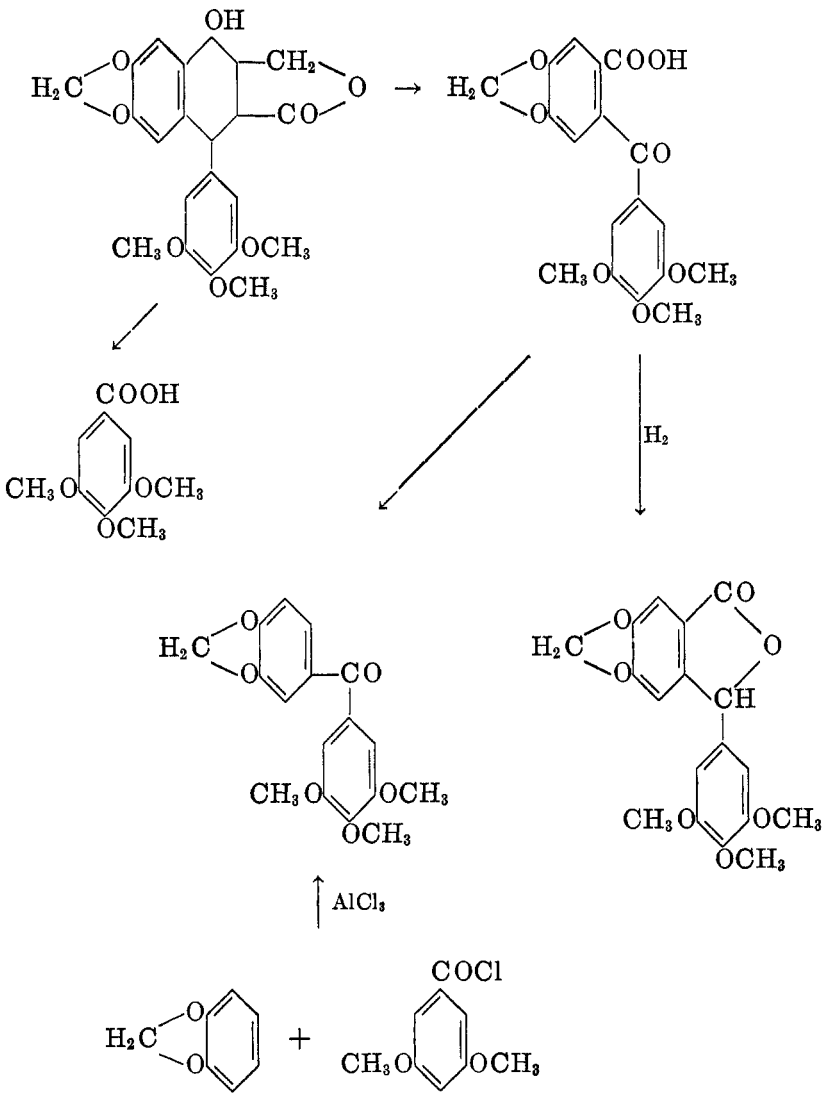


Podophyllotoxin



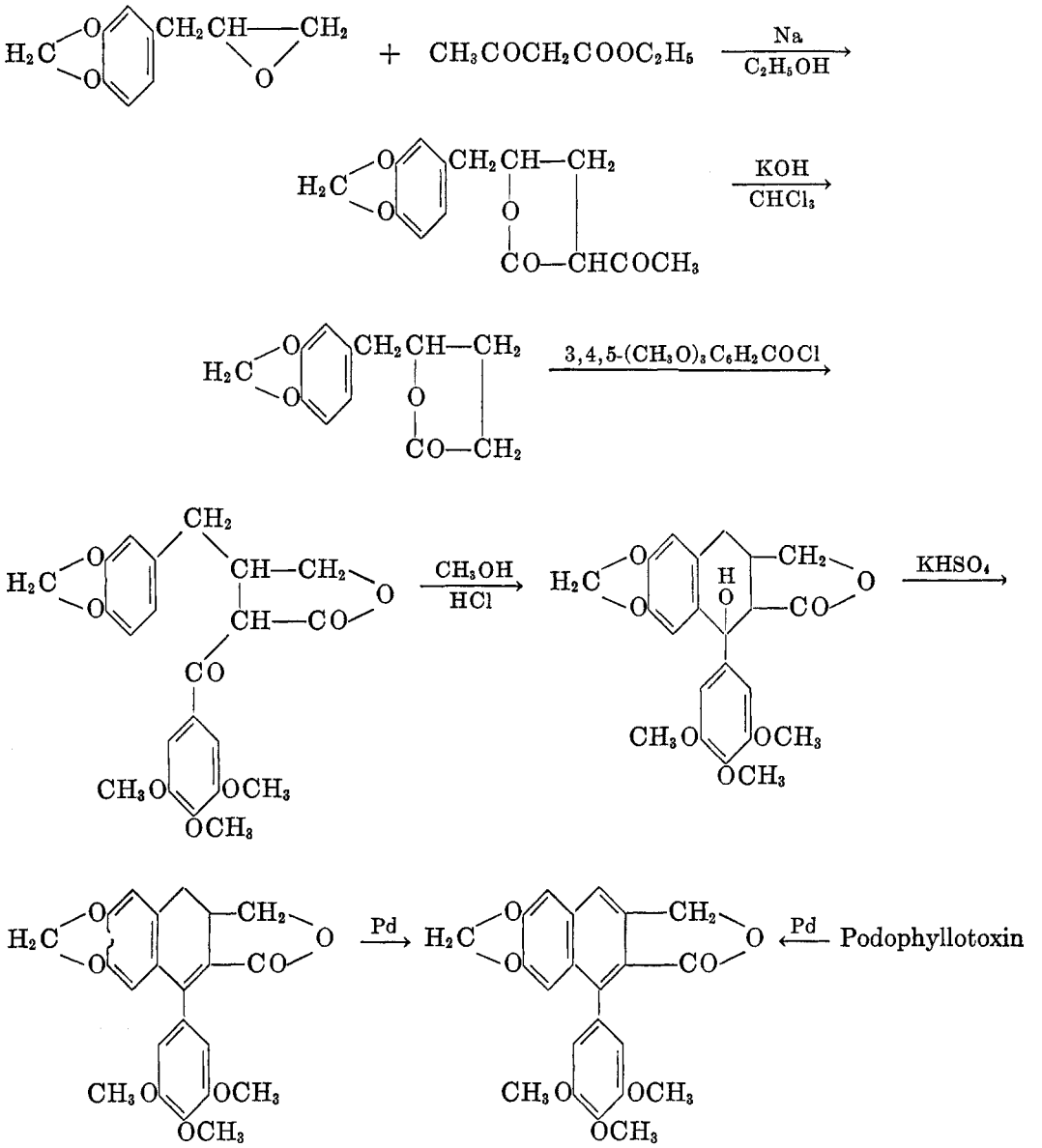
Picropodophyllin

The above formulas were arrived at by Späth, Wessely, and Nadler (282) by oxidation of podophyllotoxin to gallic acid trimethyl ether and by oxidation of podophyllotoxin or picropodophyllin to an acid which on decarboxylation gave 3,4,5-trimethoxy-3′,4′-methylenedioxybenzophenone, which they were able to synthesize. The reactions are given below:



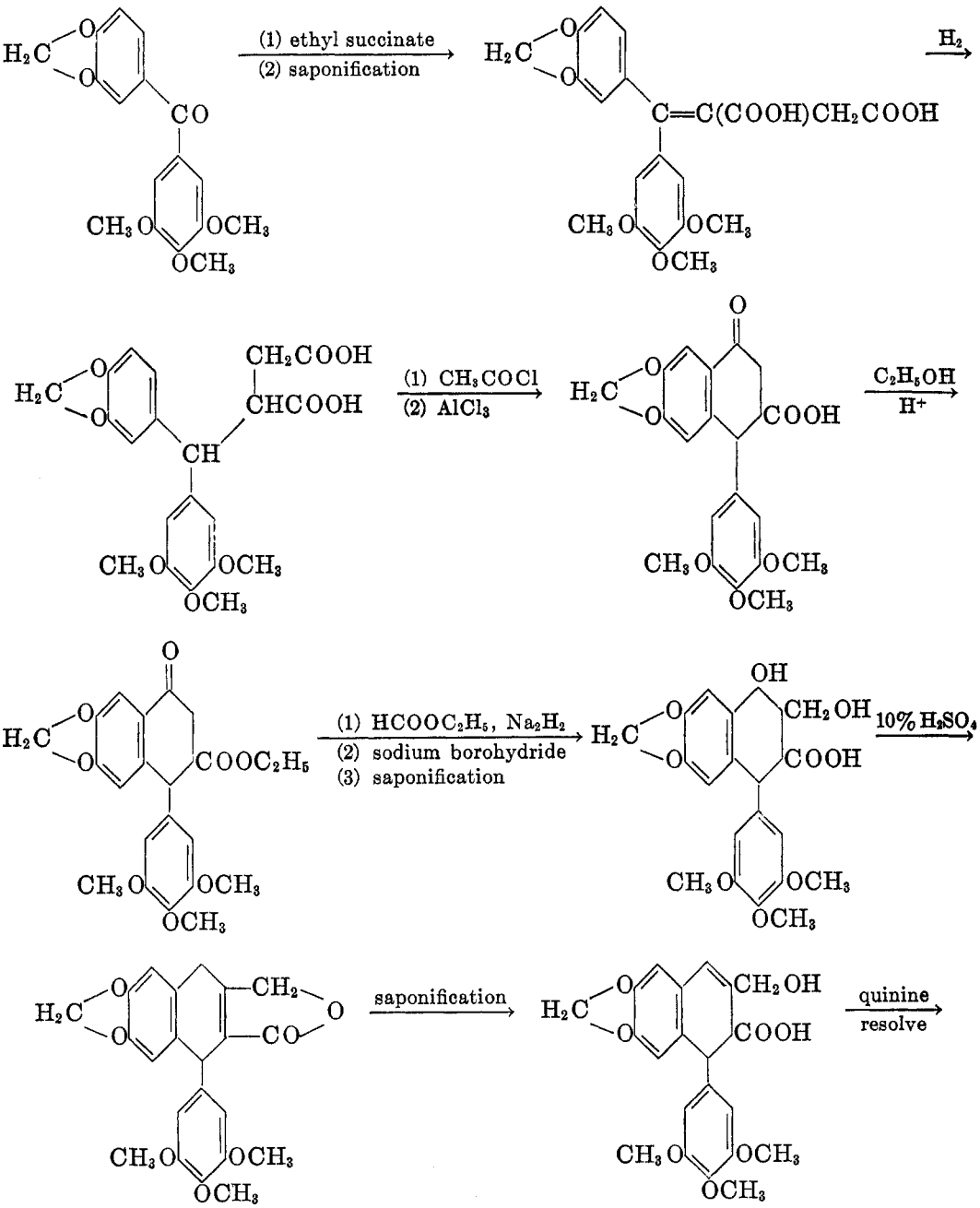
Haworth and Richardson (127, 138) synthesized dehydroanhydropicropodophyllin and found it identical with the substance produced from podophyllotoxin

by treatment with palladium black (281). The reactions for the synthesis are given below (see Schrecker and Hartwell's interpretation of the synthesis (265a)):



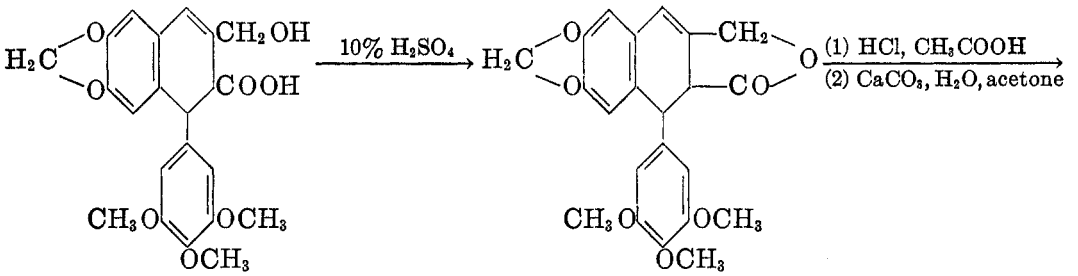
Finally, Gensler, Samour, and Wang (94a, 94b) carried out the total synthesis of optically active picropodophyllin; their product was indistinguishable from

the substance obtained from naturally occurring podophyllotoxin. The synthesis is given below:

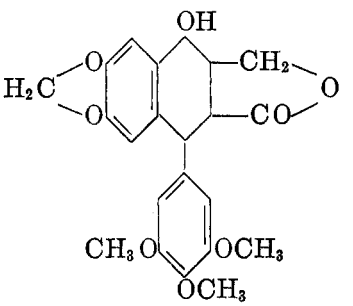


d,*l*-β-Apopicropodophyllin

d,*l*-α-Apopodophyllic acid

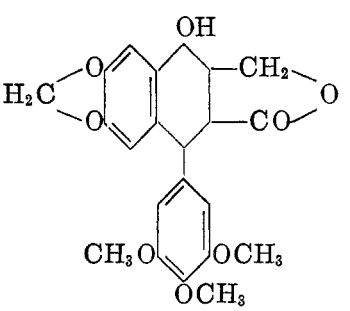


α-Apopodophyllic acid



Picropodophyllin

Recently Hartwell and Schrecker (116) have reëxamined the accepted structures of podophyllotoxin and picropodophyllin and have shown that the formulas of Borsche and Neimann (28, 29) and of Späth (281) were not correct. They have shown that both podophyllotoxin and picropodophyllin have the basic formula



and that the two materials differ only by being steric isomers. Podophyllotoxin has a *trans* configuration about carbon atoms 2 and 3, while picropodophyllin is *cis*.[3] The change from podophyllotoxin to picropodophyllin under the in-

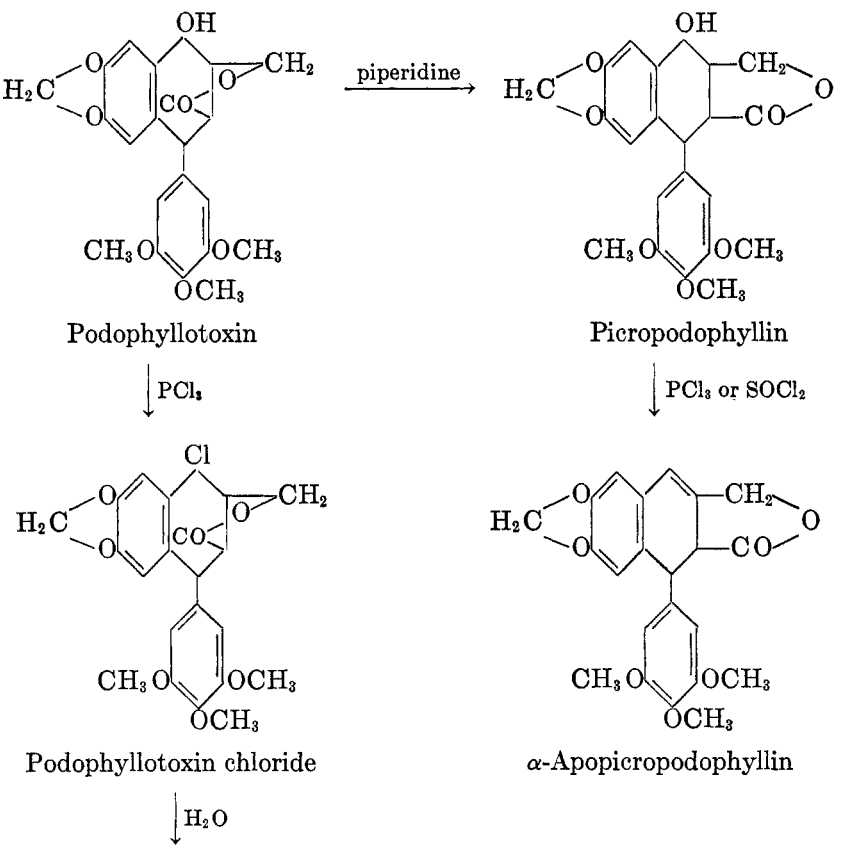
[3] Structures showing space configurations will be consistent within the discussion of any one lignan but will not necessarily agree with the spatial structures shown in other sections. The spatial interrelations of the lignans are discussed in the section on stereochemistry.

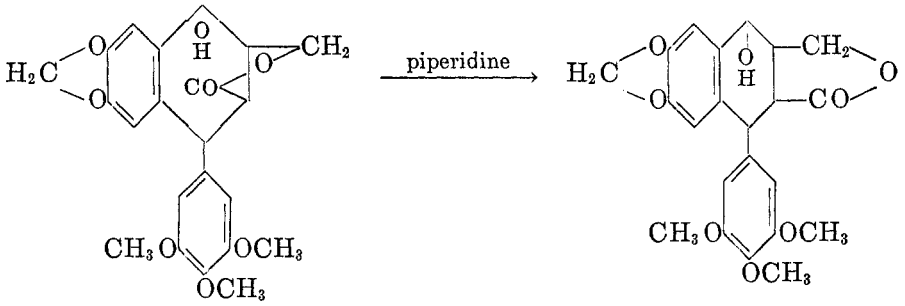
fluence of alkaline reagents occurs then by epimerization around carbon atom 3, and not by re-forming a new lactone ring, as had been previously supposed.

This type of epimerization is known to occur also in conidendrin (152, 169) and in the peltatins (113), where there is no possibility for formation of a new lactone ring.

Hartwell and Schrecker (116) also submitted new evidence that the position of the free hydroxyl group in podophyllotoxin and picropodophyllin had been correctly placed at carbon atom 1.

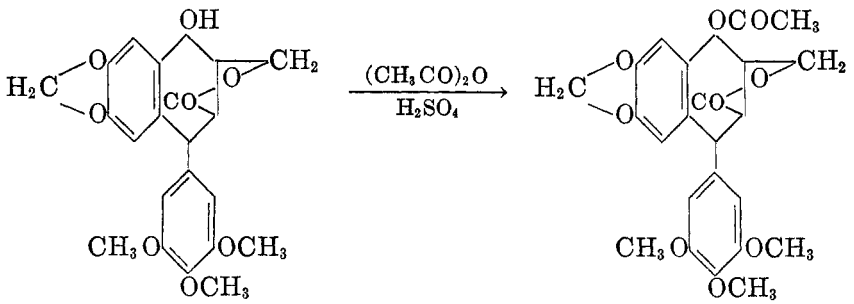
In addition, Hartwell and Schrecker (116) have prepared further diastereoisomers of podophyllotoxin and picropodophyllin where the position of the hydroxyl group on carbon atom 1 has been reversed. These new compounds have been given the prefix epi-. Epipodophyllotoxin is formed through the intermediate halide followed by hydrolysis during which a Walden inversion occurs. Epipodophyllotoxin can then be isomerized to epipicropodophyllin with piperidine. Epipicropodophyllin cannot be made *via* the halide route, since the halogenating reagents dehydrate the picropodophyllin to α-apopicropodophyllin. These reactions are summarized below:



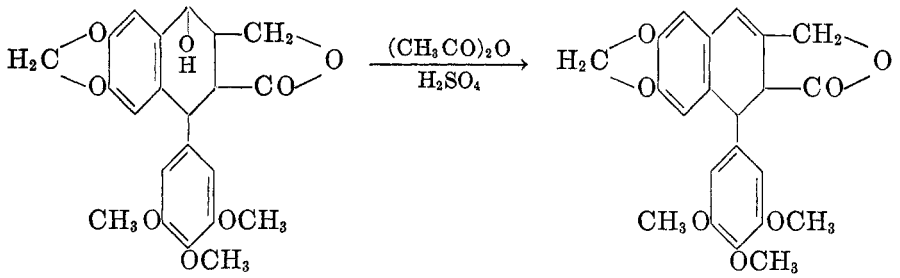


Epipodophyllotoxin — Epipicropodophyllin

Chatterjee and Chakravarti (50, 51) have suggested that the conversion of podophyllotoxin to picropodophyllin involves a change in configuration not only around carbon atom 3 but also carbon atom 1. They base this on the fact (27) that podophyllotoxin with acetic anhydride and sulfuric acid gives podophyllotoxin acetate, while picropodophyllin with the same reagents loses water and forms α-apopicropodophyllin:



Podophyllotoxin — Podophyllotoxin acetate



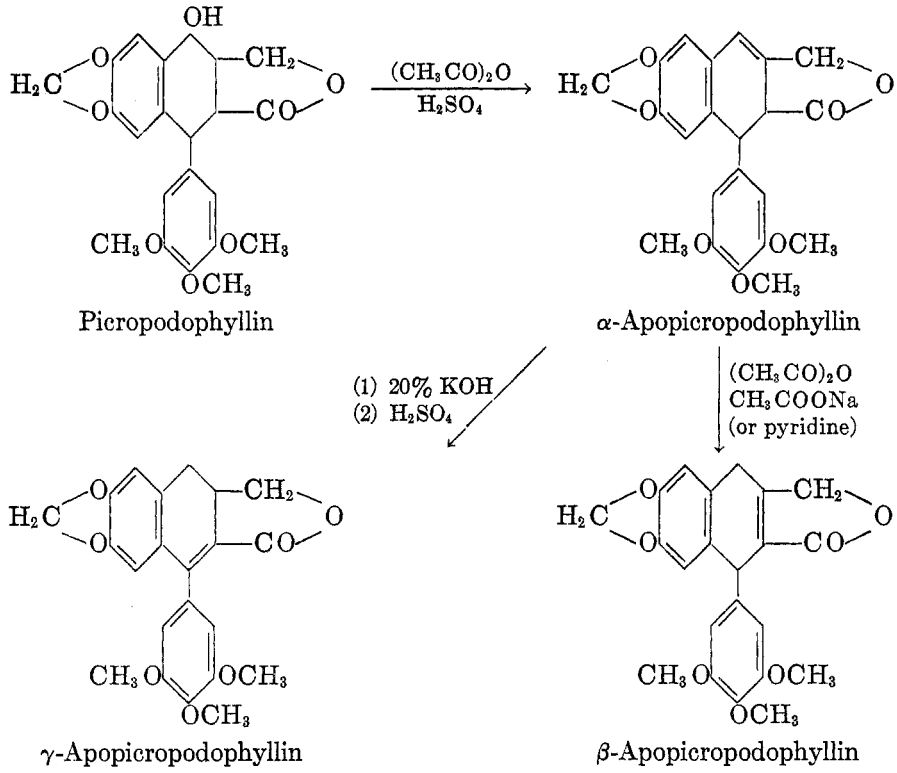
Picropodophyllin (according to Chatterjee) — α-Apopicropodophyllin

Chatterjee's double inversion, however, does not seem likely, since podophyllotoxin acetate and benzoate are easily isomerized to picropodophyllin acetate and benzoate, respectively (116), and one would expect such groups to block inversion. Furthermore, epipodophyllotoxin ethyl ether easily isomerizes to

epipicropodophyllin ethyl ether (116). Finally, Schrecker and Hartwell (267) have determined the relative configuration between all asymmetric carbon atoms in podophyllotoxin and have shown that the change of podophyllotoxin to picropodophyllin occurs through inversion around carbon atom 3 (120).

Recently (252) a different set of formulas for podophyllotoxin and picropodophyllin has been advanced, but these formulas do not correspond to most of the known chemical reactions for these materials and are almost certainly incorrect (269a). The authors apparently had inaccurate experimental data. Recently, Bartek and Santavy (16) have confirmed Hartwell's data on podophyllotoxin.

Schrecker and Hartwell (266) have also investigated the α-apopicropodophyllin of Borsche and Niemann (27) and the β-apopicropodophyllin of Robertson and Waters (257). In addition, Schrecker and Hartwell have prepared a third, γ-apopicropodophyllin, and have established the structures of all three substances. The reactions for the preparation of the three apopicropodophyllins are given below:



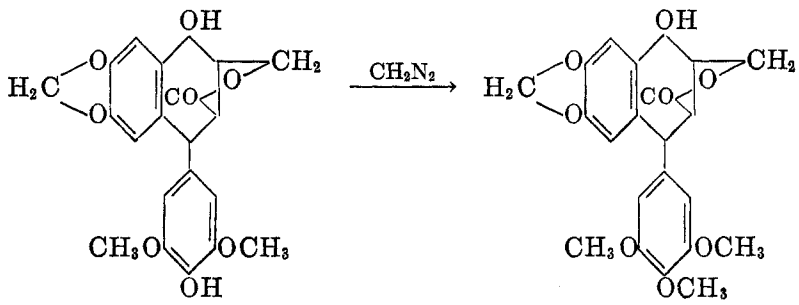
Considerable interest has been shown in podophyllotoxin as a possible therapeutic agent for the treatment of cancer. It has been shown to have a strong destructive action on Sarcoma 37 in mice (121, 205) and on five other types

of tumors (102). The toxicity of podophyllotoxin, however, has limited its use in clinical testing.

b. Demethylpodophyllotoxin

Demethylpodophyllotoxin has been found only from one source, the resin from *Podophyllum emodi* Wall. (233). The resin was extracted with alcohol, treated with benzene, and the solution chromatographed on activated alumina. Along with podophyllotoxin and picropodophyllin glucoside (discussed below), demethylpodophyllotoxin was isolated in 1.7 per cent yield based on the total resin (232).

The structure of demethylpodophyllotoxin was readily established by elemental analysis, by methoxyl determination (233), and by methylation with diazomethane to podophyllotoxin:



Demethylpodophyllotoxin Podophyllotoxin

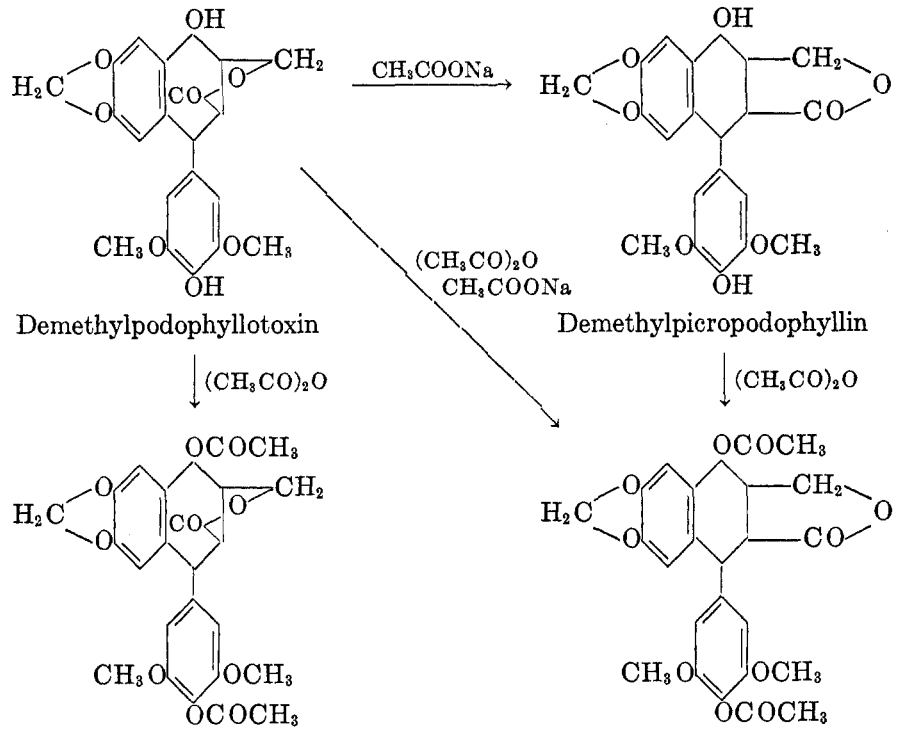
Like podophyllotoxin, demethylpodophyllotoxin is isomerized with alkaline reagents by inversion of the carbon atom carrying the carboxyl group. This change gives rise to demethylpicropodophyllin and its derivatives (232). The

TABLE 20

Demethylpodophyllotoxin and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
Demethylpodophyllotoxin	250–251.6	$[\alpha]_D^{20} = -130°$ (*c* 0.75, $CHCl_3$)	(232)
Diacetyldemethylpodophyllotoxin	230–231.2	$[\alpha]_D^{20} = -133°$ (*c* 0.5, $CHCl_3$)	(232)
Demethylpicropodophyllin	229–232	$[\alpha]_D^{20} = +7.0°$ (*c* 0.75, $CHCl_3$)	(232)
Diacetyldemethylpicropodophyllin	207–208.8	$[\alpha]_D^{20} = +27.5°$ (*c* 0.84, $CHCl_3$)	(232)
4′-Ethyldemethylpicropodophyllin	203.2–206	$[\alpha]_D^{20} = -1.7°$ (*c* 0.84, $CHCl_3$)	(232)

following series, similar to that found with podophyllotoxin, illustrates the isomerization:



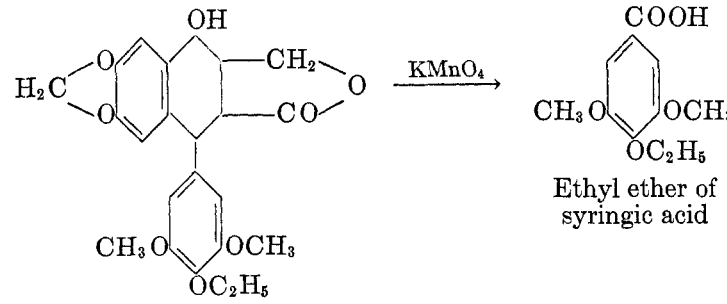
Demethylpodophyllotoxin

Demethylpicropodophyllin

Diacetyldemethylpodophyllotoxin

Diacetyldemethylpicropodophyllin

The position of the phenolic hydroxyl group was determined by permanganate oxidation of the ethyl ether of demethylpicropodophyllin to the ethyl ether of syringic acid, a compound already known:



Ethyl ether of demethylpicropodophyllin

Ethyl ether of syringic acid

Demethylpodophyllotoxin was tested in tumor-bearing mice and was found to produce hemorrhage and necrosis in Sarcoma 37 (401).

c. Demethylpodophyllotoxin β-glucoside

This glucoside was isolated by Stoll, von Wartburg, Angliker, and Renz (287b) from the dried rhizomes of *Podophyllum emodi* Wall. in 0.2–0.5 per cent yield.

The β-linkage was demonstrated by the easy hydrolysis of the glucoside with β-glucosidase. The aglucone was found to be identical with the 4′-demethylpodophyllotoxin already reported by Nadkarni, Hartwell, Maury, and Leiter (232).

TABLE 21

Demethylpodophyllotoxin β-glucoside and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
Demethylpodophyllotoxin β-glucoside	165–170	$[\alpha]_D^{20} = -75°$ (water) $[\alpha]_D^{20} = -81°$ (methanol) $[\alpha]_D^{20} = -123°$ (pyridine)	(287b)
Pentaacetyl demethylpodophyllotoxin β-glucoside	167-169	$[\alpha]_D^{20} = -77°$ (chloroform)	(287b)

TABLE 22

Picropodophyllin β-glucoside and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
Picropodophyllin β-glucoside	237–238.2	$[\alpha]_D^{20} = -11.5°$ (*c* 0.5, pyridine)	(232)
Tetraacetylpicropodophyllin β-glucoside	269–270.2	$[\alpha]_D^{20} = -5.2°$ (*c* 0.5, $CHCl_3$)	(232)

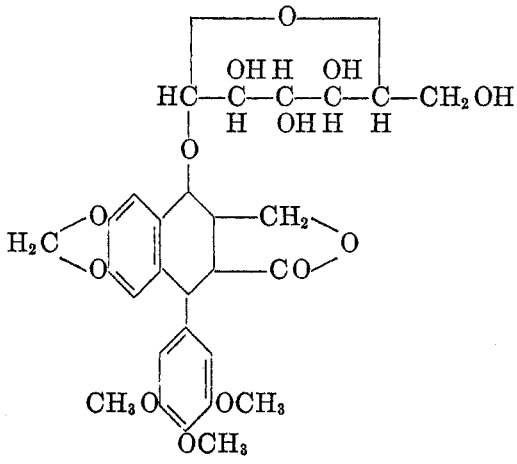
d. Picropodophyllin β-glucoside

During the chromatography of the resin from *P. emodi* Wall., Hartwell (233) found, besides podophyllotoxin and demethylpodophyllotoxin (see Section III,E,1,b), 1.8 per cent of the resin to be a glucoside of picropodophyllin. No other source for this lignan has been reported, and it is believed that this is the first instance of picropodophyllin or a derivative of it being found in nature.[4]

The glucoside, which was readily hydrolyzed by acid or emulsin, gave picropodophyllin, a substance already well known (see Section III,E,1,a), and D-glucose in mole-for-mole proportions. Failure of the glucoside to undergo hydrolysis with maltase showed the sugar linkage to have the β-configuration. These facts, coupled with the non-reducing nature of the original glucoside, indicate that it was a pyranoside. The point of attachment of the glucose seems clear, since picropodophyllin has only one free hydroxyl group. The structure

[4] Picropodophyllin glucoside may be an artifact, although picropodophyllin acetate has been found by King (187) in *Hernandia sonora*.

of picropodophyllin glucoside is therefore as follows:



Picropodophyllin glucoside

Picropodophyllin glucoside was found to have no effect on Sarcoma 37 in mice (232); this result was to be expected, since picropodophyllin itself is inactive.

e. Podophyllotoxin β-glucoside

Recently Stoll, von Wartburg, Angliker, and Renz (287a) reported the isolation of podophyllotoxin β-glucoside by methanolic extraction of *Podophyllum emodi* Wall. and *Podophyllum peltatum* Linn. after separating the resin fraction and the tannins. The yield from commercial supplies was approximately 0.5–1 per cent.

The structure of the compound was readily proved by hydrolysis with emulsin (showing a β-glucoside linkage) and characterization of the podophyllotoxin and glucose. Podophyllotoxin β-glucoside could also be rapidly and quantitatively converted to picropodophyllin β-glucoside, which had already been

TABLE 23

Podophyllotoxin β-glucoside and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
Podophyllotoxin β-glucoside	149–152	$[\alpha]_D^{20} = -65°$ (c 0.5, water)	(287)
		$[\alpha]_D^{20} = -75°$ (c 0.6, methanol)	(287)
		$[\alpha]_D^{20} = -117°$ (c 0.67, pyridine)	(287)
Picropodophyllin β-glucoside	235–236	$[\alpha]_D^{20} = -10.5°$ (c 0.65, pyridine)	(287)
Tetraacetylpodophyllotoxin β-glucoside	252–254 134–135	$[\alpha]_D^{20} = -90.8°$ (c 0.63, $CHCl_3$)	(287)

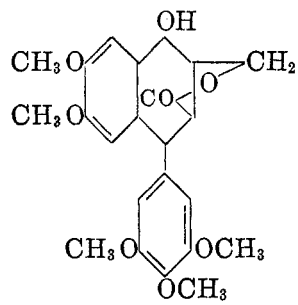
isolated by Nadkarni, Maury, and Hartwell (233) from *Podophyllum emodi* Wall.

Podophyllotoxin β-glucoside was tested against Sarcoma 37 in mice and found to be effective in doses about 100 times the minimum effective dose of podophyllotoxin itself (112).

f. Sikkimotoxin

Recently, Chatterjee and Mukerjee (53) discovered a new species of *Podophyllum* in India and named it *Podophyllum sikkimensis*. The resin from *P. sikkimensis* was investigated by Chatterjee (47, 52), who isolated from it, by solvent extraction and precipitation, a new compound which he named sikkimotoxin.

Sikkimotoxin very probably has the structure suggested by Chatterjee (49) as shown:



Sikkimotoxin

Elemental analysis of sikkimotoxin showed an empirical formula of $C_{23}H_{26}O_8$. Methoxyl determination showed five methoxyl groups to be present. Sikkimotoxin did not react with diazomethane but gave a monoacetyl derivative, thus showing the presence of one aliphatic hydroxyl group. Sikkimotoxin reacted with acetyl chloride to produce monochlorosikkimotoxin, a result which indicated that the hydroxyl group might be secondary. Saponification showed the presence of a lactone ring.

TABLE 24

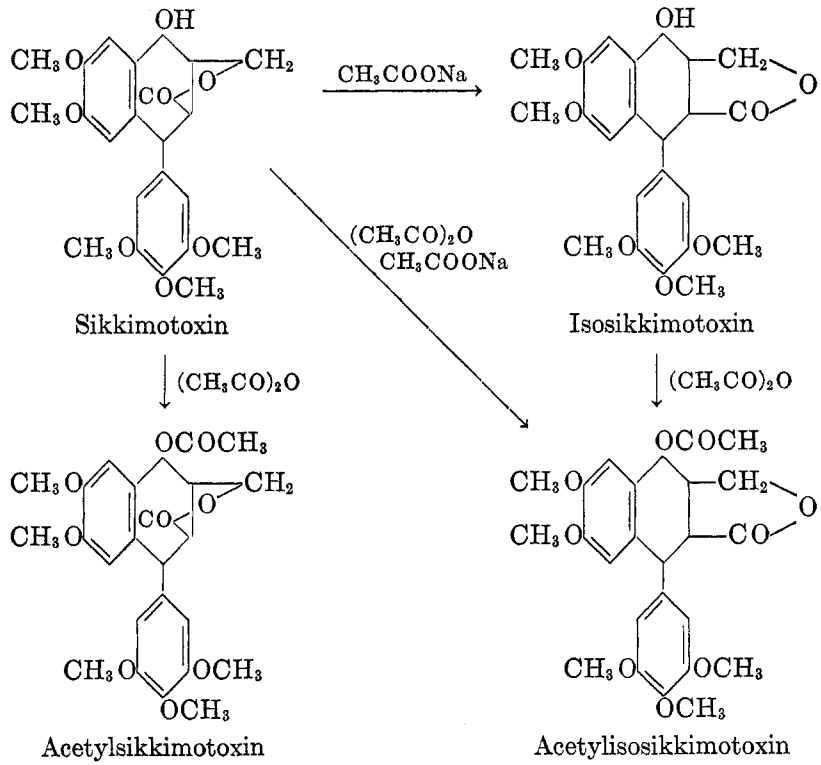
Sikkimotoxin and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
Sikkimotoxin	120	$[\alpha]_D^{25} = -91.9°$	(49)
Isosikkimotoxin	220–222	$[\alpha]_D^{25} = -1°$ (*c* 0.05, acetone)	(49)
Monoacetylsikkimotoxin	180–182		(49)
Monoacetylisosikkimotoxin	207–208		(49)
Monochlorosikkimotoxin	196–197		(49)

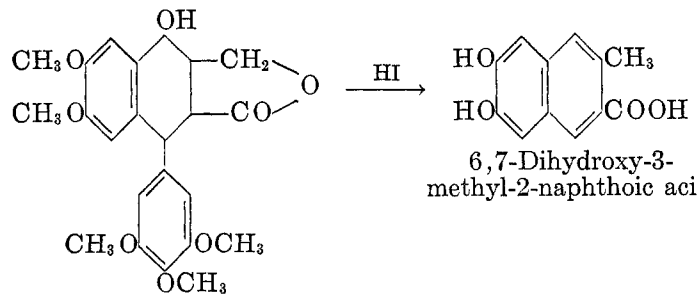
The above evidence indicated the following partial formula for sikkimotoxin:

$$C_{16}H_8\begin{cases}5\ OCH_3\\ 1\ OH\ \text{(secondary aliphatic)}\\ -COO-\end{cases}$$

Sikkimotoxin showed the same action toward alkaline reagents as did podophyllotoxin and the peltatins: *viz.*, isomerization to a new form, called isosikkimotoxin. This isomerization is illustrated in the following equations:

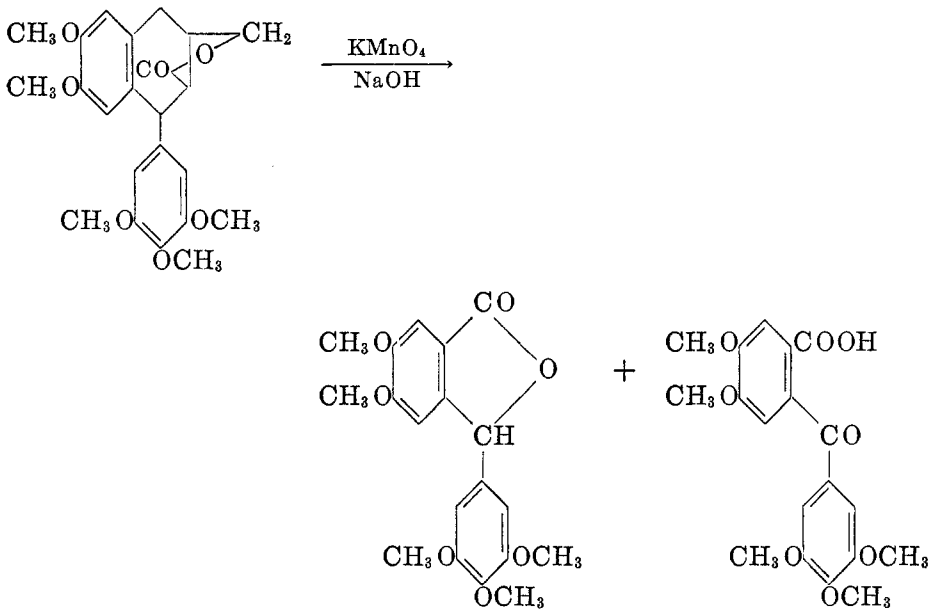


Sikkimotoxin furnished 2-methylnaphthalene on distillation with zinc dust. Isosikkimotoxin with hydriodic acid gave 6,7-dihydroxy-3-methyl-2-naphthoic acid.

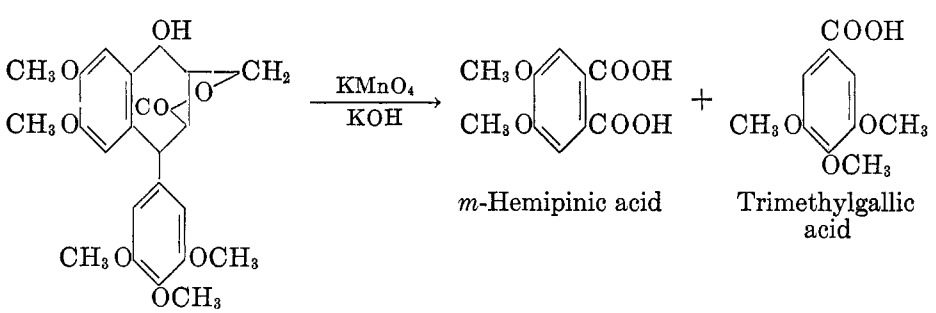


These reactions showed the basic naphthalene nucleus and the position of the lactone ring with the primary hydroxyl group in all probability on carbon atom 2.

Oxidation of sikkimotoxin with permanganate and alkali gave 3-(3,4,5-trimethoxyphenyl)-5,6-dimethoxyphthalide and 4,5-dimethoxy-2-(3,4,5-trimethoxybenzoyl)benzoic acid.



More drastic oxidation of sikkimotoxin by alkaline potassium permanganate gave *m*-hemipinic acid and trimethylgallic acid.



Sikkimotoxin

m-Hemipinic acid

Trimethylgallic acid

The above oxidations clearly show the positions of the methoxyl groups in sikkimotoxin, the attachment of the suspended benzene ring, and the alicyclic ring. Finally, Chatterjee has removed the methylene group from picropodophyllin and methylated it, giving isosikkimotoxin and thus confirming the structure of the former (48).

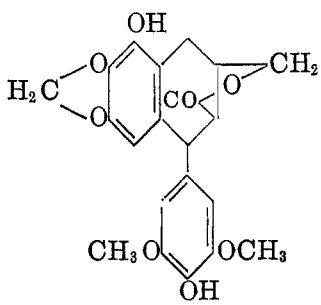
The resin from *P. sikkimensis* has been tested and found to be strongly active against Sarcoma 37 in mice. This activity may be due to the sikkimotoxin, although this has not been established (112).

2. 2-Hydroxymethyl-3-carboxylic acid lactones

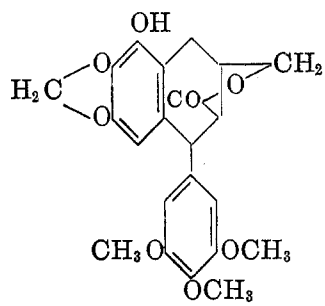
a. Peltatins

During the chromatography of the resin from *Podophyllum peltatum* L. (American May apple), Hartwell and Detty (113) discovered not only podophyllotoxin, as expected, but two new phenols which they named α- and β-peltatin. No other occurrence in plants of these materials has been reported.

The structures for these lignans have been definitely established through considerable work by Hartwell and coworkers (113, 118, 268):



α-Peltatin



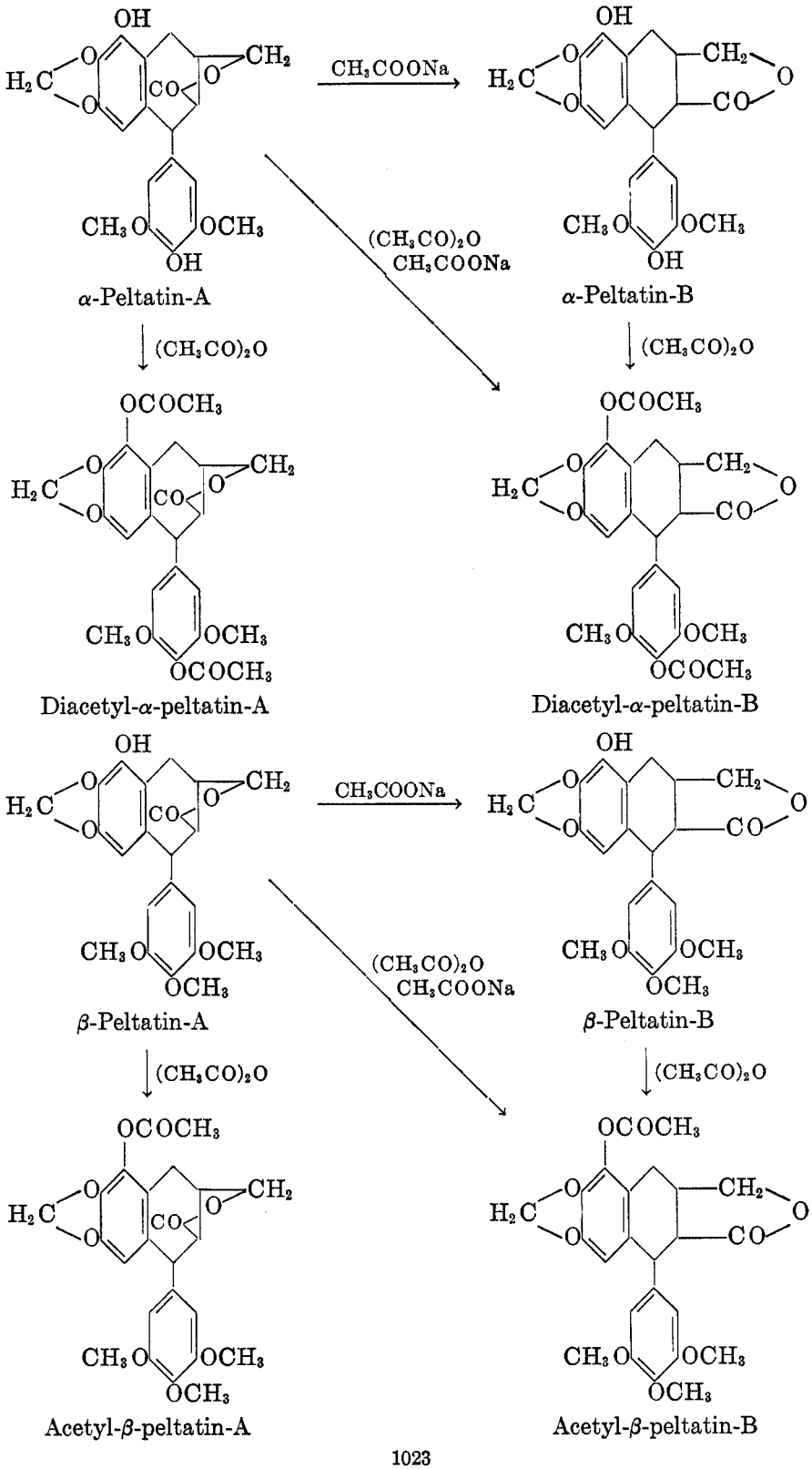
β-Peltatin

Thus, the two peltatins stand in the same relation to each other as do podophyllotoxin and demethylpodophyllotoxin (see above).

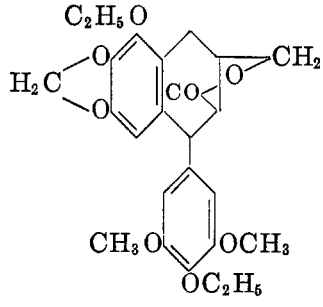
Elemental analyses of the peltatins were not entirely satisfactory (113); however, rechecks (118) gave $C_{21}H_{20}O_8$ for α-peltatin and $C_{22}H_{22}O_8$ for β-peltatin. Tests by Hartwell (113) for substituent groups are summarized below:

Test	α-Peltatin	β-Peltatin
Gaebel test for methylenedioxy	Present	Present
Zeisel methoxyl	Two present	Three present
Hydroxyl by acetylation and alkylation	Two present	One present
Phenolic hydroxyls by diazomethane	Two present	One present
Lactone ring by saponification and analysis	One present	One present

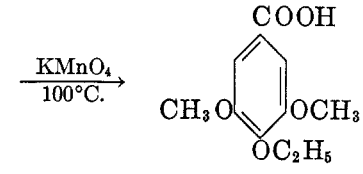
The peltatins exhibited the same isomerization with alkaline reagents as does podophyllotoxin and undoubtedly by the same mechanism, i.e., inversion of the configuration around the carbon atom bearing the carboxyl group. Hartwell (113, 118) has designated the naturally occurring form with A and the isomerized form with B after the name "peltatin." Given below are reactions (113) to show the isomerization:


OH
H_2C
O
O
CH_2
O
CO
CH_3O
OCH_3
OH
CH_3COONa
$(CH_3CO)_2O$
CH_3COONa
α-Peltatin-A
α-Peltatin-B
$(CH_3CO)_2O$
$(CH_3CO)_2O$
$OCOCH_3$
Diacetyl-α-peltatin-A
Diacetyl-α-peltatin-B
β-Peltatin-A
β-Peltatin-B
Acetyl-β-peltatin-A
Acetyl-β-peltatin-B

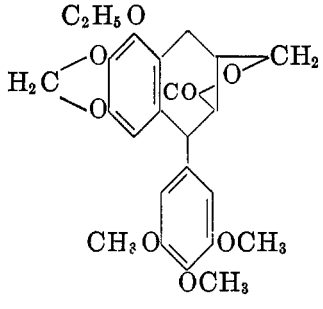
By the use of considerable logical inferences, which will not be repeated here, and by studies of the infrared spectrum Hartwell (113) arrived at the podophyllotoxin basic structure for the basic structure of peltatins. The positions of the groups in the isolated benzene ring were determined by permanganate oxidation of the ethylated peltatins. This same reaction had been used for the same purpose in picropodophyllin (28). α-Peltatin diethyl ether yielded the ethyl ether of syringic acid, while β-peltatin gave 3,4,5-trimethoxybenzoic acid (as did picropodophyllin).



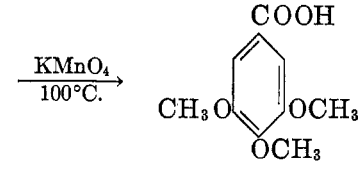
α-Peltatin diethyl ether



Syringic acid ethyl ether



β-Peltatin ethyl ether

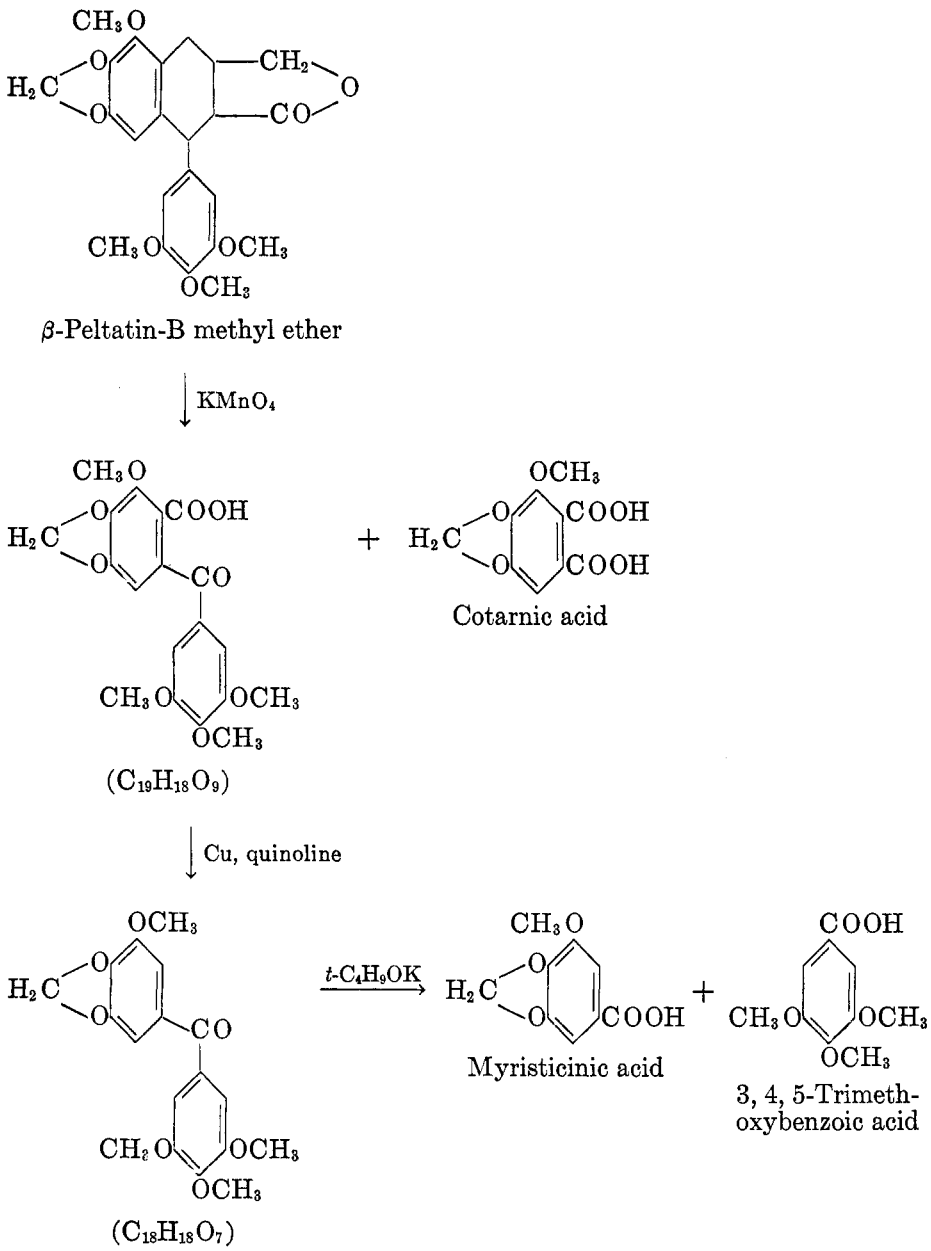


3, 4, 5-Trimethoxybenzoic acid

The interrelation of the α- and β-peltatins has been thoroughly demonstrated by Hartwell, Schrecker, and Greenberg (118) by methylation of both materials to the same product. This, together with the above oxidation studies, shows α-peltatin to be 4′-demethyl-β-peltatin.

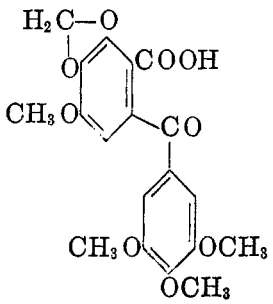
The position of the lactone ring was inferred by infrared studies which show no conjugation with a double-bond system. The substituents in the isolated benzene ring were established by the oxidation studies with permanganate. The position of the methylenedioxy and hydroxyl groups in the tetralin nucleus were established by a milder permanganate oxidation of β-peltatin-B methyl ether (268). The primary oxidation products were a substituted benzoylbenzoic acid, $C_{19}H_{18}O_9$, and cotarnic acid. The benzoylbenzoic acid on decarboxylation gave a benzophenone, $C_{18}H_{18}O_7$, which with potassium *tert*-butoxide gave

myristicinic acid and 3,4,5-trimethoxybenzoic acid:



The formation of cotarnic acid proved the structure of the benzoylbenzoic acid to be that shown rather than 2,3-methylenedioxy-4-methoxy-6-(3,4,5-

trimethoxybenzoyl)benzoic acid,



which on further oxidation would have given isocotarnic acid, although on decarboxylation it still would have given the above benzophenone.

The structure of the above substituted benzoylbenzoic acid definitely fixed the positions of the methylenedioxy and methoxyl groups.

TABLE 25

Peltatins and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
α-Peltatin	230.5–232.5	$[\alpha]_D^{20} = -120°$ (c 1.0, $CHCl_3$)	(113)
β-Peltatin	231.1–238	$[\alpha]_D^{20} = -119°$ (c 1.0, $CHCl_3$)	(113)
Dimethyl-α-peltatin-A	162.6–163.6	$[\alpha]_D^{21} = -120.6°$ (c 1.02, $CHCl_3$)	(118)
Methyl-β-peltatin-A	162.6–163.6	$[\alpha]_D^{20} = -120°$ (c 0.98, $CHCl_3$)	(118)
Dimethyl-α-peltatin-B	183.8–184.6	$[\alpha]_D^{21} = +11°$ (c 1.02, $CHCl_3$)	(118)
Methyl-β-peltatin-B	183.8–184.6	$[\alpha]_D^{21} = +10.9°$ (c 1.07, $CHCl_3$)	(118)
α-Peltatic acid	275–276 (hydrate)	$[\alpha]_D^{20} = -95°$ (c 1, 10% $NaHCO_3$)	(118)
β-Peltatic acid	202	$[\alpha]_D^{19} = -123.5°$ (c 1, 10% $NaHCO_3$)	(118)
α-Peltatin-B	275–276.5	$[\alpha]_D^{20} = +39°$ (c 1, acetone)	(113)
Diethyl-α-peltatin-B	138.8–141.1		(113)
Diacetyl-α-peltatin-A	229.1–231.4	$[\alpha]_D^{22} = -115°$ (c 1.007, $CHCl_3$)	(113)
Diacetyl-α-peltatin-B	260.1–262.9	$[\alpha]_D^{22} = -12.1°$ (c 3.05, $CHCl_3$)	(113)
β-Peltatin-A hydrazide	211–212	$[\alpha]_D^{21} = -141°$ (c 1.031, pyridine)	(113)
β-Peltatin-B	212.3–213.3	$[\alpha]_D^{21} = +40°$ (c 1.002, acetone)	(113)
Ethyl-β-peltatin-B	197.9–199.3		(113)
Acetyl-β-peltatin-A	229.4–231.6	$[\alpha]_D^{21} = -122°$ (c 0.999, $CHCl_3$)	(113)
Acetyl-β-peltatin-B	220–222	$[\alpha]_D^{21} = -6.3°$ (c 3.01, $CHCl_3$)	(113)
2-Methoxy-3,4-methylenedioxy-6-(3,4,5-trimethoxybenzoyl)benzoic acid	183–185		(268)
Cotarnic acid anhydride	160–161		(268)
Cotarnic acid methylimide	203.5–205		(268)
3,3′,4′,5′-Tetramethoxy-4,5-methylenedioxybenzophenone	164–165		(268)
3,3′,4′,5′-Tetramethoxy-4,5-methylenedioxybenzophenone oxime (2 isomers)	168–169 135–138		(268)
Myristicinic acid	209.5–212		(268)
Methyldehydro-β-peltatin	271–272		(268)

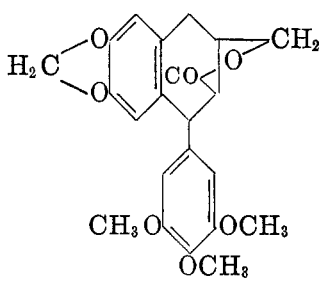
The lactone ring, while on carbon atoms 2 and 3, could be with the hydroxymethyl group on carbon 2 and the carboxyl on carbon 3 or *vice versa*. The probability is very great, however, that the lactone ring is as shown (carboxyl group on 3), since the peltatins are easily isomerized by such mild alkalies as sodium acetate (113), just as is desoxypodophyllotoxin (119) or podophyllotoxin (116). Conidendrin, a lignan having the lactone in the reverse position (carboxyl group on carbon 2), however, isomerizes only under more drastic conditions; for example, with sodium ethoxide (152).

Recently (252) other structures have been proposed for the α- and β-peltatins. However, these structures appear to be based on inaccurate analytical work and are almost certainly not correct (269a). Bartek and Santavy (16) have substantiated Hartwell's data for the peltatins.

Both peltatins are active against tumors in mice (102, 205), but the B series are completely inactive (113).

b. Desoxypodophyllotoxin

The compound



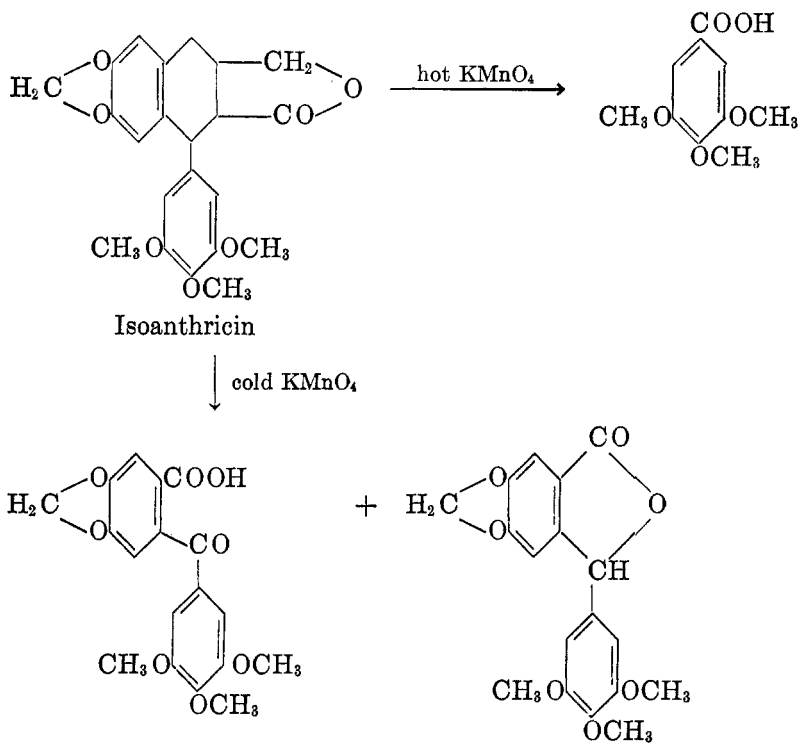
has been found independently by four different sets of workers in four different sources and has been designated by three names. Hartwell (117) recently suggested that the substance be designated desoxypodophyllotoxin, a name which would associate it with the better-known parent compound.

Noguchi and Kawanami (239) in 1940 extracted the roots of *Anthriscus sylvestris* with ether and obtained a crystalline material melting at 168°C. which they termed anthricin. Anthricin had the empirical formula $C_{22}H_{22}O_7$; it contained three methoxyl groups and no hydroxyl, carboxyl, aldehyde, or ketone groups. It did form a hydrazide with hydrazine, and from this fact they concluded that a lactone ring was present. The Liebermann reaction indicated the presence of a hydroaromatic nucleus.

The residue from the crystallization of anthricin gave on saponification another material, melting at 170°C. and having the empirical formula $C_{22}H_{22}O_7 \cdot H_2O$. This substance was named isoanthricin. The hydrazide of anthricin on alkaline hydrolysis gave isoanthricin.

Isoanthricin with hot permanganate gave 3,4,5-trimethoxybenzoic acid, while cold permanganate yielded 2-(3,4,5-trimethoxybenzoyl)-4,5-methylene-

dioxybenzoic acid and 3-(3,4,5-trimethoxyphenyl)-5,6-methylenedioxyphthalide:



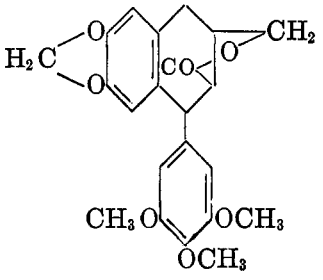
Both the latter two compounds had been obtained by Späth (283) by the permanganate oxidation of picropodophyllin. Dehydrogenation of isoanthricin with palladium gave dehydroanhydropicropodophyllin, which had been synthesized by Haworth and Richardson (138) in 1936. The above results confirmed the conclusion that isoanthricin is a 1,2,3,4-tetrahydro derivative of dehydroanhydropicropodophyllin.

In 1942, Hata (123) reported that while extracting the seeds of *Hernandia ovigera* Linn. (or *Hernandia peltata* Meissn.), he obtained a crystalline material melting at 167–168°C. This substance, which he named hernandion, had the empirical formula $C_{22}H_{22}O_7$ and with alkali, then acid, was changed to a new material of the same formula but melting at 169–170°C. which he called isohernandion. After the usual qualitative and quantitative tests were performed, Hata discovered the work of Noguchi and Kawanami reported above and sent them samples for mixed melting points. These established that hernandion is identical with anthricin and that isohernandion is the same as isoanthricin.

Finally, while screening the dried needles of many conifers for tumor-necrotizing activity, Hartwell (114) found the needles of *Juniperus silicicola* to be active. After successive extractions of the needles with different organic solvents, followed by chromatography on alumina, silicicolin was isolated in 0.11 per cent yield.

Elemental analysis and molecular weight determinations gave the empirical formula $C_{22}H_{22}O_7$. The Gaebel test showed the presence of the methylenedioxy group, and methoxyl analysis showed three such groups to be present. Slow solubility of the material in hot alkali with separation of a white gelatinous precipitate on acidification indicated the strong probability of a lactone ring. The infrared spectrum of silicicolin showed the general similarity to that of podophyllotoxin and confirmed the presence of the lactone ring and the absence of hydroxyl groups.

On the basis of the above evidence, Hartwell (114) suggested that silicicolin possesses the structure of desoxypodophyllotoxin:



Hartwell, Schrecker, and Johnson (119) then prepared desoxypodophyllotoxin (267) by the hydrogenolysis of podophyllotoxin chloride and found it identical with silicicolin. They also compared silicicolin, anthricin, and hernandion and

TABLE 26

Desoxypodophyllotoxin, desoxypicropodophyllin, and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Desoxypodophyllotoxin			
Anthricin	168	$[\alpha]_D^{26} = -142.5°$ (pyridine)	(239)
Hernandion	167–168	$[\alpha]_D^{31} = -112.4°$ ($CHCl_3$)	(123)
Silicicolin	168–169	$[\alpha]_D^{19} = -119°$ (*c* 0.40, $CHCl_3$)	(114)
		$[\alpha]_D^{19} = -196°$ (*c* 1.09, pyridine)	(119)
Desoxypicropodophyllin			
Isoanthricin	170	$[\alpha]_D^{20} = -127.87$ (pyridine)	(239)
Isohernandion	169–170	$[\alpha]_D^{30} = +36.6°$ ($CHCl_3$)	(123)
Silicicolon B	169–173	$[\alpha]_D^{19} = +30°$ (*c* 0.43, $CHCl_3$)	(119)
Cicutin	171		(221)
Desoxypicropodophyllin hydrazide	223		(239)
Methyl desoxypodophyllate (?)	173–174	$[\alpha]_D^{16} = -43.6°$	(123, 239)
Desoxypodophyllic acid	171–172	$[\alpha]_D^{20} = -165°$ (*c* 0.43, pyridine)	(119, 239)
2-(3,4,5-Trimethoxybenzoyl)-4,5-methylenedioxybenzoic acid	213.5		(239)
3-(3,4,5-Trimethoxyphenyl)-5,6-methylenedioxyphthalide	218		(239)
6,7-Methylenedioxy-1-(3,4,5-trimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid lactone	266		(239)
Dibromodesoxypodophyllotoxin	230–231		(123)

concluded that these three are the same (117). Similarly, silicicolin B (from silicicolin with sodium acetate), isoanthricin, and isohernandion are the same, and are all desoxypicropodophyllin.

Another probable occurrence of desoxypicropodophyllin was reported by Marion (221) in 1942. Extraction of the root of *Cicuta maculata* with petroleum ether and saponification of the extract with methanolic alkali yielded a crystalline material, m.p. 171°C., which he named cicutin. Cicutin had the empirical formula $C_{22}H_{22}O_7$ and contained three methoxyl groups. A potentiometric titration showed a lactone ring present. Cicutin in alkali gave a hydroxy acid which could be methylated to an ether-ester, which on saponification gave an acid with four methoxyl groups.

Marion did not further characterize cicutin; however, Hartwell (119) found the methylenedioxy group in cicutin by the Gaebel test and showed the infrared spectrum of cicutin to be practically identical with that for desoxypicropodophyllin. Recently, Hartwell (117) showed cicutin to be an impure desoxypicropodophyllin.

There is no evidence that desoxypicropodophyllin occurs as such in nature. Cicutin was obtained only under conditions which would have isomerized it to the picro form had it been in the podophyllotoxin form. Isoanthricin, isohernandion, and silicicolin B were all obtained by alkaline treatment of the parent compound.

Desoxypodophyllotoxin is at least one of the active principles of *Juniperus silicicola*, which produces destruction of Sarcoma 37 in mice (114, 119). It has also recently been found in the resin from *Podophyllum peltatum* L. (191a).

c. Peltatin β-glucosides

Stoll, von Wartburg, and Renz (287a, 287c) have isolated the β-glucosides of α- and β-peltatin from *Podophyllum peltatum* Linn. The β-linkages were demonstrated by hydrolysis of the glucosides with β-glucosidase and the aglucones were proved identical with the peltatins already reported (113). The glucose residue is attached in both cases to the hydroxyl group in the ring carrying the methylenedioxy group.

TABLE 27

Peltatin β-glucosides and derivatives

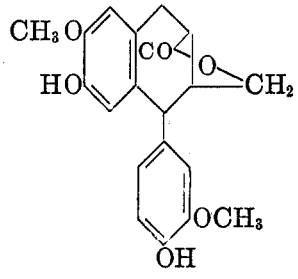
Compound	Melting Point	Optical Rotation	Reference
	°C.		
α-Peltatin-β-glucoside	168–171	$[\alpha]_D^{20} = -128.9°$ (c 0.5, methanol)	(287c)
Pentaacetyl α-peltatin-β-glucoside	222–223	$[\alpha]_D^{20} = -96.0°$ (c 0.5, chloroform)	(287c)
Methyl α-peltatin-β-glucoside	154–156	$[\alpha]_D^{20} = -122.4°$ (c 0.5, methanol)	(287c)
		$[\alpha]_D^{20} = -169.4°$ (c 0.5, pyridine)	
β-Peltatin-β-glucoside	156–159	$[\alpha]_D^{20} = -123°$ (c 0.5, methanol)	(287a)
		$[\alpha]_D^{20} = -169°$ (c 0.5, pyridine)	(287a)

3. 3-Hydroxymethyl-2-carboxylic acid lactone

a. Conidendrin

Conidendrin is one of the earliest discovered and one of the most thoroughly studied of the lignans. It occurs widely in nature and along with nordihydroguaiaretic acid represents one of the two lignans commercially available. Many derivatives of conidendrin have been made and some show promise for industrial or medical application.

Its structure has been definitely shown to be as follows (120):



Conidendrin

The old literature on conidendrin is not easy to follow because the compound has been known under the names of "sulfite waste liquor lactone," "tsugaresinol," and "tsugalactone." However, the name "conidendrin" proposed by Erdtman (78) in 1935 has now become standard.

The first isolation of conidendrin is attributed to Lindsey and Tollens (207), who extracted sulfite waste liquor (presumedly from cooking spruce) with ether. Removal of the ether left an oily residue from which crystals separated. These, however, were not further investigated. It was not until 1920 that Holmberg (166) isolated conidendrin from spruce sulfite waste liquor by extraction with ether or benzene. He demonstrated its lactone nature; hence the name "sulfite waste liquor lactone" quickly arose.

A year later Hintikka (160) repeated Holmberg's work, using liquor from birch and aspen woods, but could not find the lactone. Hintikka (161) later was able to get the lactone from spruce wood but not from spruce bark or from pine wood when cooked by the sulfite process. He found that the lactone could be detected in the liquor early in the cook and that the quantity reaches a maximum and then diminishes towards the end of the cook.

In 1932, Kawamura (181) extracted the Japanese hemlock *Tsuga sieboldii* with ether and isolated a crystalline lactone which he named "tsugaresinol." Two years later Emde and Schartner (72, 74) reported that "sulfite waste liquor lactone" and "tsugaresinol" were identical. Whether this discovery was made by these authors or by Slotta, who performed their analytical work, is the subject of a polemic (73, 276).

Up to this time it had been generally believed that conidendrin was formed during the pulping reaction; however, this was found to be in error when Emde

TABLE 28

Conidendrin and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Conidendrin	255–256	$[\alpha]_D^{22} = -53.7°$ (*c* 2.125, acetone)	(245)
	238	$[\alpha]_D^{22} = -53.7°$	(245)
Dimethylconidendrin	179–180	$[\alpha]_D^{20} = -103.6°$ (*c* 3.207, acetone)	(33)
Diacetylconidendrin	222–223	$[\alpha]_D^{21} = -73.53°$ (*c* 3.249, acetone)	(33)
Dibenzoylconidendrin	145–152	$[\alpha]_D^{19} = -62.1°$ (*c* 2.87, pyridine)	(33)
Ditosylconidendrin	195–196	$[\alpha]_D^{21} = -50.5°$ (*c* 3.233, acetone)	(33)
Conidendric acid (hydroxy acid)	185	$[\alpha]_D^{18} = +75°$ (*c* 3.346, acetone)	(167)
Amide of conidendric acid	139–140	$[\alpha]_D = +85°$ (*c* 1.761, acetone)	(167)
Monosulfonic acid of conidendrin	172–173		(167)
Tribromoconidendrin	238–240	$[\alpha]_D^{22} = +20.5°$ (*c* 2.937, acetone)	(167)
Tetrabromoconidendrin	260	$[\alpha]_D^{23} = +30.9°$ (*c* 2.7, acetone)	(167)
Dimethyl-α-conidendric acid	150–156	$[\alpha]_D^{20} = +38.9°$ (*c* 1.47, acetone)	(169)
β-Conidendrin	210–212	$[\alpha]_D^{20} = +28°$ (*c* 2.3, acetone)	(167)
	208–210	$[\alpha]_D^{25} = +32.5°$ (*c* 3.0, acetone)	(151)
Dimethyl-β-conidendrin	142–143; 156–157	$[\alpha]_D^{20} = 0.0°$ (*c* 3, acetone)	(169)
	154–155	$[\alpha]_D^{25} = 0.0°$ (*c* 4, acetone)	(151)
Dimethyl-β-conidendric acid		$[\alpha]_D^{20} = +52.6°$ (*c* 2.959, acetone)	(169)
Diacetyl-β-conidendrin	205–207	$[\alpha]_D^{25} = +25°$ (*c* 2.0, acetone)	(151)
Ditosyl-β-conidendrin	166.5–167	$[\alpha]_D^{25} = +13°$ (*c* 4.0, acetone)	(151)
α-Conidendrol	165–166 (dihydrate, 102–103)	$[\alpha]_D^{25} = -75°$ (*c* 4.0, acetone)	(151)
Tetraacetyl-α-conidendrol		$[\alpha]_D^{25} = -57.5°$ (*c* 4.0, acetone)	(151)
Tetrabenzoyl-α-conidendrol	176–177	$[\alpha]_D^{25} = -75°$ (*c* 2.0, acetone)	(151)
β-Conidendrol	251–252	$[\alpha]_D^{25} = +15°$ (*c* 5.0, acetone)	(151)
	248–249	$[\alpha]_D^{20} = +13°$ (*c* 2.0, acetone)	(88)
Tetraacetyl-β-conidendrol	179–180	$[\alpha]_D^{25} = +14°$ (*c* 4.0, acetone)	(151)
	174–175	$[\alpha]_D^{20} = +11°$ (*c* 2.0, acetone)	(88)
Bis(*p*-nitrobenzoyl)conidendrin	257–258		(181)
Diethylconidendrin	178–179		(140)
6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-2-naphthaldehyde	182–183		(43, 168)
Dimethylconidendreic acid	192–193	$[\alpha]_D^{20} = +39.3°$ (*c* 2.0, acetone)	(77)
Aromatized dimethylconidendrin	215–216		(140)
Dimethylconidendreic anhydride	204–205		(77)
Dimethyl dimethylconidendreate	148–149	$[\alpha]_D^{20} = +29.5°$ (*c* 1.0, acetone)	(77)
Aromatized dimethyl ester of dimethylconidendreic acid	165–167		(77)
Dibromodimethyl-α-conidendrin	183–184	$[\alpha]_D^{20} = -15.7°$ (*c* 5.0, acetone)	(77)
Dimethyl-α-conidendreamic acid	225–227	$[\alpha]_D^{26} = +50°$ (*c* 0.6, dioxane)	(55)
Methyl dimethyl-α-conidendreamate	230–231	$[\alpha]_D^{26} = +51°$ (*c* 5.7, dioxane)	(55)
N,*N*-Dimethyldimethyl-α-conidendreamic acid	167–168.5	$[\alpha]_D^{26} = +27°$ (*c* 5.0, acetone)	(55)
Dimethyl-α-retrodendrin	189.5–191.5	$[\alpha]_D^{26} = -58°$ (*c* 2.1, acetone)	(55)
Aromatized dimethyl-α-retrodendrin	245–249		(55)
Dimethyl-α-conidendryl alcohol (dimethylisolariciresinol)	168–172 (monohydrate)	$[\alpha]_D^{25} = +21°$ (*c* 0.5, 95% ethanol)	(55)
Anhydrodimethyl-α-conidendryl alcohol	149–150	$[\alpha]_D^{25} = -52°$ (*c* 2.1, chloroform)	(55)
Methyl dimethyl-α-conidendrate	125–126.5	$[\alpha]_D^{23} = +44°$ (*c* 2.5, acetone)	(55)
Methyl dimethyl-β-conidendrate	94–97	$[\alpha]_D^{26} = +60°$ (*c* 3.5, acetone)	(55)
Dimethyl-β-conidendryl alcohol	131–132	$[\alpha]_D^{25} = +41°$ (*c* 4.0, chloroform)	(55)
	82–84; 140–142	$[\alpha]_D^{20} = +46.2°$ (*c* 2.33, chloroform)	(43)
Anhydrodimethyl-β-conidendryl alcohol	97–98	$[\alpha]_D^{26} = -33°$ (*c* 3.2, acetone)	(55)
2,3-Bis(hydroxymethyl)-6,7-dimethoxy-4-(3,4-dimethoxyphenyl)naphthalene	188–189		(55)
Dimethyl-α-retrodendric acid	185–187 (d.)	$[\alpha]_D^{25} = +31°$ (*c* 2.6, acetone)	(55)
Methyl dimethyl-α-retrodentrate	183.5–184	$[\alpha]_D^{21} = +24°$ (*c* 0.48, $CHCl_3$)	(270a)

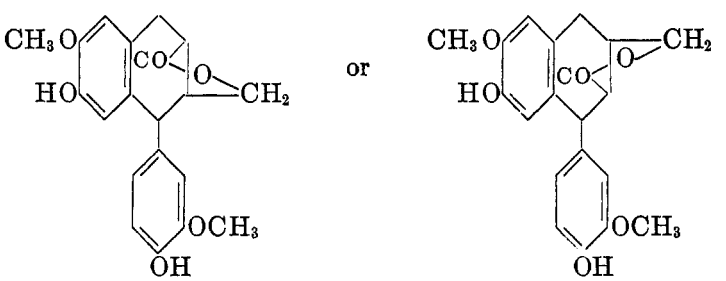
(72, 74, 75) isolated it from the rosin of *Picea excelsa* (spruce). "Tsugalactone" (181) was extracted directly from wood, and recognition of its identity with "sulfite waste liquor lactone" further confirmed the fact that this compound is actually a wood extractive and not an artifact produced during pulping.

Besides occurring in *Picea excelsa* and *Tsuga sieboldii*, conidendrin is found in *Podocarpus spicatus* (35). A thorough investigation by Erdtman (85) showed that this lignan is widely distributed in various conifers. Of fourteen spruces tested, seven were found to contain conidendrin, as did four hemlocks. None was found in pine, Douglas fir, or the larch species. One fir (*Abies arizonica*) may contain conidendrin.

During the investigation of "native" lignin from western hemlock (*Tsuga heterophylla*) Brauns (32, 33) discovered considerable quantities (0.15 per cent) of conidendrin in the wood. This observation led Pearl (245) in 1945 to study the sulfite waste liquor from the pulping of western hemlock as a source of the lignan. He found about 1.1 g. per liter of digester-strength liquor. The possibility of a continuous extraction process for getting conidendrin from sulfite waste liquor was studied by McLaughlin (224) on the basis of the work of Pearl.

Since western hemlock is the principal pulp wood in the western part of the United States for the sulfite process, a thorough investigation was made of ways to isolate conidendrin in commercial quantities. A process was devised (201) whereby the liquor is mixed with small amounts of certain organic liquids which cause the conidendrin to precipitate from solution. This process has been operated on a pilot-plant scale and several hundred pounds of the lignan produced.

Although many reactions were carried out early on conidendrin (166, 167, 168, 169, 181), it was not until 1934 that the correct basic structure was proposed by Erdtman (77). He was unable to determine, however, whether the lactone ring contained the carboxyl group on the No. 2 or the No. 3 carbon atom (and the hydroxymethyl group correspondingly on the No. 3 or the No. 2 carbon atom) (see below). The correct position of the lactone ring, however, was established



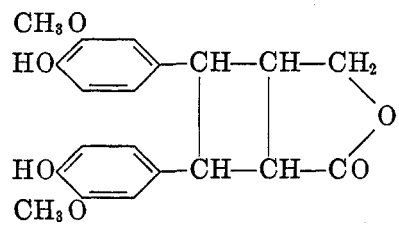
by Haworth (139, 140) and the correct structure confirmed by synthesis of the two possible naphthalene derivatives, which were compared with the corresponding naphthalene derivative made from dimethylconidendrin by dehydrogenation.

Holmberg (166) correctly determined the empirical formula to be $C_{20}H_{20}O_6$ and found two methoxyl groups by analysis and two free hydroxyl groups by

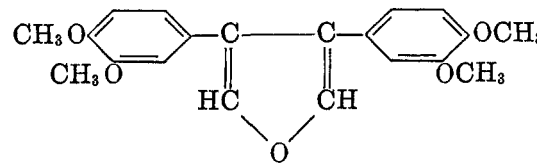
acetylation and methylation (169). He also established the presence of a lactone ring and isolated the free hydroxyl acid (167). These data led to the formula:

$$C_{17}H_{12}\begin{cases}(OH)_2\\(OCH_3)_2\\O\\CO\end{cases}$$

Of the oxidation studies on methylated conidendrin, that using sodium hypobromite proved the most fruitful. Holmberg (168) obtained three products: (A) $C_{20}H_{20}O_5$, optically inactive and insoluble in alkali; (B) $C_{22}H_{24}O_8$, an optically active dibasic acid precipitated by acetic acid; and (C) $C_{20}H_{20}O_8$, an optically inactive acid precipitated by sulfuric acid. He assumed the structure of conidendrin to be similar to that of the truxillic acids, i.e.,

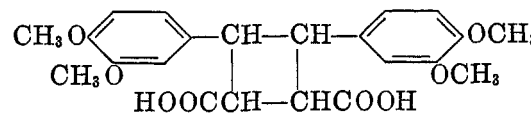


and correspondingly that A would be 3,4-bis(3,4-dimethoxyphenyl)furan, B would be tetramethoxytruxillic acid, and C would be diveratroylacetic acid.



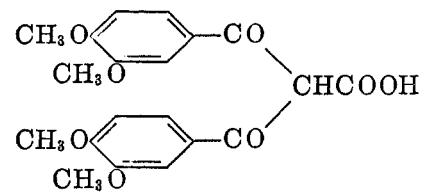
A

3,4-Bis(3,4-dimethoxyphenyl)furan



B

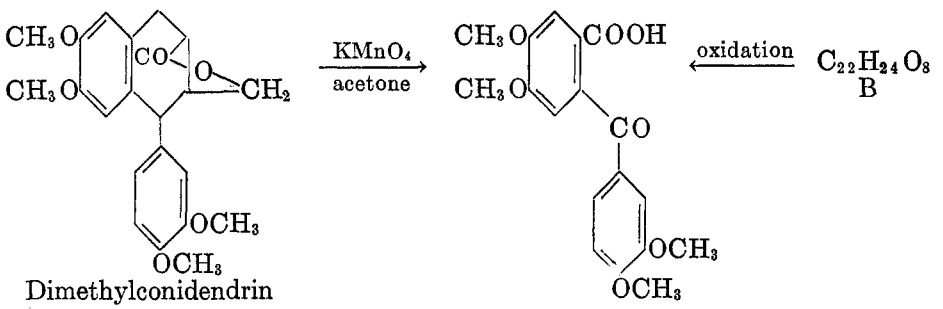
Tetramethoxytruxillic acid

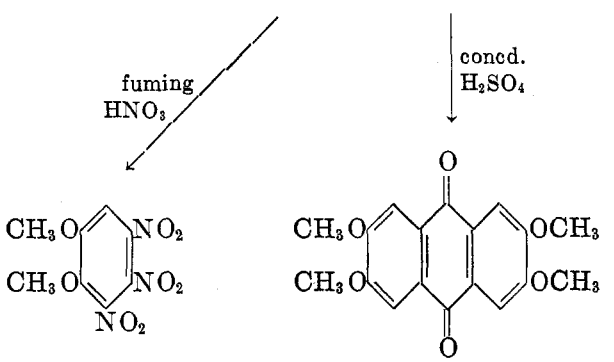


C

Diveratroylacetic acid

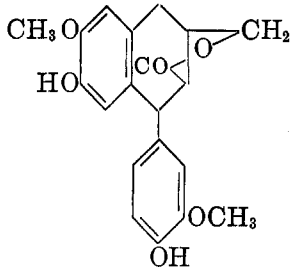
Erdtman (77) first attempted to hydrogenate dimethylconidendrin, using a platinum oxide catalyst, but found it to be saturated; therefore the cyclobutane structure of Holmberg could not be correct. He next oxidized the methylated conidendrin with potassium permanganate in acetone and obtained an acid (D), $C_{18}H_{18}O_7$, which he also could obtain by oxidation of Holmberg's acid (B) above. Acid D with fuming nitric acid gave trinitroveratrole, a result which showed for the first time that conidendrin is a derivative of guaiacol. Furthermore, acid D with concentrated sulfuric acid gave the compound $C_{18}H_{16}O_6$, which was demonstrated by mixed melting point with an authentic sample to be 2,3,6,7-tetramethoxyanthraquinone. Acid D, therefore, was shown to be 6-veratroylveratric acid, and this was again confirmed by a mixed melting point with an authentic sample (133).



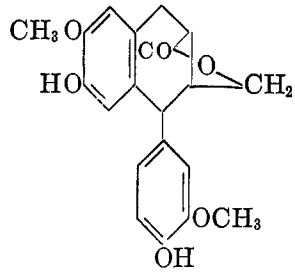


Holmberg's oxidation of methylated conidendrin to B, a dibasic acid, and its ready conversion to an anhydride, as well as the rapid ring closure of the opened lactone, showed the lactone to possess a five-membered ring. The oxidation to the dibasic acid B showed the presence of a hydroxymethyl group, which must be on a carbon atom adjacent to the carbon atom carrying the carboxyl group.

These facts, and the observation that conidendrin empirically is a dimer of coniferaldehyde, led Erdtman to suggest one of the two formulas below for conidendrin:

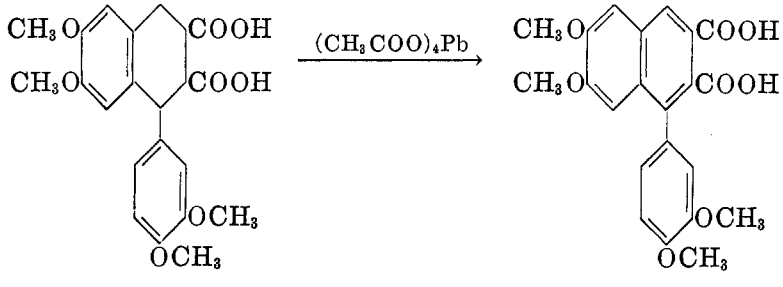


E



F

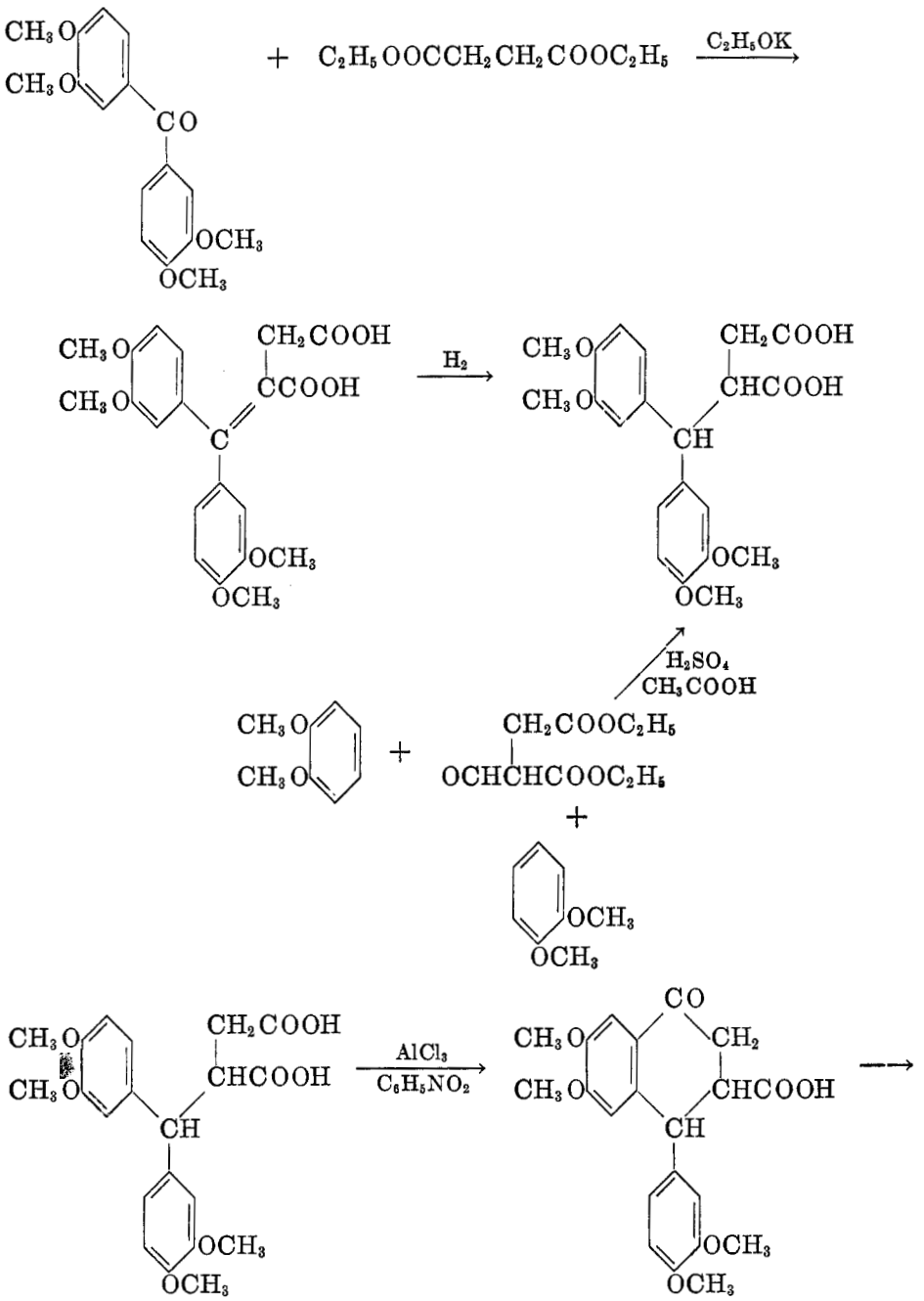
As a further test of his proposed formula, Erdtman dehydrogenated the acid $C_{22}H_{24}O_8$ (Holmberg's product B) with lead tetraacetate and obtained a new acid which by analysis corresponded to the naphthalene derivative of B.

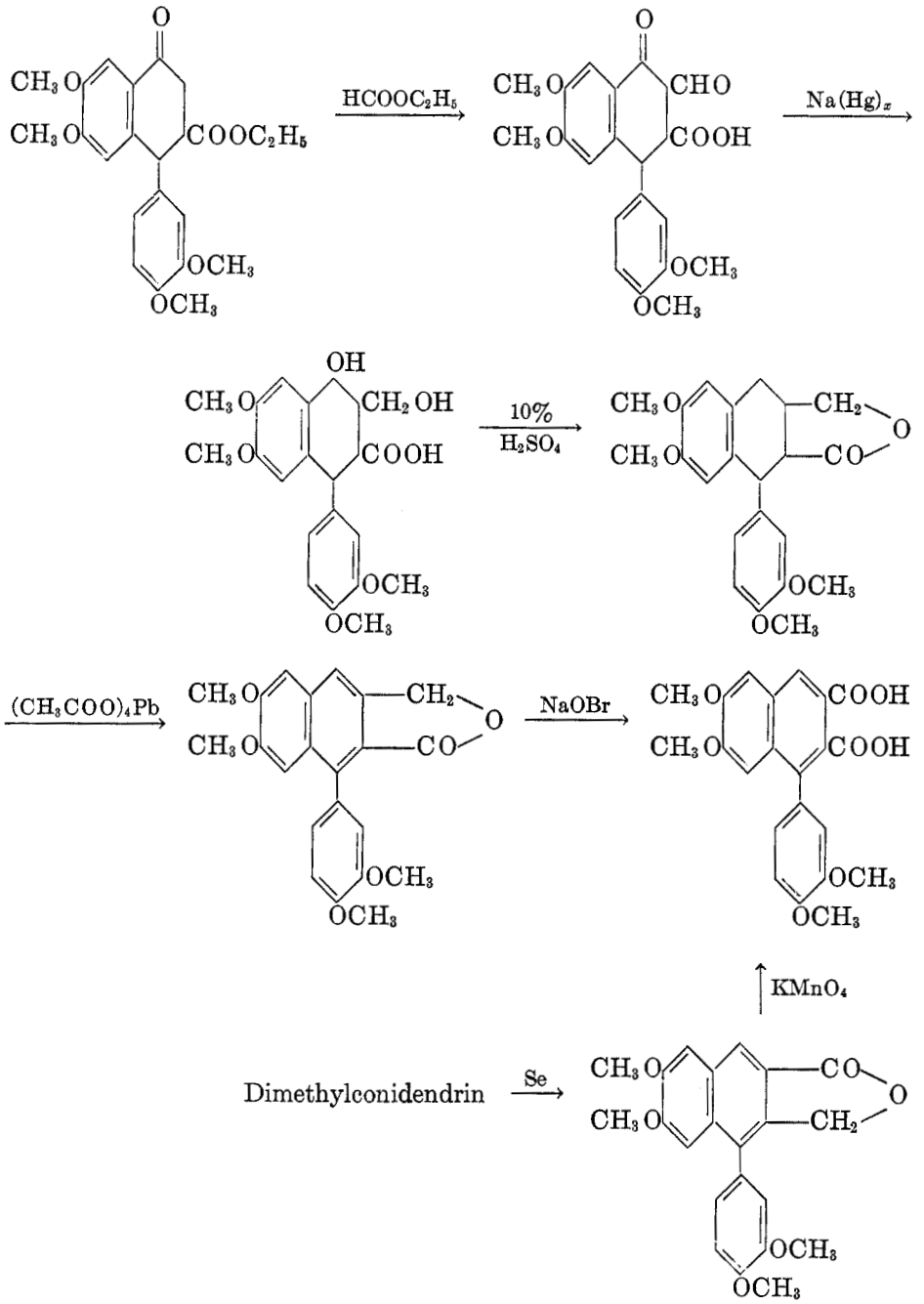


The structure of the oxidation product (A, above) obtained by Holmberg has been shown to be 6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-2-naphthaldehyde (43). B is the dibasic acid of dimethylconidendrin (dimethylconidendreic acid), and C was shown by Erdtman to be 6-veratroylveratric acid. Holmberg's analyses were inaccurate and his empirical formula for C should be $C_{13}H_{18}O_7$, instead of $C_{20}H_{20}O_8$.

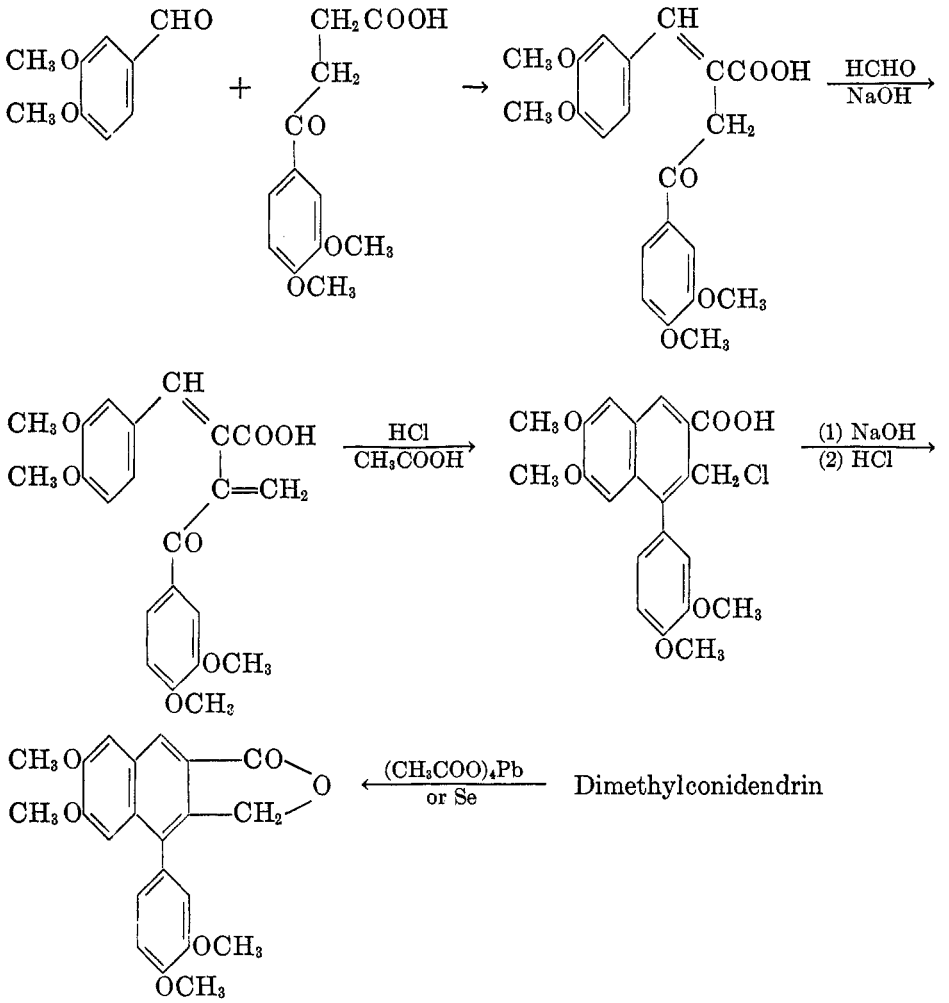
Erdtman's proposed structure was based on no absolute proof of the positions of the substituents. That it was correct, though, was demonstrated by Haworth, Richardson, and Sheldrick in 1935 (139, 140). Since the relation of the lactone ring to the phenyl group at carbon 4 was in doubt, Haworth synthesized compounds corresponding to both E and F above. To simplify the syntheses he prepared the completely methylated naphthalene derivatives corresponding to E and F. These ingenious syntheses are outlined below:

Synthesis of dimethyl aromatized E:




HCOOC2H5
Na(Hg)x
10%
H2SO4
(CH3COO)4Pb
NaOBr
KMnO4
Se
Dimethylconidendrin

Synthesis of dimethyl aromatized F:



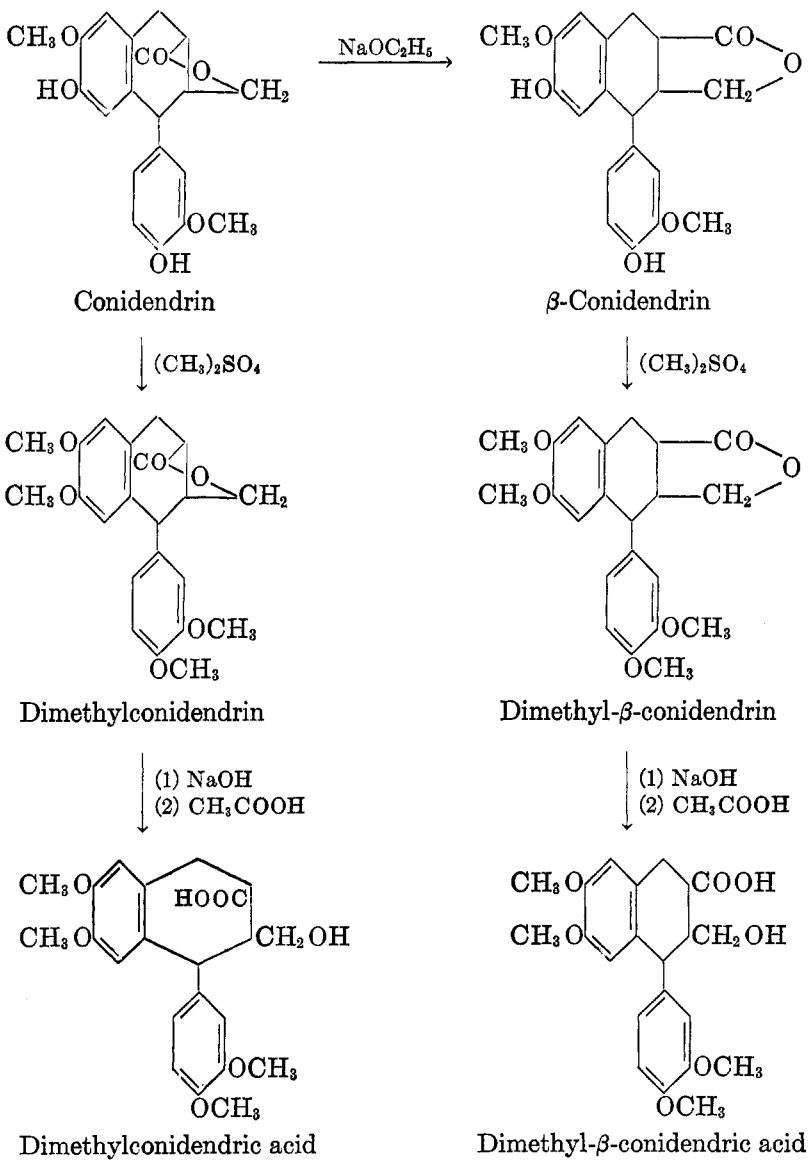
Dimethylconidendrin was easily converted to the corresponding naphthalene derivative by oxidation with lead tetraacetate. A mixed melting point then demonstrated that conidendrin corresponds to structure F above.

Conidendrin is a white crystalline solid melting at 255–256°C. It also can occur in a different crystalline form melting at 238°C.; however, the higher-melting form is the more common. Pearl (245) has discussed these two forms in some detail and corrected the erroneous observation of Briggs and Peak (35). The ultraviolet absorption spectrum of conidendrin has been reported by Erdtman and Erdtman (6) and the infrared absorption spectrum by Spearin (284).

Conidendrin is not methylated by diazomethane in ether or dioxane (33), but is methylated in methanol (263). It is oxidized by nitrobenzene in alkali to give

only a 1 per cent yield of vanillin (as compared to higher yields for other lignans) (203). Conidendrin is converted to a polysaccharide by the *Flavobacterium sp.* when grown on a medium containing conidendrin as a sole source of carbon (251).

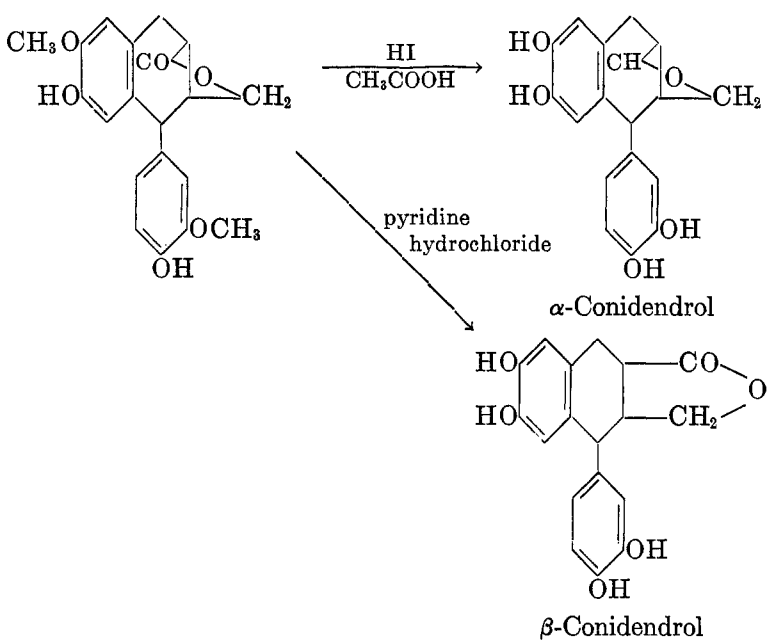
Holmberg (167), as early as 1921, noted that conidendrin, when heated dry or treated with alcoholates, was transformed to another compound melting at 210–212°C. with an optical rotation of $[\alpha]_D^{20} = +29°$ (acetone). He further



found that the methylated conidendrin could be similarly changed to an isomer. These isomeric forms have been designated β in the later literature. Dimethyl-β-conidendrin made by methylating β-conidendrin and that prepared by isomerizing dimethylconidendrin were shown to be the same.[5] The hydroxy acids from the two methylated conidendrins had different melting points and optical rotations.

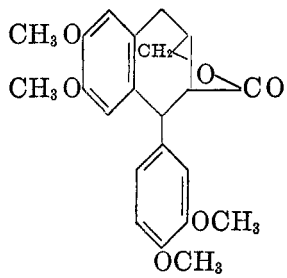
Emde and Schartner (74) explained the isomerization of conidendrin by inversion of configuration around the carbon atom carrying the carboxyl group. This reaction has been further studied (152), and Emde and Schartner's explanation is undoubtedly true. Reference should be made to the same type of isomerization which occurs with podophyllotoxin to picropodophyllin.

The conversion of conidendrin to β-conidendrin has been studied using either alcoholates (152) or heat (151). Also, the demethylation of conidendrin to the corresponding catechol derivative has been carried out using hydriodic acid. This demethylated product is called conidendrol (152). If the demethylation is performed with pyridine hydrochloride, the resulting product is not only demethylated but also inverted; hence β-conidendrol is formed (88, 152). This product has also been called β-norconidendrin. The conidendrols have shown considerable promise as antioxidants for oils and fats (91).



[5] Dimethyl-β-conidendrin is a very rare example of a compound which has optically active centers and no axes or center of symmetry and yet has a reported zero optical rotation. The corresponding hydroxy acid made with alkali does show a rotation of $[\alpha]_D^{20}$ = +52.1–52.6° (acetone) (169).

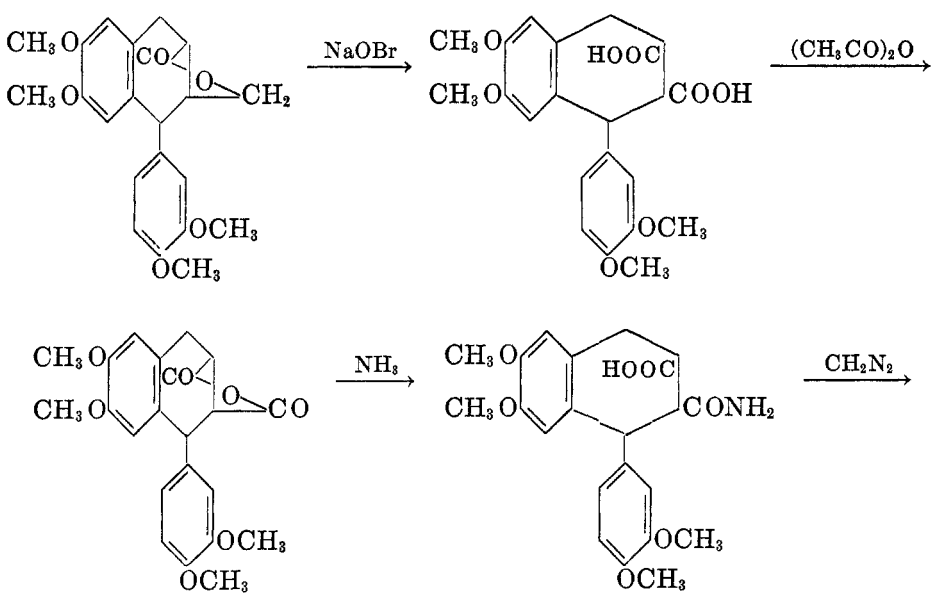
Dimethylconidendrin has been modified by reversing the lactone ring, i.e., having the carboxyl group on carbon 3 and the hydroxymethyl group on carbon 2 (55). This compound, named dimethyl-α-retrodendrin, has the following structure:

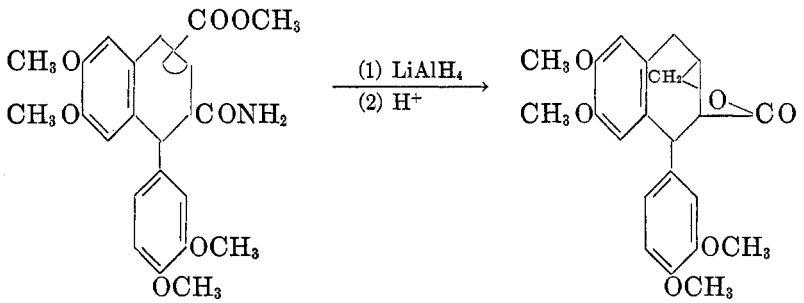


Dimethyl-α-retrodendrin

While dimethyl-α-retrodendrin has superficially the parent structure of podophyllotoxin, it is ineffective for producing necrosis in Sarcoma 37 in mice (112). α-Retrodendrin has the same steric configuration as conidendrin (2:3 *trans*, 3:4 *trans*) (270a). Schrecker and Hartwell (267) have shown that podophyllotoxin has the configuration of 2:3 *trans*, 3:4 *cis*, and this no doubt explains the failure of retrodendrin to have the tumor-necrotizing activity of podophyllotoxin.

Dimethyl-α-retrodendrin has been prepared from conidendrin by the following sequence of reactions:





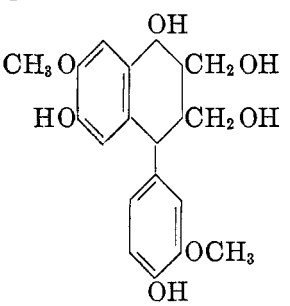
Dimethyl-α-retrodendrin

4. 2,3-Bis(hydroxymethyl) derivatives

a. Isoölivil

Isoölivil, which was first obtained by the acid-catalyzed isomerization of olivil (189), occurs naturally in the resinous deposit in the cracks of the Australian olive (*Olea cunninghamii*) (34).

Although it has not been synthesized, isoölivil is known from degradation studies to have the following structure:



Isoölivil

The hydroxyl groups of isoölivil may be reacted in stepwise fashion. Thus monoalkylation etherifies the hydroxyl group in the 4′-position (303), while

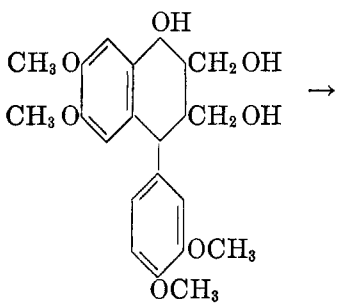
TABLE 29

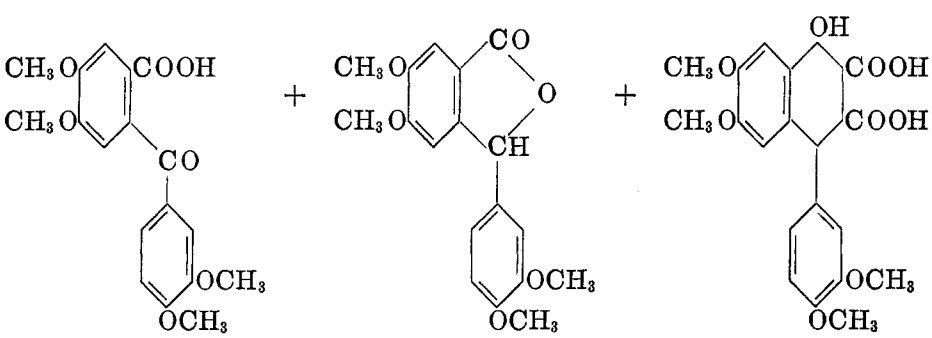
Isoölivil and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Isoölivil	167	$[\alpha]_D^{25}$ = +61.1° (alcohol)	(34, 176, 191)
Dimethylisoölivil	184.5	$[\alpha]_D^{22.5}$ = +35.6° (alcohol)	(34, 191)
Diethylisoölivil	179.5	$[\alpha]_D^{22.5}$ = +38.2° (alcohol)	(34, 191)
Trimethylisoölivil	153–154	$[\alpha]_D^{17}$ = +26.23° (chloroform)	(34)
Monomethylisoölivil	207		(191, 295)
Monoethylisoölivil	148–150		(191, 295)
Ethylmethylisoölivil	192	$[\alpha]_D^{25}$ = +50.35°	(191, 295)
Benzylmethylisoölivil	173–174		(191, 295)
Methylethylisoölivil	168	$[\alpha]_D^{25}$ = +39.36°	(191, 295)
Isoölivic acid	230 (d.)	$[\alpha]_D^{15}$ = +43.9° (c 1.71, K salt in H_2O)	(297, 298)

ordinary etherification with dimethyl sulfate or diethyl sulfate etherifies both phenolic hydroxyls (34, 191). The use of a large excess of dimethyl sulfate gave a trimethyl ether which still contained two active hydrogen atoms but which resisted attempts at esterification (34).

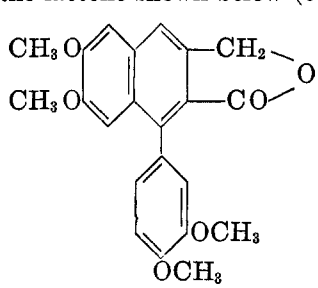
Oxidations of isoölivil dimethyl ether which provided the basis for the assignment of structure gave complex mixtures of products. With alkaline permanganate, the products included three compounds obtained in yields of 24 per cent A, 18 per cent B, and a small amount of C (which was named isoölivic acid) (296, 297, 298, 303). The structures of A and B were confirmed by synthesis (305).





A B C

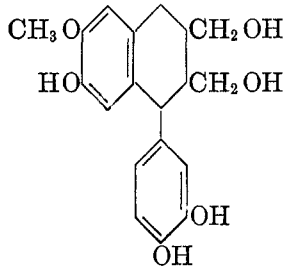
When the dimethyl ether was oxidized with potassium dichromate in acetic acid, there was obtained in addition to the veratroylveratric acid (A) and the phthalide (B), a 0.5 per cent yield of 2,3,6,7-tetramethoxyanthraquinone and a 15–20 per cent yield of the lactone shown below (68).



The lactone was identical with the synthetic product of Haworth and Sheldrick (140) and with the product obtained from the cyclodehydrogenation of dimethylmatairesinol (137). The anthraquinone did not arise from the veratroylveratric acid or the phthalide, since neither gave it under the reaction conditions. It is believed to originate from an initial condensation between the secondary hydroxyl group and the free aromatic ring prior to oxidation (68).

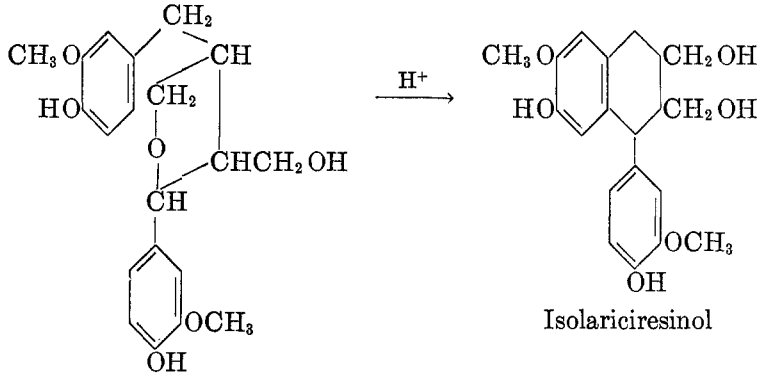
b. Isotaxiresinol

While studying the heartwood of *Taxus baccata* (the English yew), King, Jurd, and King (188) isolated a phenolic compound which they named isotaxiresinol. It has not been elsewhere reported. The structure of isotaxiresinol was proved to be:



Isotaxiresinol

Isolariciresinol has the same structure, but with a methoxyl group in the 3′-position. Isolariciresinol has not been found in nature, but is formed from lariciresinol by ring closure as follows:



Lariciresinol

Isolariciresinol

Since there is a possibility that an open-chain demethyllariciresinol ("taxiresinol") occurs in nature, this phenol was named as an "iso" compound.

Isolation of isotaxiresinol was carried out by hot water extraction of the yew

TABLE 30

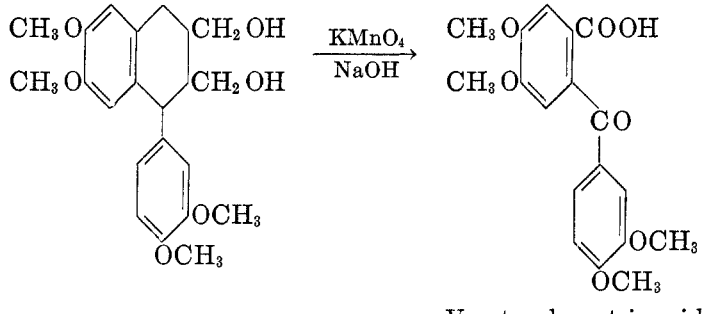
Isotaxiresinol and derivatives

Compound	Melting Point	Optical Rotation	Reference
	°C.		
Isotaxiresinol	171		(188)
Trimethylisotaxiresinol (dimethyliso-lariciresinol)	167–168	$[\alpha]_D^{18} = +19°$ (chloroform)	(188)
Triethylisotaxiresinol	140		(188)
Trimethylanhydroisotaxiresinol	149.5		(188)
Triethylanhydroisotaxiresinol	122.5–123		(188)
Triethyldiacetylisotaxiresinol	89.5		(188)
Triethyldibenzoylisotaxiresinol	125		(188)
2-(3,4-Diethoxybenzoyl)-4-ethoxy-5-methoxy-benzoic acid	173.5		(188)
Methyl 2-(3,4-diethoxybenzoyl)-4-ethoxy-5-methoxybenzoate	111		(188)

heartwood, followed by an ether extraction of the aqueous solution. The ether yielded material which was crystallized from suitable solvents until pure.

Elemental analysis gave the formula $C_{19}H_{22}O_6$, methoxyl analysis indicated one methoxyl group, and methylation showed the existence of three phenolic hydroxyls. The two remaining oxygens were proved to be alcoholic by formation of a diacetate of *O*-triethylisotaxiresinol.

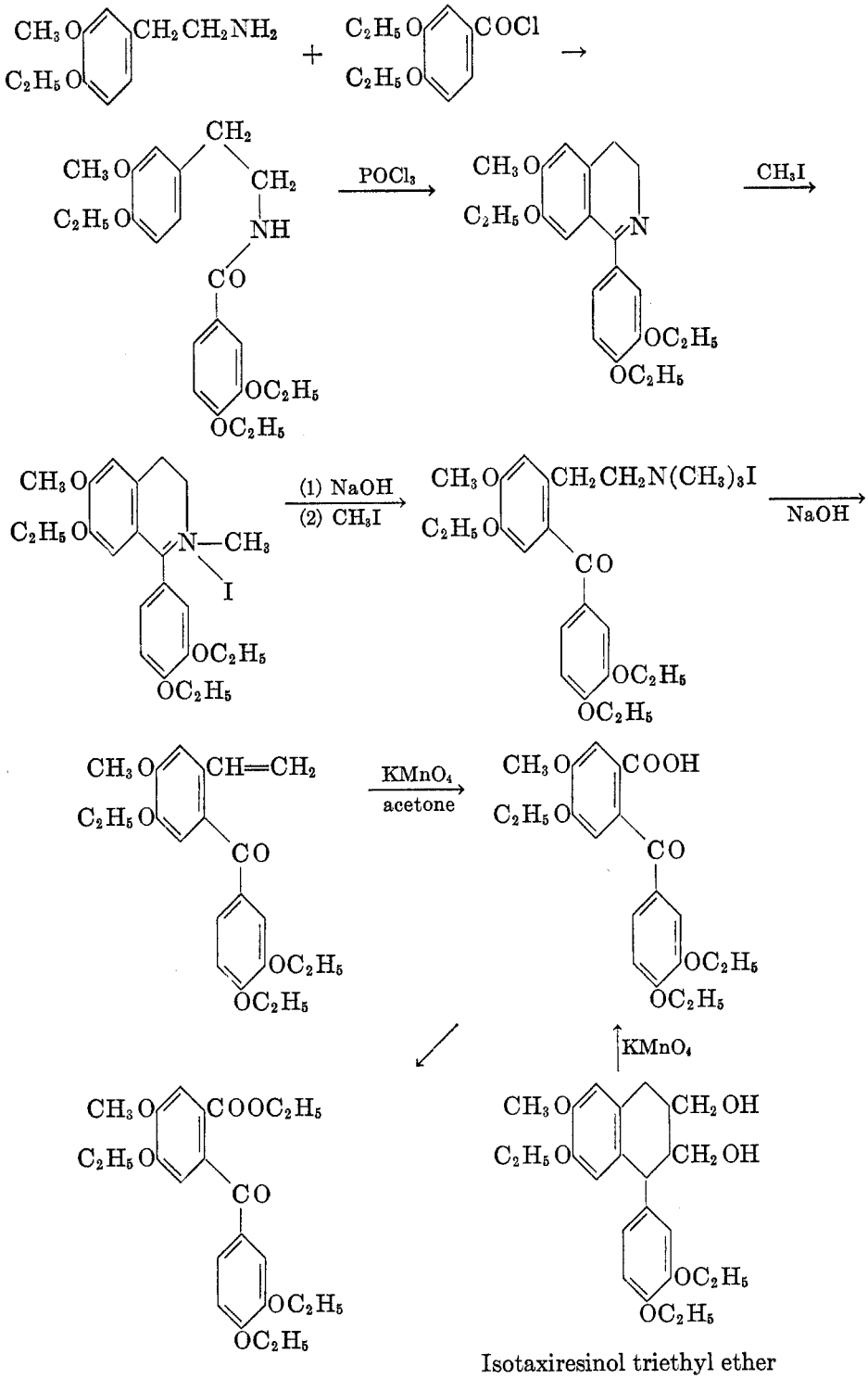
Treatment of the trimethyl ether with nitric acid gave 4,5-dinitroveratrole, while the triethyl ether under the same conditions gave 4,5-dinitrocatechol diethyl ether. Thus the existence of a catechol group was demonstrated and, by difference, a methoxyphenol group must be present. Oxidation of the trimethyl ether with alkaline permanganate gave veratroylveratric acid:



Veratroylveratric acid

A lignan was suspected to be present; a comparison of the melting points of dimethyllariciresinol and trimethylisotaxiresinol suggested their identity, which was confirmed by mixed melting point. Therefore, isotaxiresinol was established as a demethylisolariciresinol.

Oxidation of the triethylisotaxiresinol gave a tetraalkylbenzoylbenzoic acid, whose structure was proved by synthesis to be 2-(3,4-diethoxybenzoyl)-4-ethoxy-5-methoxybenzoic acid. Thus the positions of the methoxyl and phenolic hydroxyl groups were established. These reactions are given below:



Isotaxiresinol triethyl ether

To exclude the possibility of isomerization of isotaxiresinol during isolation, the extraction of yew was repeated with cold ether, which gave only the same material although in lower yield. Undoubtedly isotaxiresinol exists as such in the heartwood of *Taxus baccata*.

5. 2,3-Dimethyl derivatives

a. Galbulin

Galbulin occurs along with galcatin (*cf.* following section) and galbacin in the bark of the Australian species *Himantandra baccata* Bail. (171). The three are separated from a methanol extract, as outlined in the section on galbacin.

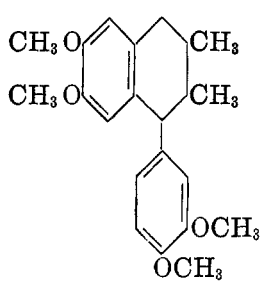
It is of interest that this tree, which belongs to a phylogenetically primitive family, should produce the only two known examples of phenyltetralin lignans with no oxygen in the alicyclic portion (171).

TABLE 31

Galbulin and galcatin and derivatives

Compound	Melting Point	Optical Rotation	References
	°C.		
Galbulin	135	$[\alpha]_D^{20} = -8.5°$ (*c* 1.90, $CHCl_3$)	(171, 270a)
Galcatin	117–118	$[\alpha]_D^{20} = -8.8°$ (*c* 2.0, $CHCl_3$)	(171)
Pentanitrogalbulin	189		(171)
Pentanitrogalcatin	165		(171)
Isogalbulin	88–89 or 101	$[\alpha]_D^{20} = +48°$ (*c* 0.296, $CHCl_3$)	(270)
Racemic isogalbulin	86	$[\alpha]_D = 0°$	(20a)

Hughes and Ritchie (171) recently showed galbulin to have the following structure:

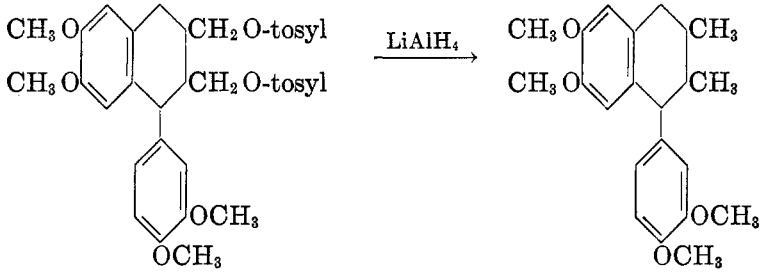


Galbulin

The assignment of structure followed from the analytical data and dehydrogenation over palladized charcoal to the corresponding naphthalene compound, which is dehydroguaiaretic acid (171). Oxidation with potassium dichromate in acetic acid gave a small yield of 2-veratroylveratric acid.

Attempts to nitrate galbulin in acetic acid failed to give a crystalline product, a result which is characteristic of the phenyltetralin lignans. However, a light-sensitive pentanitro derivative has been reported from the reaction with fuming nitric acid (171).

Galbulin has recently been synthesized independently by Carnmalm (43a) and by Schrecker and Hartwell (270a) from dimethylisolariciresinol by reduction of the ditosyl or dimesyl derivatives with lithium aluminum hydride:

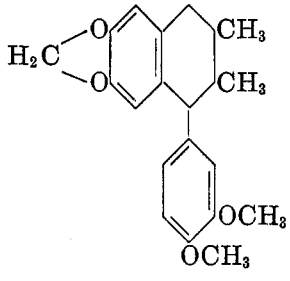


Galbulin

The corresponding reduction of the ditosyl derivative of dimethyl-β-conidendryl alcohol gave a stereoisomer of galbulin which Schrecker and Hartwell (270a) named isogalbulin.

b. Galcatin

In galcatin the two aromatic rings bear different substituents as below (171):



Galcatin

Dehydrogenation of galcatin over palladized charcoal produced the corresponding naphthalene, along with some of the naphthol resulting from the opening of the methylenedioxy ring (171). Methylation of the latter produced dehydroguaiaretic acid.

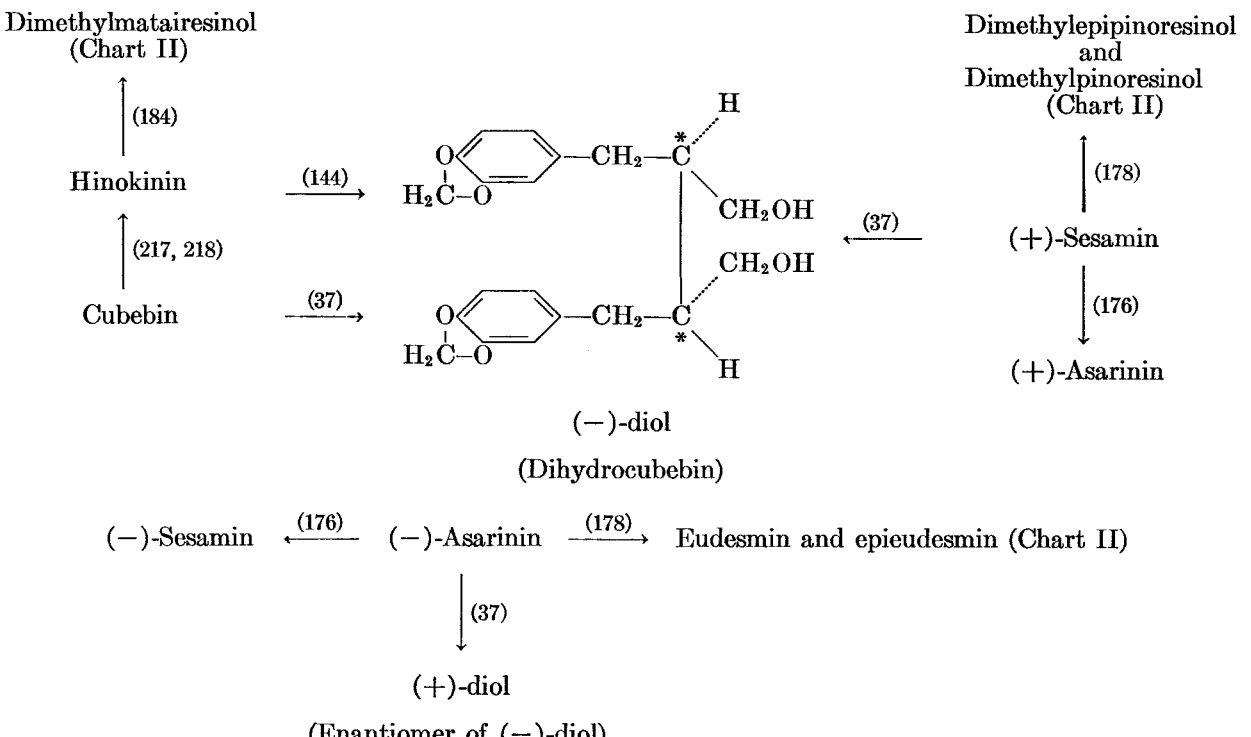
The formation of dehydroguaiaretic acid served to establish the position of the four oxygen atoms. The question as to which ring bore the methylenedioxy group was resolved by reductive opening of the methylenedioxy ring with sodium in ammonia and oxidation of the resulting phenol with permanganate. A small yield of veratric acid was obtained (171).

IV. Stereochemistry of the Lignans and their Interrelations

Justification for the concept of the lignans as a family is strengthened by examination of their stereochemistry. Despite the widely divergent botanical sources, there exists a constant steric pattern about the β-carbon atoms through which joining of the C_6-C_3 units occurs.

Chart I

Interconversions of lignans containing two methylenedioxy groups



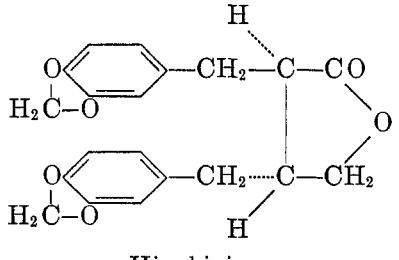
Much of the stereochemical information about the lignans derives from the many lignan interconversions which have been effected. These interconversions are summarized in charts I, II, III, and IV. The numbers accompanying the arrows in the charts refer to the literature references; in order to condense the charts, structural formulas are given only for certain key compounds. The grouping into charts is based on the functional groups situated on the aromatic rings because the structural correlation between lignans bearing different groups is weak, owing to the severe reaction conditions required for interconversion of methylenedioxy groups and methoxyl groups.

Lignans which contain two methylenedioxy groups have been interrelated as shown in chart I. The aldehyde group of cubebin is easily oxidized to give hinokinin or reduced to give the levorotatory diol. The same diol also results when the furofuran structure of (+)-sesamin is opened by mild hydrogenolysis. (−)-Sesamin, which also occurs naturally, results from isomerization of (−)-asarinin, which in turn undergoes hydrogenolysis to a dextrorotatory diol that is enantiomorphic with the diol from cubebin or sesamin. The spatial situation of the groups attached to the two β-carbon atoms (starred in chart I) is constant for this group of lignans, being one or the other of two enantiomorphic configurations.

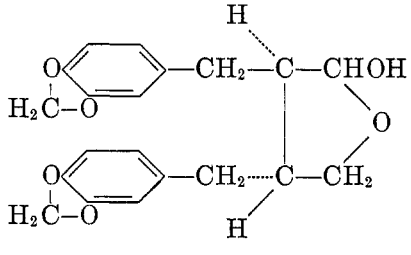
The configurations correspond to the diol diagrammed in chart I or its mirror image because this diol, or its enantiomer, resulted from hydrogenations as indicated. Had the configuration been inverted about either of the β-carbons, the diol would have been *meso*.

Since hinokinin and cubebin have only two asymmetric carbon atoms, the above considerations serve to show the configurations to be as below or the mirror image thereof.

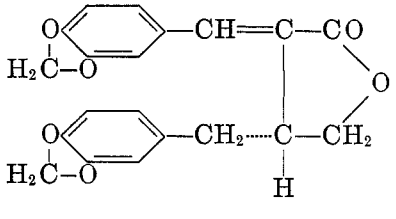
The one asymmetric carbon atom in savinin has the same configuration as the C_3 of hinokinin, since savinin forms isohinokinin upon hydrogenation (270).



Hinokinin



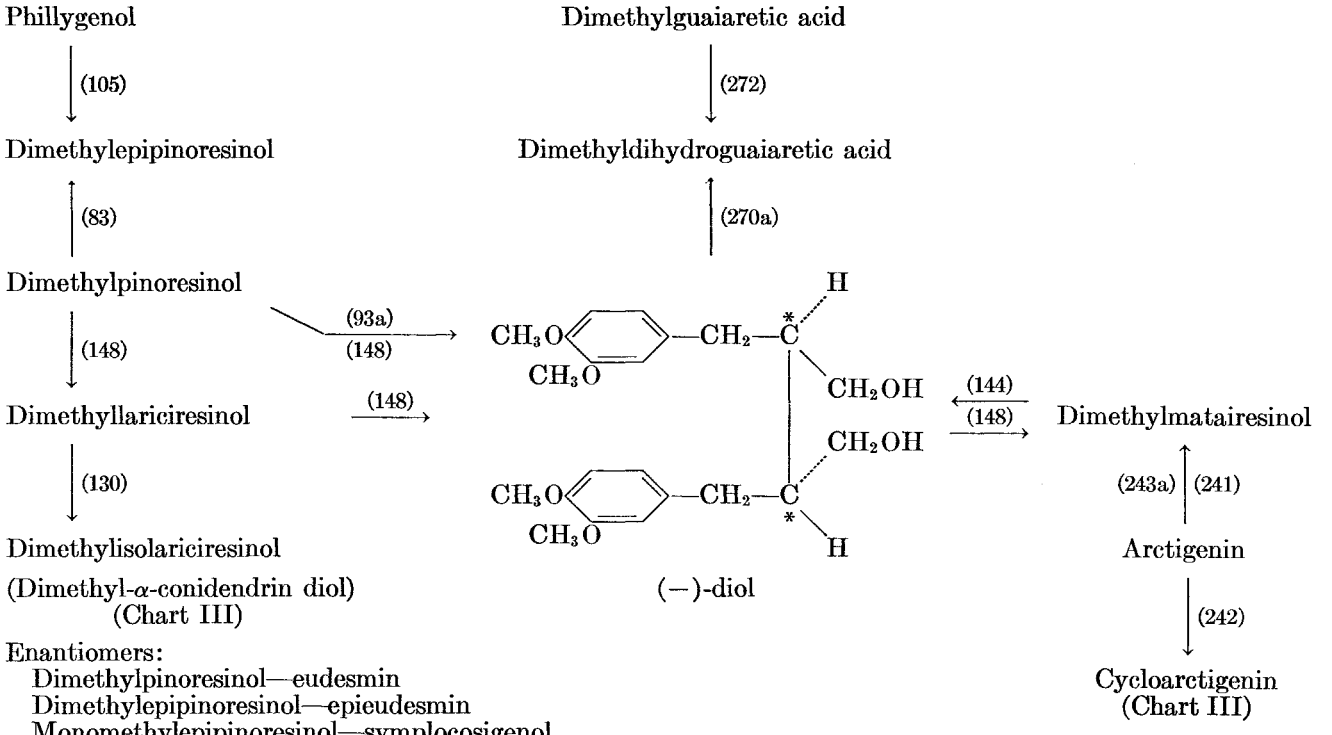
Cubebin



Savinin

Chart II

Interconversions of lignans containing methoxyl and hydroxyl groups

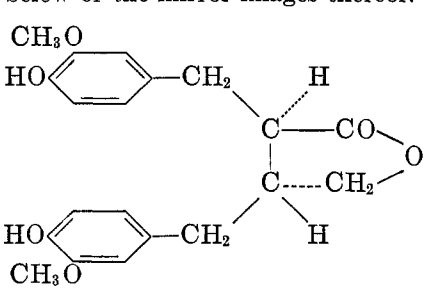


Sesamin and asarinin each have two additional carbon atoms and the stereochemistry about these remains unsolved. Production of the levorotatory diol by hydrogenolysis requires that the hydrogens on the carbon atoms common to the two fused rings be *cis*. Asarinin probably has one of the two possible symmetrical structures, and sesamin is epimeric to it at one of the benzyl carbon atoms.

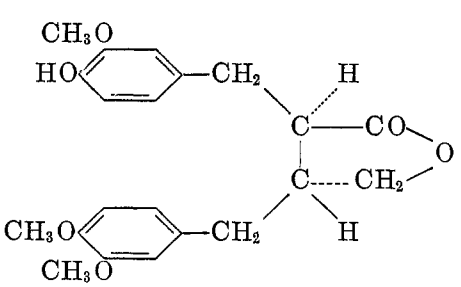
In three cases the methylenedioxy groups have been cleaved (by heating for 8 hr. at 180°C. with alcoholic potassium hydroxide) and the products methylated to give the analogs containing four methoxyl groups (*cf.* chart I). In the cases of (+)-sesamin and (−)-asarinin, which are epimeric about both β-carbon atoms, the configuration about these β-carbons was not changed during the conversion because the products, dimethylpinoresinol and eudesmin, are enantiomorphs. Since a mixture of the normal and epi compound resulted in each case, the configurations about the carbon atoms alpha to the rings were altered.

The interconversions in those methoxyl-containing lignans shown in chart II follow a pattern similar to that given above. The key intermediate in this group is the levorotatory diol which results from hydrogenolysis of the lactone ring of dimethylmatairesinol or of the tetrahydrofuran rings of dimethyllariciresinol and dimethylpinoresinol. Methylation of phillygenol gives dimethylepipinoresinol, which is also formed reversibly by acid treatment of dimethylpinoresinol. Similarly, methylation of arctigenin gives dimethylmatairesinol. Dimethyldihydroguaiaretic acid is obtained by reducing the ditosylate of the levorotatory diol and also results from hydrogenating dimethylguaiaretic acid. Each of these lignans thus possesses the same configuration about the β-carbon atoms (starred in chart II).

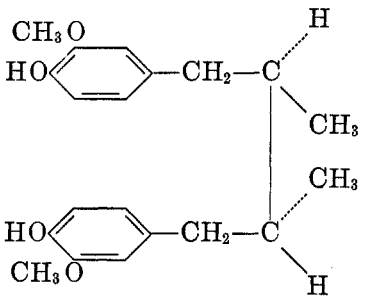
The basis for assigning spatial relationships to the atoms attached to the β-carbon atoms parallels that given for the methylenedioxy analogs. Thus, dimethylmatairesinol was synthesized from the appropriate levorotatory dibenzylsuccinic acid *via* anhydride formation and reduction. If no inversion occurred in these steps, the configuration would correspond to the diol pictured or its mirror image. If the hydrogens on the carbon atoms common to the two furan rings of pinoresinol are *cis*, the same diol configuration would be predicted, and if the hydrogens were not *cis* the diol resulting from hydrogenolysis would be the *meso* form. These considerations establish that the configurations of matairesinol, arctigenin, dihydroguaiaretic acid, and guaiaretic acid are those given below or the mirror images thereof.



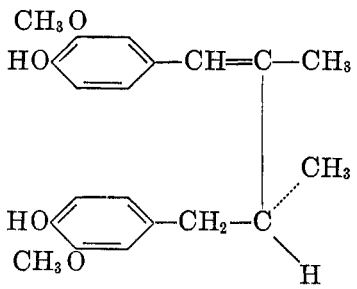
Matairesinol



Arctigenin

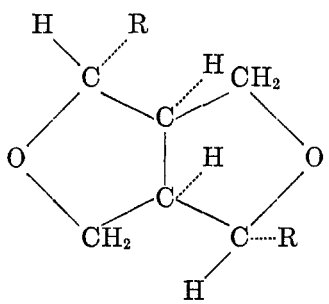


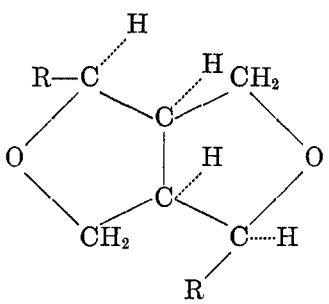
Dihydroguaiaretic acid



Guaiaretic acid

The configurations of the tetrahydrofuran and the tetrahydrofurofuran lignans are further complicated in that they possess additional asymmetric carbon atoms. In the case of pinoresinol the equivalence of the methylated ethyl ethers and ethylated methyl ethers shows that the molecule must possess a rotating axis of symmetry. Only two *dl* pairs fulfill these requirements and it is not yet possible to choose between them. They are (R is 4-hydroxy-3-methoxyphenyl) as follows:





Lariciresinol, which has one less asymmetric carbon atom, has the configuration formed by opening one of the furan rings of pinoresinol by hydrogenolysis. Epipinoresinol (and also phillygenol) has the configuration formed by inversion at one of the pinoresinol benzyl carbon atoms.

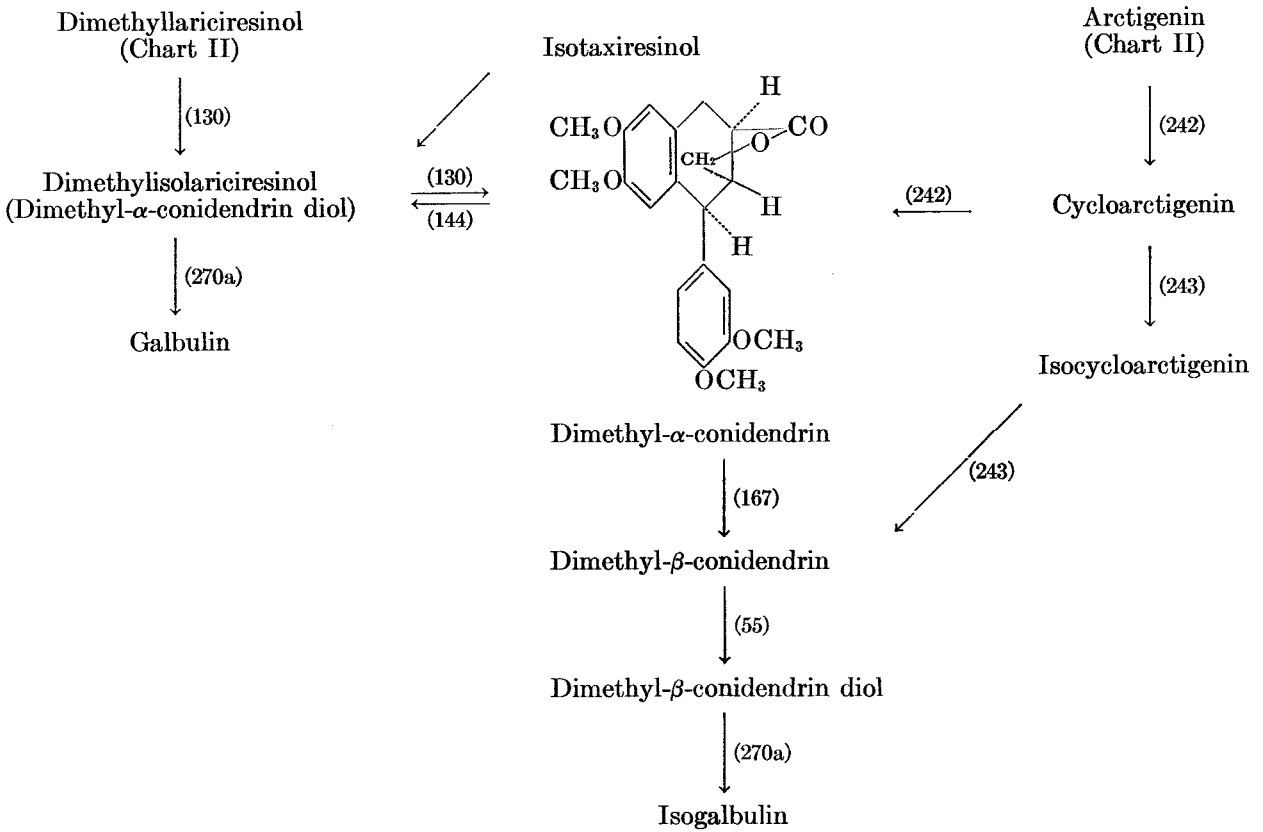
The three pairs of enantiomers noted in chart II show again the occurrence of configurations corresponding to both antipodes of the diol.

Two conversions serve to correlate the configurations about the β-carbon atoms of the above lignans with the corresponding carbon atoms of the phenyltetralin lignans shown in chart III. The facile isomerization of lariciresinol to isolariciresinol almost certainly occurs without altering the configuration about the two β-carbon atoms. The more difficult dehydrogenation of arctigenin to cycloarctigenin probably also occurs without disturbing the configuration at these carbon atoms. The hydrogen atoms at the 2- and 3-positions of isolariciresinol and cycloarctigenin thus are *trans*.

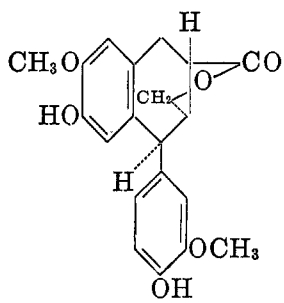
Isolariciresinol and cycloarctigenin have the same configuration as α-conidendrin at the 4-position as well as at the 2- and 3-positions, since the latter gives dimethyl-α-conidendrin by methylation while reduction of dimethyl-α-conidendrin gives dimethylisolariciresinol. Since the isomerizations were stereospecific, it is likely that the hydrogen atoms on the 3- and 4-positions are

Chart III

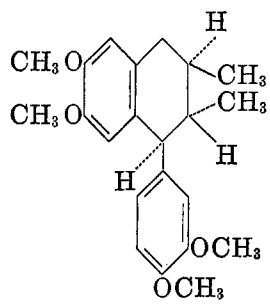
Phenyltetralin lignans containing methoxyl and hydroxyl groups



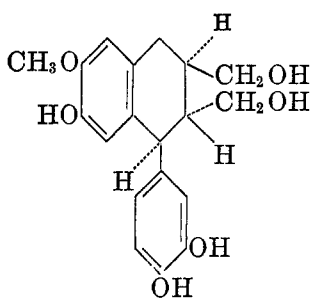
also *trans* and the configuration is that shown in chart III, or its mirror image. Better evidence for the *trans* arrangement of the hydrogens at the 3- and 4-positions has recently been obtained by comparing optical rotational data and alkali stability of dimethyl-α-retrodendrin, which has the α-conidendrin configuration, with isodesoxypodophyllotoxin (270a) (see below). The formation of galbulin by reduction of the ditosyl derivative of dimethylisolariciresinol and the conversion of isotaxiresinol to dimethylisolariciresinol by methylation show these to have the same configuration at carbon atoms 2, 3, and 4. The three naturally occurring lignans in this group thus most likely are correctly represented as one of the enantiomers corresponding to the following structures:



Conidendrin

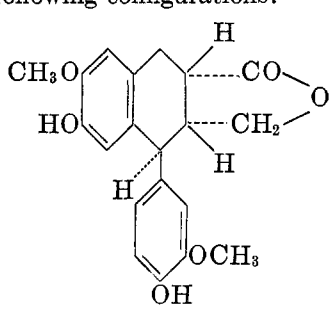


Galbulin

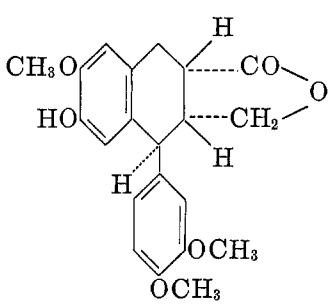


Isotaxiresinol

Both α-conidendrin and cycloarctigenin can be isomerized about the carbon attached to the carboxyl, giving the structures in which the hydrogen atoms on the 2- and 3-positions are *cis*. Thus, β-conidendrin and isocycloarctigenin have the following configurations:



β-Conidendrin



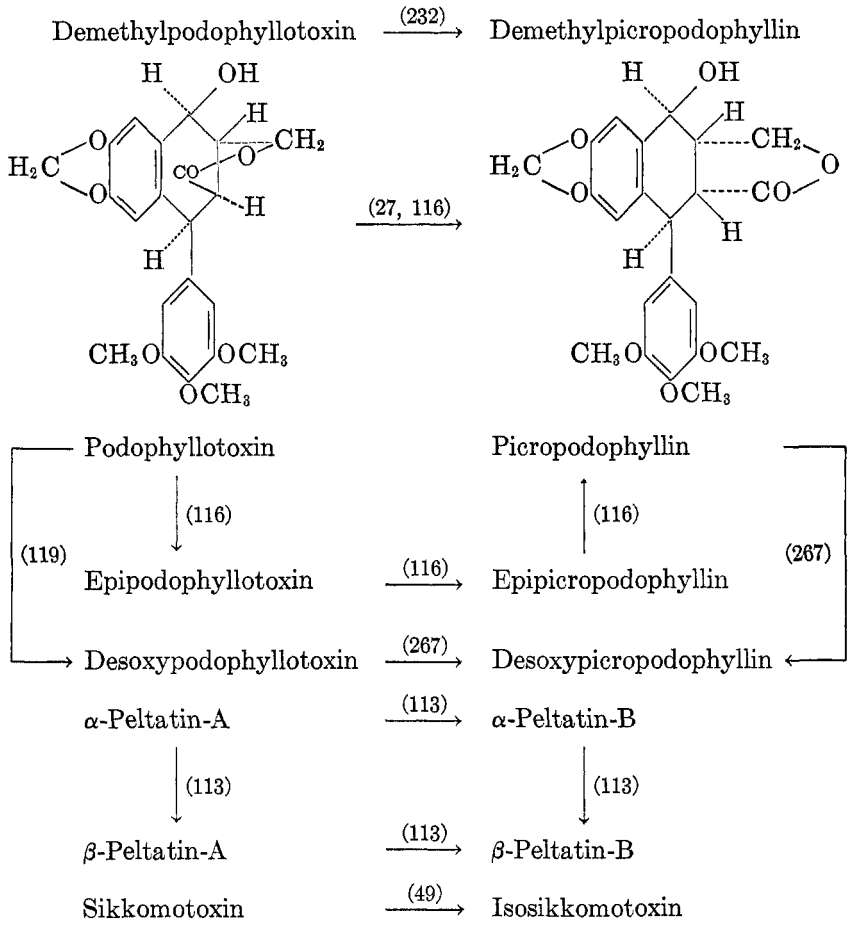
Isocycloarctigenin

The lignans related to podophyllotoxin form a group whose steric configurations are related to the other lignans only by optical rotational data, as outlined below.

These lignans, as shown in chart IV, are grouped either in the podophyllotoxin series or the picropodophyllin series depending on the configuration at the 3-position (116) (*cf.* the section on podophyllotoxin for the basis for this conclusion). The interconversions in each series are parallel. Thus, demethylpodophyllotoxin is methylated to give podophyllotoxin. By a proper choice of reagent, the hydroxyl group of podophyllotoxin can be replaced by chlorine; hydrolysis of this product gives the inverted configuration, which is epipodophyllotoxin. The intermediate chloride can be reduced to form desoxypodophyllotoxin. Some of the corresponding interconversions have also been obtained in the picropodophyllin series. The conversions from the podophyllotoxin series

Chart IV

Interconversions of lignans related to podophyllotoxin



to the picropodophyllin series characteristically occur easily under mild basic conditions.

The assignment of relative configurations at the No. 1 and No. 2 carbon atoms was based on the thermal elimination of benzoic acid from the benzoyl ester (267). Thus, the benzoates of podophyllotoxin and picropodophyllin, in which the hydroxyl group and the No. 2 hydrogen atom are *cis*, decomposed more rapidly than the corresponding epi configurations. The hydrogen atoms on the 1- and 2-positions thus are *trans*, as pictured.

The assignment of configuration at positions 2, 3, and 4 is based largely on hydrogenations of α-, β-, and γ-apopicropodophyllins (267). Upon hydrogenating the 1,2 double bond of the α-apo compound, a mixture of desoxypicropodophyllin and an isomer with the opposite configuration about the 2-position (isodesoxypicropodophyllin) was obtained (267). This shows that the α-apo compound has the picropodophyllin configuration. On the other hand, hydrogenating either the 2,3 double bond of the β-apo compound or the 3,4 double bond of the γ-apo compound yielded predominantly a single new isomer, which probably is the isomer in which the hydrogens at the 2-, 3-, and 4-positions are all *cis* (267). If the assumption of *cis* addition is correct, the configurations at the 2-, 3-, and 4-positions are fixed. Since desoxypicropodophyllin and isodesoxypicropodophyllin are epimeric at the 2-position, the hydrogen atoms at the 3- and 4-positions must be *trans*, because otherwise either desoxypicropodophyllin or isodesoxypicropodophyllin would have the *cis*, *cis* arrangement at the 2-, 3-, and 4-positions. Consequently, the hydrogen atoms in the 3- and 4-positions in the picropodophyllin series must be *trans* and in the podophyllotoxin series must be *cis*.

The hydrogen atoms at the 2- and 3-positions in desoxypodophyllotoxin must be *trans*, because otherwise the compound would then have the *cis*,*cis* structure. Since picropodophyllin differs from it only in the configuration at C_3, the hydrogen atoms in the 2- and 4-positions in it must also be *trans*. The relative configurations of the two series thus are those given in chart IV or mirror images thereof.

It is of interest that only those lignans of the podophyllotoxin series (hence *trans*-(2:3),-*cis*-(3:4) arrangement of hydrogen atoms) show activity against experimental tumors (119a).

The α- and β-peltatins are related, since the latter is a monomethyl ether of the former (118). Both the A series of peltatins and sikkomotoxin have the podophyllotoxin configuration, since they are easily isomerized by alkalies, giving the B series and isosikkomotoxin, respectively, and also are active against Sarcoma 37 in mice.

In a recent correlation of optical rotational data (120) the contributions of each asymmetric center toward the molecular rotations of various lignans were calculated. The molecular rotations calculated from these values were in general in good agreement with observed values and provide evidence for correlations which have not been achieved chemically.

Comparisons of the molecular rotation of analogous members in the coni-

dendrin and podophyllotoxin series showed that the values were approximately equal but of opposite sign for several pairs (270a). Three such pairs were dimethyl-α-retrodendrin and isodesoxypodophyllotoxin, dimethyl-β-conidendryl alcohol and desoxypicropodophyllyl alcohol, and anhydrodimethyl-β-conidendryl alcohol and anhydrodesoxypicropodophyllyl alcohol. The configurations of podophyllotoxin and α-conidendrin thus seem to be epimeric about the 4-position.

V. Commercial Uses for Lignans

Relatively few lignans have gained commercial importance. Of those which have, nordihydroguaiaretic acid (NDGA) has found the largest market. Conidendrin (as conidendrol) has shown promise of commercialization, while others, principally sesamin, have been seriously investigated for industrial use. Podophyllotoxin, the peltatins, and similar lignans will also be mentioned for their potential use in medicine.

NDGA was for several years the principal antioxidant for food materials. Because of its high price, however, more recently other food antioxidants have appeared and NDGA no longer holds as large a market. Nevertheless, it is a potent, relatively non-toxic antioxidant for a variety of food substances (92, 93, 209).

NDGA is particularly good as an antioxidant to prevent rancidity of both vegetable and animal fats (61, 159, 222, 255, 202). It is also effective in protecting against rancidity in bacon (277), fish (275, 288), fish oils (38, 101), and walnuts (58). It has been tested widely in dairy products (196, 253, 289, 290), where it is effective in reducing spoilage by oxidation. NDGA has a protective action against the oxidation of vitamin A (19, 20, 60) and vitamin E (59). The effectiveness of NDGA can often be improved by the addition of synergists (56, 195). The mechanism of how NDGA works as an antioxidant has also been studied (208, 286).

The α- and β-conidendrols, derived from conidendrin by demethylation, are being marketed in limited commercial production (4) as antioxidants. They are reported equal or superior to other stabilizers in current use for GR-S type polymers and as additives for inhibiting the polymerization of vinyl-type monomers (210). They are also effective for food oils (91), although more effective for stabilizing lard than cottonseed oils (230). They may find particular value in food products because of their low toxicity (313).

Both sesamin and asarinin have been mentioned as possible insecticides (256), although the former has been more extensively studied. The effect of sesamin on the brain and muscles of the housefly has been found to be due to vacuolation of the large nerve cells (122). However, sesamin has been studied principally as a synergist with other insecticides such as pyrethrins (108, 109, 223, 271). Other lignans, such as asarinin, pinoresinol, eudesmin, and isosesamin, have been mentioned as possible insecticide synergists (23, 107).

While podophyllotoxin and related lignans have not achieved large-scale production, they have shown promise in medicine and will be mentioned. Podophyllotoxin, α-peltatin, and β-peltatin have each been found to produce

severe damage to tumors in experimental animals (102, 205). A more complete review of the physiological effects of podophyllotoxin has been prepared by Kelly and Hartwell (186). The tumor-damaging activity of podophyllotoxin and the peltatins is apparently associated with the tetrahydronaphthalene nucleus and lactone ring on the No. 2 and No. 3 carbon atoms. In agreement with this, demethylpodophyllotoxin (232), desoxypodophyllotoxin (114, 119), and possibly sikkimotoxin (48) are active. However, the steric configuration of the compound is important, since dimethyl-α-retrodendrin (112) was found to be entirely inactive. Probably a 2:3 *trans*, 3:4 *cis* configuration (as found in podophyllotoxin) is needed. (α-Retrodendrin has a configuration of 2:3 *trans*, 3:4 *trans*.)

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