761. *The Chemistry of Extractives from Hardwoods. Part XXXVI.* The Lignans of* Guaiacum Officinale *L.*

By F. E. King and J. G. Wilson.

The presence in "lignum vitae," the heartwood of *Guaiacum officinale* L., of at least nine lignans has been demonstrated by the isolation of their ethers from the methylation and ethylation products of a light-petroleum extract. In addition to guaiaretic acid and its dihydro-compound, dehydroguaiaretic acid and two new tetrahydro-derivatives, guaiacin and isoguaiacin, have been found.

The accompanying dimethoxydihydric phenol, furoguaiacin, and its monomethyl ether afford examples of the unusual furano-lignans. The occurrence of two optically inactive tetrahydrofurans, tetrahydrofuroguaiacin-A and -B, was also established and there is some evidence of a tetrahydromethylfuroguaiacin.

The hardwood, *Guaiacum officinale*, which is found in the West Indies and Central America, and to a lesser extent *G. sanctum*, are important as the source of the heavy durable commercial timber "lignum vitae." The name recalls fomer medicinal applications of the resin obtained from it by heat or by extraction with alcohol. Guaiacum resin constitutes some 18—25% of the wood and has been the subject of many investigations since the early nineteenth century. An alcoholic solution of the extract gives a royal blue colour in air and this has been used as a sensitive test for oxidising agents, including oxidases. Fractionation of the resin, by solvents, pyrolysis, etc., resulted in numerous products. Outstanding among these is the dihydric phenol, guaiaretic acid, readily isolated as its sparingly soluble sodium salt. Its constitution (I; R = H) was largely elucidated by Doebner [1,2] and particularly by Schroeter and their co-workers.[3] The natural acid, which is *l*-rotatory, belongs to the D-series [4] and is accompanied by *meso*- and *l*-dihydroguaiaretic acid (II; R = H) (see ref. 5) but the majority of the resin constituents are amorphous, or inadequately characterised, for example α-guaiaconic acid,[6] the unknown precursor of Guaiacum Blue.

Our own investigation of guaiacum resin was based on the assumption that an improved fractionation would result from extraction of the heartwood with solvents less powerful than boiling ethanol. We are indebted to Mr. D. Irvine, Messrs. Irvine and Sellers Ltd., Liverpool, for generous gifts of lignum vitae in the form of sawdust. Extraction of it with boiling light petroleum led to the discovery of a group of new phenolic lignans.

The highly viscous petroleum extract, 3—4% of the wood, was divided by trituration

* Part XXXV, Janes, King, and Morgan, *J.*, 1963, 1356.

[1] Doebner and Lucker, *Arch. Pharm.*, 1896, **234**, 590.
[2] Doebner and Sauer, *Arch. Pharm.*, 1896, **234**, 610.
[3] Schroeter, Lichtenstadt, and Irineu, *Ber.*, 1918, **51**, 1587.
[4] Schrecker, *J. Amer. Chem. Soc.*, 1957, **79**, 3823.
[5] Haworth, Mavin, and Sheldrick, *J.*, 1934, 1423.
[6] Richter, *Arch. Pharm.*, 1906, **244**, 90.

with boiling methanol into soluble and insoluble portions. Only from the former were any definite products obtainable, the first being guaiaretic acid which was precipitated as the sodium salt. The remaining phenolic resin, liberated by carbon dioxide, yielded no further pure product until resolution of the methylated resin on alumina gave some crystalline fractions. Thereafter, large-scale chromatographic separation of the fully methylated materials became the principal technique of investigation. Ethylation was later applied to prepare a corresponding series of crystalline ethyl ethers, and, by comparison of their degradation products with those of the related methyl ethers, the substituents originally present as hydroxyl groups were located. In all, five methyl ethers and eight ethyl compounds were obtained, thus enabling the constitutions to be deduced of at least six lignans not previously known in nature.

Light petroleum–benzene (1 : 1 to 1 : 3), then benzene–ether (9 : 1 to 1 : 1), and finally ether alone were used to elute the methylated compounds, and seven principal fractions were obtained (M1—M7). With similar solvents the mixed ethylated phenols were separated into nine fractions (E1—E9). A summary of the compounds identified is given in the Table.

Lignans identified in *Guaiacum officinale* L.

Lignan	Isolated ethers
Guaiaretic acid (I; R = H) *	Dimethyl and diethyl
Dihydroguaiaretic acid (II; R = H) *	Dimethyl and diethyl
Dehydroguaiaretic acid (III; R = H)	Dimethyl † and diethyl
Isoguaiacin (VII; R = H)	Dimethyl and diethyl
Guaiacin (X; R = H)	Diethyl
Furoguaiacin (XI; R = H)	Dimethyl † and diethyl
Methylfuroguaiacin (XII; R = H)	Ethyl
Tetrahydrofuroguaiacin-A (XVb)	Dimethyl † and diethyl
Tetrahydrofuroguaiacin-B (XIVb)	Dimethyl † and diethyl

* Previously isolated from guaiacum resin.[1-3] † Previously known but not isolated from guaiacum resin.

Owing to the incomplete removal of guaiaretic acid by sodium salt precipitation, its dimethyl and diethyl ethers (M2 and E4) were among the products isolated. Both compounds were contaminated with 10—12% of the corresponding dihydro-compounds since the isomeric *l*- and *meso*-dihydro-acids also occur in guaiacum resin and are difficultly separable from the unsaturated acid, a circumstance which has been the cause of some confusion in the earlier literature of guaiaretic acid.[5] The ethers of dehydroguaiaretic acid (III; R = H) were also easily recognised minor products (M3 and E3), thus pointing to the occurrence of this acid as a constituent of the resin, an observation not hitherto reported.

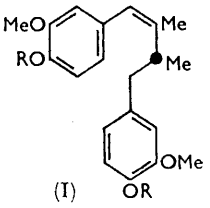
The least strongly absorbed fraction (M1) consisted of a saturated *l*-rotatory tetramethoxy-compound, $C_{22}H_{28}O_4$, containing two *C*-methyl groups. It exhibited ultraviolet absorption and colour reactions identical with those of the ethyl ether, $C_{24}H_{32}O_4$, (four *C*-methyl groups) from E1. E2 consisted of an isomeric more soluble *d*-rotatory methyl ether but the analogous methyl ether was not observed among the methylation products. These derivatives must therefore arise from isomeric lignans, $C_{20}H_{22}O_4$, which later became known as guaiacin, parent compound of the ether E2, and isoguaiacin corresponding to the ethers M1 and E1.

Working with the more abundant isoguaiacin ethers, 4,5-dinitroveratrole and 2-ethoxy-4,5-dinitroanisole, respectively, were obtained by their oxidation with nitric acid. Oxidation of the dimethyl ether with chromic acid or potassium dichromate in acetic acid gave a yellow compound, $C_{14}H_{14}O_4$. Its decolourisation with zinc and acid and rapid reoxidation in air indicated the quinonoid nature of this product, which was identified as 6,7-dimethoxy-2,3-dimethylnaphthaquinone (methylpyroguaiacin quinone)[7] (IV; R = Me) by mixed melting point with an authentic specimen kindly provided by Professor Roger Adams.

[7] Adams and Wicks, *J. Amer. Chem. Soc.*, 1944, **66**, 1315.

Chromic acid oxidation of diethylisoguaiacin gave the homologous quinone, $C_{15}H_{16}O_2$, the known 2,6-diethoxy-3,7-dimethoxyanthraquinone (V; R = Et),[8,9] and an unidentified red compound. With dichromate–acetic acid, in addition to the naphthaquinone (IV; R = Et), the benzoylbenzoic acid (VI; R = H) was obtained. The constitutions of the acid and corresponding anthraquinone were confirmed when identical products were obtained by dichromate oxidation of diethyldi-isoeugenol,[10] specimens of the respective methyl esters (VI; R = Me) also having congruent melting points.

From these oxidations it follows that isoguaiacin is a lignan of the phenyltetralin group, *i.e.*, (VII), but its derivatives are not dehydrogenated to the corresponding phenylnaphthalenes as readily as are galbulin and galcatin,[11] isogalbulin,[12] and podophyllotoxin.[13]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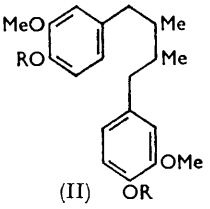
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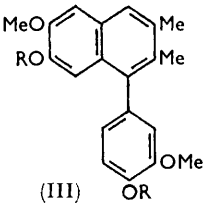
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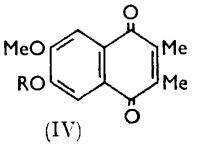
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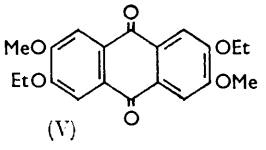
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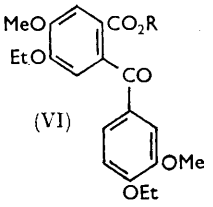
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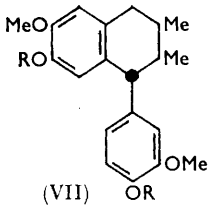
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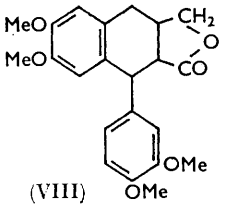
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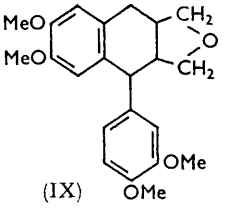
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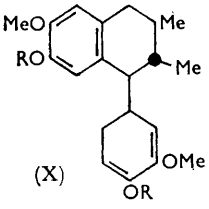
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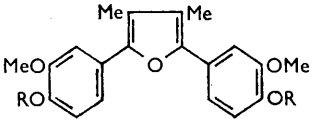
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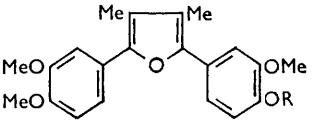

(XII)

Other phenyltetralins resistant to aromatisation are the lactone (VIII) and the anhydrodimethylisolariciresinol (IX).[14] Isoguaiacin methyl and ethyl ethers were finally dehydrogenated without solvent at 300—320° in presence of palladised charcoal, or better, using tetrachloro-*o*-benzoquinone, the products being (III; R = Me, Et). Under the latter

[8] Vanzetti and Dreyfuss, *Gazzetta*, 1934, **64**, 382.
[9] Muller, Toldy, Halmi, and Meszaros, *J. Org. Chem.*, 1951, **16**, 481.
[10] Muller, Raltschewa, and Papp, *Ber.*, 1942, **75**, 692.
[11] Hughes and Ritchie, *Austral. J. Chem.*, 1954, **7**, 104.
[12] Carnmalm, *Acta. Chem. Scand.*, 1954, **8**, 1827.
[13] Spath, Wessely, and Kornfeld, *Ber.*, 1932, **65**, 1536.
[14] Haworth and Richardson, *J.*, 1935, 633.

conditions the analogous diethylguaiacin was likewise dehydrogenated to dehydrodiethylguaiaretic acid, thus establishing the stereochemical relationship of guaiacin and isoguaiacin.

In all, eight optically-active isomers of a given tetralin of this type are feasible, of which galbulin (IX; R = Me) from the Australian species *Himantandra baccata* [11] is the *l*-rotatory *trans*-2,3-*trans*-3,4-dimethyl ether,[12] whilst the *d-cis*-2,3-*trans*-3,4-compound (isogalbulin) (VII; R = Me) is known as a transformation product of dimethyl-β-conidendrin.[12,15] A comparison of melting points and specific rotations strongly suggested that dimethylisoguaiacin was the *l*-rotatory isomer of isogalbulin. The identity of the infrared spectra (sample kindly supplied by Dr. A. W. Schrecker) provided unequivocal proof of this relationship.

	M. p.	$[\alpha]_D^{23}$
Dimethylisoguaiacin	86—87 or 101—102°	−46 (23°)
Isogalbulin	88—89 or 100—100·5	+48 (20°) [15]
	85—85·5	+45° [12]

Failure to isolate dimethylguaiacin from the lignum vitae resin did not permit direct comparison in the isomeric series but the relative optical rotations of diethylguaiacin ($[\alpha]_D^{17}$ +4°) and of galbulin ($[\alpha]_D^{20}$ −8·8°) [11] do not conflict with the view that guaiacin may be the *d-trans*-2,3-*trans*-3,4-isomer (X; R = H).

Furoguaiacin and 4-Methylfuroguaiacin. Fractions M4, E5, and E6 were distinguished from the others by the bluish fluorescence of their solutions. The methylated product M4, $C_{22}H_{24}O_5$, contained four methoxyl and two *C*-methyl groups. Oxidation gave small amounts of veratric acid (permanganate) and of 4,5-dinitroveratrole (nitric acid). The fifth oxygen was assumed to be part of a heterocyclic system, possibly furan. The u.v. absorption, $\lambda_{max.}$ 326 mμ (log ε 4·47), was similar to that of 1,4-diphenylbutadiene [$\lambda_{max.}$ 328 mμ (log ε 4·61)[16]] thus implying a bisdimethoxyphenyldimethylfuran structure for this methylated product. Its properties were concordant with those of 2,5-bis-(3,4-dimethoxyphenyl)-3,4-dimethylfuran (XI; R = Me) obtained by Atkinson and Haworth [17] by the action of selenium on pinoresinol and epipinoresinol dimethyl ether, and a mixed melting point determination with an authentic specimen, kindly supplied by Professor R. D. Haworth, F.R.S., established their identity.

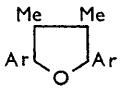
The ethyl ether, E5, $C_{24}H_{28}O_5$, containing 4 *C*-methyl groups, similarly gave, with nitric acid, 2-ethoxy-4,5-dinitroanisole and its u.v. absorption was indistinguishable from that of the furan (XI; R = Me). The conversion into *O*-ethylvanillic acid on permanganate oxidation was 90%. The formation of the diethyl ether therefore indicated the presence in guaiacum resin of 2,5-di-(4-hydroxy-3-methoxyphenyl)-3,4-dimethylfuran (XI; R = H), hereafter termed furoguaiacin in view of its derivation and structure.

The colour reactions and u.v. absorption of the minor constituent E6, which was altogether absent from some samples of the wood, indicated its close resemblance to furoguaiacin. From the molecular formula, $C_{23}H_{26}O_5$, containing one methylene group more than that of dimethylfuroguaiacin, and three C-methyl groups it appeared to have been formed from a methylfuroguaiacin. Although, like other furoguaiacin ethers, somewhat resistant to permanganate, a small amount of ethylvanillic acid was isolated fom the acid products of the oxidation. The structure thus deduced, (XII; R = H), was later confirmed by synthesis of the ethyl ether. Furoguaiacin and methylfuroguaiacin constitute a new series of lignans in being the only natural compounds of this group having a fully aromatised furan ring.

Tetrahydrofuroguaiacin-A and -B. Fractions M5—M7 and E7—E9 consisted of products eluted in the last stages of the chromatographic separation with benzene–ether and ether. Two pure isomeric methyl derivatives were obtained, both optically inert, one, m. p. 120°, from M6 and the other, m. p. 132—133°, from the small final eluate, M7.

[15] Schrecker and Hartwell, *J. Amer. Chem. Soc.*, 1955, **77**, 432.
[16] Braude, *Ann. Reports*, 1945, **42**, 105.
[17] Atkinson and Haworth, *J.*, 1938, 1681.

Fraction M5 appeared to consist of a mixture of the isomers but fractional crystallisation gave only the former completely pure. Both ethers had the molecular formula $C_{22}H_{28}O_5$



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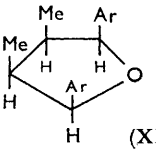
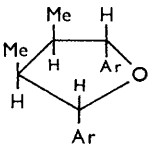


(XIV)



(XV)

a, Ar = 3,4-dimethoxyphenyl. b, Ar = 4-hydroxy-3-methoxyphenyl. c, Ar = 4-ethoxy-3-methoxyphenyl.

and contained four methoxyl and two *C*-methyl groups, and seemed probably to be tetrahydrofuroguaiacin dimethyl ethers. The properties of the isomer of m. p. 120° tallied with those of the lignan, galgravin, isolated from *Himantandra belgraveana* by Hughes and Ritchie [11] who regarded it as one of the *meso*-forms of structure (XIIIa), and a mixed melting point determination with a specimen kindly made available by Professor A. J. Birch, F.R.S., confirmed that the two were identical.

Corresponding in spectra and colour reactions to these methyl ethers were two optically neutral ethylated compounds, one, m. p. 100°, from fraction E7 and the other, m. p. 105°, from E8. Their formulae, $C_{24}H_{32}O_5$, and the presence of two additional *C*-methyl groups per molecule signified their derivation from dihydric phenols which on general grounds were assumed to be isomers of tetrahydrofuroguaiacin (THFG) (XIIIb). Oxidation of the ether of m. p. 100° with nitric acid to give 2-ethoxy-4,5-dinitroanisole, and with chromic acid to *O*-ethylvanillic acid, confirmed this interpretation for one of the isomers, and other evidence discussed below established the stereochemical relationship of the two isomers. The parent phenols have therefore been designated tetrahydrofuroguaiacin-A and -B and their existence in guaiacum resin seemingly accounts for some, if not all, of the galgravin and its isomer in products M6 and M7.

Fraction E9 gave a small amount of a third ethyl ether, m. p. 114—115°, of similar u.v. absorption and sulphuric acid colour. Analyses indicated it to have the formula, $C_{23}H_{30}O_5$, and to contain three *C*-methyl groups. In view of the identification of a methylethylfuroguaiacin (XII) among the ethylation products, the occurrence of an analogous tetrahydro-derivative would not be unexpected, but insufficient material was available for the experiments necessary to prove this speculative structure.

The inter-relationship of dimethyl- and diethyl-THFG-A and -B was demonstrated by dehydrogenation experiments. The action of palladised charcoal on galgravin (dimethyl-THFG-A) is known [11] to cause both cyclodehydration and loss of two atoms of hydrogen to give dehydrodimethylguaiaretic acid (III; R = Me), the product also obtained by preliminary dehydration followed by palladised-charcoal treatment of the intermediate anhydro-compound. Palladium dehydrogenation of diethyl-THFG-A similarly afforded dehydrodiethylguaiaretic acid (50%) thus demonstrating the configurational identity of the two ethers. Dimethyl-THFG-B on the other hand underwent normal aromatisation to dimethylfuroguaiacin (XI; R = Me) (25%), and diethylfuroguaiacin (XII; R = H) (30%) was formed by dehydrogenation of diethyl-THFG-B.

It is possible to deduce from the nature of the dehydrogenation products the steric pattern of the tetrahydrofuran substituents. Figs. (XIV) and (XV) depict the two possible *meso* structures of the THFG ethers in which the hydrogen atoms are, respectively, all-*cis* and semi-*trans*. In structure (XIV), the hydrogen atoms are more accessible to the catalyst, a condition which would more readily favour dehydrogenation to a furan rather than a phenylnaphthalene. Accordingly, THFG-B and its ethers were assigned the fully *cis*-structure (XIV) and THFG-A and its derivatives the structure (XV). Further evidence in support of these conclusions was obtained from the catalytic hydrogenation of dimethyl- and diethyl-furoguaiacin using 5% palladised charcoal in dimethylformamide at 55°, when both products were the ethers of THFG-B.

Similar assignments with respect to the methyl ethers were made by Blears and Haworth [18] from the hydrogenation of synthetic dimethylfuroguaiacin (10% palladised charcoal at room temperature and 30 atm.) to an optically inactive tetrahydro-derivative having the same melting point as dimethyl-THFG-B and with which there was no melting point depression (determination made by Professor Haworth). This hydrogenation product in turn underwent isomerisation (perchloric acid in acetic acid for 30 minutes) to galgravin. In accordance with the views of Linstead *et al.*,[19] on the stereochemistry of catalytic hydrogenation, the product was considered to have the all-*cis* structure (XIVa) and galgravin the semi-*trans* structure (XVa). The ready isomerisation to galgravin was interpreted as resulting from a release of steric compression due to interference of aromatic rings with adjacent methyl groups in (XIVa). Birch *et al.*[20] from other considerations also suggested the semi-*trans* structure (XVa) for galgravin.

Evidence consonant with the structures (XVb) and (XIVb) for THFG-A and -B, respectively, has been obtained from nuclear magnetic resonance measurements (in CS_2), those for the A isomer being in excellent agreement with the values recently reported by Crossley and Djerassi [21] for galgravin (in $CDCl_3$), the small upfield shift (0·1—0·3 τ) in our values being obviously due to a solvent effect. The authors are indebted to Dr. R. L. Erskine and Dr. S. A. Knight, British Petroleum Company Ltd., Research Centre, Sunbury-on-Thames, for running the spectra and for the following note.

The n.m.r. spectra of carbon disulphide solutions of dimethyl-THFG-A (galgravin) and of its B-isomer to which the *meso*-structures (XVa) and (XIVa) have been ascribed, have similar aromatic absorption at about 3·3 τ and methoxyl at about 6·3 τ.[22] The absorption due to the methyl groups attached to the tetrahydrofuran ring of dimethyl-THFG-B occurs at a higher field (doublet 9·41, 9·50 τ) than that of dimethyl-THFG-A (8·98, 9·03 τ). Inspection of molecular models indicates that this may be caused by the methyl group restricting the rotation of a *cis*-aromatic substituent and thus becoming shielded by it. Similarly the absorption of the β-ring hydrogen atoms at a higher field strength in dimethyl-THFG-A (complex multiplet *ca.* 7·9 τ) than in dimethyl-THFG-B (complex multiplet *ca.* 7·4 τ) indicate a *cis*-relationship with the aromatic ring. The separation of the doublets due to the α-ring hydrogen atoms is almost the same for both isomers (A, $J = 6{\cdot}2$ c./sec.; B, $J = 6{\cdot}5$ c./sec.), and it is therefore assumed that the tetrahydrofuran ring is distorted to give approximately equal coupling constants for both *cis*- and *trans*-configurations of the α- and β-hydrogen atoms. However, the absorption of the α-protons of dimethyl-THFG-B (doublet 5·01, 5·09) at a lower field strength than that those of the A-isomer (doublet 5·65, 5·73) could again be a consequence of restricted rotation of the aromatic ring by a *cis*-methyl group.

Experimental

Light petroleum had boiling point 60—80°.

Extraction of the Heartwood of Guaiacum officinale *L.*—The finely comminuted heartwood (sawdust) (4·0 kg.) was extracted with light petroleum (*ca.* 3·5 l.) for 22 hr. in a metal Soxhlet apparatus of 4—5 kg. wood capacity. Evaporation of the solvent left a viscous, greenish-yellow gum (185 g., 4·5%); wood shavings gave a smaller extract (*ca.* 3·0%).

The product (280 g.) from shavings (10 kg.) was exhaustively extracted with boiling methanol (*ca.* 3 l.) until the extracts were almost colourless. Evaporation left a brown-yellow gum (53 g.) which was dissolved in warm 2% sodium hydroxide (600 ml.). Next day the precipitated sodium salt of guaiaretic acid was removed, the concentration of alkali in the filtrate was increased to 7% and the remaining salt allowed to separate over several hours. The two fractions

[18] Blears and Haworth, *J.*, 1958, 1985.
[19] Linstead, Doering, Davis, Levine, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985.
[20] Birch, Milligan, Smith, and Speake, *J.*, 1958, 4471.
[21] Crossley and Djerassi, *J.*, 1962, 1459.
[22] Jackman, "Applications of N.M.R. Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959.

were combined, washed with a little acetone, and after suspension in water, decomposed with a rapid stream of carbon dioxide which precipitated the free phenol as a finely divided, pale fawn solid. The crude material, washed with water and dried *in vacuo*, amounted to 35·8 g. (0·36% of the wood). Treatment with carbon dioxide of the dark brown filtrate from the sodium salt precipitation caused the separation of a soft, dark brown resin which slowly solidified (15·4 g., 0·15% of the wood) (" the resinous phenolic fraction," *vide infra*). The yields of crude guaiaretic acid varied from 0·36—0·60%, the resinous phenolic material being 0·15—0·32%.

Ether, acetone, and ethanol each removed from the wood large amounts of dark resin which acquired a bluish colour when exposed to air and gave an intense blue ferric reaction in ethanol solution. These extracts were not further investigated.

Guaiaretic Acid and Derivatives.—Guaiaretic acid (I; R = H). Several recrystallisations of crude guaiaretic acid (20 g.) from light petroleum, 60% methanol (twice), and finally ethanol afforded plates (2 g.), m. p. 100—101°, $[\alpha]_D^{16}$ −91° (*c* 1·1, in ethanol) (lit., m. p. 99—100·5°, $[\alpha]_D$ −94°;[3] m. p. 101°, $[\alpha]_D^{20}$ −91°[15]) $\lambda_{max.}$ 207 and 260 mμ (log ε 4·64 and 4·28) (Found: C, 72·9; H, 7·7; OMe, 18·4. Calc. for $C_{20}H_{24}O_4$: C, 73·1; H, 7·6; 2 OMe, 18·3%). Methylation (15% potassium hydroxide–methyl sulphate) gave dimethylguaiaretic acid as tiny needles (0·6 g.), m. p. 94° (from methanol), $[\alpha]_D^{16}$ −92° (*c*, 0·6, in ethanol) (lit., m. p. 94—94·5°, $[\alpha]_D$ −94°;[3]; m. p. 92—93°, $[\alpha]_D^{20}$ −94°),[4] $\lambda_{max.}$ 211 and 259 mμ (log ε 4·45 and 4·20) (Found: C, 74·0; H, 8·3; OMe, 33·6. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9; 4OMe, 34·3%). Colour with concentrated sulphuric acid: cherry red.

meso-*Dihydrodimethylguairetic acid* (II; R = Me). Prepared by catalytic reduction of the above dimethyl ether, this formed needles, m. p. 101—102° (from methanol) (lit., 101—102°;[3] 101·5—102°),[15] $[\alpha]_D^{16}$ 0°, $\lambda_{max.}$ 229 and 281 mμ (log ε 4·30 and 3·79) (Found: C, 74·0; H, 8·5. Calc. for $C_{22}H_{30}O_4$: C, 73·7; H, 8·4%). The compound gave no colour with concentrated sulphuric acid. The dinitro-derivative, pale yellow prisms, had m. p. 151—152° (lit., 150°,[3] 151—152°,[5] 153—153·5°)[4] (Found: C, 59·2; H, 6·6; N, 5·9. Calc. for $C_{22}H_{28}N_2O_8$: C, 58·8; H, 6·2; N, 6·2%).

Diethylguaiaretic acid (I; R = Et). Prepared analogously to the dimethyl ether, this was obtained as lustrous plates, m. p. 91—91·5° (from methanol), $[\alpha]_D^{20}$ −80° (*c* 0·22, in ethanol), (previous m. p.s, 95—96°, $[\alpha]_D^{19}$ −48°[14] and 100—102°,[23] probably refer to samples contaminated with the dihydro-derivative) (Found: C, 74·8; H, 8·5. Calc. for $C_{24}H_{32}O_4$: C, 75·0; H, 8·4%).

meso-*Diethyldihydroguaiaretic acid* (II; R = Et). Prepared as for the dimethyl ether, this formed plates, m. p. 98—99° (from methanol) (lit.,[14] 98—99°), $[\alpha]_D^{16}$ 0° (Found: C, 74·9; H, 9·0. Calc. for $C_{24}H_{34}O_4$: C, 74·6; H, 8·8%). The dinitro-derivative, pale yellow needles from ethanol, had m. p. 111° (lit.,[14] 111—112°[14]) (Found: C, 60·3; H, 6·9; N, 5·5. Calc. for $C_{24}H_{32}O_8N_2$: C, 60·5; H, 6·7; N, 5·9%). *Diacetylguaiaretic acid* (I; R = Ac). This separated from methanol in prisms, m. p. 84·5°, $[\alpha]_D^{20}$ −66° (lit. m. p. 86—87°;[17] 84—85°, $[\alpha]_D^{20}$ −66°[4]) (Found: C, 69·9; H, 6·6; OMe, 15·2. Calc. for $C_{24}H_{28}O_6$: C, 69·9; H, 6·8; OMe, 15·1%).

meso-*Diacetyldihydroguaiaretic acid* (II; R = Ac). Prepared by reduction of diacetylguaiaretic acid over 5% palladised charcoal, this crystallised from methanol in prisms, m. p. 115° (lit. 112°,[17] 115—116°[4]), $[\alpha]_D^{16}$ 0° (Found: C, 69·3; H, 7·0; OAc, 18·7. Calc. for $C_{24}H_{30}O_6$: C, 69·6; H, 7·2; 2OAc, 20·8%). The *dinitro-derivative* crystallised from alcohol as pale yellow prisms, m. p. 199—201° (decomp.) (Found: C, 56·9; H, 5·8; N, 5·1. $C_{24}H_{28}N_2O_{10}$ requires C, 57·2; H, 5·6; N, 5·6%).

meso-*Dihydroguaiaretic acid* (II; R = H). Obtained by deacetylation of diacetyldihydroguaiaretic acid, this separated from 60% methanol as plates, m. p. 87—88° (lit.,[4] 88—88·5°) (Found: C, 73·0; H, 7·8; OMe, 18·9. Calc. for $C_{20}H_{26}O_4$: C, 72·7; H, 7·9; OMe, 18·9%).

Dehydrodimethylguaiaretic acid (III; R = Me). Prepared by cyclisation of dimethylguaiaretic acid (10·0 g.) with Hubl's iodine, this formed small lustrous needles (4·0 g.), m. p. 178—179° (from glacial acetic acid then methanol) (lit.,[3] 179°), $\lambda_{max.}$ 237, 284, 314, and 329 mμ (log ε 5·01, 4·14, 3·62, and 3·74) (Found: C, 75·2; H, 6·7. Calc. for $C_{22}H_{24}O_4$: C, 75·0; H, 6·8%).

Dehydrodiethylguaiaretic acid (III; R = Et). Prepared as above, this *derivative* formed prisms, m. p. 162—163° (from ethyl acetate), $\lambda_{max.}$ 239, 284, 315, and 329 mμ (log ε 4·87, 4·00, 3·52, and 3·58) (Found: C, 75·9; H, 7·4. $C_{24}H_{28}O_4$ requires C, 75·8; H, 7·4%).

[23] Herzig and Schiff, *Montash.*, 1898, **19**, 95.

The Presence of Dihydroguaiaretic Acid in the Crude Guaiaretic Acid Fraction.—The methyl sulphate–alkali methylation product from crude guaiaretic acid (20 g.) was chromatographed in benzene on alumina. Two crystallisations from methanol of the residue from the benzene eluate afforded tiny needles (9·0 g.), m. p. 95° (Found: C, 74·3; H, 7·9; OMe, 34·3. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9; 4OMe, 34·8%). The specific rotation, $[\alpha]_D^{16}$ −74°, was little changed by further crystallisation or chromatography.

(i) *Hydrogenation.* A solution of the product in ethyl acetate containing 10% palladised charcoal absorbed 0·84 mole of hydrogen with the formation of the pure *meso*-dihydro-compound, m. p. 101—102°, undepressed by a sample obtained from pure dimethylguaiaretic acid, $[\alpha]_D^{20}$ 0° (Found: C, 74·0; H, 8·5%). The product gave no colour with concentrated sulphuric acid. On long standing the mother-liquor gave flat needles, m. p. 83—85°, probably the optically active ether (lit.,[3] m. p. 86—87°, $[\alpha]_D$ −27°). Ethylation and acetylation of crude guaiaretic acid gave derivatives, m. p. 91—91·5°, $[\alpha]_D^{16}$ −71° and m. p. 88—89°, $[\alpha]_D^{20}$ −42°, respectively, each of which absorbed *ca.* 0·85—0·90 mole of hydrogen.

(ii) *Oxidation.* Powdered potassium permanganate (3·0 g.) was added over 2 hr. to a refluxing acetone solution (100 ml.) of crude dimethylguaiaretic acid (1·0 g.), and, after further heating for 1 hr., the mixture was concentrated to *ca.* 40 ml. The addition of water (20 ml.) refluxing for 10 min., and treatment with more water (20 ml.) gave a precipitate, which was removed. The combined filtrate and washings were distilled, the small amount of solid which separated was taken up into ether, and the ethereal solution was washed with 2N-sodium carbonate (2 × 10 ml.), the washings being added to the aqueous solution. Evaporation of the dried ($MgSO_4$) ether extract left an oil which rapidly solidified and afforded *meso*-dihydro-dimethylguaiaretic acid (0·115 g., 11·5%), m. p. and mixed m. p. 101—102° (from methanol). Acidification of the aqueous solution gave veratric acid (0·3 g.). Permanganate oxidation of the diacetyl derivative of crude guaiaretic acid permitted the isolation of *meso*-diacetyl-dihydroguaiaretic acid (10·5%), m. p. and mixed m. p. 114°. No acidic fraction was obtained from this reaction.

Resinous Phenolic Fraction.—Alkylation. After the phenolic resin (15·2 g.) and methyl sulphate (25 ml.) had been refluxed in dry acetone (250 ml.) with anhydrous potassium carbonate (30 g.) for 40 hr., solids were removed and the filtrate and acetone washings evaporated to small bulk. Water and dilute ammonia were added and the methylated product was isolated with ether as a pale yellow-brown gum (15·5 g.). The use of either ethyl sulphate or ethyl iodide in the above procedure likewise resulted in a thick, syrupy product (27 g. from 34 g. of resin).

Chromatographic resolution of the alkylated phenolic fraction. Chromatography was carried out on columns (diameter *ca.* 6 cm.) of alumina (Spence Type H) and elution was begun with either 25 or 50% benzene–light petroleum. The eluates were collected in small aliquots; after removal of solvent the residues, usually gummy, were taken up in methanol and allowed to crystallise. These solid products, alone or combined with other obviously related fractions, were either recrystallised to constant m. p. or fractionally crystallised to provide pure compounds. A large number of chromatographic resolutions was carried out on material derived from different batches of wood, and as not all were identical, the most effective procedure is illustrated by reproducing details of one example each of the fractionation of the methylated and ethylated products.

Methylated phenolic fraction. When the methylated gum (23 g.) was dissolved in 50% benzene–light petroleum, crystals immediately began to separate. These were collected, washed with a little of the solvent, and recrystallised from methanol to give fluorescent needles of dimethylfuroguaiacin (1·0 g.), m. p. 167—169°. The original filtrate was poured on to a column of alumina (700 g.) and elution with benzene–light petroleum, benzene, ether–benzene, and ether followed by crystallisation of the products gave ten main crystalline fractions (A—J).

Products A, B, and the second crop of C, combined and recrystallised twice from methanol, gave dimethylisoguaiacin (0·9 g., 0·01%), m. p. 99—101°. Warm methanol dissolved the bulk of C (first crop), leaving a residue of prisms which were removed. The filtrate desposited a mixture, m. p. 93—94°, of dimethylguaiaretic acid and its dihydro-derivative (0·3 g.). Recrystallisation of the undissolved crystals gave prismatic rods of dimethyldehydroguaiaretic acid (0·06 g., 0·0006%), m. p. 179—180°.

Products D and E, combined and recrystallised from methanol, afforded dimethylfuroguaiacin (0·45 g. in all, 0·015%), m. p. 169—170°, as flat, lustrous, fluorescent needles. On recrystallisation from methanol, products G and H gave lustrous plates (1·9 g.), m. p. 108—110°.

Recrystallisation from light petroleum (20 ml.) then methanol gave flat needles of dimethyl-THFG-A (galgravin) (0·08 g., 0·002%), m. p. 120°. Crystals obtained by concentrating the petroleum liquors had m. p. 108—110°, and further recrystallisation only served to widen the m. p. range.

Combinations of products I and J and recrystallisation from methanol gave dimethyl-THFG-B (0·15 g., 0·0015%), plates, m. p. 132—133·5°.

Ethylated phenolic fraction. Ethylated phenolic resin (27 g.) was chromatographed on a column of alumina (750 g.) and eluted with the same series of solvents, the fractions being crystallised from methanol.

Fraction 1 consisted of diethylisoguaiacin (0·3 g.), m. p. 105—106·5°. Slow cooling of a solution of fraction 2 in methanol produced diethylfuroguaiacin (0·1 g.), m. p. 150—151°. When the filtrate was cooled in ice, a product (2·5 g.), of m. p. 80—95°, separated which, when crystallised from methanol, gave needles (*ca.* 0·05 g.) m. p. 150°, then fluffy needles (1·4 g.), m. p. 95—102°. Two crystallisations of the latter fraction afforded felted needles (0·8 g.), m. p. 104—106°, of diethylisoguaiacin (in all, 0·01%).

Recrystallisation of fractions 3 and 4 from methanol gave flat, fluorescent needles (0·2 g.), m. p. 150—151°, of diethylfuroguaiacin (in all, 0·003%). Fractions 6—10, combined and recrystallised, afforded ethylmethylfuroguaiacin (0·6 g.), m. p. 138—140° (0·005%), as fluorescent needles from methanol.

Three recrystallisations from methanol of the combined fractions 12—14 gave small prisms of diethyl-THFG-A (0·1 g.), m. p. 98—100° (0·001%). From another chromatogram, fractions containing this lignan required recrystallisation alternately from methanol and light petroleum before yielding a pure product.

Combined fractions 15—18 were crystallised thrice from methanol to provide diethyl-THFG-B, lustrous plates (0·3 g.), m. p. 103—104° (0·003%). Repeated crystallisation of fractions 19 and 20 resulted in lustrous plates (0·06 g.), m. p. 114—115°, of the tentatively designated ethylmethyl-THFG.

In another chromatographic resolution of the ethylated mixture of phenols, further lignan ethyl ethers were isolated. From the mother-liquors of the fractions (25% benzene–light petroleum) which gave diethylisoguaiacin, silky needles (0·2 g.), m. p. 113—115°, of an isomer, diethylguaiacin, separated. From the later fractions (50 and 75% benzene–light petroleum) a small amount (5 mg.) of dehydrodiethylguaiaretic acid, m. p. 160—161°, was obtained, as well as a considerable quantity (1·65 g.) of a mixture, m. p. 89—90°, of diethylguaiaretic acid and its dihydro-derivative.

Dimethylisoguaiacin, (VII; R = Me).—An analytical sample formed small, tightly packed clusters of felted *needles*, m. p. 101—102° (from hexane or methanol) $[\alpha]_D^{23}$ −46° (*c* 5·2, in $CHCl_3$), $\lambda_{max.}$ 283 mμ (log ε 3·83) (Found: C, 73·8, 74·1; H, 7·8, 8·0; OMe 35·0; *C*-Me, 7·4. $C_{22}H_{28}O_4$ requires C, 74·1; H, 7·9; 4OMe, 34·8; 2*C*-Me, 8·4%). On one occasion a form, m. p. 86—87°, was obtained from hexane by rapid cooling, but on subsequent recrystallisation from methanol it reverted to the higher-melting modification. With concentrated sulphuric acid, dimethylisoguaiacin produced a deep orange colour. When one drop of concentrated nitric acid was added to its solution in glacial acetic acid a transient blue colour developed which changed to green and finally golden yellow. No hydrogen uptake was observed on attempted hydrogenation.

Oxidation (i) *With chromic acid.* Chromic oxide (0·9 g.) dissolved in pure acetic acid (4 ml.) and water (0·5 ml.) was added during 2 hr. to a refluxing acetic acid solution (7·5 ml.) of the lignan (0·5 g.). The mixture was poured into water and next day the red resinous precipitate was collected, washed well with water, and dissolved in ethanol. The orange powder, m. p. 223—227°, which separated was sublimed at 130—140°/0·1 mm., affording yellow needles of 6,7-dimethoxy-2,3-dimethylnaphthaquinone (IV; R = Me), m. p. and mixed m. p. 239—240°, $\lambda_{max.}$ 276, 345, and 404 mμ (log ε 4·48, 3·32, and 3·05) (Found: C, 68·7; H, 5·4; OMe 25·4%; *M*, 242. Calc. for $C_{14}H_{14}O_4$: C, 68·3; H, 5·7; OMe, 25·2%; *M*, 246). It formed a green solution in concentrated sulphuric acid. The naphthaquinone did not darken with hydrochloric acid or alkali, nor react with Brady's reagent. Its alcoholic solution was decolourised by zinc and dilute hydrochloric acid and, after filtration, the colour was restored and yellow needles of the quinone separated. The quinone very slowly liberated iodine from hydriodic acid, gave a positive iodoform reaction, and decolourised warm acetone solutions of permanganate.

(ii) *With potassium dichromate.* Dimethylisoguaiacin (0·5 g.) and potassium dichromate (3·0 g.) in acetic acid (40 ml.) were heated on a steam-bath for 8 hr., and the solution poured into water and thoroughly extracted with ether. Evaporation of the washed (water, sodium hydrogen carbonate, 2N-sodium hydroxide, and water) and dried ($MgSO_4$) extract left a yellow solid (0·1 g.), which, when recrystallised and sublimed at 130—140°/0·1 mm., gave 6,7-dimethoxy-2,3-dimethylnaphthaquinone, yellow needles, m. p. and mixed m. p. 241°. Acidification of the alkaline washings precipitated a brown resinous solid (crimson with concentrated sulphuric acid) which was esterified with diazomethane and sublimed at 110—120°/0·3 mm., but it failed to yield a purifiable ester.

Dehydrogenation. Dimethylisoguaiacin (70 mg.) was heated at 300—320° with 30% palladised charcoal (20 mg.) for 2 hr. The mixture, in 50% benzene–light petroleum, was chromatographed on alumina and the blue fluorescent band (u.v. light) eluted with the same solvent. Evaporation of the eluate left a gum which crystallised from methanol as prisms (*ca.* 10 mg.), m. p. 165—175°. Two recrystallisations gave dehydrodimethylguaiaretic acid as needles, m. p. 177—178°, which did not depress the melting point of an authentic sample, m. p. 178—179°.

Diethylisoguaiacin (VII; R = Et).—This *compound* crystallised from methanol in clusters of long felted needles, m. p. 108°, $[\alpha]_D^{23}$ −32° (*c* 4·7, in $CHCl_3$), $\lambda_{max.}$ 283 mμ (log ε 3·85) (Found: C, 75·0, 75·3; H, 8·5, 8·6; *C*-Me, 14·1, 14·1. $C_{24}H_{32}O_4$ requires C, 75·0; H, 8·4; 4*C*-Me, 15·6%). It was quite soluble in ether, benzene, and acetone but rather less soluble in methanol, ethanol, and hexane. It gave a pale orange-yellow colour with concentrated sulphuric acid.

Oxidation. (i) *With nitric acid.* Diethylisoguaiacin (0·4 g.) was boiled with concentrated nitric acid (8 ml.) for 5 min., and the clear yellow solution poured into water. The ether extract, after being washed with 2N-sodium carbonate and evaporated, yielded a yellow solid which was exhaustively extracted with boiling light petroleum. The yellow material (50 mg.) crystallising from the petroleum extracts gave 2-ethoxy-4,5-dinitroanisole, plates, m. p. and mixed m. p. 147—148° (from methanol). Nitric acid oxidation of dimethylisoguaiacin afforded a small amount of 4,5-dinitroveratrole.

(ii) *With chromic acid.* A solution of chromic oxide (0·9 g.) in acetic acid (4 ml.) and water (1 ml.) was added during 1 hr. to a refluxing acetic acid solution (7 ml.) of diethylisoguaiacin (0·5 g.), refluxed for 1 hr., cooled, and poured into water (200 ml.). The mixture was extracted thoroughly with ether and the insoluble solid (A) which settled at the interface was collected. The red alkali-washed ether extract was dried ($MgSO_4$) and evaporated to give a red gum, which deposited from ethanol red crystals interspersed with a few clusters of golden needles (40 mg.). Two recrystallisations afforded clusters of red needles, m. p. 161—162° (B). Sublimation at 130—140°/0·2 mm. of the gummy residue, obtained by evaporating the first liquor from the crystallisation of (B) yielded only yellow needles, m. p. 142° (from ethanol) (C). Crystallisation of (A) from acetic acid gave 2,6-diethoxy-3,7-dimethoxyanthraquinone, needles, m. p. 295°, alone or mixed with a sample, m. p. 296°, obtained by dichromate oxidation of diethyldiisoeugenol. The anthraquinone (A) gave a green sulphuric acid colour and compound (B) blue changing to green. Alcoholic solutions of (B) and phenylhydrazine caused an immediate colour change to straw yellow. With Brady's reagent (B) gave a dark red solution and a red precipitate slowly separated. Acetone solutions of permanganate were slowly decolourised, and on warming an alcoholic solution of (B) with zinc and dilute hydrochloric acid, the red colour faded to a straw yellow. It gave a positive iodoform test. No empirical formula could be derived from the analytical figures (Found: C, 67·3; H, 5·9%; *M*, 331) and there was insufficient material for further examination.

Product (C) was 6-*ethoxy*-7-*methoxy*-2,3-*dimethylnaphthaquinone* (IV; R = Et) (Found: C, 68·6; H, 6·3. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%), $\lambda_{max.}$ 277, 346, and 408 mμ (log ε 4·51, 3·35, and 3·10). It dissolved in concentrated sulphuric acid forming a green solution.

(iii) *With potassium dichromate.* A mixture of diethylisoguaiacin (0·5 g.) and powdered potassium dichromate (3·0 g.) in acetic acid (40 ml.) was heated on a steam-bath for 7 hr., and the green mixture was diluted with water and extracted with ether. The extract, when washed with 2N-sodium carbonate (these washings yielded no precipitate on acidification) and extracted with dilute sodium hydroxide, yielded by evaporation a yellow gum (0·18 g.) subliming at 130°/0·1 mm., to yellow oily needles. Recrystallisation from ethanol gave golden-yellow needles (*ca.* 5 mg.), m. p. 141—142°, of the above naphthaquinone (IV; R = Et). Acidification

of the sodium hydroxide extract precipitated a solid (0·16 g.), m. p. 165—178°. Recrystallisation from aqueous methanol and twice from benzene–light petroleum gave 4-ethoxy-3-methoxy-6-(3-methoxy-4-ethoxybenzoyl)benzoic acid (VI; R = H), m. p. 206—207·5° (lit., 213°; [8] 215° [9]), also prepared from diethyldi-isoeugenol (Found: C, 64·4; H, 5·7. Calc. for $C_{20}H_{22}O_7$: C, 64·2; H, 5·9%). The acid gave a red solution in concentrated sulphuric acid. A sample, m. p. 207—209°, kindly supplied by Professor Muller, had with the above acid mixed m. p. 206—208°. With diazomethane the *methyl ester* was obtained as needles from methanol, m. p. 135°, alone or mixed with the ester, m. p. 134—135°, from diethyldi-isoeugenol (Found: C, 64·9, H, 6·1. $C_{21}H_{24}O_7$ requires C, 64·9; H, 6·2%).

Dehydrogenation. (i) Diethylisoguaiacin (60 mg.) and 30% palladised charcoal (20 mg.) were heated at 310—315° for 2 hr. The mixture, taken up in chloroform and passed through alumina, gave a light brown eluate which was further chromatographed on alumina in 50% benzene–light petroleum thus eluting a strongly (u.v.) fluorescent band. Evaporation *in vacuo* left a gum, prisms (*ca.* 10 mg.), m. p. 159—160° (from methanol). Mixed with a sample of pure dehydrodiethylguaiaretic acid, m. p. 162°, the dehydrogenation product melted at 159—161°, and its infrared spectrum (kindly determined by Dr. T. R. R. McDonald, British Celanese Laboratories) was identical with that of dehydrodiethylguaiaretic acid.

(ii) The lignan (50 mg.) was refluxed with tetrachloro-*o*-benzoquinone (70 mg.) in benzene (5 ml.) for 24 hr. and the red product was passed through alumina and eluted with benzene. The (u.v.) fluorescent eluate was evaporated *in vacuo* leaving a slightly coloured gum which deposited the above phenylnaphthalene as prisms (30 mg., 60%), m. p. and mixed m. p. 160—161° (from methanol).

Diethylguaiacin (X; R = Et) formed discrete silky needles, m. p. 114—115° (from methanol or light petroleum), $[\alpha]_D^{17}$ +4° (*c* 1·1, in $CHCl_3$), $\lambda_{max.}$ 283 mμ (log ε 3·86) (Found: C, 75·1; H, 8·0; *C*-Me, 13·4. $C_{24}H_{32}O_4$ requires C, 75·0; H, 8·4; 4*C*-Me, 15·6%). It gave a rose colour in sulphuric acid. Dehydrogenation by refluxing the compound with tetrachloro-*o*-benzoquinone in benzene for 24 hr. afforded dehydrodiethylguaiaretic acid (III; R = Et) (66%).

Methyl and Ethyl Ether Mixtures of Guaiaretic and Dihydroguaiaretic Acids.—(i) *Methyl ethers.* This crystalline fraction, m. p. 94°, $[\alpha]_D^{16}$ −74° (*c* 0·7, in EtOH) (Found: C, 74·0; H, 7·8; OMe, 33·6. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9; 4OMe, 34·8%) absorbed 0·85 mole of hydrogen on catalytic (5% Pd–C) reduction. The dihydro-compound (*ca.* 10% of the mixture) which remained after permanganate oxidation of the mixture, formed needles, $[\alpha]_D^{20}$ 0°, m. p. and mixed m. p. 101—102° (from methanol).

(ii) *Ethyl ethers.* This fraction crystallised in plates from methanol, m. p. 90—91° $[\alpha]_D^{16}$ −69° (*c* 0·85, in EtOH) (Found: C, 74·9; H, 8·5. Calc. for $C_{24}H_{34}O_4$: C, 75·0; H, 8·4%) and took up 0·92 mole of hydrogen on reduction. Permanganate oxidation permitted the isolation of the dihydro-component, $[\alpha]_D^{16}$ 0°, m. p. and mixed m. p. 99°.

Dehydrodimethylguaiaretic acid. (III; R = Me) separated as prisms, m. p. and mixed m. p. 179—180° (from methanol), $\lambda_{max.}$ 237, 283, 314, and 329 mμ (log ε 4·85, 4·10, 3·47, and 3·57) (Found: C, 75·2; H, 6·9; OMe, 31·3. Calc. for $C_{22}H_{24}O_4$: C, 75·0; H, 6·8; 4OMe, 35·3%). With sulphuric acid the compound produced a straw-yellow solution. Dehydrodiethylguaiaretic acid (III; R = Et) prisms, m. p. 160—161° (from methanol or glacial acetic acid), was identified by mixed m. p.

Dimethylfuroguaiacin (XI; R = Me).—This separated from methanol in tiny lustrous pale blue fluorescent plates, m. p. and mixed m. p. 170—171°. Its intense green colour in sulphuric acid slowly changed to turquoise. In formic acid a reddish brown colour developed. The compound was soluble in acetone, ethyl acetate, and chloroform, slightly soluble in benzene and sparingly soluble in ether, methanol, ethanol, and acetic acid, and had $\lambda_{max.}$ 252 and 326 mμ (log ε 4·11 and 4·47) (Found: C, 71·6, 71·2; H, 6·4, 6·3; OMe, 33·4, 33·1; *C*-Me, 7·4, 5·2%; *M*, 361, 347. Calc. for $C_{22}H_{24}O_5$: C, 71·7; H, 6·5, 4OMe, 33·7; 2*C*-Me, 8·2%; *M*, 368).

Oxidation. (i) *With permanganate.* Powdered potassium permanganate (0·5 g.) was added during 1 hr. to a refluxing solution of dimethylfuroguaiacin (0·2 g.) in purified acetone (30 ml.), and, after further heating to halve the volume, water (10 ml.) was added and refluxing continued (10 min.). Solids were removed from the hot solution and washed thoroughly with acetone and hot water. When filtrate and washings were combined and the remaining acetone distilled, the cooled solution deposited unchanged dimethylfuroguaiacin (0·1 g.), m. p. 168—170°. The filtrate was acidified and extracted with ether, yielding a solid which twice recrystallised from ethyl acetate gave veratric acid (15 mg.), m. p. 179—180°.

(ii) *With nitric acid.* Dimethylfuroguaiacin (0·2 g.) was added to concentrated nitric acid (4 ml.), the solution boiled for 5 min., and poured into water. The precipitate was collected in ether and the extract was shaken repeatedly with 2N-sodium carbonate to remove colour and then evaporated. The semi-solid residue, exhaustively extracted with light petroleum, gave 4,5-dinitroveratrole (30 mg.), yellow needles, m. p. 127—129° (from ethanol,) identified by mixed m. p.

Hydrogenation. Dimethylfuroguaiacin (0·22 g.) in glacial acetic acid (15 ml.) and dimethylformamide (15 ml.) with 5% palladium–charcoal (0·1 g.) was shaken in hydrogen at *ca.* 55° (infrared lamp). After 15 hr. hydrogen absorption was 1·5 moles. Filtration from catalyst and evaporation under reduced pressure left a gum which rapidly crystallised giving with warm methanol, needles (0·15 g.) of dimethylfuroguaiacin. Concentration and cooling of the filtrate gave a mixture of needles and plates, m. p. 124—129°, which was dissolved in light petroleum and cooled to give plates (18 mg.), m. p. 132—133°, undepressed on admixture with dimethyl-THFG-B, followed by a second crop, m. p. 124—130°.

Diethylfuroguaiacin (XI; R = Et).—This *lignan* crystallised from methanol in flat needles with a blue fluorescence (very intense in solution), m. p. 151°, $\lambda_{max.}$ 252 and 326 mμ (log ε 4·08 and 4·49) (Found: C, 72·8; H, 6·9; *C*-Me, 13·3. $C_{24}H_{28}O_5$ requires C, 72·7; H, 7·1; 4*C*-Me, 15·1%). Its solution in sulphuric acid was green slowly changing to turquoise. Its solubility was similar to that of the dimethyl analogue; however it was somewhat more soluble in methanol and ethanol.

Oxidation. (i) *With permanganate.* The procedure used was that employed for the dimethyl ether, and the ethyl compound (0·2 g.) afforded *O*-ethylvanillic acid, needles (90 mg.), m. p. and mixed m. p. 195—197° (from ethyl acetate). Starting material (0·1 g.) was recovered.

(ii) *With nitric acid.* Oxidation of the lignan (0·2 g.) by the method used for dimethylfuroguaiacin afforded a product (80 mg.) which, after two crystallisations from ethanol, was obtained as tiny, pale yellow plates, m. p. 147—149°, mixed m. p. with 2-ethoxy-4,5-dinitroanisole, 148—149°.

Hydrogenation. Diethylfuroguaiacin (0·4 g.) in glacial acetic acid (20 ml.) and dimethylformamide (20 ml.) was added to a suspension of 5% palladised charcoal (0·1 g.) in glacial acetic acid (10 ml.) previously hydrogenated (100 ml. absorbed). The mixture, shaken in hydrogen at 55° (infrared lamp), absorbed the theoretical volume (55 ml., 2 moles) in 6 hr. Removal of the catalyst and evaporation under reduced pressure left a gum which crystallised from methanol and then from light petroleum as flat needles (0·15 g.), m. p. 105—106°, alone or mixed with diethyl-THFG-B (Found: C, 72·2; H, 8·1. Calc. for $C_{24}H_{32}O_5$: C, 72·0; H, 8·0%).

Ethylmethylfuroguaiacin (XII; R = Et).—This *lignan* was obtained as fluorescent needles, m. p. 140° (from methanol), $\lambda_{max.}$ 252 and 325 mμ (log ε 4·09 and 4·47) (Found: C, 71·9; H, 7·0; *C*-Me, 11·7. $C_{23}H_{26}O_5$ requires C, 72·2; H, 6·9; 3*C*-Me, 11·8%). Its colour in sulphuric acid resembled that of compound (XI; R = Et). It dissolved in acetone and chloroform, but was sparingly soluble in benzene, methanol, and ethanol.

Oxidation with permanganate. Powdered potassium permanganate (1·5 g.) was extracted (Soxhlet) into a refluxing solution of the furan (0·3 g.) in acetone (80 ml.) for 4 hr. The solution was then concentrated, water (40 ml.) added, and the manganese dioxide removed by sulphur dioxide. The remaining acetone was evaporated and the aqueous suspension thrice extracted with ether. The ethereal solution was extracted with 2N-sodium carbonate (2 × 30 ml.) and water. The alkaline extract and washings were acidified with concentrated hydrochloric acid and the precipitate (0·09 g.) collected with ether (2 × 30 ml.). The crystalline residue obtained after evaporating the dried ($MgSO_4$) solution crystallised from ethyl acetate in needles, m. p. 194—196°, undepressed on admixture with *O*-ethylvanillic acid. Evaporation of the dried ether solution left starting material (0·15 g.).

(*Dimethyl-THFG-A*) (*Galgravin*) (XVa).—This crystallised from methanol or light petroleum in flat needles, m. p. and mixed m. p. 120° $[\alpha]_D^{16}$ 0°, $\lambda_{max.}$ 231 and 279 mμ (log ε 4·27 and 3·80) (Found: C, 70·9; H, 7·6. Calc. for $C_{22}H_{28}O_5$: C, 71·0; H, 7·5%).

Diethyl-THFG-A (XVc).—This *compound* was obtained as small prisms, m. p. 100° (from methanol or light petroleum) $[\alpha]_D^{20}$ 0°, $\lambda_{max.}$ 233 and 280 mμ (log ε 4·29 and 3·81) (Found: C, 72·0, 72·1; H, 7·9, 8·0; *C*-Me, 14·7. $C_{24}H_{32}O_5$ requires C, 72·0; H, 8·0; 4*C*-Me, 15·0%). In sulphuric acid a deep cherry-red colour was produced. Hydrogen was not absorbed over palladised charcoal (10%).

Oxidation. (i) *With nitric acid.* Diethyl-THFG-A (0·3 g.) and concentrated nitric acid

(4 ml.) were heated on a steam-bath for 30 min. The yellow solid (0·24 g.) precipitated by water was recrystallised from ethanol to give 2-ethoxy-4,5-dinitroanisole plates, m. p. and mixed m. p. 147—148°.

(ii) *With chromic acid.* Chromium trioxide (0·25 g.) dissolved in glacial acetic acid (2·5 ml.) and water (3 drops), and a solution of diethyl-THFG-A (0·25 g.) in glacial acetic acid (5 ml.) were heated on a steam-bath for 45 min. The mixture was diluted with water and extracted with ether, and the ethereal solution shaken with 2N-sodium carbonate. The alkaline extract was acidified and the precipitate collected and crystallised from aqueous ethanol giving *O*-ethylvanillic acid as tiny needles, m. p. and mixed m. p. 193—195°.

(iii) *With permanganate.* Finely powdered potassium permanganate (1·3 g.) was added to a refluxing solution of diethyl-THFG-A (0·2 g.) in pure acetone (35 ml.) during 4 hr. After further refluxing (1 hr.) and concentration of the solvent, water was added and the mixture saturated with sulphur dioxide. When the remaining acetone was distilled the milky solution was extracted thrice with ether which, in turn, was twice shaken with 2N-sodium carbonate. Evaporation of the dried ($MgSO_4$) ether extract left a gum (0·18 g.) which crystallised from methanol as plates, m. p. 100°, of starting material. Ether extraction of the acidified alkaline extract gave no significant product.

Dehydrogenation. Diethyl-THFG-A (0·2 g.) was refluxed for 3 hr. with 30% palladised charcoal (0·1 g.) in freshly distilled diphenyl ether (3 ml.). The cooled mixture, diluted with boiling light petroleum (10 ml.) and filtered from the catalyst, was kept in a refrigerator for 36 hr. The product (0·105 g.) yielded diethyldehydroguaiaretic acid, prisms, m. p. 163° (from ethyl acetate) (Found: C, 76·0; H, 7·3. Calc. for $C_{24}H_{28}O_4$: C, 75·8; H, 7·4%), identical (mixed m. p. and u.v. spectrum) with a sample prepared from diethylguaiaretic acid.

Acid rearrangement and dehydration. To a solution of diethyl-THFG-A (0·25 g.) in glacial acetic acid (0·4 ml.) concentrated sulphuric acid (2 drops) was added and the brown solution left at room temperature for 1 week. Dilution with dilute sodium hydroxide and extraction with ether gave an uncrystallisable gum (0·17 g.) which was refluxed with 30% palladised charcoal (0·1 g.) in diethylene glycol (2 ml.) for 4 hr. After removal of the catalyst, which was washed with acetone, the filtrate and washings were poured into water and the gummy precipitate extracted with ether. Evaporation left a gum which gave dehydrodiethylguaiaretic acid, m. p. and mixed m. p. 162° (from ethyl acetate), $\lambda_{max.}$ 240, 284, 315, and 330 mμ (log ε 4·79, 3·98, 3·55, and 3·61).

Dimethyl-THFG-B (XIVa).—This *isomer* was obtained as lustrous plates from methanol, m. p. 132—133°, $[\alpha]_D^{23}$ 0°, $\lambda_{max.}$ 231 and 279 mμ (log ε 4·44 and 3·95) (Found: C, 70·8; H, 7·1; OMe, 33·2; *C*-Me, 8·2. $C_{22}H_{28}O_5$ requires C, 71·0; H, 7·5; 4 OMe, 33·3; 2*C*-Me, 8·1%), having a cherry-red colour in sulphuric acid.

Dehydrogenation. The pure lignan (80 mg.) was refluxed with 30% palladised charcoal (50 mg.) in diphenyl ether (2 ml.) for 1·5 hr. The solution was filtered and filtrate and washings, diluted with light petroleum to *ca.* 20 ml., were left for 24 hr. in a refrigerator. The resulting product, flat needles (20 mg.), m. p. 167—169°, gave *dimethylfuroguaiacin* as fluorescent needles, m. p. and mixed m. p. 169—170° (from methanol), which, in sulphuric acid, exhibited a green colour which slowly changed to turquoise.

Diethyl-THFG-B (XIVc).—This *lignan* crystallised from methanol or light petroleum as lustrous plates, m. p. 105°, $[\alpha]_D^{23}$ 0°, giving a cherry-red colour with sulphuric acid. It did not absorb any hydrogen during attempted reduction over 10% palladised charcoal, and had $\lambda_{max.}$ 232 and 279 mμ (log ε 4·31 and 3·81) (Found: C, 72·1; H, 8·0; *C*-Me, 14·3. $C_{24}H_{32}O_5$ requires C, 72·0; H, 8·0; 4*C*-Me, 15·0%).

Dehydrogenation. Diethyl-THFG-B (0·11 g.) was refluxed in diphenyl ether (2 ml.) with 30% palladised charcoal (50 mg.) for 1·5 hr. The mixture, worked up in the usual way, yielded diethylfuroguaiacin, flat needles (30 mg.), m. p. and mixed m. p. 150° (from methanol), which gave a green sulphuric acid reaction which slowly changed to turquoise.

Ethylmethyl-THFG.—This *lignan* separated from methanol as lustrous plates, m. p. 114—115°, insufficient for optical rotation measurement. The compound gave a cherry-red colour with sulphuric acid, did not undergo catalytic reduction, and had $\lambda_{max.}$ 232 and 280 mμ (log ε 4·26 and 3·81) (Found: C, 71·5, 71·4; H, 7·8, 7·6; *C*-Me, 9·6, 9·9. $C_{23}H_{30}O_5$ requires C, 7·14; H, 7·8; 3*C*-Me, 11·7%).

Dimethyldi-isoeugenol.—Dimerisation of isoeugenol with methanolic hydrochloric acid [24]

[24] Haworth and Mavin, *J.*, 1931, 1363.

gave a small yield of di-isoeugenol, m. p. 177—179°, converted by methyl sulphate and alkali into the dimethyl ether which crystallised from ethanol as tightly packed clusters of small needles, m. p. 105—106·5° (lit.,[24] 105—106°).

Oxidation with dichromate. A mixture of dimethyldi-isoeugenol (5 g.), potassium dichromate (20 g.), and acetic acid (200 ml.) was stirred on a steam-bath for 6 hr. The dark green solution was diluted with water (800 ml.) and thoroughly extracted with ether. Yellow crystals of 2,3,6,7-tetramethoxyanthraquinone at the interface were collected, washed with ethanol, and recrystallised from glacial acetic acid as needles (*ca.* 10 mg.), m. p. 335—336° (lit.,[24] 336°). The ethereal extract was washed with sodium hydrogen carbonate and shaken with 2N-sodium hydroxide until no more colour was removed, but acidification of the alkaline extracts gave only a trace of solid. A yellowish brown gum (2 g.) isolated from the ether solution, when dissolved in ethanol, slowly deposited prisms, m. p. 140—150°, which were not further investigated.

Diethyldi-isoeugenol.—The crude oily product obtained by ethylating isoeugenol with ethyl sulphate and alkali was dimerised by means of concentrated sulphuric acid [10] and the product crystallised from ethanol to form white, felted needles, m. p. 127° (lit.,[10] 131°), $\lambda_{max.}$ 283 mμ (log ε 3·89).

Oxidation with dichromate. Diethyldi-isoeugenol (5 g.) and potassium dichromate (20 g.) in acetic acid (200 ml.) were heated with stirring on a steam-bath for 7 hr. Pouring into water (800 ml.) precipitated a solid which was collected and warmed with dilute potassium hydroxide, the undissolved material being removed and treated with boiling methanol. On cooling, the filtered solution deposited crystals (0·33 g.), m. p. 120—146°, which after three recrystallisations from ethanol formed prisms, m. p. 155—156°, but were not further examined. The methanol-insoluble solid crystallised from acetic acid in yellow needles (40 mg.), m. p. 296° (Vanzetti and Dreyfuss [8] reported m. p. 288° for 2,6-diethoxy-3,7-dimethoxyanthraquinone) (Found: C, 67·7; H, 5·5. Calc. for $C_{20}H_{20}O_6$: C, 67·4; H, 5·6%). The quinone gave the recorded [8] green colour with sulphuric acid. Acidification of the alkaline extract gave crude acid (0·53 g.).

An ether extract of the original aqueous filtrate, washed with sodium hydrogen carbonate to remove acetic acid, was extracted with dilute potassium hydroxide. The washed and dried ethereal solution was evaporated and a methanol solution of the residue (1·0 g.) deposited small clusters of prisms, m. p. 130—136°, raised by recrystallisation from ethanol to 195—196°, but this product was not further examined.

The alkali-soluble portion (0·67 g.) was liberated and two crystallisations from benzene–light petroleum gave prisms (0·42 g.), m. p. 204—206°, with sintering from 200°. Crystallisation from aqueous ethanol afforded 4-ethoxy-3-methoxy-6-(3-methoxy-4-ethoxybenzoyl)benzoic acid, as soft needles, m. p. 206—207·5° exhibiting a deep red colour in sulphuric acid (Found: C, 64·0; H, 5·8. Calc. for $C_{20}H_{22}O_7$: C, 64·2; H, 5·9%). The *methyl ester*, prepared with diazomethane, crystallised from methanol in needles, m. p. 134—135° (Found: C, 65·2; H, 6·2. $C_{21}H_{24}O_7$ requires C, 64·9; H, 6·2%).

C.S.I.R.O., Division of Plant Industry, P.O. Box 109, Canberra City, A.C.T, Australia.

[Present address (F. E. K.): The British Petroleum Co., Ltd., Brittanic House, Finsbury Circus, London E.C.2.]

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