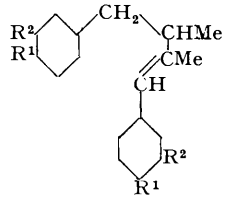
The Chemistry of the Lignan Group of Natural Products.

THE TILDEN LECTURE DELIVERED BEFORE THE CHEMICAL SOCIETY AT BRISTOL AND LONDON ON MAY 14TH AND 21ST RESPECTIVELY.

By R. D. HAWORTH, D.Sc., Ph.D.

THE predominant type of aromatic compounds found in nature contains the benzene nucleus united to a normal chain of three carbon atoms. Familiar examples include eugenol and *iso*eugenol from oil of cloves and nutmeg respectively, coniferyl alcohol occurring in the cambium sap of the Conifereæ, ferulic acid present in the resin of *Asafoetida*, numerous coumarins and the amino-acids β-phenylalanine and tyrosine. In addition the *n*-propylbenzene nucleus is molecularly associated with *iso*pentane units in many compounds, *e.g.*, osthol and ammoresinol, included in the fish poison and resin groups, and with aliphatic or aromatic C_6 units in many glycosides and plant pigments.

In 1918 Schroeter and co-workers (*Ber.*, 1918, **51**, 1587) suggested structure (I; R^1 = OH, R^2 = OMe) for *l*-guaiaretic acid, the principal constituent of the resin from *Guaiacum officinale* (Zygophyllaceæ) and drew attention to the derivation of the " bis-coniferyl " structure from two molecules of *iso*eugenol. The carbon framework of *l*-guaiaretic acid is now known to be of frequent occurrence in natural products and as safrole may replace the coniferyl structure the term " bis-coniferyl " is inadequate. In 1936 (*Ann. Reports*, 1936, **33**, 270) the generic term, lignan, was introduced to include members of a family of natural products characterised by the βγ-dibenzylbutane skeleton (II). This structure, in which two *n*-propylbenzene units are united by the β-carbon atom of the side chain, is retained in a variety of modifications, including the 1-phenyltetralin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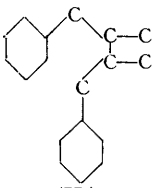
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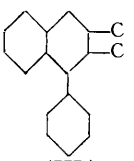
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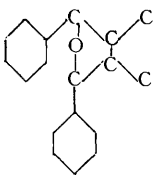
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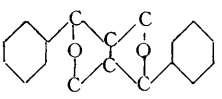
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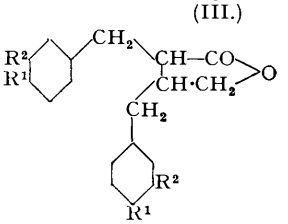
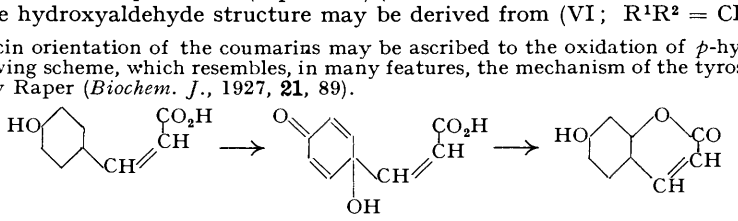

(VI.)

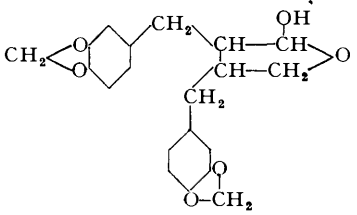
(III), the αα′-diphenylfuran (IV) and the furanofuran (V) types. The term associates the lignans with woody tissue, and the heartwood and overflow resin (Überwallungsharz) of the Conifereæ are a plentiful source of these substances. Their occurrence is not limited, however, to this Order and representatives have been obtained from the wood, rhizomes, roots, seeds, oils and resins of diverse plant families. The phenolic or phenolic ether groups attached to the aromatic nuclei are invariably of the 3 : 4-dihydroxyphenyl type associated with the naturally occurring monomeric *n*-propylbenzenes,* but considerable variation occurs in the aliphatic portion, which may contain ethereal, alcoholic, aldehydic or lactonic groups, and exhibit a state of oxidation from one to six with the value of four predominating.

The lignans are conveniently classified in accordance with the type structures (II)—(V). *l*-Guaiaretic acid (I; R^1 = OH; R^2 = OMe) is unique in containing an oxygen-free side chain. *l*-Matairesinol (VI; R^1 = OH; R^2 = OMe), obtained from the heartwood of *Podocarpus spicatus* (Conifereæ) (Easterfield and Bee, J., 1910, **97**, 1028), its monomethyl ether *l*-arctigenin (VI; R^2 and R^1 in upper ring = OMe; R^1 in lower ring = OH), occurring as a glycoside in the seeds of *Arctium lappa* (Compositeæ) (Shinoda and Kawagoe, *J. Pharm. Soc. Japan*, 1929, **49**, 565, 1165), and *l*-hinokinin (VI; R^1R^2 = CH_2O_2), isolated from *Cupressus obtusa* (Conifereæ) (Yoshiki and Ishiguro, *ibid.*, 1933, **53**, 11), form a closely related group of αβ-dibenzylbutyrolactones. *l*-Cubebin (VII), obtained from the fruit of *Piper cubeba* (Piperaceæ) (Mameli, *Gazzetta*, 1907, **37**, ii, 453), is readily oxidised to *l*-hinokinin, and the hydroxyaldehyde structure may be derived from (VI; R^1R^2 = CH_2O_2) by reduction.

* The unusual resorcin orientation of the coumarins may be ascribed to the oxidation of *p*-hydroxypropylbenzenes as indicated in the following scheme, which resembles, in many features, the mechanism of the tyrosine–melanin pigment conversion suggested by Raper (*Biochem. J.*, 1927, **21**, 89).



l-Conidendrin (VIII; R^1 = OH; R^2 = OMe), occurring in the woods of *Tsuga sieboldii* (Conifereæ) (Kawamura, *Bull. Imp. Forestry Exp. Stat. Tokyo*, 1932, **31**, 73) and *Picea excelsa* (Conifereæ) (Emde and Schartner, *Naturwiss.*,



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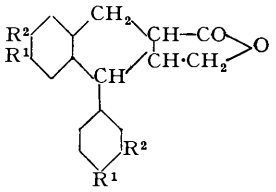

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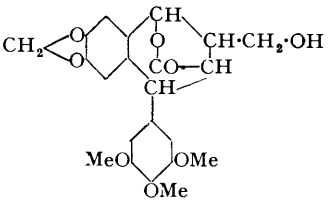
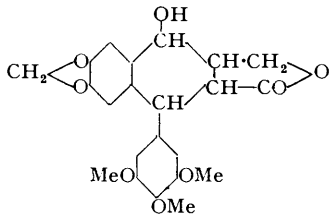
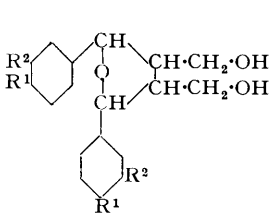


(IX.)

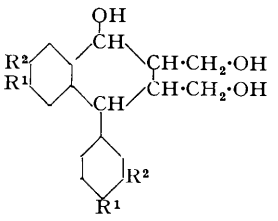
1934, **22**, 743), was first isolated from waste sulphite liquors by Tollens and Lindsay (*Annalen*, 1892, **267**, 353). The phenyltetralin structure (VIII) may be derived from (VI) by dehydrogenation, and the association of small amounts of *l*-conidendrin with *l*-matairesinol in the heartwood of *Podocarpus spicatus* (Haworth, Richardson, and Sheldrick, J., 1935, 1576) suggests that the relationship may be biological as well as structural. The phenyltetralin structure is present in *l*-podophyllotoxin (IX), isolated from the root resins of several species of *Podophyllum* (Berberidaceæ), which is readily isomerised by bases to *d*-picropodophyllin (X) (Borsche and co-workers, *Annalen*, 1932, **494**, 126; Späth and co-workers, *Ber.*, 1932, **65**, 1526). *l*-Podophyllotoxin is the only representative of the lignans containing dissimilarly substituted aromatic nuclei, and the position of the secondary alcoholic group indicates a relationship with the αα′-diphenylfuran type. *l*-Olivil (XI; R^1 = OH; R^2 = OMe), isolated from the resin of *Olea europea* (Oleaceæ), is an αα′-diphenylfuran, isomerised by acids into the phenyltetralin, *d*-*iso*olivil (XII; R^1 = OH; R^2 = OMe) (Korner and Carnelutti, *Rend. R. Ist. Lomb. Sci.*, 1882, **15**, II, 654; Vanzetti, *Monatsh.*, 1929, **52**, 163) which occurs naturally in the wood of *Olea Cunninghamii* (Briggs and Freiberg, J., 1937, 271). *d*-Lariciresinol (XIII; R^1 = OH; R^2 = OMe), occurring in the resin of *Larix decidua* (Conifereæ) (Bamberger, *Monatsh.*, 1897, **18**, 481), is a β-benzyl-α-phenyltetrahydrofuran



(X.)

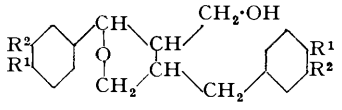


(XI.)



(XII.)

closely related to the furanofuran (V) type. *d*-Lariciresinol is converted by acids into the phenyltetralin, *d*-*iso*lariciresinol (XIV; R^1 = OH; R^2 = OMe), and the rapid isomeric change misled early investigators. Interesting relationships are found in the furanofuran lignans. *d*-Pinoresinol (XV; R^1 = OH; R^2 = OMe) occurs in the resins of *Picea abies*, *Pinus nigra* and *sylvestris* (Conifereæ) (Bamberger, *Monatsh.*, 1891, **12**, 441), and a diastereoisomeric or *epi*-modification of its monomethyl ether, *d*-forsythigenol, occurs as a glycoside in the leaves of *Forsythia koreana* (Oleaceæ) (Kunimine and Suzuki, *J. Pharm. Soc. Japan*, 1938, **58**, 25, 182).



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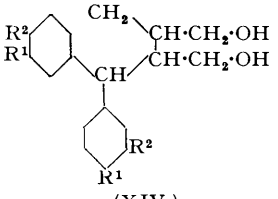

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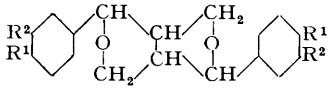


(XV.)

l-Eudesmin (XV; R^1 = R^2 = OMe), which occurs in the kinos of *Eucalyptus hemiphloia* (Mystaceæ) (Robinson and Smith, *J. Proc. Roy. Soc. N.S.W.*, 1915, **48**, 449), is the optical antipode of *d*-pinoresinol dimethyl ether. The methylenedioxy-analogue (XV; R^1R^2 = CH_2O_2) (Bertram and co-workers, *Biochem. Z.*, 1928, **197**, 1; Böeseken and co-workers, *ibid.*, 1928, **201**, 544), *d*-sesamin, occurs in the oil from the seeds of *Sesamum indicum* (Pedaliaceæ) and its antipode, *l*-sesamin, is isolated, together with a diastereoisomer, *l*-asarinin, from *Asarum sieboldii* (Aristolchiaceæ) (Kaku and co-workers, *J. Pharm. Soc. Japan*, 1936, **56**, 80; 1937, **57**, 184). The discovery of new representatives of the lignan group may be expected and it is probable that gmelinol, obtained from the wood of *Gmelina leichardii* (Verbenaceæ) (Harradence and Lions, *J. Proc. Roy. Soc. N.S.W.*, 1940, **74**, 117), and *d*-sesamolin (Adriani, *Z. Unters. Lebensmittel*, 1928, **56**, 187), from *Sesamum indicum*, are hydroxy-substitution products of eudesmin and sesamin respectively.

Isolation and Methods of Investigation of the Lignans.

The lignans are usually obtained from ethereal or alcoholic extracts of the plant material. *l*-Matairesinol and *l*-olivil are obtained in a high state of purity from the hot filtered extract of the wood and exuded resin

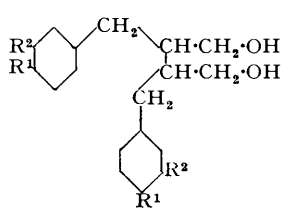
respectively, and several phenolic lignans, *e.g.*, *l*-guaiaretic acid, *d*-lariciresinol and *d*-pinoresinol, are isolated in the form of sparingly soluble sodium or potassium salts. In other cases more elaborate fractionation may be necessary, and the lignans are frequently associated with small amounts of high molecular weight impurities of tannin nature which cannot be removed by repeated crystallisation. These impurities, which have no appreciable effect on the melting point and optical rotation of the lignan, are probably responsible for the unreliable analytical results of several early workers, and the preparation of analytically pure specimens frequently necessitates the filtration of appropriate solutions of the lignan through a layer of alumina or distillation in a high vacuum.

Standard methods are used in the detection and estimation of functional groups, and methylenedioxy-derivatives are related to the methoxy-analogues by demethylenation and subsequent methylation; *e.g.*, *l*-hinokinin and *l*-asarinin have been converted into *l*-matairesinol dimethyl ether and *l*-eudesmin respectively (Keimatsu and Ishiguro, *J. Pharm. Soc. Japan*, 1936, **56**, 61; Huang-Minlon, *Ber.*, 1937, **70**, 951; Kaku and Ri, *J. Pharm. Soc. Japan*, 1937, **57**, 289). Occasionally difficulties are experienced in the preparation of crystalline acyl derivatives of alcoholic lignans, but Zerewitinoff determinations and indirect evidence may be used in the detection of alcoholic groups.

The known lignans occur naturally in an optically active form and the structural problem has been greatly simplified by the isolation of inactive degradation products from nitration, reduction, oxidation, and dehydrogenation experiments. It is usual to protect the phenolic lignans by alkylation prior to degradation.

The elimination of α-oxygenated side chains during nitration of catechol ethers may be employed in the detection of the furanofuran type (V). Nitration of *l*-pinoresinol dimethyl ether (XV; $R^1 = R^2 = OMe$) in acetic acid solution yields the 6 : 6′-dinitrolignan together with 4-nitroveratrole, but nitration with concentrated acid results in complete elimination of the side chain with the formation of 4 : 5-dinitro- or trinitro-veratrole (Erdtman, *Annalen*, 1935, **516**, 162). Ethers of the αβ-dibenzylbutyrolactone type (VI), on the other hand, yield dinitro- or tetranitro-substitution products retaining the lignan structure, but the phenyltetralin type (III) is usually converted into amorphous products by nitric acid (Haworth and Richardson, J., 1935, 633). Not only do these reactions serve to characterise the furano-group, but the yield of dinitrocatechol ether frequently indicates the number of such groups in the molecule. An additional application has been realised with *d*-pinoresinol; the diethyl ether is converted into the 6 : 6′-dibromolignan, which with nitric acid affords 4-bromo-5-nitro-2-ethoxyanisole in 80% yields, thus indicating the presence of two furan groups and also locating the phenolic group in *d*-pinoresinol (Erdtman, *Svensk Kem. Tids.*, 1938, **50**, 68).

The susceptibility of benzyl ethers to catalytic reduction provides another method for the detection of the furan types (IV) and (V). It has been shown that *d*-pinoresinol dimethyl ether (XV; $R^1 = R^2 = OMe$) may be reduced either partially to *d*-lariciresinol dimethyl ether (XIII; $R^1 = R^2 = OMe$) or completely to the *l*-diol (XVI; $R^1 = R^2 = OMe$) (Haworth and Woodcock, J., 1939, 1054). *d*-Sesamin has been reduced similarly to the methylenedioxy-analogue (XVI; $R^1R^2 = CH_2O_2$), which is also obtained by reducing *l*-cubebin (VII) with amalgamated aluminium (Bruchhausen and Gerhard, *Ber.*, 1939, **72**, 830). These catalytic reduc-



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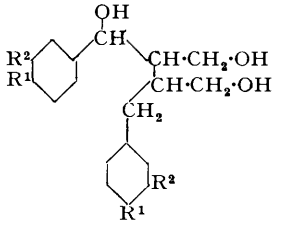

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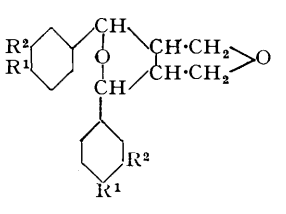


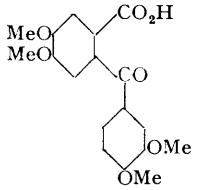
(XVIII.)

tions are confined to the benzyl ether linkages and *l*-olivil dimethyl ether (XI; $R^1 = R^2 = OMe$) yields the triol (XVII). The conversion of *d*-pinoresinol and *d*-sesamin into the *l*-diol therefore provides strong support for the furanofuran structures and excludes alternatives based upon the anhydro-olivil structure (XVIII).

A decision between the αβ-dibenzylbutyrolactone (VI) and phenyltetralin (III) types can be made by oxidation experiments. The former are oxidised by permanganate to substituted benzoic acids, and, as the diethyl ether of *l*-matairesinol (VI; $R^1 = OEt$; $R^2 = OMe$) gives 3-methoxy-4-ethoxybenzoic acid in yields exceeding 50%, the presence of two guaiacyl groups is established (Haworth and Richardson, J., 1935, 633). Phenyltetralin types are oxidised to substituted *o*-benzoylbenzoic acids by the action of permanganate, and oxidation of the ethyl ethers locates the hydroxyl groups in the lignans. On the other hand, oxidation with hypobromite yields a mixture of substituted *o*-benzoylbenzoic acid and phenyltetralin dibasic acids containing the complete carbon content of the lignan; *e.g.*, *l*-conidendrin dimethyl ether (VIII; $R^1 = R^2 = OMe$) gives *o*-veratroylveratric acid (XIX) and the optically active dibasic acid (XX) (Holmberg, *Ann. Acad. Sci. Fennicæ*, 1927, **29**, No. 6; Erdtman, *Annalen*, 1934, **513**, 229).

The establishment of the lignan framework has, in a few cases, been obtained by synthesis of the optically active lignan, but usually the evidence rests upon the synthesis of optically inactive products containing the entire carbon content of the lignan, obtained by dehydrogenation with lead tetra-acetate or selenium. The active acid (XX) is dehydrogenated with lead tetra-acetate to the optically inactive acid (XXI), which has been

synthesised by dimerisation of 3 : 4-dimethoxyphenylpropiolic acid with acetic anhydride (Haworth and Sheldrick, J., 1935, 636), a reaction discovered by Michael for the preparation of 1-phenylnaphthalene-2 : 3-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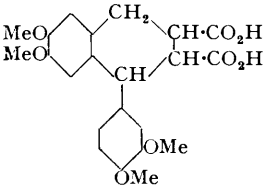
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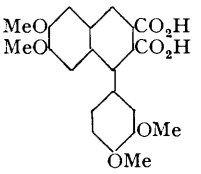
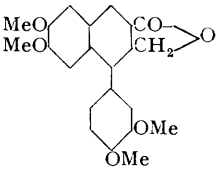

(XXI.)

dicarboxylic acid. Selenium or preferably lead tetra-acetate may be employed for the conversion of *l*-conidendrin dimethyl ether (VIII; $R^1 = R^2 = OMe$) into the inactive lactone (XXII). This lactone (XXII) is also obtained together with an inactive isomer (XXIII) by the action of tetra-acetate on *l*-matairesinol dimethyl ether (VI; $R^1 = R^2 = OMe$) (Haworth and Richardson, J., 1935, 633; Haworth and Sheldrick, *ibid.*, p. 636), and a similarly constituted lactone, dehydroanhydropicropodophyllin (XXIV), has been prepared from podophyllotoxin (Späth and co-workers, *Ber.*, 1932, **65**, 1536). Special methods, described below, have been developed for the synthetical confirmation of these lactonic structures. The cyclisation observed during the conversion of *l*-matairesinol dimethyl ether into (XXII) and (XXIII) can also be realised with phenolic lignan acetates, and by limiting the amount of lead tetra-acetate *l*-matairesinol (VI; $R^1 = OH$; $R^2 = OMe$) and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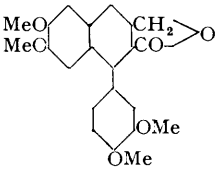
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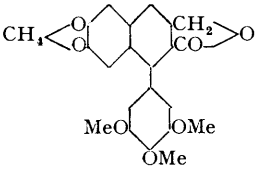
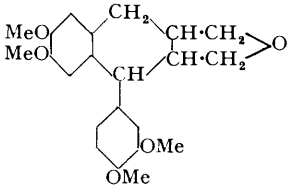

(XXIV.)

l-arctigenin have been converted into *l*-conidendrin (VIII; $R^1 = OH$; $R^2 = OMe$) and its monomethyl ether respectively (Omaki, *J. Pharm. Soc. Japan*, 1937, **57**, 42). The dehydrogenating action of lead tetra-acetate is not confined to lactones and carboxylic acids and an interesting application is found in the chemistry of *d*-lariciresinol. *d-iso*Lariciresinol dimethyl ether (XIV; $R^1 = R^2 = OMe$) is converted by acids into the *l*-cyclic ether (XXV), which is smoothly dehydrogenated to the inactive ether (XXVI) (Haworth and Kelly, J., 1937, 1645), and a method, described below, has been developed for the synthesis of this ether (XXVI).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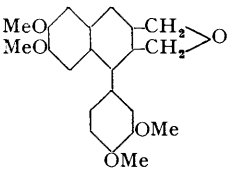
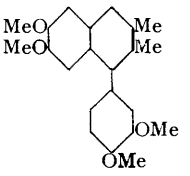
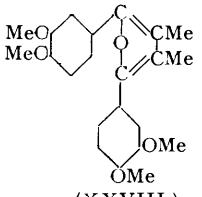
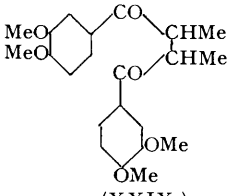
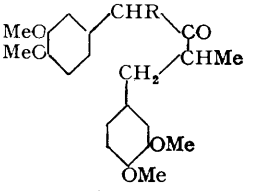

(XXVI.)


(XXVII.)

The lignan ethers are dehydrogenated by selenium and, although poor yields (3%) are obtained, the results are of considerable interest (Atkinson and Haworth, J., 1938, 1681). The dimethyl ethers of *l*-guaiaretic acid, *l*-olivil, *d*-lariciresinol and *d-iso*lariciresinol yield the inactive dehydroguaiaretic acid dimethyl ether (XXVII), for which two syntheses are described below, but the dimethyl ethers of *d*-pinoresinol and *d-epi*pinoresinol and *l*-eudesmin resist naphthalene formation and yield the inactive furan (XXVIII), which is readily synthesised by heating β-bromopropioveratrone with copper and dehydrating the resultant γ-diketone (XXIX) with methyl-alcoholic hydrogen chloride. It will be observed that the characteristic lignan framework is preserved in (XXVIII) in spite of the profound changes which occur during the dehydrogenation.


(XXVIII.)


(XXIX.)

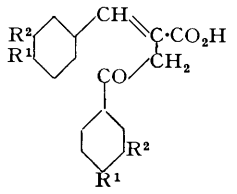

(XXX.)

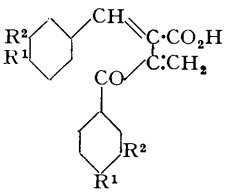
Synthetical Methods.

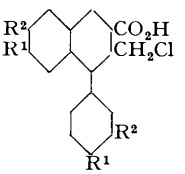
In addition to the syntheses of (XXI) and (XXVIII) mentioned above, methods have been developed for the synthesis of the compounds (XXII), (XXIII), (XXIV), (XXVI), and (XXVII) and for the preparation of lignans of the αβ-dibenzylbutyrolactone type (VI) in *dl*- and optically active forms.

(a) *Synthesis of* dl-*Guaiaretic Acid Dimethyl Ether* (I; $R^1 = R^2 = OMe$).—The α-cyano-ketone (XXX; R = CN), obtained from **3 : 4**-dimethoxyphenylacetonitrile and methyl β-**3 : 4**-dimethoxyphenyl-α-methylpropionate, was converted into the corresponding amide and thence into the ketone (XXX; R = H) by acid and alkaline hydrolysis respectively. Dehydration of the carbinol, obtained by the action of methylmagnesium iodide on the ketone (XXX; R = H), yielded *dl*-guaiaretic acid dimethyl ether (I; $R^1 = R^2 = OMe$), which gave a *meso*-dihydro-derivative identical with the major product obtained by catalytic reduction of *l*-guaiaretic acid dimethyl ether (Haworth, Mavin, and Sheldrick, J., **1934**, **1423**).

(b) *Synthesis of Dehydroguaiaretic Acid Dimethyl Ether* (XXVII) *and the Cyclic Ether* (XXVI).—(i) The synthetic *dl*-guaiaretic acid dimethyl ether was converted into (XXVII) by the action of iodine (Haworth, Mavin, and Sheldrick, *loc. cit.*). (ii) Reduction of the inactive acid (XXI) with sodium amalgam led to an


(XXXI.)

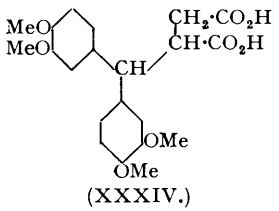

(XXXII.)

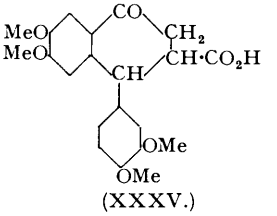

(XXXIII.)

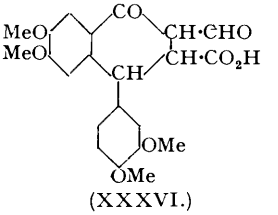
inactive form of the dibasic acid (XX), the diethyl ester of which was converted into a *dl*-form of *iso*lariciresinol dimethyl ether (XIV; $R^1 = R^2 = OMe$) by Bouveault reduction. Dehydration of this ether with selenium provided a second synthesis of dehydroguaiaretic acid dimethyl ether (XXVII), and the *dl*-cyclic ether (XXV) obtained from (XIV; $R^1 = R^2 = OMe$) by the action of methyl-alcoholic hydrogen chloride was dehydrogenated with lead tetra-acetate to the inactive cyclic ether (XXVI), identical with the product from *d*-lariciresinol (Haworth and Woodcock, J., **1939**, **1237**).

(c) *Synthesis of Lactones of* 1-*Phenyl*-2-*hydroxymethylnaphthalene*-3-*carboxylic Acid.*—In **1914** Borsche observed that aromatic aldehydes and β-benzoylpropionic acids react under the conditions of the Perkin reaction to yield acids of type (XXXI). These acids condense with formalin to give acids of type (XXXII), which are converted by hydrochloric acid into the 1-phenylnaphthalene derivatives of type (XXXIII), yielding the desired products on lactonisation (Haworth, Richardson, and Sheldrick, J., **1935**, **1576**). In the case where $R^1 = R^2 = OMe$, the product was identical with the lactone (XXII) obtained from *l*-conidendrin, and the synthesis established the orientation of the lactonic group in the lignan, excluding an alternative obtained by transposing the CO and CH_2 groups. The reactions are of wide application and may be used for the synthesis of lactones with dissimilarly substituted aromatic nuclei; by starting with piperonal and β-**3 : 4 : 5**-trimethoxybenzoylpropionic acid, a lactone isomeric, but not identical, with dehydroanhydropicropodophyllin (XXIV) was obtained (*loc. cit.*).

(d) *Synthesis of Lactones of* 1-*Phenyl*-3-*hydroxymethylnaphthalene*-2-*carboxylic Acid.*—(i) The dibasic acid (XXXIV) obtained from veratrole and ethyl hydroxymethylenesuccinate was converted into (XXXV) by the action of aluminium chloride on the anhydride, and the tetralone structure (XXXV) was established and the alternative hydrindone structure excluded. Condensation of the ethyl ester of (XXXV) with ethyl formate


(XXXIV.)


(XXXV.)

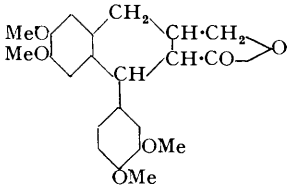

(XXXVI.)

gave (XXXVI), from which a small yield of (XXXVII) was obtained by reduction. Dehydrogenation of the lactone (XXXVII) gave the lactone (XXIII), identical with one of the products obtained by dehydrogenating *l*-matairesinol dimethyl ether (Haworth and Sheldrick, J., **1935**, **636**). As this method was unsuitable for the synthesis of lactones with dissimilarly substituted aromatic nuclei, other routes were investigated, but it is important to note that the method rigidly establishes the structure of (XXIII).

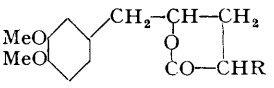
(ii) It has been found that the reactive methylene group of ethyl acetoacetate or malonate reacts with ethylene oxides, *e.g.*, *O*-methyleugenol oxide, with the formation of compounds of type (XXXVIII; R = $CO{\cdot}CH_3$ or CO_2Et), which yield γ-benzylbutyrolactones (XXXVIII; R = H) by hydrolytic removal of the acetyl or carbethoxy-group. The constitution of the lactone (XXXVIII; R = H) was determined by an independent synthesis : the ester (XXXIX), obtained from **3 : 4**-dimethoxyphenylacetyl chloride and ethyl acetosuccinate, was hydrolysed to β-**3 : 4**-dimethoxyphenylacetylpropionic acid, which gave the lactone (XXXVIII; R = H) by reduction and lactonisation.

Substituted benzylcyanoacetates react similarly with *O*-methyleugenol oxide, giving, after hydrolysis and lactonisation, αγ-dibenzylbutyrolactones (XXXVIII; R = substituted benzyl), and a structural isomer of

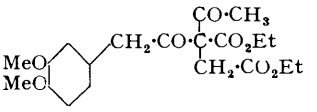
l-matairesinol dimethyl ether has been prepared by this method. This isomer failed to give the cyclodehydrogenation products (XXII) and (XXIII) with lead tetra-acetate and marked differences in the rates of formation



(XXXVII.)



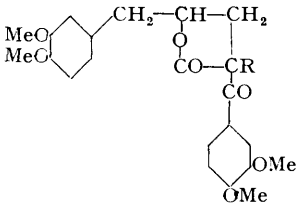
(XXXVIII.)



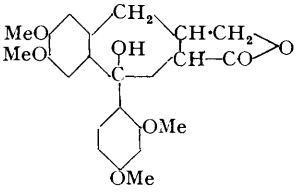
(XXXIX.)

of the lactones from the corresponding hydroxy-acids were observed in the αγ- and αβ-dibenzylbutyrolactone series.

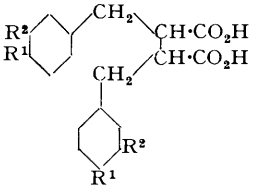
In spite of the apparently unfavourable structure, compounds of type (XXXVIII; R = CO·CH_3) provide important starting products for the synthesis of 1-phenylnaphthalene lactones with the CO group in position 2. Condensation of (XXXVIII; R = CO·CH_3) with veratroyl chloride yields the β-diketone (XL; R = CO·CH_3), which leads to (XL; R = H) by elimination of the acetyl group. In the presence of acids (XL; R = H) undergoes cyclisation and pinacolinic change to give (XLI), which yields the lactone (XXIII) by dehydration and dehydrogenation. The product was identical with that prepared by method d(i) and the establishment of



(XL.)



(XLI.)



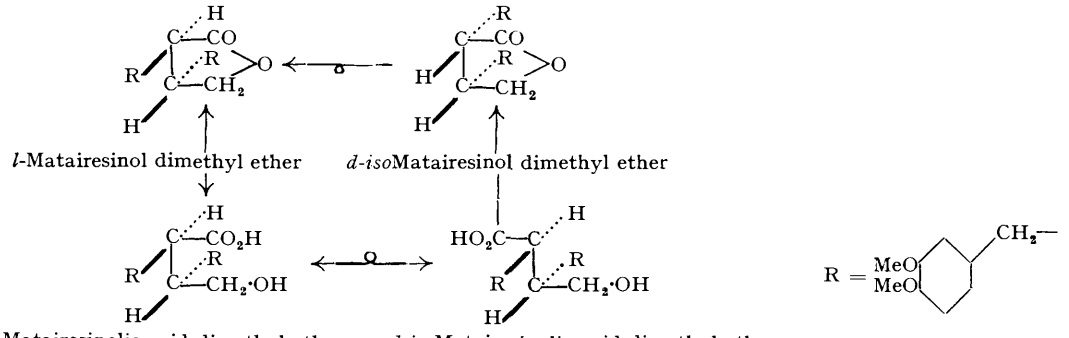
(XLII.)

the constitution of starting and end products necessitates the assumption of the pinacolinic change in the interpretation of the synthesis. The method is of extensive application and condensation of safrole oxide with ethyl acetoacetate, followed by combination of the product with 3 : 4 : 5-trimethoxybenzoyl chloride, leads to a lactone (XXIV) identical with dehydroanhydropicropodophyllin.

(e) *Synthesis of αβ-Dibenzylbutyrolactones.*—Reduction of αβ-dibenzylidenesuccinic acids, obtained from aromatic aldehydes and ethyl succinate, yields a mixture of *meso*- and *dl*-forms of αβ-dibenzylsuccinic acids (XLII) with the former predominating. The *meso*-acid is converted into the *dl*-anhydride by warming with acetic anhydride, and subsequent reduction with aluminium amalgam gives the αβ-dibenzylbutyrolactones (VI). *dl*-Matairesinol dimethyl ether and *dl*-hinokinin have been prepared in this way. The *dl*-form of the dibasic acid may be resolved into *d*- and *l*-modifications, which lead similarly to the *d*- and *l*-forms of the αβ-dibenzylbutyrolactones. The optically active forms of hinokinin and matairesinol dimethyl ether have been synthesised in this way (Haworth and Woodcock, J., 1938, 1985; 1939, 154) and by protection of the phenolic group as the benzyl ether a synthesis of *l*-matairesinol has been realised (Haworth and Slinger, J., 1940, 1098).

Stereochemistry of the Lignans.

Unless optical inversion occurs during the reduction of the *l*-anhydride of the dibasic acid (XLII), the synthesis of *l*-matairesinol establishes the *trans*-configuration of the two asymmetric centres and this arrangement is confirmed by the oxidation of the *l*-diol (XVI; $R_1 = R_2 =$ OMe) to *l*-matairesinol dimethyl ether (Haworth and Woodcock, J., 1939, 1056).

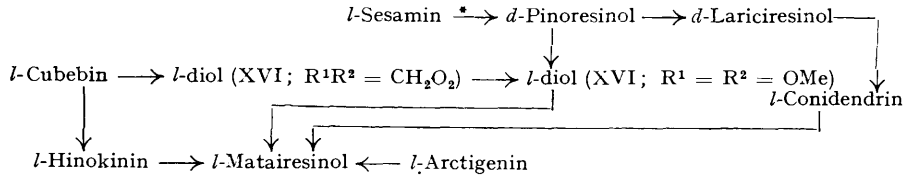


l-Matairesinol dimethyl ether *d-iso*Matairesinol dimethyl ether

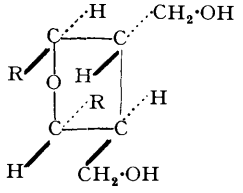
l-Matairesinolic acid dimethyl ether *d-iso*Matairesinolic acid dimethyl ether

l-Matairesinol dimethyl ether is slowly hydrolysed to the methyl ether of *l*-matairesinolic acid by cold alkali, but when heated with sodium hydroxide solution to 180° about one-third of this hydroxy-acid is converted by

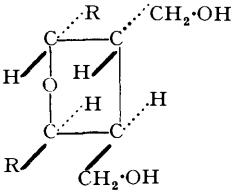
inversion at the CH·CO centre into a diastereoisomer, *d-iso*matairesinolic acid dimethyl ether. The isomer is converted by warm acids into *d-iso*matairesinol dimethyl ether, but the change is much slower than the lactonisation of *l*-matairesinolic acid dimethyl ether, and the difference is only consistent with the suggested *trans*-configuration for *l*-matairesinol, which allows of a closer approach of the CH_2·OH and CO_2H groups in the " equilibrium position " of the dimethyl ether of *l*-matairesinolic acid (Haworth and Atkinson, J., 1938, 797). Another interesting point is the rapid conversion of *d-iso*matairesinol dimethyl ether into *l*-matairesinol dimethyl ether by cold alkali, the Walden inversion occurring more rapidly than hydrolysis of the lactone group. Diastereoisomeric modifications of *l*-hinokinin and *l*-arctigenin have been prepared similarly (Keimatsu and Ishiguro, *J. Pharm. Soc. Japan*, 1936, **56**, 19; Omaki, *ibid.*, 1935, **55**, 159; 1937, **57**, 89). *l*-Conidendrin dimethyl ether is partly converted into an *iso*lactone by the action of sodium ethoxide and of the two hydroxy-acids that corresponding to the *iso*-form is lactonised more rapidly (Holmberg, *Ber.*, 1921, **54**, 2389, 2406). As rotation around the *n*-propylbenzene junction is prevented in the phenyltetralin series, the observed rates of lactonisation suggest a *trans*-lactonic structure for *l*-conidendrin. In 1936 it was tentatively suggested that the *l*-matairesinol configuration is retained throughout the lignan group and this is supported by more recent evidence. During the many interconversions of lignans, some of which are summarised below, two points are noteworthy. (i) The interconversions result in the formation of the new lignan in a stereochemically homogeneous form, identical (except in the asterisked case, which receives special mention later, below) with the



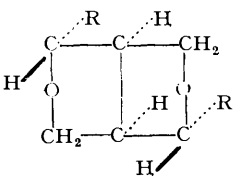
form in which the new member occurs naturally; a common stereochemical configuration throughout the family is consistent with these observations. (ii) The conversion of *l*-cubebin, *d*-pinoresinol and *d*-lariciresinol into the optically active diols of type (XVI) is convincing evidence that the *l*-matairesinol configuration is present in these lignans. Further important stereochemical observations have been made by Vanzetti (*Rend. R. Accad. Lincei*, 1937, **25**, 133) and Erdtman (*Svensk Kem. Tids.*, 1936, **48**, 230) on *l*-olivil and *d*-pinoresinol respectively. If the *trans*-configuration of *l*-matairesinol is retained in these compounds, the two hydrogen atoms of the β-C–C bond should be *trans* in *l*-olivil, but *cis* in *d*-pinoresinol, because in the latter the aromatic nuclei have taken up remote positions by rotation round the β-C–C linkage. Both *l*-olivil and *d*-pinoresinol are optically active, but the two phenolic groups are symmetrically disposed, *e.g.*, monomethylation and subsequent ethylation and reversal of this alkylation procedure yield identical products. The molecules therefore have a symmetry axis, but lack planes, centres or alternating axes of symmetry, and these requirements reduce the stereochemical formulæ to two possibilities for each lignan. These structures for *l*-olivil, (XI*a*) and (XI*b*), where R = guaiacyl, have a *trans*-arrangement at the β-C–C bond and those for *d*-pinoresinol (XV*a*) and (XV*b*) also retain the matairesinol configuration.



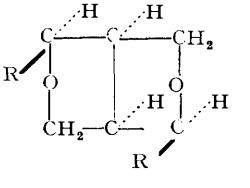
(XI*a*.)



(XI*b*.)



(XV*a*.)



(XV*b*.)

The configurations at the α-asymmetric centres in *l*-olivil and *d*-pinoresinol have not been determined, but inversion may be effected at these ether linkages by the action of mineral acids. The change is complicated by cyclisation in the case of *l*-olivil, but *l*- and *d*-eudesmin are partially converted into *l*- and *d-epi*eudesmin respectively by inversion at one or both of the α-carbon atoms. Similarly *d*- and *l*-sesamin are partially converted into *d*- and *l*-asarinin respectively (Kaku and co-workers, *J. Pharm. Soc. Japan*, 1936, **56**, 80; 1937, **57**, 289, 3217; Huang-Minlon, *loc. cit.*; Erdtman, *Svensk Kem. Tids.*, 1938, **50**, 161). Similar epimerisations occur during the replacement of the methylenedioxy-groups of asarinin and sesamin by methoxy-groups; *l*-asarinin yields a mixture of *l*-eudesmin and *l-epi*eudesmin, and *d*-sesamin gives *d*-eudesmin and *d-epi*eudesmin. It is probable that asarinin and sesamin have the eudesmin and *epi*eudesmin configuration respectively. The α_D values given in the following table show that nitration of eudesmin and asarinin is accompanied by a change in sign of α_D value, which is not observed during the nitration of sesamin and *epi*eudesmin (compare Erdtman, *Svensk Kem. Tids.*, 1936, **48**, 250) :

d- and *l*-Eudesmin,	$\alpha_D \pm 64°$	Dinitro-compound	$\alpha_D \mp 124°$	Diff.	188°
d- and *l*-Asarinin,	$\alpha_D \pm 119$	,, ,,	$\alpha_D \mp 29$	,,	148
d- and *l-epi*Eudesmin,	$\alpha_D \pm 143$	,, ,,	$\alpha_D \pm 74$	,,	70
d- and *l*-Sesamin,	$\alpha_D \pm 67$	,, ,,	$\alpha_D \pm 35$	,,	32

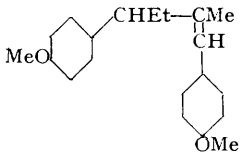
The configuration of the α-asymmetric centre in *l*-conidendrin and *d-iso*lariciresinol is equally uncertain, but the conversion of the latter into the former (Haworth and Kelly, J., 1937, 384) suggests a common configuration. The only experimental evidence bearing on these α-asymmetric centres is derived from experiments on 1-phenyltetralin-2 : 3-dicarboxylic acid, which was isolated in four inactive isomeric forms. The stability of the isomeric acids, esters, and anhydrides was compared and by using *cis*- and *trans*-tetralin-2 : 3-dicarboxylic and *cis*- and *trans*-cinnamic acids as models for the 2 : 3- and 1 : 2-linkages respectively, it was concluded that the most stable of the four acids (XX; H instead of OMe) had the *trans* (1 : 2), *trans* (2 : 3) structure (Haworth and Slinger, J., 1940, 1321). In *l*-podophyllotoxin (IX) the bridged lactonic structure suggests a *cis*-arrangement of the 2 : 4-positions, from which the *trans* (1 : 2), *trans* (2 : 3), *trans* (3 : 4) structure may be developed.

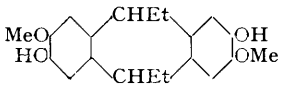
Biological Relationships.

Schroeter (*loc. cit.*) suggested that *l*-guaiaretic acid could be derived from two molecules of *iso*eugenol, and Vanzetti (*loc. cit.*), pointing out that *n*-propenylbenzenes such as cinnamic acid and *iso*eugenol occur naturally in the stable *trans*-forms, favoured the stereochemical arrangement (XI*a*) for olivil because this structure is derivable from two molecules of *trans*-coniferyl alcohol. Similar arguments favour (XV*a*) for *d*-pinoresinol, but the natural occurrence of both sesamin and its *epi*-form, asarinin, shows the weakness of the biogenetic derivation of stereochemical configuration.

Many *n*-propenylbenzene derivatives are polymerised by the action of heat, acids, etc., but the dimeric products do not possess the characteristic lignan structure; anethole and *iso*eugenol are readily dimerised to (XLIII) and (XLIV) respectively by the action of methyl-alcoholic hydrogen chloride. It seems probable that

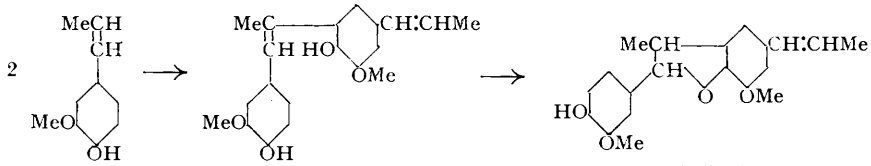
(XLIII.)





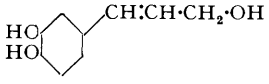
(XLIV.)

the exclusive union of two *n*-propenylbenzene derivatives at the β-carbon atom is effected by oxidation. The oxidation of phenols to peroxides, diphenyl ethers, 2 : 2′- or 4 : 4′-dihydroxydiphenyls involves coupling at anionoid centres, and the β-carbon atom of the side chain of a *p*-hydroxypropenylbenzene may acquire this character in virtue of the extended conjugation and analogous coupling may be expected. The oxidation of *iso*eugenol to dehydrodi*iso*eugenol (XLV) (Erdtman, *Annalen*, 1933, **503**, 283) * involves a coupling of the anionoid centre in the side chain with the *o*-position relative to the phenolic group in a second molecule, followed by a cyclisation to the furan involving the phenolic group. The lignan structure corresponds to the union of two propenylbenzene units at the anionoid centres of the side chain. The selection of the alcohol type (XLVI) of precursor must be regarded as arbitrary, but oxidative coupling along the lines suggested above leads to structure (XLVII), or a biological equivalent such as (XLVIII), from which the naturally occurring lignan

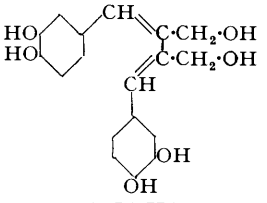


(XLV.)

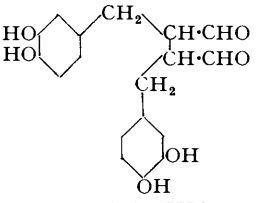
structures (VI), (VIII), (XI), (XIII), and (XV) may be derived by dismutations or cyclisations which are capable of realisation or for which there are numerous analogies.



(XLVI.)



(XLVII.)

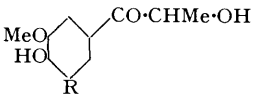


(XLVIII.)

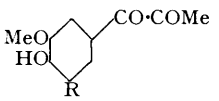
The structural relationship together with the occurrence of lignans in essential oils, where they are associated with terpenes and *n*-propylbenzenes, and in resins, where they occur with diterpenes, suggests that the *n*-propylbenzene–lignan and terpene–diterpene relationships are formally analogous. There are no indications of a group of natural products containing three propylbenzene units corresponding to the triterpenes, but it is possible that lignin represents the polyterpene of the propylbenzene metabolism. The structure of this complex

* My thanks are due to Professor J. Kenner for drawing my attention to this important work.

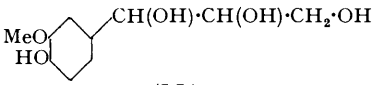
substance is obscure, but the few established structural features indicate a relationship with the *n*-propylbenzenes. Lignin contains the 3 : 4-dihydroxyphenyl grouping and the *n*-propylphenols (XLIX; R = H) and (L ; R = H) have been obtained by the action of methyl-alcoholic hydrogen chloride on soft wood lignin;



(XLIX.)



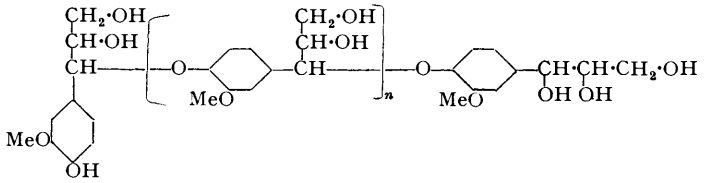
(L.)



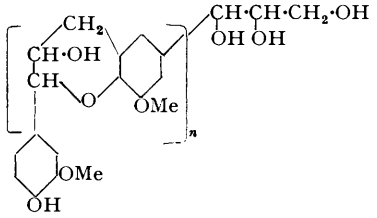
(LI.)

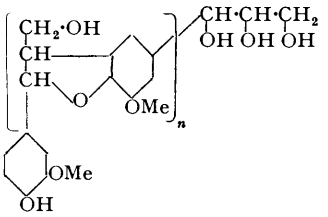
from hard wood lignin the syringyl analogues (XLIX; R = OMe) and (L; R = OMe) are also obtained (Hibbert and co-workers, *J. Amer. Chem. Soc.*, 1939, **61**, 509, 2190, 2198). It is probable that lignin is a product resulting from the condensation of *n*-propylphenolic units, but as lignin, unlike the lignans, retains few if any phenolic groups, these must be involved in the condensation. Oxidation of *n*-propenylbenzene units at anionoid centres and subsequent cyclisation as in the formation of dehydrodi*iso*eugenol provide a satisfactory explanation

(LII.)



(LIII.)

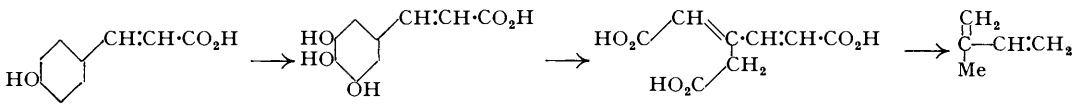




(LIV.)

of this loss of phenolic properties. Freudenberg (*Ann. Review Biochem.*, 1939, **8**, 81) regards (LI) or a biological equivalent as the lignin precursor, and suggests an alternative condensation mechanism involving etherification to type (LII), followed in part by cyclisation to type (LIII) or (LIV). It is probable that lignin is a mixture of the closely related types (LII), (LIII), and (LIV) together with the corresponding types derived from biological equivalents of (LI) or from other precursor units. In addition some of the guaiacol residues are replaced by syringyl residues in hard wood lignins and it is recognised that lignin varies in composition with the nature and age of the tree in which it occurs, and that isolated lignin differs from the substance existing in the wood. The wide distribution of the *n*-propylbenzenes and the lignans in unrelated plant families is a strong indication of their association with a general metabolic process and, in spite of the inconclusive state of knowledge concerning the constitution of lignin, the relationships are sufficiently striking to indicate that the *n*-propylbenzenes and the lignans are connected with the lignification process.

Of the simple structural units employed in the construction of natural products, the *n*-propylbenzene and *iso*pentane structures possess the common feature of branching carbon chains, and the frequent co-occurrence of these structures may signify a common origin. A derivation of the *iso*pentane structure by oxidation of



the *p*-hydroxycinnamic acid type along the lines indicated below is not unreasonable, but all suggestions concerning the formation of aromatic compounds or terpenes from hexose or hexose breakdown products are devoid of experimental confirmation.