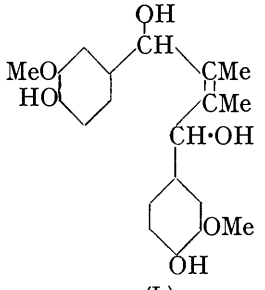
80. *The Constituents of Natural Phenolic Resins. Part VIII. Lariciresinol, Cubebin, and Some Stereochemical Relationships.*

By Robert D. Haworth and William Kelly.

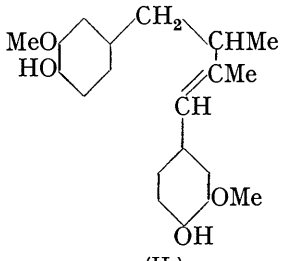
Injury of the bark of the European larch (*Larix decidua*) leads to the exudation of resin (Überwallungsharz), from which Bamberger (*Monatsh.*, 1897, **18**, 481; 1899, **20**, 647, 745; 1900, **21**, 564; 1902, **23**, 1022; 1903, **24**, 209; 1917, **38**, 457) isolated vanillin, caffeic acid, and the phenolic resinol, lariciresinol. The molecular formula, $C_{19}H_{22}O_6$, was adopted for the resinol, and the presence of two methoxyl, two phenolic, and two alcoholic hydroxyl groups was suggested. Meyer and Jacobson ("Lehrbuch der Organischen Chemie," 1924, II, **4**, 166), however, without producing any additional experimental evidence, suggested $C_{20}H_{24}O_6$, and advanced structure (I) to account for the reactions of the resinol. The orientation of the methoxyl and phenolic groups was inferred from Bamberger's isolation of dinitroguaiacol by the action of nitric acid on lariciresinol, and the formation of guaiacol and pyroguaiacin by distillation of the resinol indicated a relationship with guaiaretic acid (II). In view of the biogenetic relationships of other phenolic resinols,

a C_{20} formula was preferable, and the results of a re-examination of the chemistry of lariciresinol are reported in the present communication.

An improved method of isolation has been developed, and new analyses made on the dextrorotatory resinol and its derivatives support the formula $C_{20}H_{24}O_6$. Zeisel determinations on lariciresinol confirmed the existence of two methoxyl groups, but Zerewitinoff estimations indicated the presence of only three hydroxyl groups. Of these, two are phenolic, and alkali-insoluble *dimethyl* and *diethyl ethers*, m. p. 80° and 104°, respectively, have been prepared by alkylation in alkaline solution. These ethers contained one hydroxyl group only, and as gummy hydrogen phthalates were obtained by the action of phthalic anhydride on the ethers in boiling benzene solution, the hydroxyl group is probably primary alcoholic in character. The ethers were saturated and stable towards alkaline and carbonyl reagents, and were recovered unchanged after treatment with methylmagnesium iodide; the sixth oxygen atom is therefore ethereal in nature.



(I.)



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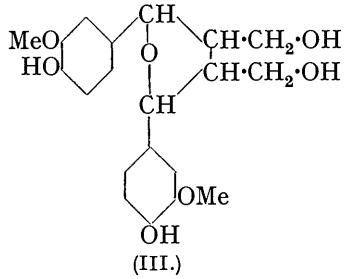
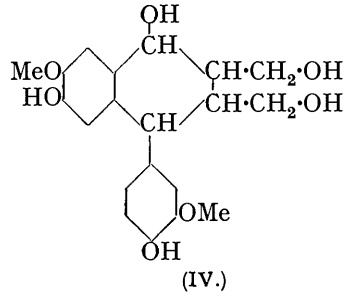


(III.)

Attempts to prepare nitro- or bromo-substitution products of lariciresinol and its ethers were unsuccessful, and this abnormality was traced to the extreme sensitivity of the resinol towards acidic reagents. Lariciresinol was isomerised by boiling with dilute formic acid or with methyl alcohol containing traces of either hydrochloric or acetic acid; the isomer, d-iso*lariciresinol*, m. p. 112°, separated with water of crystallisation, and the anhydrous form contained two methoxyl and four hydroxyl groups. The isomerisation therefore involved the conversion of the ethereal oxygen atom of lariciresinol into a hydroxyl group, and this was supported by analyses of d-iso*lariciresinol dimethyl* and *diethyl ethers*. The stability of lariciresinol towards water, alkalis, and Grignard reagents was inconsistent with an ethylene oxide structure, and the lariciresinol–*iso*lariciresinol change resembled the conversion of olivil (III) into *iso*olivil (IV) (Vanzetti, *Gazzetta*, 1929, **59**, 373), which is also catalysed by very dilute acids. Potassium permanganate oxidised



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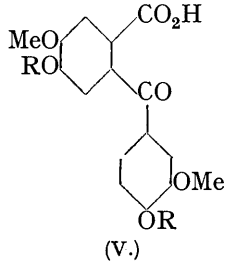

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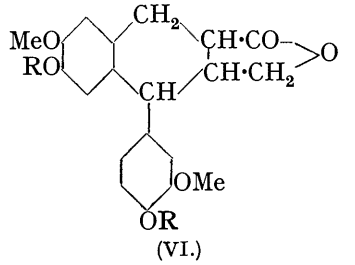
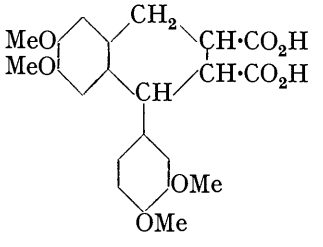


(VI.)

the dimethyl and the diethyl ether of lariciresinol to veratric and 3-methoxy-4-ethoxybenzoic acids respectively; it follows that lariciresinol contains at least one guaiacol group, but the yields of oxidation products were insufficient to establish the presence of two such groups. When *iso*lariciresinol dimethyl ether was oxidised with permanganate, it yielded 2-veratroylveratric acid (V; R = Me) and a similar oxidation of the diethyl ether gave 5-methoxy-4-ethoxy-2-(3′-methoxy-4′-ethoxybenzoyl)benzoic acid (V; R = Et). These observations confirm the view that the conversion of lariciresinol into *iso*lariciresinol involves the cyclisation of a diarylbutane into a 1-phenylnaphthalene derivative, and the

isolation of (V; R = Et) proves that *iso*lariciresinol, and consequently lariciresinol, contain two guaiacol groups. Valuable results have been obtained from a study of the oxidation of *iso*lariciresinol dimethyl ether with sodium hypobromite. *l*-Conidendrin dimethyl ether (" sulphite-liquors lactone " dimethyl ether) (VI; R = Me) was obtained, and identified by comparison with an authentic specimen, and also by dehydrogenation to the lactone of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-2-hydroxymethylnaphthalene-3-carboxylic acid (J., 1935, 636). From the acidic oxidation products 2-veratroylveratric acid (V; R = Me) and the dibasic acid (VII) were isolated, and the latter was identified with a specimen prepared by Erdtman (*Annalen*, 1934, **513**, 219) by the action of sodium hypobromite on (VI; R = Me). The formation of (VI; R = Me) and (VII), in which the carbon framework of lariciresinol is retained, indicates formulæ (VIII; R = H) and (IX; R = H), the latter containing a primary alcoholic group, for *iso*lariciresinol and lariciresinol respectively, and the conversion of (IX; R = H) into (VIII; R = H) is analogous to the olivil–*iso*olivil change.



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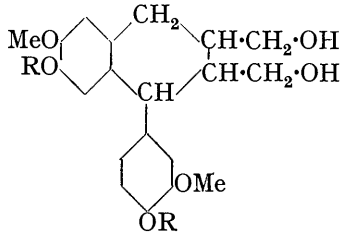
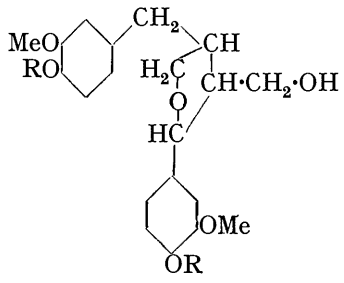


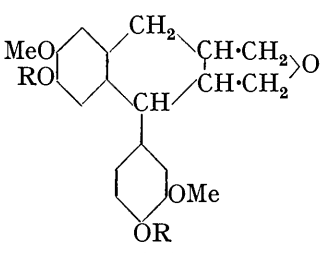
(VIII.)



(IX.)

The failure to recognise the facile conversion of lariciresinol (IX; R = H) into *iso*lariciresinol (VIII; R = H) is responsible for several errors in Bamberger's communications (*loc. cit.*). All the compounds described as normal derivatives of lariciresinol (IX; R = H) in his memoirs are derivatives of *iso*lariciresinol (VIII; R = H), and their formation from lariciresinol is due to the influence of acidic reagents. The action of acetyl chloride–pyridine or acetic anhydride–sodium acetate on lariciresinol yielded, in our hands, uncrystallisable products, but lariciresinol was converted by boiling with acetyl chloride into iso*lariciresinol tetra-acetate*, m. p. 162° (previously described as the normal tetra-acetate), giving *iso*lariciresinol (VIII; R = H) on alkaline hydrolysis, and identical with the tetra-acetate obtained by the action of acetic anhydride–sodium acetate on *iso*lariciresinol. Indefinite products were also obtained by the action of non-acidic acetylating agents on the dialkyl ethers of lariciresinol; boiling acetyl chloride, however, converted the ethers into the *diacetates* of the corresponding *iso*-derivatives (previously described as normal diacetates). On alkaline hydrolysis, these diacetates yielded iso*lariciresinol dimethyl* (VIII; R = Me) and *diethyl* (VIII; R = Et) *ethers*, m. p. **167°** and **168°** respectively (previously described as normal ethers), identical with the ethers obtained by alkylating *iso*lariciresinol. These ethers could not be prepared by alkylation of lariciresinol in alkaline solution as described previously (*Monatsh.*, 1899, **20**, 647, 745), although they were produced if alkylation conditions became acid for a short period. The substance, m. p. 95—97°, prepared by Bamberger (*ibid.*, p. 647) by the action of sodium ethoxide on lariciresinol, is probably impure *iso*lariciresinol, but as lariciresinol is stable to prolonged boiling with sodium ethoxide, the earlier result must be due to the use of excessive acidic conditions during the isolation of the product (see footnote, p. 388). The formation of a diphenolic anhydro-compound (Hermann, *ibid.*, 1902, **23**, 1022) by the action of alcoholic hydrogen chloride on lariciresinol has been confirmed. Alkylation of the anhydro-product, $C_{20}H_{22}O_5$, gave *dialkyl ethers*, and as these were also obtained by heating the dialkyl ethers of either lariciresinol or *iso*lariciresinol with potassium hydrogen sulphate at 180°, it follows that the anhydro-product, $C_{20}H_{22}O_5$, is *anhydro*iso*lariciresinol* (X; R = H). Its *dimethyl ether* (X; R = Me) is saturated and remarkably stable; it was recovered unchanged after treatment with acids, alkalis, sodium in boiling alcohol, acetylating agents, carbonyl reagents, and by sublimation from palladium-black.

During the present research, we were attracted by the possibility that cubebin, the resinol constituent of *Piper cubeba*, might be the methylenedioxy-analogue of lariciresinol. The molecular formula, $C_{20}H_{20}O_6$, containing two methylenedioxy-groups (compare Mameli, *Gazzetta*, 1907, **37**, 483; 1909, **39**, 477, 494; 1912, **42**, 546, 551; 1921, **51**, 353) was consistent with this idea, but the feeble reducing action of lariciresinol dimethyl ether towards Tollens's reagent did not support the analogy. Our thanks are due to Professor G. McOwan of Raffles College, Singapore, for the gift of an alcoholic extract of fresh



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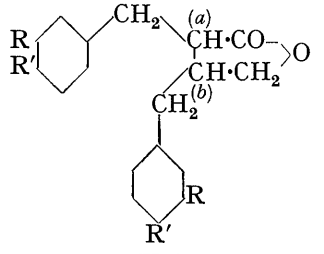

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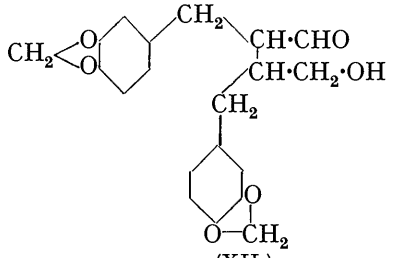
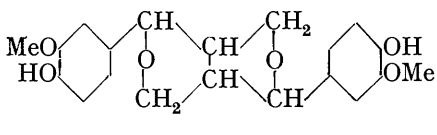


(XII.)

unripe fruit of *Piper cubeba*, from which cubebin was isolated. Analyses confirmed Mameli's formula, Zerewitinoff determinations showed the presence of one hydroxyl group only, but the preparation of a crystalline *semicarbazone* proved that the sixth oxygen atom was aldehydic and not ethereal in function. These results, together with the facile oxidation of cubebin into cubebinolide (XI; RR′ = CH_2O_2) (Mameli, *loc. cit.*), established formula (XII), or the corresponding *cyclo*-acetal formula for cubebin, but contemplated confirmatory experiments were abandoned on the appearance of a communication by Ishiguro (*J. Pharm. Soc. Japan*, 1936, **56**, 68) in which similar conclusions were reached.

A comparison of the formulæ of guaiaretic acid (II), matairesinol (XI; R = OMe; R′ = OH), olivil (III), lariciresinol (IX; R = H), pinoresinol (XIII; Erdtman, *Annalen*, 1935, **516**, 162), and conidendrin (VI; R = H) reveals an intimate structural relationship



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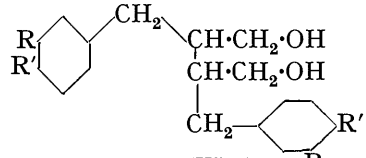

(XIV.)

which extends also to the methylenedioxy-analogues. Matairesinol (XI; R = OMe; R′ = OH) is capable of existing in two resolvable forms, and in the absence of optical inversion, the conversion of *d*-cubebinolide (*l*-hinokinin) (XI; RR′ = CH_2O_2; Keimatsu and Ishiguro, *J. Pharm. Soc. Japan*, 1936, **56**, 61) and *l*-arctigenin (Omaki, *ibid.*, 1935, **35**, 9) into *l*-matairesinol dimethyl ether (XI; R = R′ = OMe) establishes the common stereochemical configuration of the three compounds. During recent experiments, Ishiguro (*ibid.*, 1936, **56**, 68) reduced cubebin (XII) catalytically to the diol (XIV; RR′ = CH_2O_2), which was isolated as an optically active and not as a *meso*-form. From this observation, the significance of which is not indicated in the available abstract (*Centr.*, 1936, ii, 2936), it follows that hinokinin, arctigenin, and matairesinol possess the *trans*-configuration, and it is probable that the synthetic racemates (J., 1936, 725) are the corresponding *cis*-isomers.* The association of *l*-conidendrin and *l*-matairesinol in matai resin, the occurrence of *l*-conidendrin and *d*-pinoresinol in the wood and resin respectively of the spruce, and the conversion of *d*-lariciresinol into *l*-conidendrin described above, suggest that other members of the class may be stereochemically related. By employing

* The terms "*cis*" and "*trans*" refer throughout to the configurations of the centres corresponding to those marked (*a*) and (*b*) in formula (XI), and the arrangement of other asymmetric centres is not considered.

the optically active diol (XIV; R = OMe; R′ = OH) as the hypothetical precursor, and assuming the absence of optical inversion around the centres (*a*) and (*b*) (see footnote, p. 387), it may be deduced that olivil (III) and 1-phenylnaphthalene derivatives, *e.g.*, conidendrin (VI; R = H), possess the *trans*-configuration, and pinoresinol (XIII) and lariciresinol (IX; R = H) represent *cis*-forms. The configurations derived above for olivil and pinoresinol have also been arrived at recently by Erdtman (*Svensk Kem. Tidskr.*, 1936, **48**, 236), without the aid of biogenetic hypotheses, in order to account for the optical activity and the presence of an axis of symmetry in these phenols. Finally, it may be observed that the *cis*-fusion of the two five-membered rings in pinoresinol is consistent with modern views concerning the stability of bicyclic systems, but the configurations for conidendrin and anhydro*iso*lariciresinol (X; R = H) involve a strained *trans*-fusion of five- and six-membered rings.

Experimental.

Lariciresinol (IX; R = H).—The resin was collected from European larches growing in County Durham, particularly from the woods of the Forestry Commission at Chopwell and those belonging to Colonel W. St. A. Warde-Aldam at Healey. Recently felled trees provided the most convenient source of the resin, which exudes from wounds, and was abundant in trees damaged by storm. An old exudate was brittle, transparent, and brown, but a recent flow yielded a viscous, cream-coloured, opaque resin.

The resin (2500 g.), freed as far as possible from bark and wood, was extracted with two lots of boiling alcohol (8 l.), and the extract filtered and concentrated in a vacuum until frothing prevented further removal of solvent. The brown, viscous residue (1500 g., containing approximately 70% of resin) was dissolved in hot alcohol (1 l.), and a solution of potassium hydroxide (900 g.) in water (300 c.c.) was added with stirring. The mixture boiled, darkened in colour, and the potassium salt of lariciresinol, which gradually separated on cooling, was collected after 12 hours, dissolved in water, filtered, and impurities removed with ether. The alkaline liquors were acidified to Congo-red by addition of concentrated hydrochloric acid with stirring, and the excess acid was immediately destroyed by addition of sodium bicarbonate.* The brown gum, which solidified on standing, was collected after 12 hours and washed several times with warm sodium bicarbonate solution, in order to remove most of the coloured impurity. The dried buff-coloured solid (270 g.) was dissolved in warm methyl alcohol (1500 c.c.), filtered through a column of alumina, and the filtrate concentrated to 400 c.c.; after 12 hours, almost pure lariciresinol (170 g.), m. p. 164—166°, was collected. For analysis, the cream-coloured product was crystallised twice from methyl alcohol (carbon); small felted needles, m. p. 167—168°, were obtained (Found: C, 66·6, 66·5; H, 6·8, 6·7; OMe, 17·3, 17·3; OH, 15·1, 14·7, 14·5. Calc. for $C_{20}H_{24}O_6$: C, 66·7; H, 6·7; 2OMe, 17·2; 3OH, 14·1%); in acetone (*c*, 2·232) $[\alpha]_D^{14°} = 19·7°$. Lariciresinol was readily soluble in hot methyl or ethyl alcohol, and the solutions gave a green ferric test. It was sparingly soluble in ether, benzene, chloroform, and ethyl acetate. Unsuccessful attempts were made to reduce the resinol catalytically and by the action of sodium amalgam in alkaline solution. Lariciresinol (0·5 g.), sodium (1 g.), and alcohol (10 c.c.) were boiled for 10 hours. The alcohol was removed, water added, the solution acidified, and excess acid neutralised by addition of sodium bicarbonate. The solid was collected, and crystallised from methyl alcohol; lariciresinol (0·48 g.), m. p. 165—166°, was recovered.

Lariciresinol Dimethyl Ether (IX; R = Me).—Methyl sulphate (0·6 c.c.) was gradually added to a solution of lariciresinol (1 g.) in methyl alcohol (10 c.c.) containing potassium hydroxide (0·3 g.). The mixture was boiled for 0·5 hour on the water-bath, further quantities of methyl sulphate (0·6 c.c.) and potassium hydroxide (0·3 g.) were added, and the boiling continued for another 0·5 hour. The methyl alcohol was removed, water added, and the product, isolated with benzene (A), crystallised from ether in colourless prisms (0·7 g.), m. p. 79—80° (Found: C, 67·7, 68·2; H, 7·2, 7·3; OMe, 31·6; OH, 4·5, 5·1. $C_{22}H_{28}O_6$ requires C, 68·0; H, 7·3; 4OMe, 32·0; 1OH, 4·4%). Kuhn–Roth estimations showed the absence of *C*-methyl groups. In acetone (*c*, 2·051) $[\alpha]_D^{14°} = 22°$. An identical product was obtained by methylating lariciresinol with methyl iodide according to Bamberger's directions. *Lariciresinol dimethyl ether* was readily soluble in the usual organic solvents except light petroleum; it separated from concentrated benzene solution in stout colourless prisms, m. p. 40—45°,

* The addition of bicarbonate was necessary to prevent isomerisation of the gummy lariciresinol in the presence of acids. Attempts to liberate the resinol from alkaline solution with carbon dioxide precipitated a monopotassium salt of lariciresinol.

containing benzene of crystallisation, which is readily lost in a vacuum. It gave a copious white precipitate on the addition of methylmagnesium iodide to its ethereal solution; boiling, followed by decomposition with ammonium chloride, resulted in a quantitative recovery of the unchanged ether, m. p. 79—80°. The ether was not reduced by hydrogen in presence of palladium–carbon or Adams's catalyst. The dimethyl ether (0·4 g.) was boiled with concentrated nitric acid (4 c.c.) for 10 minutes, and water added. The product was extracted with ether, washed with sodium bicarbonate solution, and the ether removed; the residue, crystallised from methyl alcohol, yielded 4 : 5-dinitroveratrole (0·2 g.), m. p. 130°, unchanged by admixture with an authentic specimen. Acidification of the bicarbonate washings precipitated an amorphous acid which has not been identified. Lariciresinol dimethyl ether (0·5 g.), phthalic anhydride (0·2 g.), and benzene (10 c.c.) were refluxed for 2 hours. The cold solution was washed with sodium bicarbonate solution, and the washings were acidified; an amorphous acid, almost insoluble in hot water, was precipitated, but this has not been obtained in a crystalline state.

After the extraction of lariciresinol dimethyl ether with benzene (A, above), the alkaline aqueous layer was acidified; the turbid solution gradually deposited crystals of a *monomethyl ether* of iso*lariciresinol*, which separated from methyl alcohol with solvent of crystallisation, and crystallised from benzene in colourless nodules, m. p. 134—135° (Found : C, 67·6; H, 7·1; OMe, 24·5. $C_{21}H_{26}O_6$ requires C, 67·3; H, 7·0; 3OMe, 24·9%). This ether was converted into *iso*lariciresinol dimethyl ether (VIII; R = Me), m. p. 166°, by the action of methyl sulphate and sodium hydroxide.

Lariciresinol diethyl ether (IX; R = Et), prepared in 70% yields by ethylating lariciresinol with ethyl sulphate or ethyl iodide, crystallised from methyl alcohol in colourless rectangular prisms, m. p. 103—104°, which were insoluble in alkali and gave no ferric test (Found : C, 69·0, H, 7·8; OH, 5·1, 4·9. $C_{24}H_{32}O_6$ requires C, 69·2; H, 7·7; 1OH, 4·1%); boiled with concentrated nitric acid (2 c.c.), it (0·2 g.) yielded 4 : 5-dinitro-*O*-ethylguaiacol (0·09 g.), m. p. 150°, and some unidentified acidic material.

iso*Lariciresinol* (VIII; R = H).—(a) Lariciresinol (1 g.) was boiled with water (16 c.c.) and formic acid (4 c.c.) for 0·5 hour; most of the formic acid was then removed in steam, and *iso*lariciresinol (0·8 g.) separated on cooling.

(b) Lariciresinol (3·5 g.) was boiled with methyl alcohol (35 c.c.) containing two drops of concentrated hydrochloric acid for 0·5 hour. Water was added, most of the alcohol removed, and iso*lariciresinol* (2·8 g.) separated on cooling. It crystallised from aqueous methyl alcohol in colourless, stout prisms, m. p. 112° (with frothing), containing solvent of crystallisation (Found : C, 61·6; H, 6·7%), which was removed by drying over phosphoric oxide in a vacuum at 40—50° for 3 days (Found : C, 66·4; H, 6·8; OMe, 17·1; OH, 19·5. $C_{20}H_{24}O_6$ requires C, 66·7; H, 6·7; 2OMe, 17·2; 4OH, 18·9%). In acetone (*c*, 3·418), $[\alpha]_D^{14°} = 69·4°$. *iso*Lariciresinol gave a green ferric test; it was not converted into lariciresinol by crystallisation from benzene (compare Bamberger, *Monatsh.*, 1899, **20**, 745).

iso*Lariciresinol tetra-acetate*. (*a*) *iso*Lariciresinol (1 g.) was gently boiled with acetic anhydride (10 c.c.) and sodium acetate (1 g.) for 2 hours, the mixture was diluted with water, and the solid (1·4 g.) collected after 12 hours. (*b*) *iso*Lariciresinol (1 g.) was dissolved in pyridine (10 c.c.), and acetyl chloride (5 g.) gradually added; after 2 hours, the mixture was diluted and the product (1·4 g.) collected. (*c*) Lariciresinol (2 g.) and acetyl chloride (20 c.c.) were gently refluxed for 2 hours. Excess acetyl chloride was removed by distillation, the residue was poured into water, and the solid (2·8 g.) collected after 12 hours. The *tetra-acetate*, obtained by the three methods, crystallised from alcohol in colourless felted needles, m. p. 162° (Found : C, 63·6; H, 5·9; OMe, 11·8; $CH_3{\cdot}CO$, 32·6. $C_{28}H_{32}O_{10}$ requires C, 63·6; H, 6·1; 2OMe, 11·8; $4CH_3{\cdot}CO$, 32·6%). In acetone (*c*, 2·285) $[\alpha]_D^{15°} = 18·4°$. It was insoluble in sodium hydroxide solution and did not give a ferric test. Hydrolysis with methyl-alcoholic potassium hydroxide yielded *iso*lariciresinol, m. p. 112° (with frothing).

iso*Lariciresinol dimethyl ether* (VIII; R = Me), obtained in 95% yields by methylating *iso*lariciresinol with methyl sulphate and sodium hydroxide in the usual way, separated from aqueous methyl alcohol in colourless needles, m. p. 166—167°, containing solvent of crystallisation (Found, after drying at 100° : C, 65·0; H, 7·1; OMe, 30·4, 30·7. $C_{22}H_{28}O_6,H_2O$ requires C, 65·0; H, 7·4; 4OMe, 30·5%. Found, after drying over phosphoric oxide in a vacuum at 100° : C, 67·9; H, 7·4; OMe, 32·0; OH, 9·4. $C_{22}H_{28}O_6$ requires C, 68·0; H, 7·3; 4OMe, 32·0; 2OH, 8·8%). Kuhn–Roth estimations proved the absence of *C*-methyl groups. In chloroform (*c*, 1·950) $[\alpha]_D^{14°} = 20°$. Unsuccessful attempts were made to reduce the ether catalytically. Lariciresinol dimethyl ether (IX; R = Me) was boiled for 2 hours with acetyl

chloride (10 parts). The product, which was not purified, was hydrolysed with 10% methyl-alcoholic potassium hydroxide; *iso*lariciresinol dimethyl ether (VIII; R = Me), m. p. 166—167°, was obtained.

iso*Lariciresinol diethyl ether* (VIII; R = Et), prepared similarly by ethylating *iso*lariciresinol with ethyl sulphate, separated from alcohol in colourless needles, m. p. 168° (Found: C, 68·8; H, 7·8; OH, 8·9. $C_{24}H_{32}O_6$ requires C, 69·2; H, 7·7; 2OH, 8·2%). The *diacetate*, prepared either (*a*) by boiling *iso*lariciresinol diethyl ether (0·5 g.) with acetic anhydride (5 c.c.) and sodium acetate (0·5 g.) for 2 hours, or (*b*) by boiling lariciresinol diethyl ether (0·5 g.) with acetyl chloride (5 c.c.) for 2 hours, separated from methyl alcohol in felted needles, m. p. 114—115° (Found: C, 66·9; H, 7·1; CH_3·CO, 16·8. $C_{28}H_{36}O_8$ requires C, 67·2; H, 7·25; 2CH_3·CO, 17·2%). In acetone (*c*, 2·869) $[\alpha]_D^{15°} = 21·7°$. This diacetate was not reduced catalytically, and on hydrolysis with methyl-alcoholic potassium hydroxide it yielded *iso*lariciresinol diethyl ether (VIII; R = Et), m. p. 168°.

*Anhydro*iso*lariciresinol* (X; R = H).—Lariciresinol (2 g.) and saturated methyl-alcoholic hydrogen chloride (7 c.c.) were refluxed for 3 hours; a crystalline compound separated. The mixture was steam-distilled—the distillate had a pronounced odour of guaiacol—and the non-volatile portion deposited an oil, which solidified on cooling. This was collected, and crystallised from methyl alcohol; *anhydro*iso*lariciresinol* (1·3 g.) separated in colourless prisms, m. p. 209—210° (Found: C, 70·0; H, 6·6; OH, 10·8. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·5; 2OH, 9·9%), which gave a green ferric test. In glacial acetic acid (*c*, 2·157) $[\alpha]_D^{14°} = 7·9°$. The methyl-alcoholic mother-liquors contained *iso*lariciresinol, m. p. 112° (with frothing), which was isolated by dilution with water.

*Anhydro*iso*lariciresinol dimethyl ether* (X; R = Me), obtained (*a*) by methylating the above phenol (X; R = H) with methyl sulphate and sodium hydroxide or (*b*) by heating the dimethyl ether of either lariciresinol or *iso*lariciresinol with potassium hydrogen sulphate (2 parts) at 180° for 0·5 hour, crystallised from methyl alcohol in jagged prisms, m. p. 146—147° (Found: C, 71·2; H, 6·9. $C_{22}H_{26}O_5$ requires C, 71·4; H, 7·1%). In acetone (*c*, 2·904) $[\alpha]_D^{16°} = -33·4°$. Zerewitinoff estimations showed the absence of hydroxyl groups. This ether was heated with palladium-black at 230° for 0·5 hour, and was recovered in 95% yield by subliming at 250°/0·1 mm.

*Anhydro*iso*lariciresinol diethyl ether* (X; R = Et), prepared as for the dimethyl ether (method *b*), crystallised from methyl alcohol in long, rectangular prisms, m. p. 132—133° (Found: C, 72·0; H, 7·5. $C_{24}H_{30}O_5$ requires C, 72·4; H, 7·6%).

Oxidations with Potassium Permanganate.—(*a*) Finely divided permanganate (2 g.) was gradually added during 2 hours to a vigorously stirred suspension of lariciresinol dimethyl ether (IX; R = Me) (0·5 g.) in water (200 c.c.) at 100°. After passage of sulphur dioxide through the cold mixture, the solution was concentrated to 50 c.c., acidified with dilute sulphuric acid, and extracted three times with ether. The extract was washed with sodium bicarbonate solution, the acid recovered, and collected (0·25 g.); recrystallisation from hot water gave veratric acid (0·20 g.), m. p. 180°, unchanged by admixture with an authentic specimen.

(*b*) A similar oxidation of the diethyl ether (IX; R = Et) yielded an acid (0·15 g.), m. p. 194°, unchanged by admixture with 3-methoxy-4-ethoxybenzoic acid.

(*c*) Finely powdered permanganate (7·2 g.) was added during 5 hours to a stirred suspension of *iso*lariciresinol dimethyl ether (VIII; R = Me) (1·5 g.) in water (450 c.c.) at 40—45°. The acidic product (0·1 g.), isolated as described in (*a*) above, separated from aqueous acetic acid in colourless prisms (0·05 g.), m. p. and mixed m. p. with 2-veratroylveratric acid (V; R = Me), 222°. The identity was confirmed by preparing the methyl ester, m. p. 161° (Vanzetti and Dreyfuss, *Gazzetta*, 1934, **64**, 391), and by converting the acid into 2 : 3 : 6 : 7-tetramethoxyanthraquinone, m. p. 344° (Haworth and Mavin, J., 1931, 1365). The neutral oxidation products have not been investigated.

(*d*) Similar oxidation of the *iso*diethyl ether (VIII; R = Et) yielded 5-methoxy-4-ethoxy-2-(3′-methoxy-4′-ethoxybenzoyl)benzoic acid (V; R = Et) (0·06 g.), m. p. 214°, unchanged by admixture with an authentic specimen (Vanzetti and Dreyfuss, *loc. cit.*).

Oxidation of iso*Lariciresinol Dimethyl Ether* (VIII; R = Me) *with Sodium Hypobromite.*—A solution of sodium hypobromite, prepared by the addition of bromine (1·2 c.c.) to 10% sodium hydroxide solution (30 c.c.), was added to a solution of *iso*lariciresinol dimethyl ether (1 g.) in dioxan (8 c.c.). After being heated on the water-bath for 0·5 hour, the solution was boiled for 2 hours, cooled, saturated with sulphur dioxide, acidified with dilute sulphuric acid, and extracted with chloroform. The chloroform solution was extracted several times with sodium

bicarbonate solution (A), and the extract acidified and boiled for 15 minutes. Excess sodium bicarbonate was added, and the mixture digested on the water-bath for 0·5 hour. The solid lactone was collected (B), and crystallised from methyl alcohol; slender needles, m. p. and mixed m. p. with *l*-conidendrin dimethyl ether (VI; R = Me), 174—175° (Found: C, 68·6; H, 6·4. Calc. for $C_{22}H_{24}O_6$: C, 68·7; H, 6·3%). This lactone was dehydrogenated with lead tetra-acetate as described previously (J., 1935, 636); the lactone of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-2-hydroxymethylnaphthalene-3-carboxylic acid, m. p. and mixed m. p. 214—215°, was obtained. The bicarbonate liquors (B), from which the conidendrin dimethyl ether had separated, were acidified with acetic acid (C), the solid collected, dried, and esterified by boiling with 10% methyl-alcoholic sulphuric acid (50 parts) for 5 hours. The crude methyl ester, isolated with chloroform, was subjected to fractional crystallisation from methyl alcohol. The sparingly soluble ester separated in long rectangular prisms, m. p. 161° (Found: C, 63·2; H, 5·6. Calc. for $C_{29}H_{20}O_7$: C, 63·3; H, 5·6%), which gave no depression in m. p. with a specimen of methyl 2-veratroylveratrate. Hydrolysis of the ester yielded 2-veratroylveratric acid (V; R = Me), m. p. and mixed m. p. 221—222°. The more soluble ester separated from the mother-liquors; a second crystallisation from methyl alcohol yielded slender needles, m. p. 148—149° (Found: C, 64·8; H, 6·5. Calc. for $C_{24}H_{28}O_8$: C, 64·9; H, 6·4%), which gave no depression in m. p. with methyl 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-1 : 2 : 3 : 4-tetrahydronaphthalene-2 : 3-dicarboxylate (Erdtman, *loc. cit.*). Hydrolysis yielded the corresponding acid (VII), m. p. and mixed m. p. 192°. Addition of dilute sulphuric acid to the acid liquors (C) precipitated a further quantity of acid, which was esterified; a further yield of methyl 2-veratroylveratrate was obtained. The chloroform solution (A) was evaporated, and the residual oil refluxed with 10% methyl-alcoholic potassium hydroxide for 1 hour; the alcohol was removed, water added, and unchanged *iso*lariciresinol filtered off. Acidification of the filtrate gave a further crop of *l*-conidendrin dimethyl ether (VI; R = Me), m. p. 175°, and an amorphous acid which has not been investigated further.

Cubebin (XII).—The alcoholic extract of *Piper cubeba* was concentrated, and the residual green oil (200 g.) distilled in steam in order to remove the essential oil. The hot residue was made alkaline with sodium hydroxide, cooled, and extracted with ether. The solvent was removed from the dried extract, and the residue crystallised four times from methyl alcohol (carbon); cubebin (2 g.) was obtained as slender prisms, m. p. 132° (Found: C, 67·4, 67·3; H, 5·7, 5·7; OH, 5·2, 5·4. Calc. for $C_{20}H_{20}O_6$: C, 67·4; H, 5·7; 1OH, 4·8%). In acetone (*c*, 2·757) $[\alpha]_D^{14°} = -17·1°$, changed by a drop of ammonia to $-49·7°$. The *semicarbazone* was prepared by boiling cubebin (0·1 g.) with semicarbazide hydrochloride (0·05 g.) and sodium acetate (0·04 g.) in alcohol (7 c.c.) for 6 hours. Most of the alcohol was removed, water added, and the solid collected and crystallised from methyl alcohol; colourless nodules (0·08 g.), m. p. 144°, were obtained (Found: C, 60·7; H, 5·8; N, 10·3. $C_{21}H_{23}O_6N_3$ requires C, 61·0; H, 5·6; N, 10·2%).

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