LIGNIN POLYMERS AND RELATED BUILDING UNITS

by

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A Thesis presented to the Faculty of Graduate Studies and Research of McGill University in partial fulfilment of the requirements for the Degree of Doctor of Philosophy.

McGill University
September 1943

ACKNOWLEDGMENTS

The writer wishes to express his sincere
gratitude, appreciation and thanks to

Professor Harold Hibbert

for his invaluable advice, encouragement
and inspiration given throughout the
entire course of this work

and to

Dr. T. H. Evans

for his co-operation
and helpful criticism

Grateful acknowledgment is also made
to the Canadian Pulp and Paper Association
and to the Spruce Falls Power and Paper
Company for kind financial assistance

CLAIMS TO ORIGINAL RESEARCH

1. The synthesis of three dimers from monomolecular propylphenol units related to lignin progenitors has been carried out. These are:
    - (a) 2,2'-Divanilloyl diethyl ether
    - (b) 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone
    - (c) 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

2. Ethanolysis of each of the dimers, under the same conditions as employed in the ethanolysis of wood, was without effect on (b), while with (a) and (c) a small and large amount respectively of condensation product was formed. No monomolecular products were isolable similar to those obtained in wood ethanolysis.

3. No change occurred with any of the dimers on refluxing with dilute acid or alkali.

4. High pressure hydrogenation of the three dimers over Raney nickel at 160-165° resulted, in each case, in the primary reduction of the side chain carbonyl groups. This was followed in the case of (a) and (b) by chain fission at the oxygen-ether linkage to the extent of 50-60 per cent; the remainder was recovered in the form

of the reduced-carbonyl dimers in which cleavage did not occur. With dimer (c) no side chain fission occurred even at much higher temperatures, although under the latter conditions, reduction of the aromatic nucleus occurred accompanied by considerable gasification.

5. Experimental evidence has been obtained indicating the ease with which carbonyl groups, assumedly present in the side chains of native lignin, readily undergo reduction to methylene groups. Furthermore, lignin polymers containing side chain ether linkages in either the beta or gamma position should readily undergo hydrogenolysis at the ether union. On the other hand, if such polymers are united by a carbon-to-carbon linkage of the side chains, such linkages should be resistant to chain fission by hydrogenolysis even at relatively high temperatures.

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I.

GENERAL INTRODUCTION

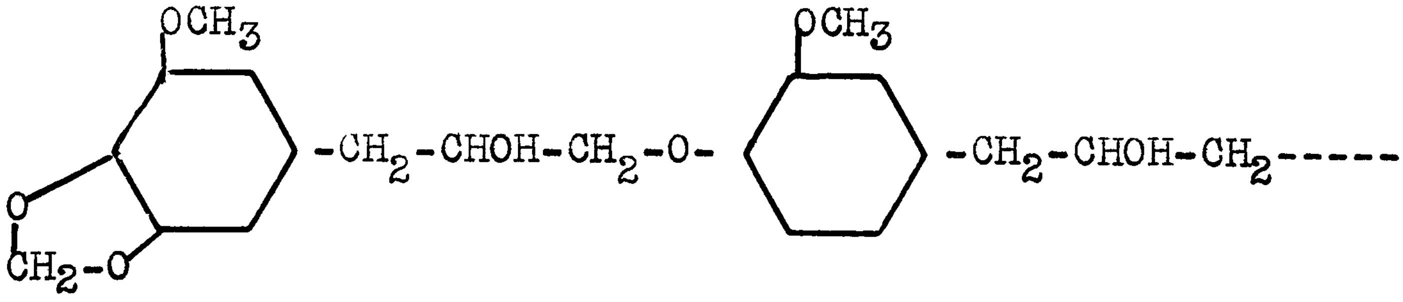
A. Early Theories

Theories on the structure of lignin have undergone many modifications since Klason (1) published his early "Coniferyl-oxyconiferyl alcohol hypothesis". Data derived from studies on the ethanolysis of spruce lignin sulfonic acids, on the occurrence of protocatechuic acid, guaiacol, and catechol among the products in lignin alkali-fusion reaction mixtures (2), and the occurrence of coniferyl alcohol in the tissues of many young plants (3) were the bases of Klason's (4) theory.

Organic-solvent extracted woodmeals upon treatment with various concentrated acids yield, in part, an amorphous product arbitrarily known as lignin. Sulfuric (5), hydrochloric (6), and mixtures of hydrochloric and phosphoric (7) acids were used in the isolation of the lignin. Analyses of this amorphous product showed the presence of methoxyl, hydroxyl, and carbonyl groups together with guaiacyl and/or syringyl nuclei.

It is obvious that drastic changes in the nature of the protolignin can occur on treatment of woodmeal with these powerful chemical reagents. Hilpert (8) has suggested that extracted lignins are actively synthesized by the action of the acids on plant carbohydrate material and therefore, they do not actually exist as such in wood. Creighton, McCarthy and Hibbert (22) have shown that with certain species of wood, over 50 per cent of the lignin is aromatic in character, thus indicating Hilpert is not justified in his assumptions (8). The alcoholysis of wood, as developed by Hibbert and co-workers (9), is a much milder procedure for the isolation of lignin.

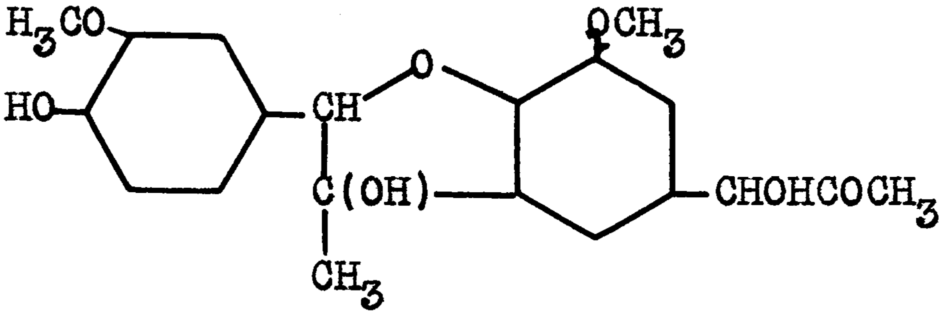
Freudenberg (10) isolated small amounts of catechol, protocatechuic acid and formaldehyde from spruce lignin. These results, together with analyses of the lignin, led him to postulate a linear-type of lignin polymer (I). The side



I

chains visualized by Freudenberg were $RCH_2CHOHCH_2OH$, $RCHOHCH_2CHO$ and $RCHOHCOCH_3$ (10, page 135). These compounds were assumed to be in equilibrium with one another, in vivo.

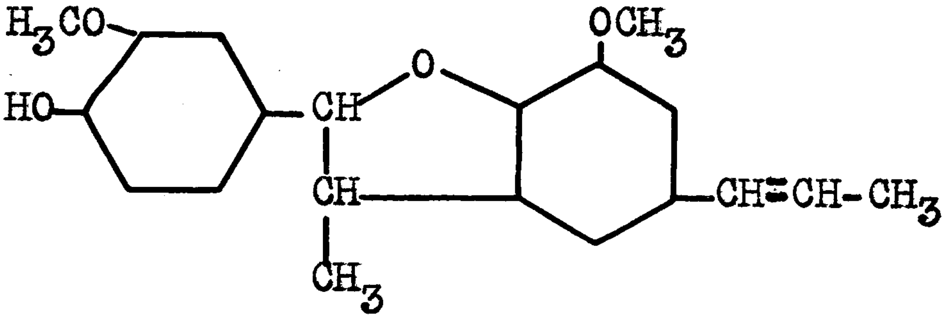
Later investigations (11,12,13) on cuproxam lignin led him to discard his earlier structure (I) (10) in favor of a carbon-to-carbon type linkage involving an oxygen bridge between the side chain and the aromatic nucleus (II) (14, page 95). This structure (II) is similar to that of



II

(from two molecules of $RCHOHCOCH_3$, where R is the guaiacyl nucleus)

dehydrodiisoeugenol (III), suggested by Erdtman (15).



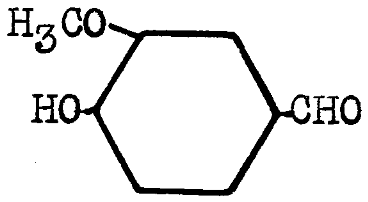
III

It is of interest to note that this type of polymer (II) could not be derived from the syringyl nucleus, in hardwoods, since the position ortho to the phenol group is blocked by a methoxyl group. Thus, if the Freudenberg dimer (II) were accepted as the possible structure of lignin in softwoods, a different type of linkage is required for that in hardwoods.

B. Recent Experimental Methods for Determination of Lignin Structure

1. Alkaline Oxidation

The action of alkali on spruce lignin sulfonic acid yields 6-7 per cent of vanillin (IV) (16), a smaller amount of 4-hydroxy-3-methoxyacetophenone (V) (17), and guaiacol (VI) (18). From oak lignin sulfonic acid syringaldehyde (VII) (19), 4-hydroxy-3,5-dimethoxyacetophenone (VIII) (20), and 1,3-dimethoxypyrogallol (IX) (21) are obtained in addition to (IV), (V) and (VI).



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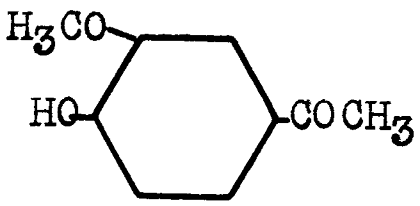

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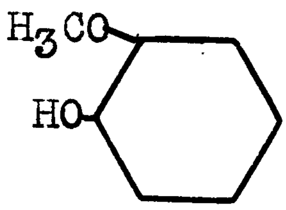

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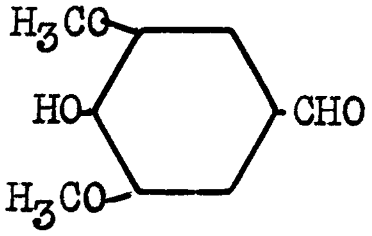
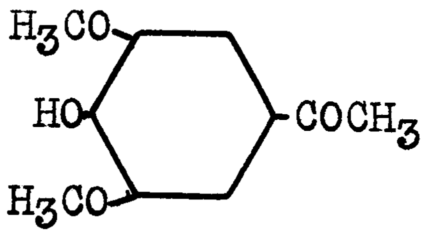
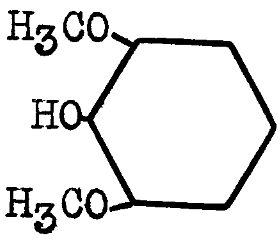


VII



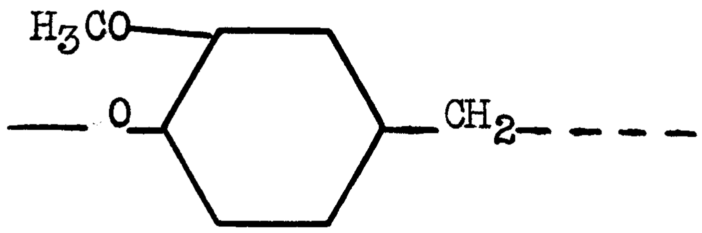
VIII



IX

Recently (22), Freudenberg's alkali-nitrobenzene oxidation technique (23) has been applied to maple and aspen woods. Combined yields, based on the Klason lignin content of the wood, of 46 and 48 per cent respectively of a mixture of vanillin (IV) and syringaldehyde (VII) were obtained. If these aromatic aldehydes are derived from propylphenol units, similar to those obtained by the ethanolysis of maple wood, then 58-62 per cent of the protolignin in these angiosperms (hardwoods) is aromatic in nature. Thus Klason's original assumption (1) that lignin is essentially aromatic receives substantial confirmation.

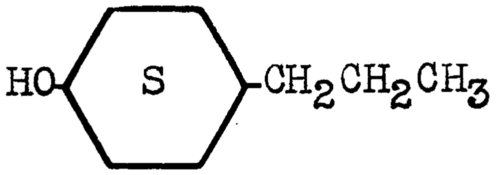
Lautsch and Piazolo (24) obtained 4-hydroxy-3-methoxy-5-bromobenzaldehyde in 8 per cent yields on alkali-nitrobenzene oxidation of a brominated spruce lignin. Since this product cannot be obtained directly from vanillin it appears that the lignin building units are united by an ether type linkage in the 4-position (X).



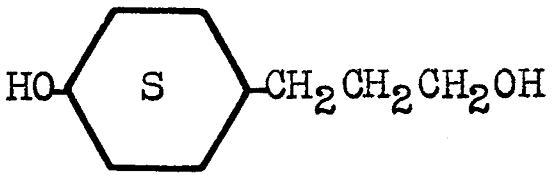
X

2. Hydrogenation

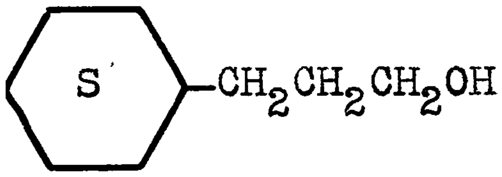
Complete liquefaction of wood has been achieved by means of high-pressure catalytic hydrogenation (25). The protolignin is converted, in part, to 4-*n*-propylcyclohexanol (XI), 3-(4-hydroxycyclohexyl)-1-propanol (XII) and 3-cyclohexyl-1-propanol (XIII) in yields of 9.9, 5.8 and 12.6 per cent respectively (based on the Klason lignin content of the wood) (25,26,27).



XI



XII



XIII

These isolated products (XI), (XII), (XIII) serve to establish the presence of propylphenol units in lignin and further studies (27,28,29) have shown that a relatively high proportion of the propylcyclohexane units contain oxygen atoms attached to the terminal carbon atoms in the propyl side chains

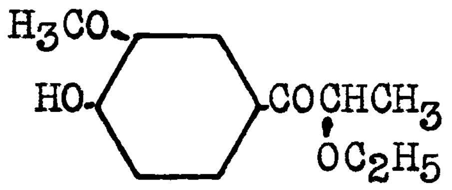
3. Chromic Acid Oxidation of Wood and Lignin

Exhaustive chromic acid oxidation of wood and lignin

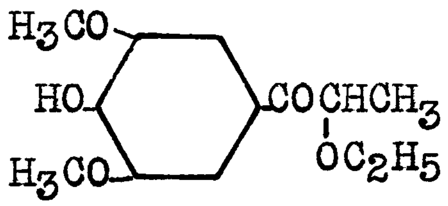
(30) has shown that Freudenberg (14) is not justified in his representation of the structure of lignin (II). MacGregor (30) obtained no acetic acid by the oxidation of maple wood, spruce wood or extracted maple lignin, and only a small amount (5 per cent) from extracted spruce lignin. This would not be the case if protolignin contained terminal methyl groups.

4. Ethanolysis of Wood

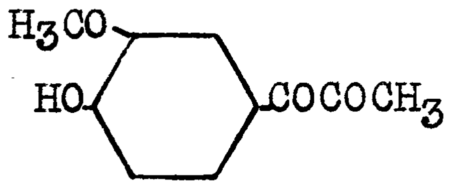
More recent work on the elucidation of the structure of lignin has been concerned with the investigation of the lignin water-soluble oils obtained by means of the ethanolysis reaction (31). Approximately one-third of the oil isolated from maple wood has been shown to consist of vanillin (IV) (32), syringaldehyde (VII) (32), 2-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (XIV) (33), 2-ethoxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone (XV) (34), 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (XVI) (35) and 1-(4-hydroxy-3,5-dimethoxyphenyl)-1,2-propanedione (XVII) (36). More recently, workers in these laboratories (37,38) have isolated 1-(4-hydroxy-3-methoxyphenyl)-2-propanone (XVIII), 1-(4-hydroxy-3,5-dimethoxyphenyl)-2-propanone (XIX) (37) from maple wood and 1-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone (XX) (38) from spruce wood, although in very low yields. The latter (XX) and its syringyl analogue presumably also are present in the water-soluble lignin ethanolysis oils from maple (hardwood), but, owing to the difficulties in connection with their isolation have not yet been separated and identified.



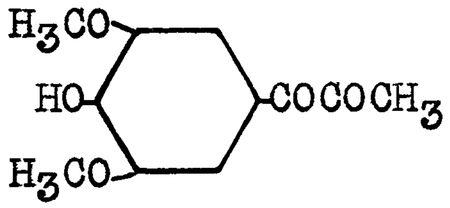
XIV



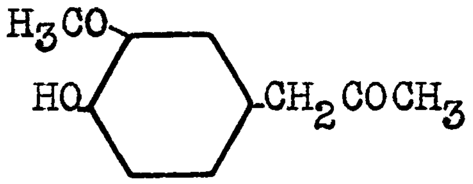
XV



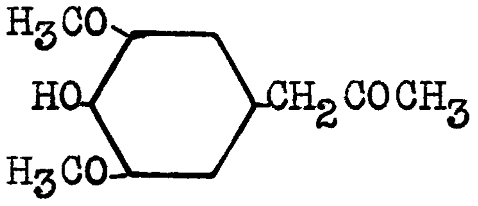
XVI



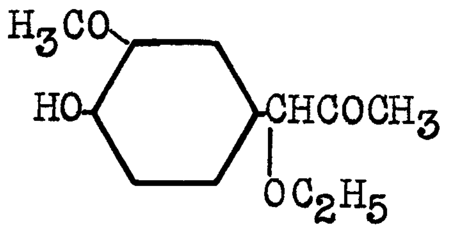
XVII



XVIII



XIX



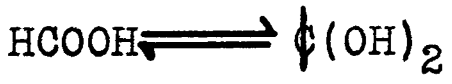
XX

The lignin derivatives (XIV) to (XX) inclusive isolated from maple and spruce woods, by means of the ethanolysis reaction, are apparently not the true lignin progenitors but rather stabilized end-products formed from the more reactive lignin building blocks representing the source of the true protolignin. It is more than likely that the lignin molecule contains one or more very unstable propylphenol units and during the ethanolysis reaction these rearrange into more stable structures, namely (XIV), (XV), (XVI), (XVII), (XVIII), (XIX) and (XX).

C. Genesis of Propylphenol Derivatives in Plant Tissue

The mechanism of the plant synthesis of the propylphenol units is not yet known. Various theories are based on the assumed transformation of hexoses (39,40). More recent theories (9) consider the formation of phenols as arising from plant respiratory products.

(a) One theory, the Free Radical Theory (41) is concerned with a possible keto-enol tautomerism originating among such simple compounds as formic acid (XXI), acetaldehyde (XXII) and glycollic aldehyde (XXIII), during various periods of plant growth.

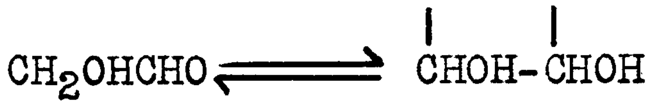


$HCOOH \rightleftharpoons C(OH)_2$

XXI

$CH_3CHO \rightleftharpoons CH_2-CHOH$

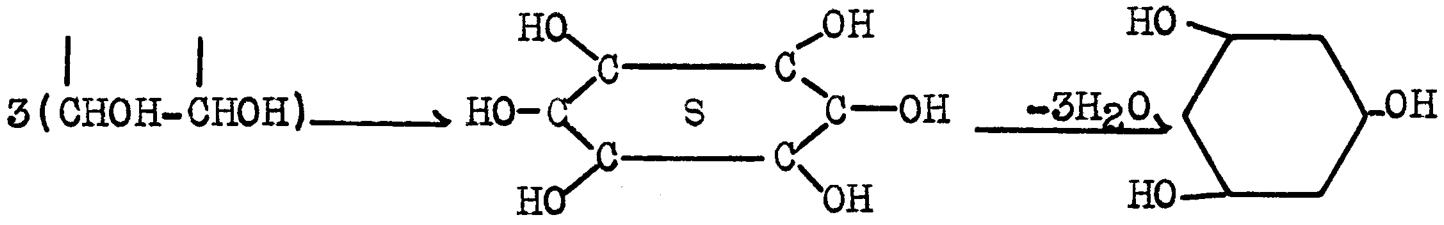
XXII



$$CH_2OHCHO \rightleftharpoons \overset{|}{C}HOH-\overset{|}{C}HOH$$

XXIII

The free radicals may unite to form hydroaromatic substances which, by loss of water, could yield phenols, as for example, in the formation of phloroglucinol (XXIV) from glycollic aldehyde.

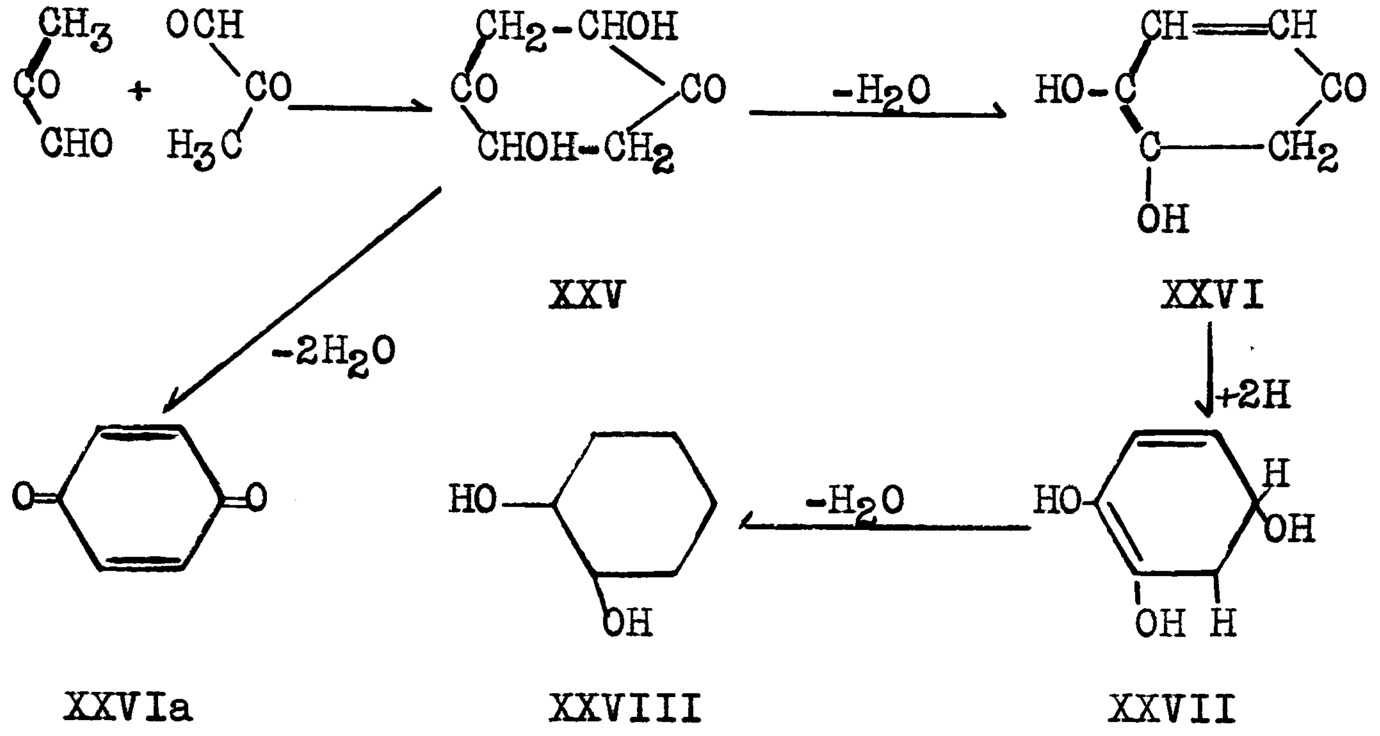


XXIII

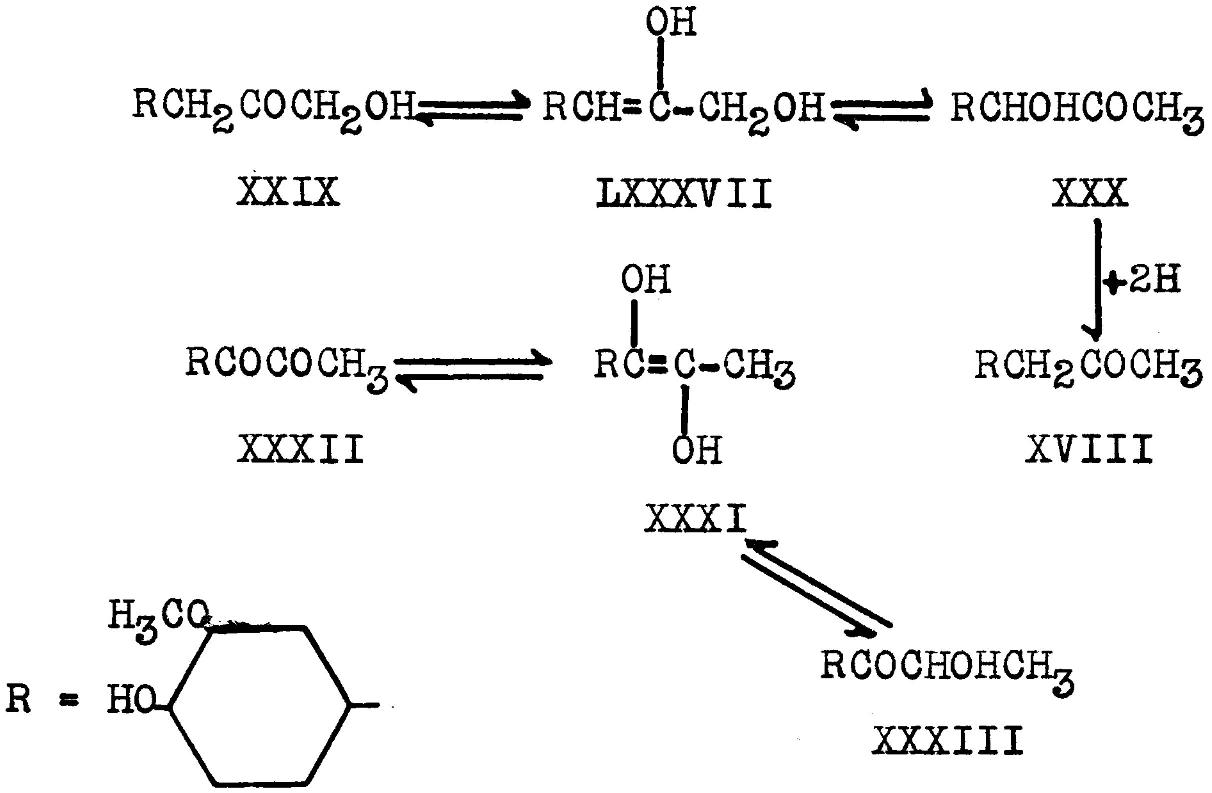
inositol

XXIV

(b) The Methyl Glyoxal Theory offers a more complete hypothesis of the plant synthesis of propylphenol units from simpler compounds. Methyl glyoxal has been isolated from a number of higher plants (42) and since it is known to be an intermediate in animal cell respiration (43, page 244), it may function in a similar manner in plants. Hibbert (44) has suggested that two molecules of methyl glyoxal undergo condensation to yield the cyclic dihydroxydiketone (XXV) which is then presumed capable of undergoing the indicated reactions to form 1,2-dihydroxy-4-ketocyclohexadiene (XXVI) and para quinone (XXVIa). The ketohexadiene (XXVI) could give rise to the hydroxy-enediol (XXVII) which in turn could yield



catechol (XXVIII) upon the loss of one molecule of water. Another molecule of methyl glyoxal could condense with the "methylated" ketohexadiene (XXVI) followed by the loss of one molecule of water and then reduction to yield RCH_2COCH_2OH (XXIX). This, in turn, could undergo an allylic isomerization to give (XXX), the ethyl ether of which has recently been isolated (38). The latter (XXX) could accept one molecule of hydrogen with formation of the desoxybenzoin (XVIII) (37) or, might undergo a keto-enol dismutation change to form the ene-diol (XXXI). The ene-diol, on loss of one molecule of hydrogen, could yield the diketone (XXXII). Ketonization of the ene-diol (XXXI) could yield (XXXIII).



The equilibrium (XXX)$\rightleftharpoons$(XXXIII) finds ample support in the Lobry de Bruyn - van Ekenstein transformation of glucose$\rightleftharpoons$mannose$\rightleftharpoons$fructose. Evidence for the rearrangement of (XXIX) to yield the diketone (XXXII) is given by an experiment carried out by Bradley and Eaton (45). They observed that 1-acetoxy-1-phenyl-3-chloro-2-propanone (XXXIV) on heating with a solution of sodium acetate in methanol-glacial acetic acid was converted, in nearly quantitative yield, into benzoyl methyl ketone (XXXV). The same chloroketone (XXXIV) decomposed spontaneously into (XXXV) on standing at room temperature for one year. It seems justifiable to assume that during this period of time the chloroketone (XXXIV) underwent slow hydrolysis to $\phi CHOHCOCH_2OH$ (XXXVI) followed by molecular rearrangement to the diketone (XXXV), as indicated.

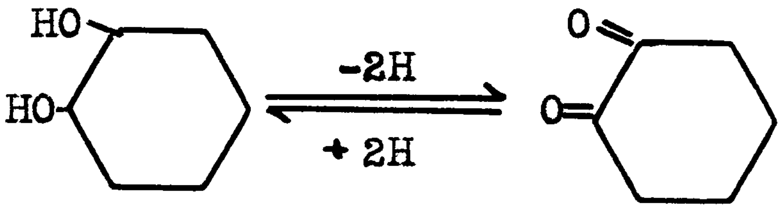
$$\begin{tikzcd}
\underset{\text{XXXIV}}{\phi CH(OAc)COCH_2Cl} \arrow[r, "NaOAc", "MeOH-HOAc"'] \arrow[dd] & \underset{\text{XXXV}}{\phi CO-CO-CH_3} \\
 & \phi C(OH)_2C(OH)=CH_2 \arrow[u] \\
\underset{\text{XXXVI}}{\phi CHOHCOCH_2OH} \arrow[r, shift left] & \phi C(OH)=C(OH)-CH_2OH \arrow[l, shift left] \arrow[u]
\end{tikzcd}$$

D. <u>Plant Respiratory Catalysts as a Source of Protolignin</u>

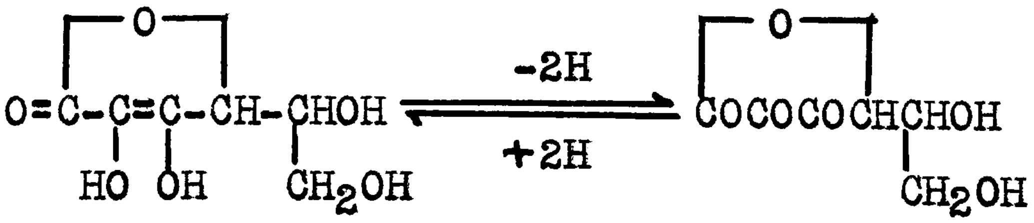
Most workers in the field of animal cell respiration (43) believe that the energy required by the animal cell for its metabolic processes is liberated by the transformation of carbohydrates into water and carbon dioxide. This transformation consists of a series of decarboxylation and dehydrogenation reactions. It should be noted that the water is not produced by a simple one-step reaction from the carbohydrates, but takes place through a series of intermediate reactions, until the lowest energy state is reached in the final reaction between hydrogen and oxygen to yield water. The reaction mechanism through which carbon dioxide is produced releases very little energy, thus it is the hydrogenation-dehydrogenation reactions that are of supreme importance.

The transformation of carbohydrates is, in reality, a "stepwise" liberation of energy necessary for the metabolism of the animal cell. The carbohydrates in the cell undergo degradation into simpler molecular units upon which dehydrogenase enzymes act to remove hydrogen. This latter is transported by an enzyme, a "carrier", or "hydrogen transporter". Thus hydrogen is transferred from one chemical compound to another through a series of hydrogenation-dehydrogenation reactions. The final stage is the union of this transported hydrogen with the oxygen in the cell.

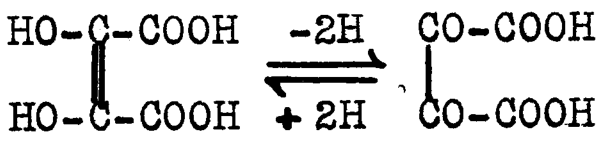
Szent-Györgyi has demonstrated the presence of a number of dehydrogenase-catalyst systems in various plants such as those of the catechol (XXXIX) (46), ascorbic acid (XXXVII) (47) and dioxymaleic acid (XXXVIII) (48) systems.



XXXIX



XXXVII



$$\begin{array}{l} \mathrm{HO\text{-}C\text{-}COOH} \\ \quad\ \| \\ \mathrm{HO\text{-}C\text{-}COOH} \end{array} \underset{+2H}{\overset{-2H}{\rightleftharpoons}} \begin{array}{l} \mathrm{CO\text{-}COOH} \\ \ | \\ \mathrm{CO\text{-}COOH} \end{array}$$

XXXVIII

Each of these (XXXVII), (XXXVIII) and (XXXIX) can function as a redox system, the oxidized molecule being a 1,2-diketone and the reduced molecule an ene-diol.

Hibbert (9) has pointed out that some of the water-soluble ethanolysis products from maple and spruce woods represent ene-diol-1,2-diketone redox systems. Compounds (XXXII), (XVIII) and (XXXIII) presumably represent stabilized end products, their forerunners (XXX) and/or (XXIX) being the lignin progenitors that act as hydrogen transport-catalysts.

The presence of coniferin in the cambial sap of many young plants (3) and other considerations have led Hibbert (9) to postulate a plant hydrogen-transport system, analogous to the Szent-Györgyi C_4-dicarboxylic acid system (49).

<u>Plant System (Hibbert)</u>	<u>Animal System (Szent-Györgyi)</u>
(A) $R\text{-}CH_2\text{-}CO\text{-}CH_2OH$	(A') $HOOC\text{-}CH_2\text{-}CO\text{-}COOH$
$+2H \downarrow\uparrow -2H$	$+2H \downarrow\uparrow -2H$
(B) $R\text{-}CH_2\text{-}CHOH\text{-}CH_2OH$	(B') $HOOC\text{-}CH_2\text{-}CHOH\text{-}COOH$
$\downarrow -H_2O$	$\downarrow -H_2O$
(C) $R\text{-}CH{=}CH\text{-}CH_2OH$	(C') $HOOC\text{-}CH{=}CH\text{-}COOH$
$+2H \downarrow\uparrow -2H$	$+2H \downarrow\uparrow -2H$
(D) $R\text{-}CH_2\text{-}CH_2\text{-}CH_2OH$	(D') $HOOC\text{-}CH_2\text{-}CH_2\text{-}COOH$

R = Syringyl or Guaiacyl radical

The first member (A) of the Hibbert system, corresponding to oxalacetic acid (A') of the Szent-Györgyi system, is the keto alcohol believed to be obtained from the condensation of three molecules of methyl glyoxal (page 12). The isomeric form of (A), $RCOCH_2CH_2OH$, may also function similarly to (A) in the new system, while (B) and its isomeric form would provide analogues of citric and isocitric acids which are the components of the Krebs animal cell oxidation system (50). The passage from Hibbert's (51) new system to the ene-diol-1,2-diketone system can take place by an allylic rearrangement of the oxyconiferyl or oxysyringyl alcohol isomer, as represented above (page 12).

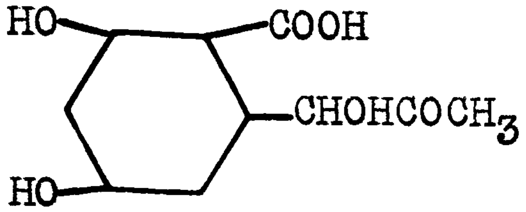
E. Mycophenolic Acids and their Relationship to Lignin

Raistrick and co-workers (52) have carried on a comprehensive program of investigation on the biochemistry of mold action. Many new products from different genera and species of molds were isolated and identified. Of these, the benzoins, benzoquinones, quinols, anthraquinones, pyrones, desoxybenzoins, and diketones are of special interest and appear to be of marked biochemical importance.

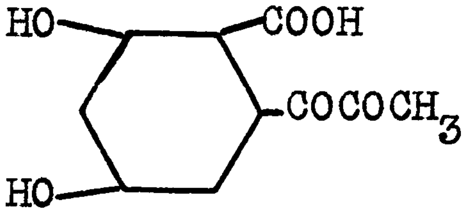
The molds were grown on the Czapek-Dox medium which is a 5 per cent glucose solution containing mineral salts. The medium was sterilized and inoculated with the mold spores.

The time of incubation, pH of medium, and temperature were varied to suit the particular species or strain of mold. Raistrick was thus able to demonstrate that the products of mold metabolism usually differed for different genera and in many cases for different species of the same genus.

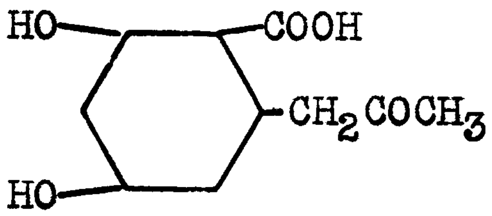
Fifteen species of Penicillium all yielded the same three mycophenolic acids (XL), (XLI) and (XLII), and in addition, other similar acids whose constitutions have not yet been determined. It is therefore interesting to note that Hibbert and co-workers (33,35,37) have isolated from the ethanolysis mixtures aromatic derivatives having a three-carbon side chain identical with those present in (XL), (XLI) and (XLII), but, in which the aromatic nucleus is represented by the guaiacyl and syringyl radicals (page 8). The introduction of the carboxyl group is not significant to the mold synthesis of (XL), (XLI) and (XLII) in the light of the ease with which carboxylation of polyhydric phenols, such as phloroglucinol, occurs on treatment with aqueous sodium bicarbonate at 50°-100° (53,54). Actually at room temperature an equilibrium mixture of phenol and carboxylic acid is obtained(55).



XL



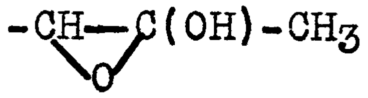
XLI



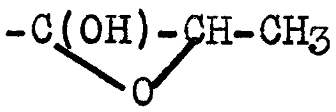
XLII

Oxford and Raistrick (52) point out that the structure of the side chain of (XL) is uncertain and that it may be either one or other of the following:

$-CO-CHOH-CH_3$, $-C(OH)=C(OH)-CH_3$,



$-\underbrace{CH-C}_{O}(OH)-CH_3$



$-\underbrace{C(OH)-CH}_{O}-CH_3$

or an equilibrium mixture of several of these possible isomers. They found that (XL) was optically inactive and explained this as due to the presence of an equilibrium between this and its ene-diol form. The three compounds (XL), (XLI), and (XLII) were found to be readily interconvertible.

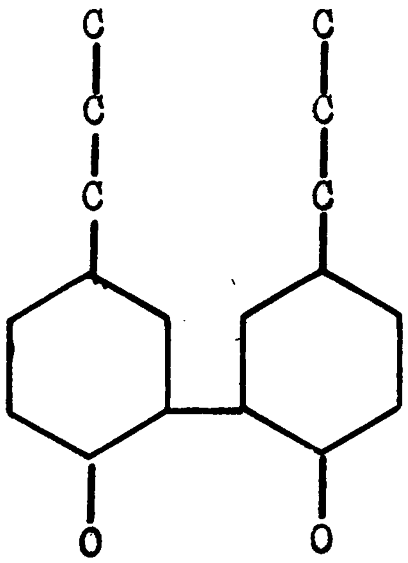
In most cases the principal constituent of the metabolic mixture was the diketone (XLI). The yields of (XLII) were quite low in all experiments, about 3 per cent of the total mixture. These three metabolic products, (XL), (XLI) and (XLII) show a remarkable parallelism, both in regard to side chain structure and interconvertibility, with the aromatic derivatives isolated from the ethanolysis products of wood, namely the ethyl ether of 2-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (XIV), 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (XVI) and 1-(4-hydroxy-3-methoxyphenyl)-2-propanone (XVIII) (37).

The interesting question of the possible function of the latter as redox systems in the life of higher plants is thus raised. Inasmuch as they have been shown to be derived from lignin (9,37), this similarity in type seems to support Hibbert's view that lignin is a mixture of products arising from a group of monomolecular compounds of the C_6-C-C-C type, whose primary function is that of respiratory catalysts (51). Actual experimental support is to be found in the fact that when Raistrick's molds were developed on a "starvation diet" only the diketone was obtained. Presumably the ene-diol form derived from (XL) gave up hydrogen to form water whereby the desired energy was provided. It is presumably justifiable to assume that Raistrick's and the analogous wood ethanolysis products actually represent stabilized end-products rather than progenitors.

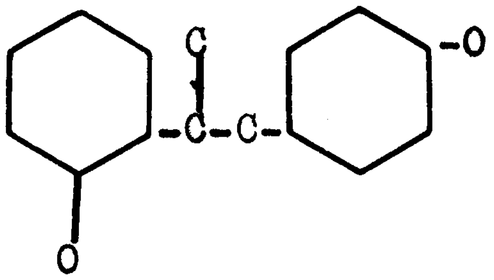
F. Plant Resins (Lignans)

Freudenberg's speculations (14) regarding polymer types and mechanism of polymerization of propylphenol units in spruce lignin have aroused a greater interest in the chemistry of plant resins. Hibbert (51) has proposed three possible lignin dimers and they are significantly related structurally to the plant resins.

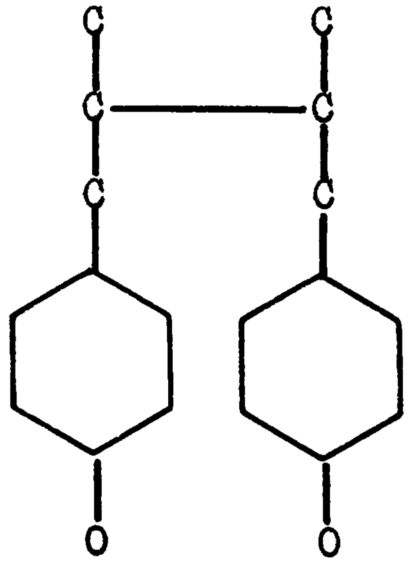
Erdtman (56), Haworth (57) and their co-workers have been the chief contributors in this field and they consider the resins to be dimeric propylphenol units linked according to one or other of the following skeletal schemes:



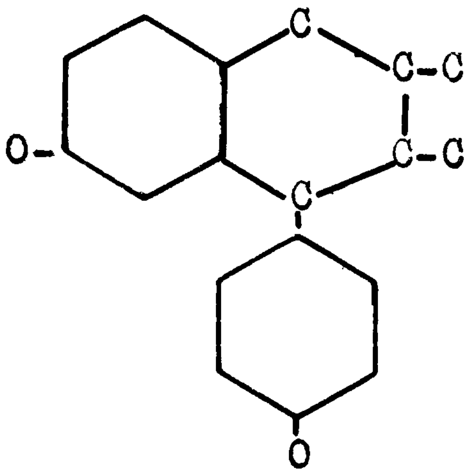
XLIII



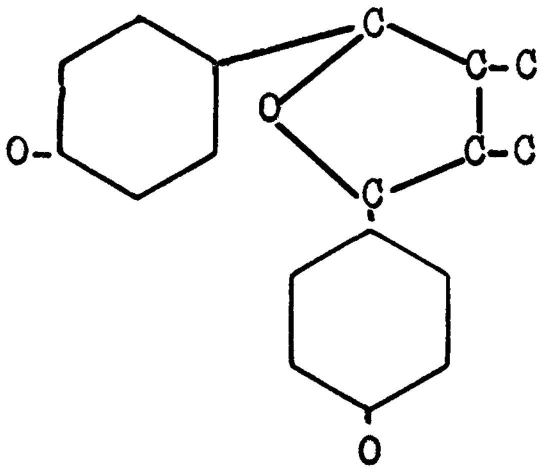
XLIV



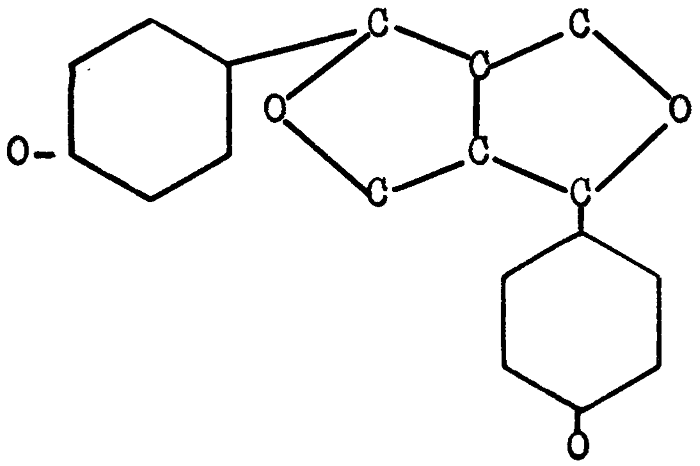
XLV



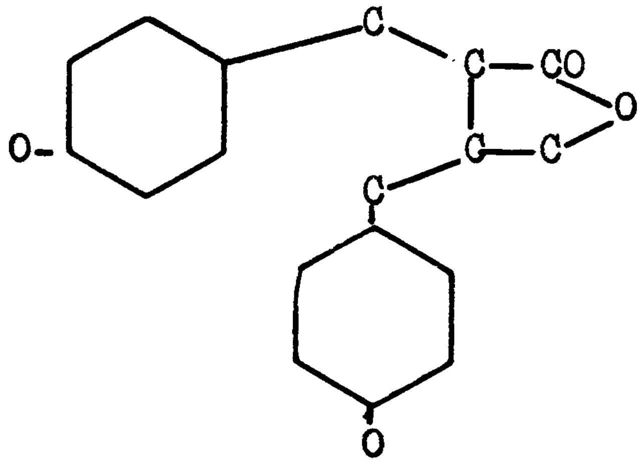
XLVI



XLVII

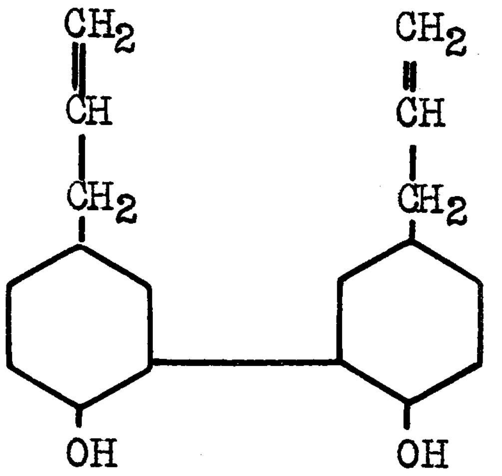


XLVIII

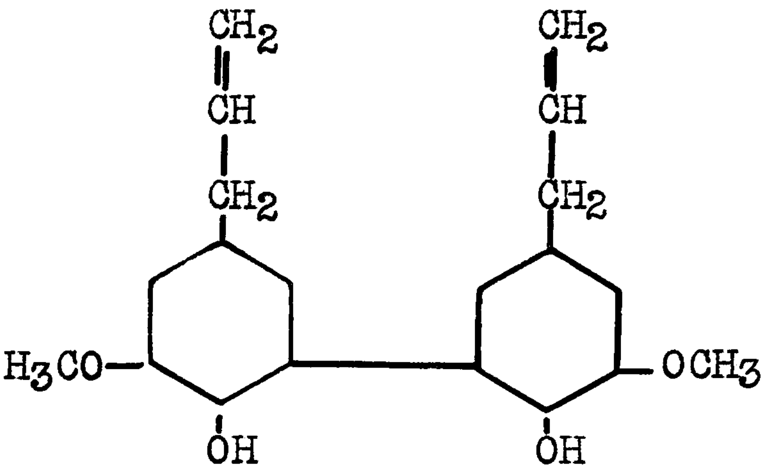


XLIX

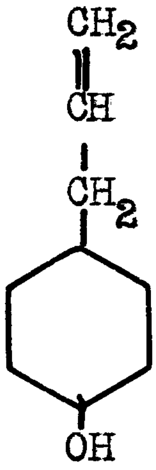
The structure (XLIII) is found in maginolol (L) and dehydrodieugenol (LI). These dimers (L), (LI) can be synthesized from the monomers (LII) and (LIII) respectively both by enzymatic dehydrogenation and ferric chloride oxidation (58).



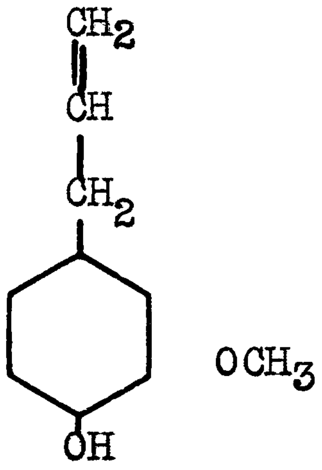
L



LI

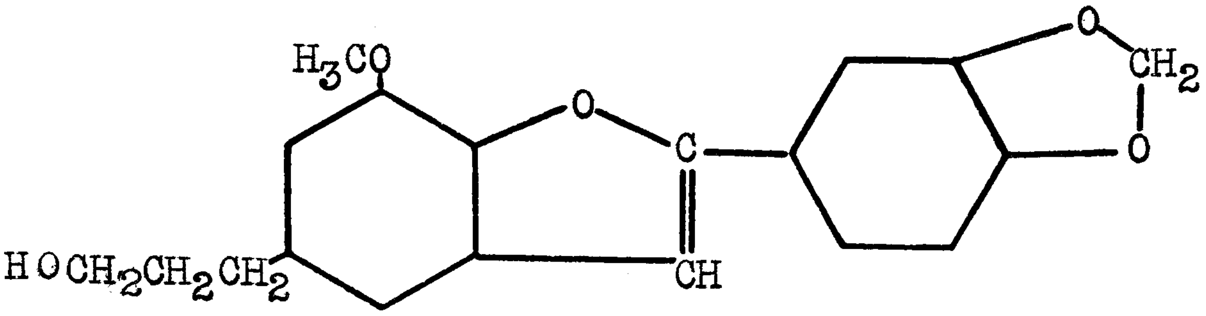


LII



LIII

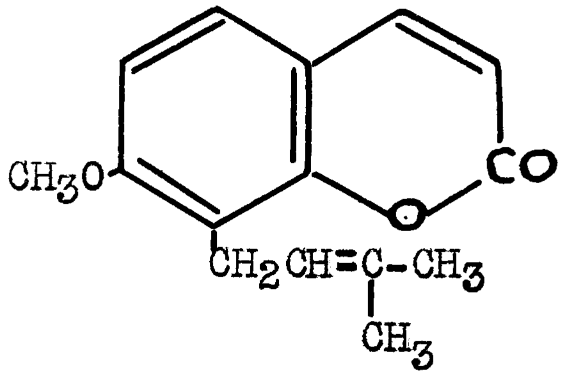
The structure (XLIV) is found in egonol (LIV), which of all the natural dimeric products, is most closely related to Freudenberg's (II) and Hibbert's (51) structures for lignin.



LIV

The larger number of plant resins appear to have the skeletal structures indicated in (XLVI), (XLVII), (XLVIII) and (XLIX). They all consist of dimeric propylphenol units united by carbon to carbon linkages at the β carbon atom of the propyl side-chain.

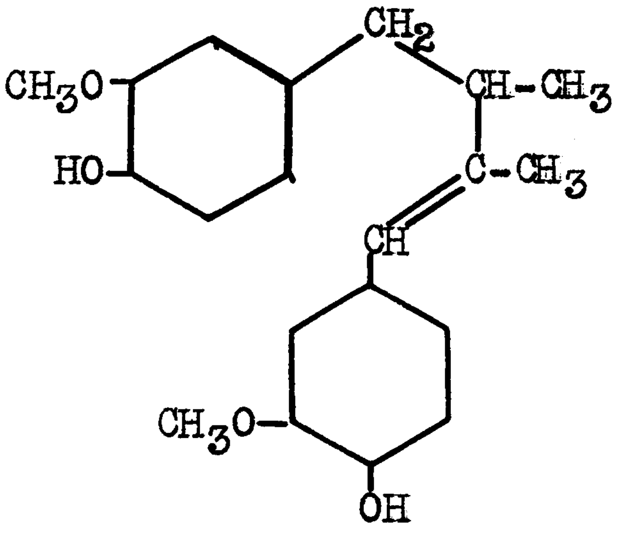
The predominant type of aromatic compounds found in nature contains the guaiacyl and/or syringyl nuclei united with a propyl side-chain. In addition, the n-propylbenzene nucleus is found associated with the isopentene units in many compounds, for example, osthol (LV) and ammoresinol, the latter structure not yet having been completely established.



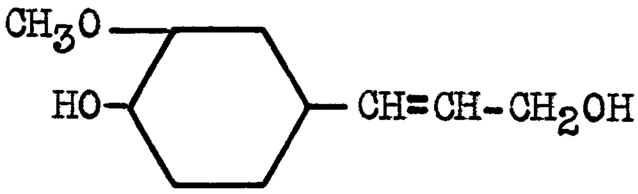
LV

It is also found united with aliphatic or aromatic C_6 units in many plant pigments (anthocyanins), glycosides and lignin monomers.

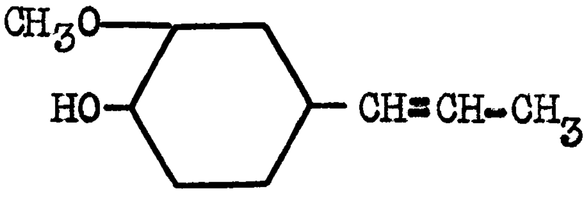
Schroeter and co-workers (59) suggested that the principal constituent of the resin from Guaiacum officinale, l-guaiaretic acid (LVI), had a "bis-coniferyl" structure. Klason (2), as early as 1897, emphasized that lignin was in all probability related to coniferyl alcohol (LVII). Thus interest is centered around the lignans, as both lignin monomers and the lignans contain the basic structure of isoeugenol (LVIII).



LVI



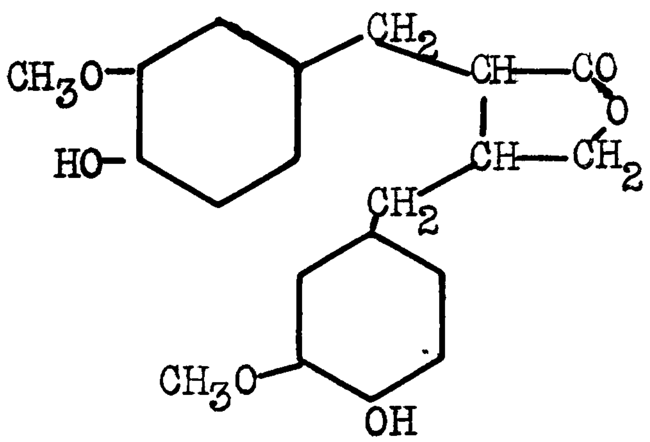
LVII



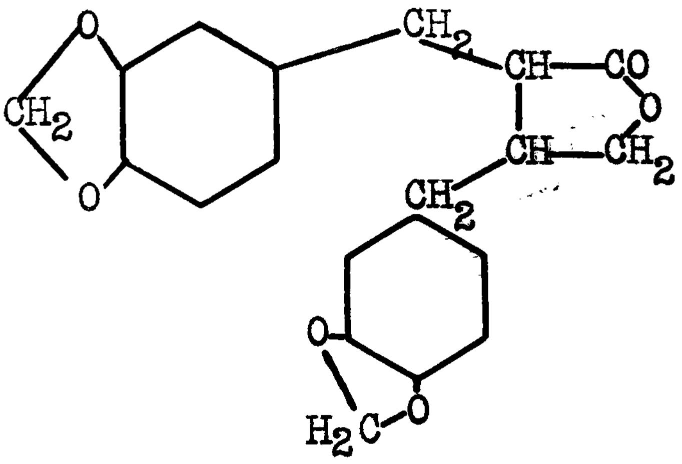
LVIII

Haworth (57,60) introduced the term "lignan" to designate those dimeric types of compounds which are characterized by two aromatic nuclei, each containing a propyl side chain. The propyl side chains are linked at their β carbon atoms and usually contain one or two oxygen atoms. The lignans are conveniently classified into six main types, referred to on pages 20, 21, three of which , 1-phenyltetralins (XLVI), $\alpha\alpha'$-diphenylfurans (XLVII) (XLVIII), and dibenzylbutyrolactones (XLIX), are discussed below.

1-Matairesinol (LIX), isolated from the heartwood of Podocarpus spicatus (61); its monomethyl ether 1-arctigenin, occurring as the glycoside in the seeds of Arctium lappa (62); and 1-hinokinin (LX), isolated from Cupressus obtusa (63) form a closely related group of $\alpha\beta$ dibenzylbutyrolactones (XLIX).

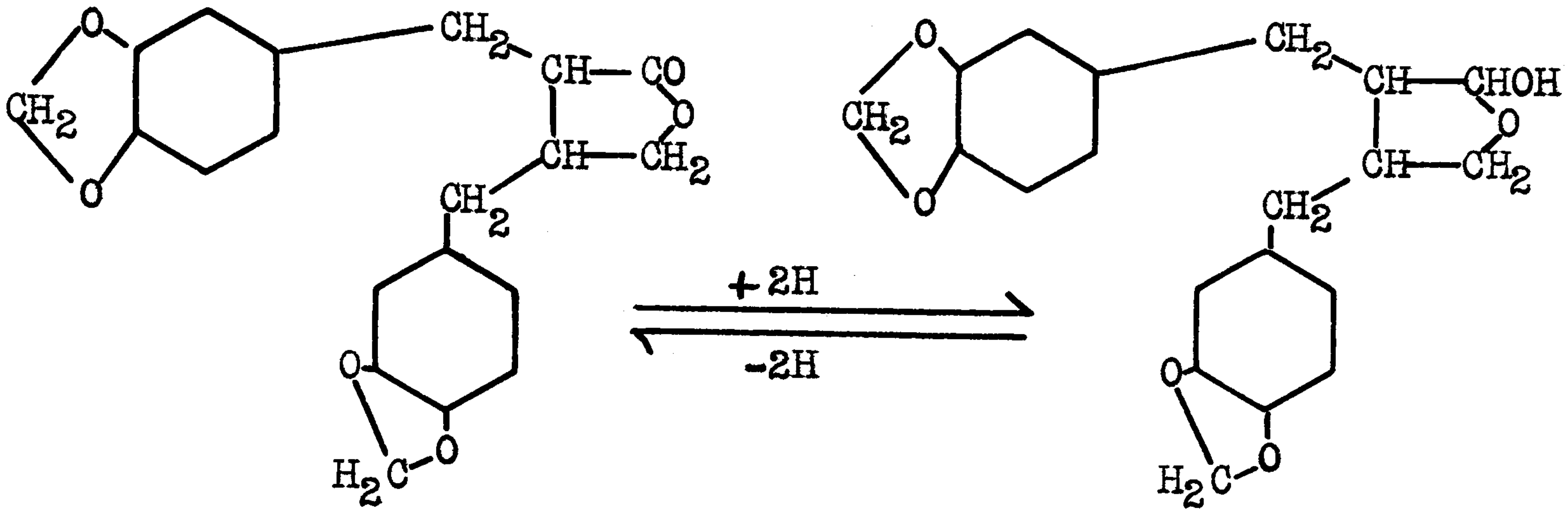


LIX



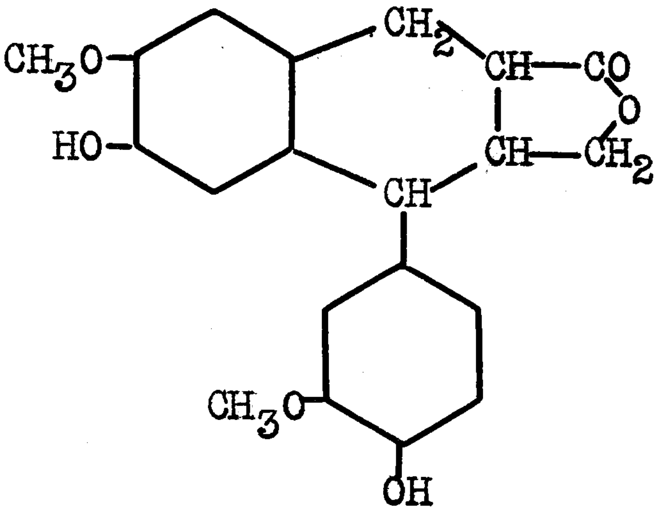
LX

l-Cubebin (LXI), found in Piper cubeba (64), is readily converted to l-hinokinin (LX) on mild oxidation. The former may be obtained from the latter on mild reduction.



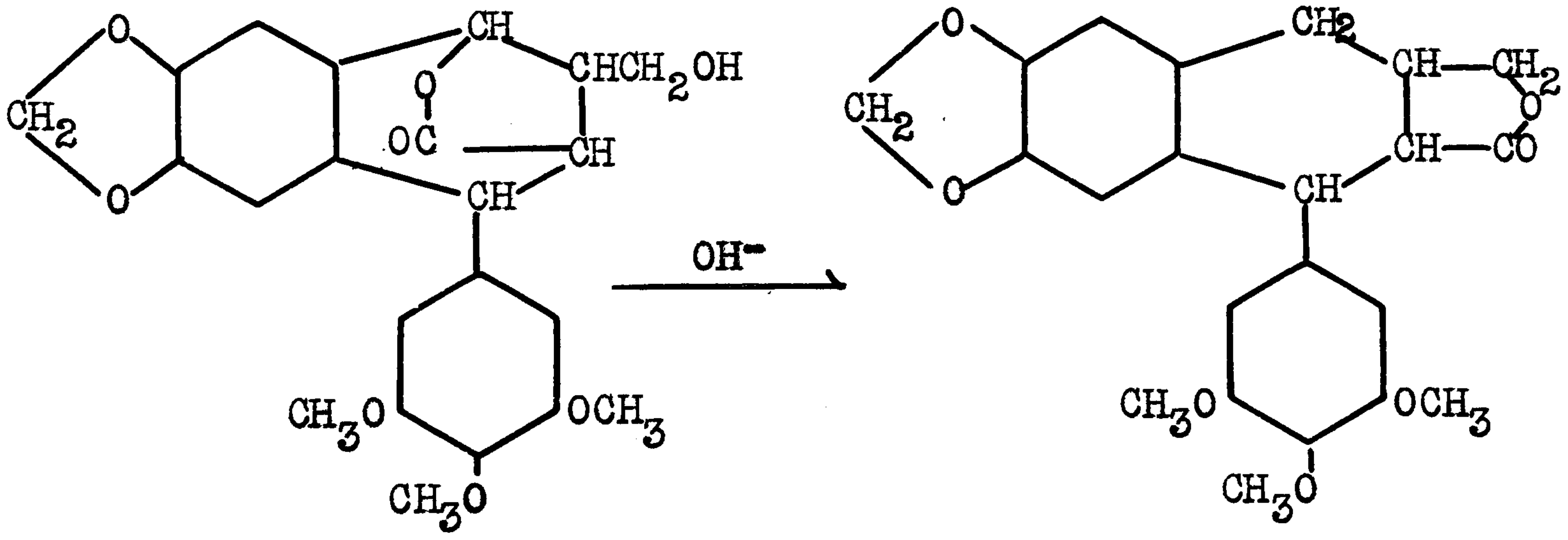
LX LXI

Tollens and Lindsay (65) first isolated l-conidendrin (LXII) (sulfite liquor lactone) from waste sulfite liquor. This lignan occurs in Tsuga siebaldii (66) and Picea excelsa (67). The phenyltetralin structure (LXII) may be derived from (LIX) by dehydrogenation in the plant tissue, and the association of small amounts of l-conidendrin (LXII) with l-matairesinol (LIX) in the heartwood of Podocarpus spicatus (68) suggests that the relationship may be biological as well as structural. It is significant that dehydrogenation would have to occur to form the phenyltetralin (LXII) from (LIX).



LXII

The phenyltetralin structure is also present in l-podophyllotoxin (LXIII), isolated from the root resins of several species of Podophyllum. Bases readily isomerize l-podophyllotoxin to d-picropodophyllin (LXIV) (69,70), the isomerization being irreversible.

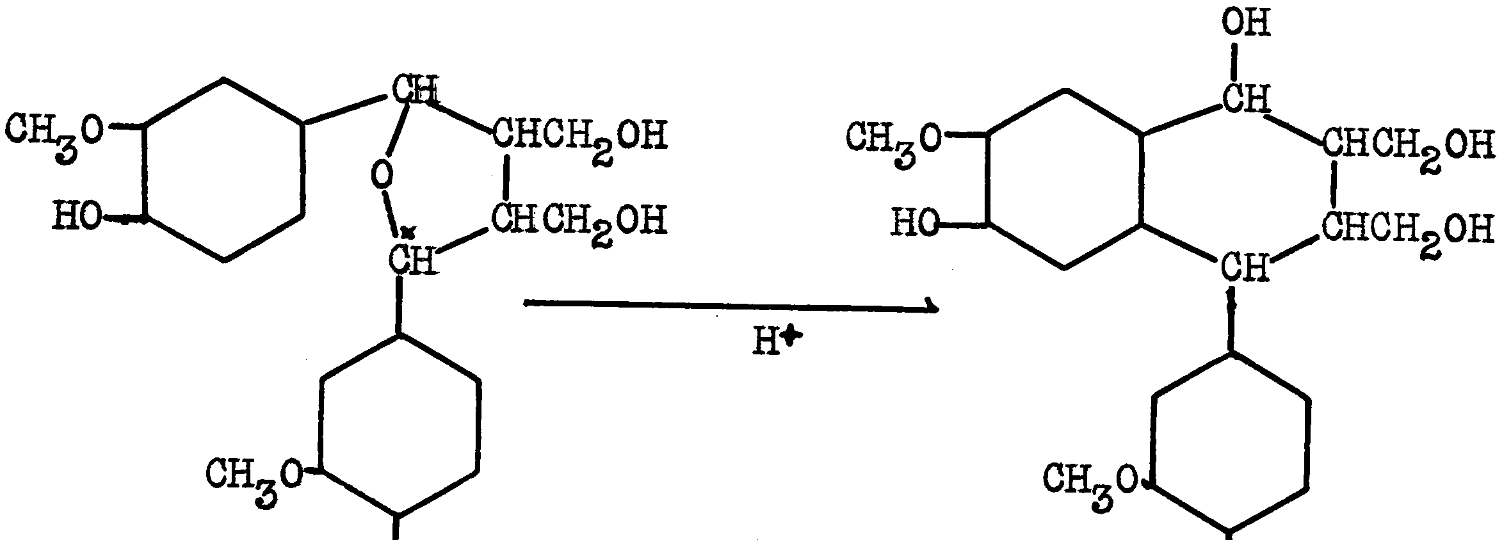


LXIII

LXIV

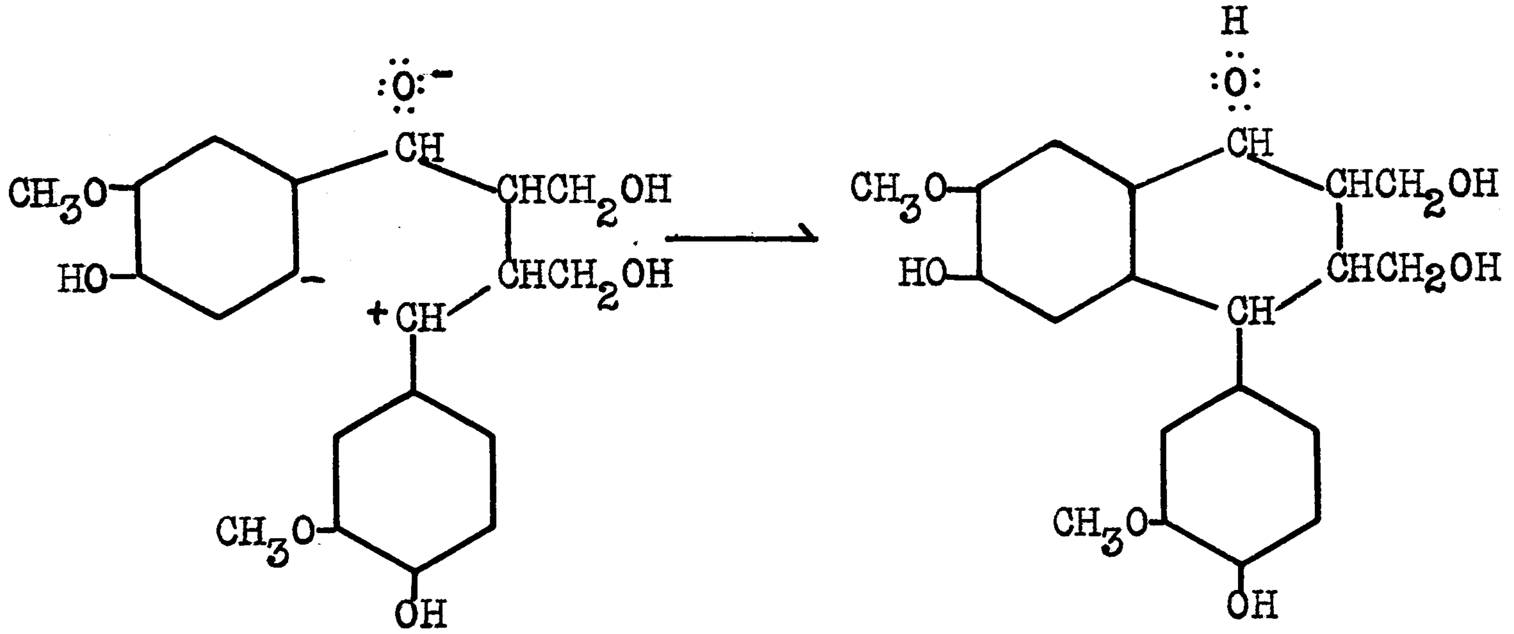
1-Podophyllotoxin (LXIII) is the only representative of the lignan resins containing dissimilarly substituted aromatic nuclei and the position of the secondary alcoholic group indicates a relationship with the $\alpha\alpha'$-diphenylfuran type (XLVII). This dissimilarity in the substituted aromatic nuclei may have some relationship to possible lignin dimers in hardwoods.

1-Olivil (LXV), isolated from the resin of <u>Olea europa</u>, is an $\alpha\alpha'$-diphenylfuran (XLVII). It is converted by mild acid treatment into iso-olivil (LXVI), a phenyltetralin (XLVI) (71,72,73).



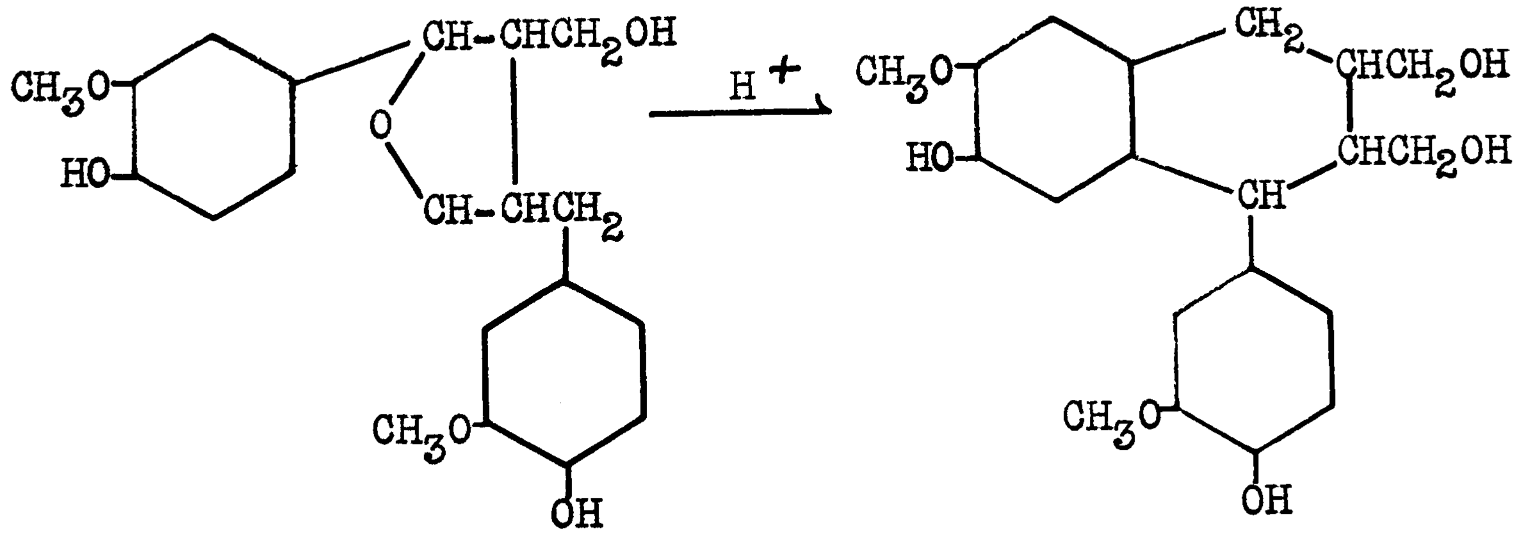
LXV LXVI

Apparently, ring fission occurs between the oxygen and carbon atoms in (LXV), leaving the oxygen with a complete octet of electrons and the carbon atom* with a deficiency of electrons. This anionoid carbon atom can then substitute in the aromatic ring by the general mechanism postulated by Price (74). The cationoid oxygen atom then unites with an anionoid hydrogen atom, either from the ring, or more probably, from the hydrogen ions of the acid solution necessary to effect the change to the phenyltetralin form (LXVI):



LXVI

d-Lariciresinol (LXVII) is also converted into a phenyltetralin, d-iso-lariciresinol (LXVIII), in acidic media; a similar substitution mechanism being involved.



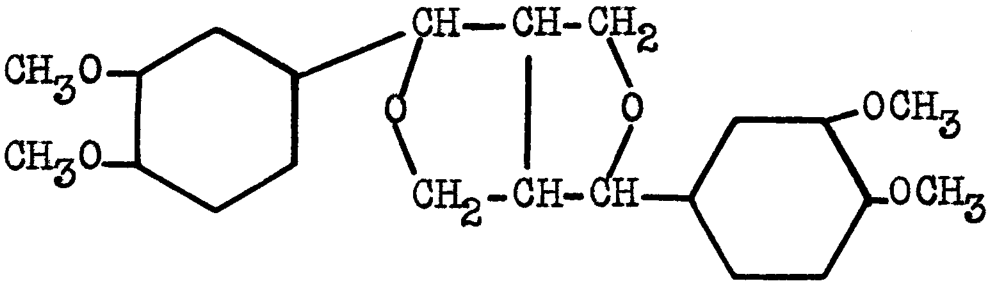
LXVII

LXVIII

This phenomenon would seem to have a marked application to lignin chemistry and a section of Part G, page 48 is devoted to it.

The known lignans occur naturally in optically active modifications and the structural problem has been largely simplified by the isolation of inactive degradation products from reduction, oxidation, dehydrogenation and nitration experiments. The phenolic hydroxyls are protected by methylation or ethylation prior to degradation.

The elimination of α-oxygenated side chains during nitration of catechol ethers may be employed for the detection of the furanofuran lignans (XLVIII). Nitration of l-pinoresinol dimethyl ether (LXIX) yields the 6,6'-dinitrolignan together with 4-nitroveratrole, but nitration with fuming nitric acid results in complete elimination of the side chain with formation of dinitro- or trinitroveratrole (75).

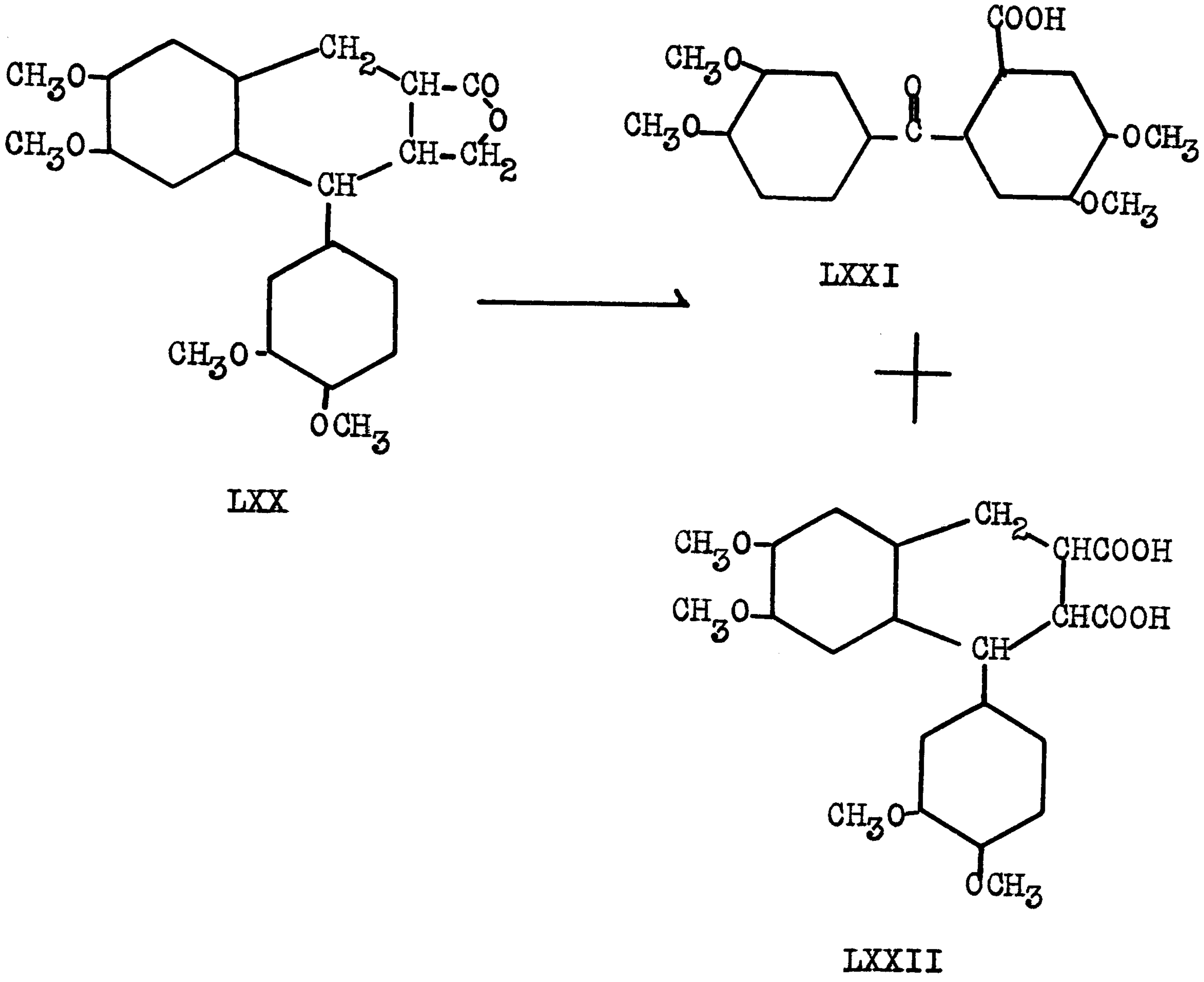


LXIX

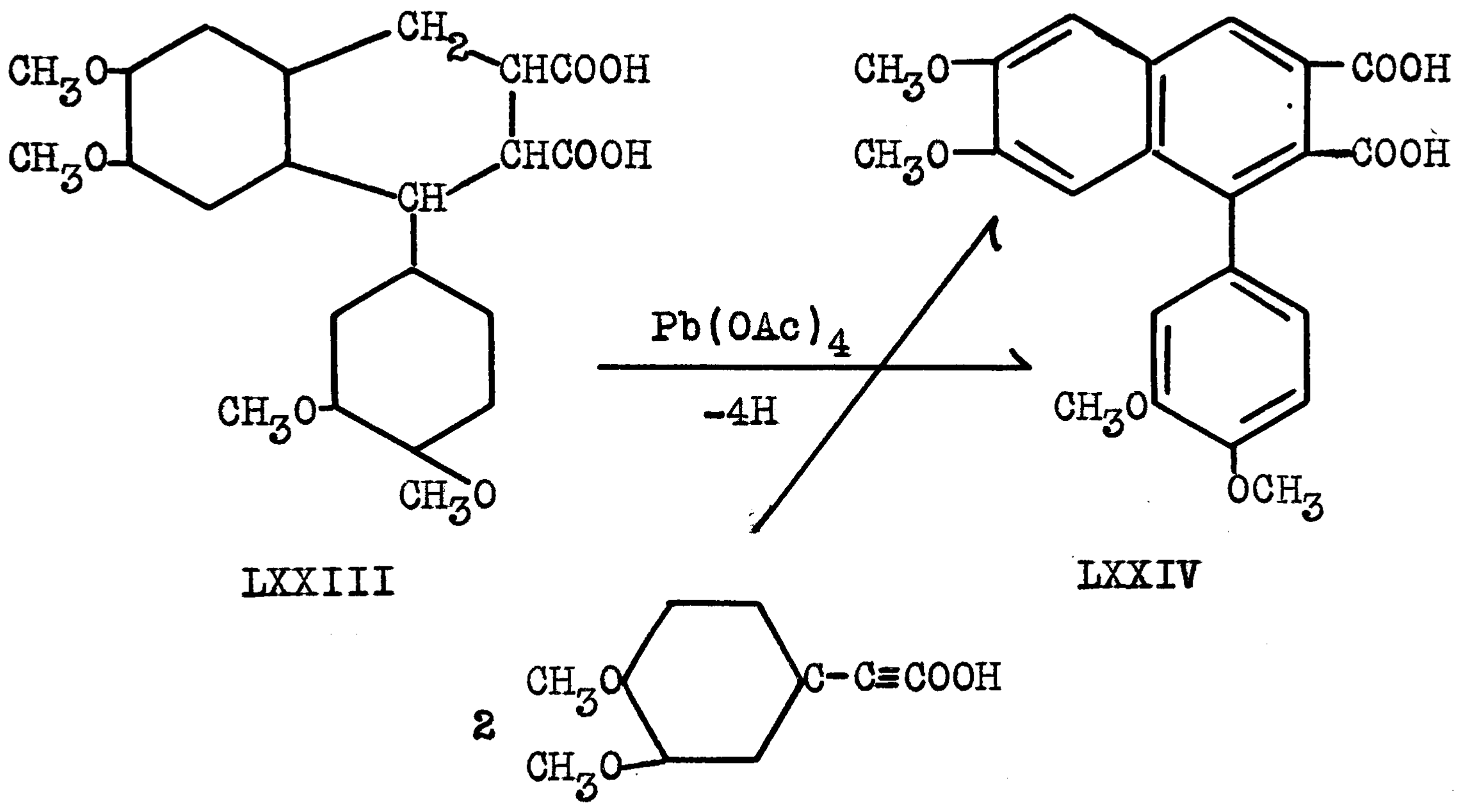
Ethers of the α,β-dibenzylbutyrolactone type (XLIX) yield dinitro- or tetranitro-substitution products, retaining the complete lignan structure. The phenyltetralin type (XLVI) is usually converted into amorphous products (76) on treatment with nitric acid.

The reactions referred to above serve to characterize the furanofuran (XLVIII) and furan (XLVII) lignans. The yields of dinitroveratrole, assuredly semi-quantitative, indicate the number of furan groups in the molecule. Other methods for the determination of the number of furan groups involve the use of bromination or hydrogenation techniques.

The structures of the $\alpha\beta$-dibenzylbutyrolactone (XLIX) and phenyltetralin (XLVI) type lignans can be differentiated by simple oxidation experiments. The former are oxidized by permanganate to substituted benzoic acids and as the diethyl ether of l-matairesinol (LIX) gives 3-methoxy-4-ethoxybenzoic acid in yields exceeding fifty per cent, the presence of two guaiacyl nuclei is established (76). The latter are oxidized to substituted ortho benzoylbenzoic acids by the action of permanganate, and oxidation of the ethyl ethers and subsequent identification of the resulting acids, locates the hydroxyl groups. Further structural evidence is obtained from hypobromite oxidation which yields a mixture of substituted ortho benzoylbenzoic acids and phenyltetralin dibasic acids containing the complete carbon content of the original lignan. Thus conidendrin dimethyl ether (LXX) gives ortho veratroylveratric acid (LXXI) and the phenyltetralin dibasic acid (LXXII) (77,78).



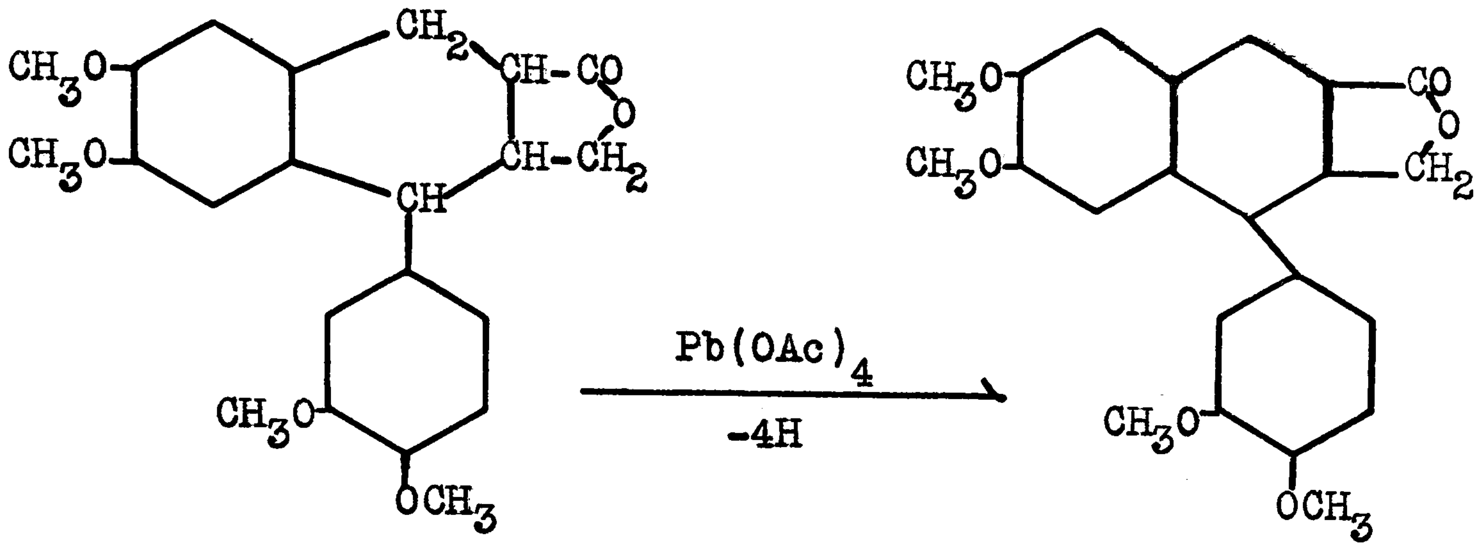
The establishment of the lignan structure has been obtained in a few cases by synthesis of the optically active lignan, but in cases similar to the above it is usually sufficient to effect the synthesis of the optically inactive acid containing the entire lignan structure. For example, in the case of the proof of structure of conidendrin dimethyl ether (LXX), the dicarboxylic acid which can be obtained on oxidation of (LXX) can be dehydrogenated to form the optically inactive acid (LXXIV). This acid, in turn has been synthesized by dimerization of 3,4-dimethoxyphenyl propiolic acid with acetic anhydride (79).



LXXIII

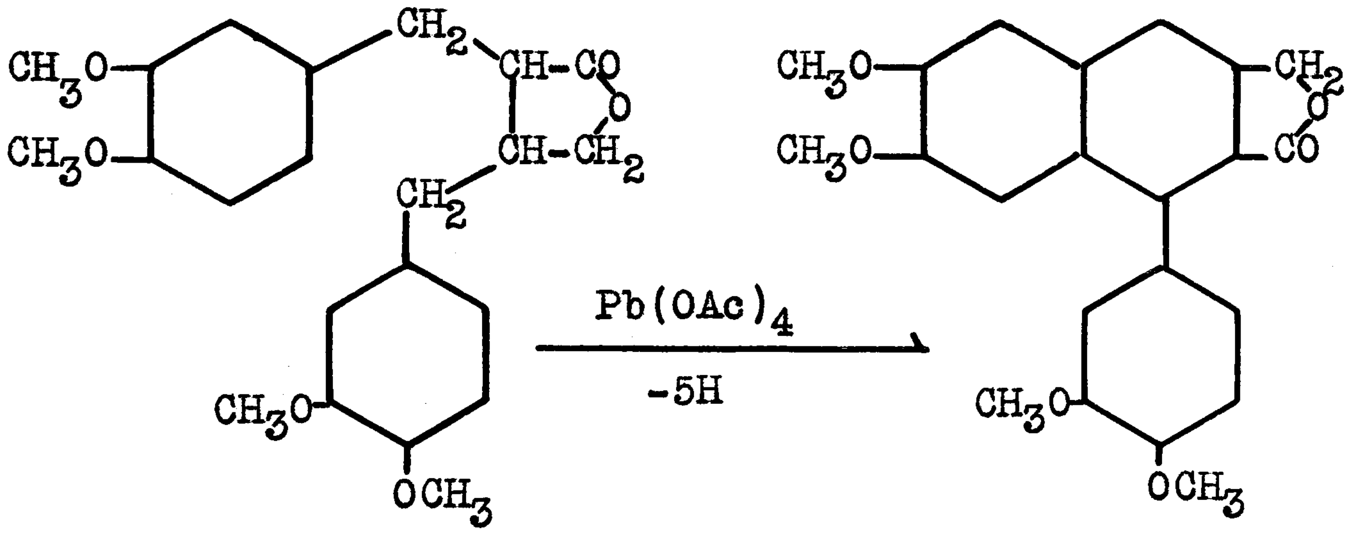
LXXIV

Selenium, or preferably lead tetra-acetate may be used for the conversion of l-conidendrin dimethyl ether (LXXV) into the inactive lactone (LXXVI). This lactone is also obtained, together with an inactive isomer (LXXVII), by the action of lead tetra-acetate on the dimethyl ether



LXXV LXXVI

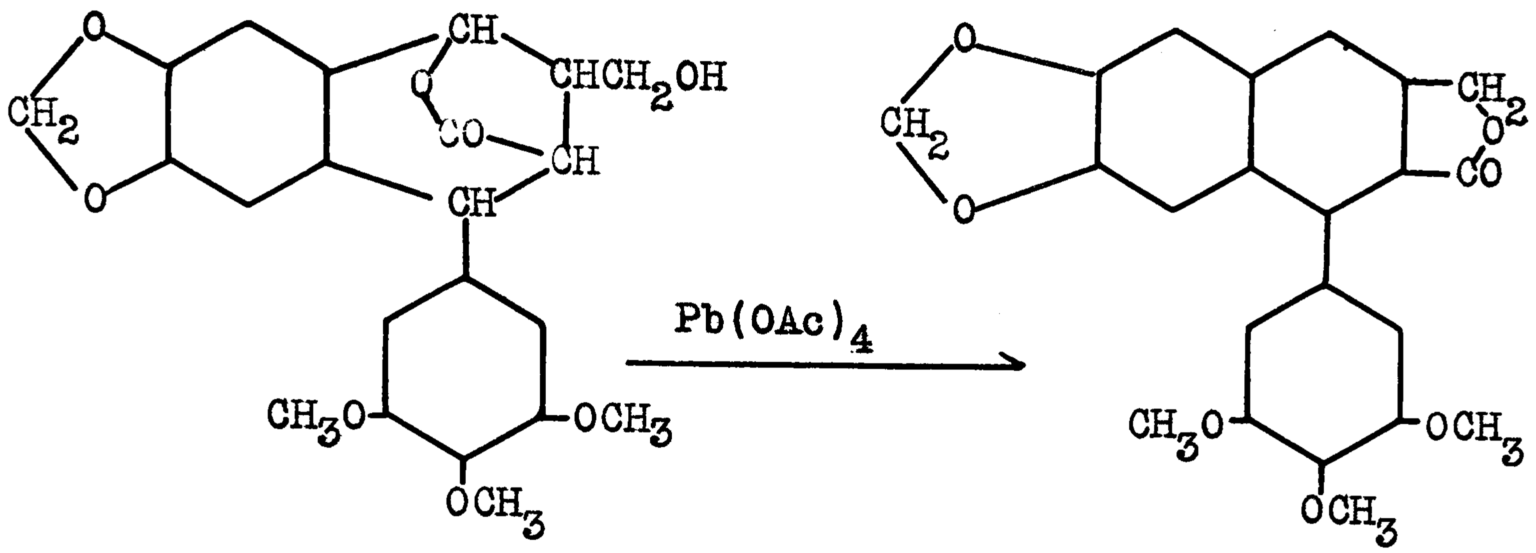
of l-matairesinol (LXXVIII) (76,79). Apparently ring closure occurs during one stage of the dehydrogenation.



LXXVI

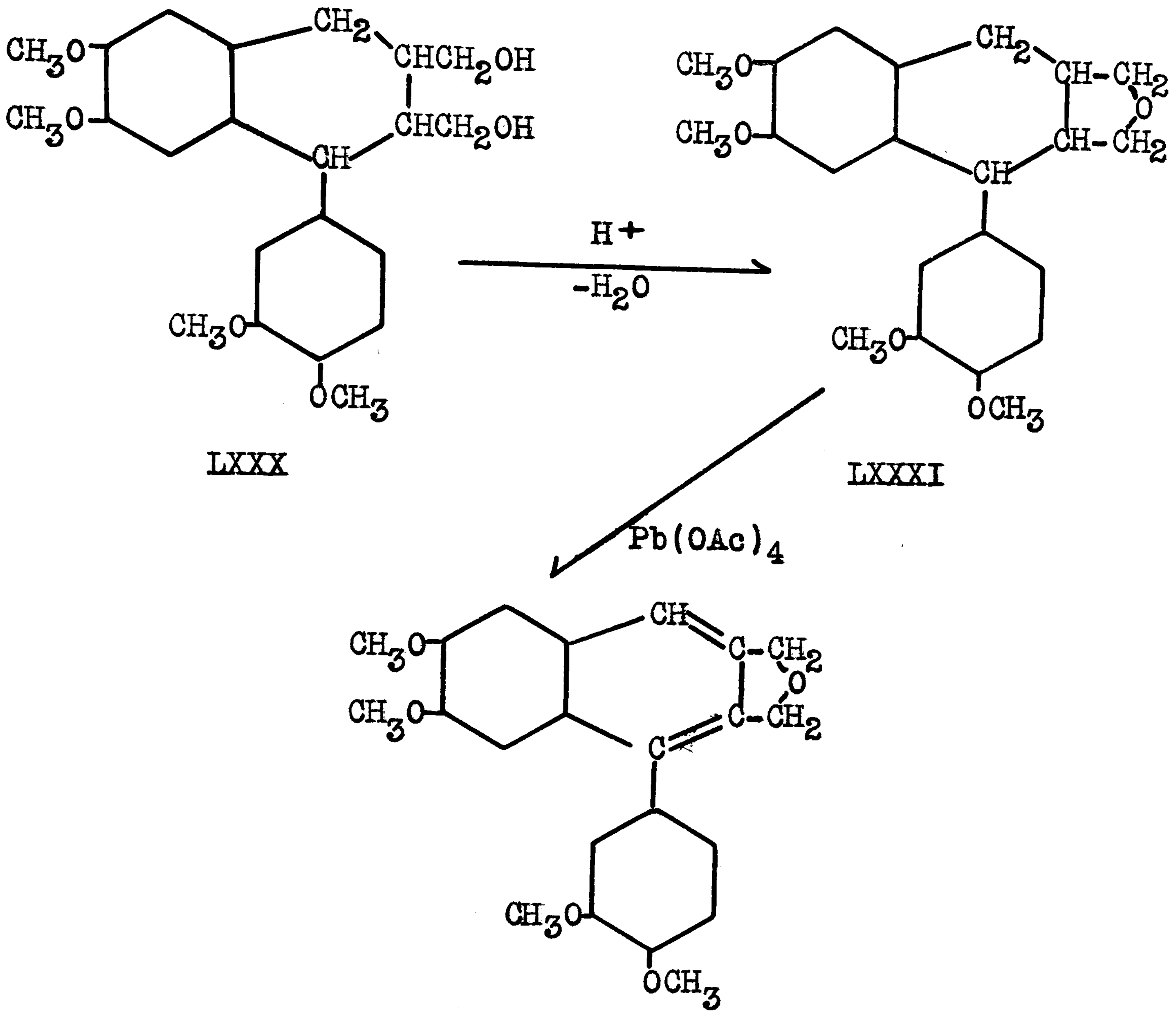
LXXVIII LXXVII

A similarly constituted lactone, dehydroanhydropicropodophyllin (LXXIX) has been prepared from podophyllotoxin (LXIII) (80).



LXIII LXXIX

The dehydrogenative 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 (LXXX) is converted by acids into the l-cyclic ether (LXXXI), which is smoothly dehydrogenated to the inactive ether (LXXXII) (81).



LXXX

LXXXI

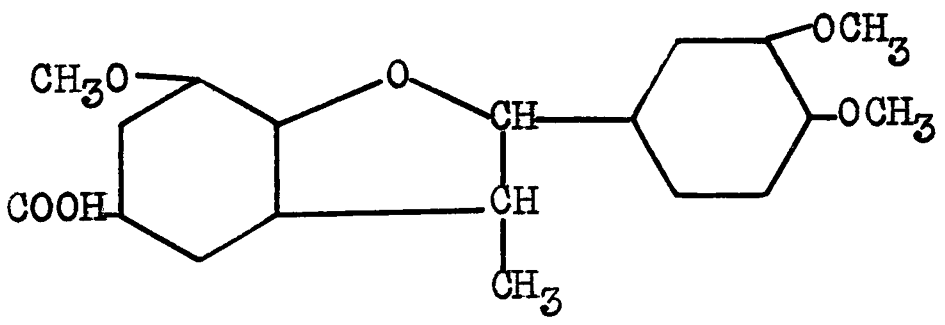
LXXXII

The lignan ethers may be dehydrogenated by means of selenium, rather than lead tetra-acetate, but the yields are very low.

G. Formation of Protolignin from Propyl Phenol Units

(a) Polymers of the Guaiacyl Type

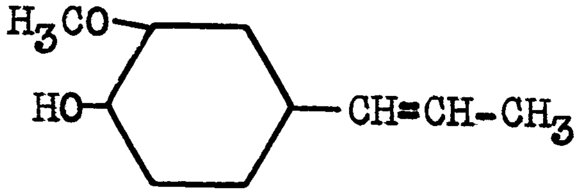
The investigations on the plant resins have shown (57,60) that a group of natural products exist that are presumably derived from propyl phenol units by dehydrogenative coupling. Erdtman (82) has suggested that the same phenomenon of dehydrogenative coupling of single molecules probably plays an important role in the biogenesis of lignin. He therefore commenced a series of investigations on the so-called "Erdtman's acid" (LXXXIII). This structure agrees exceptionally well with those of Freudenberg's dimer (II) and Hibbert's dimers (LXXXVIII) (XC) (XCII) (51).



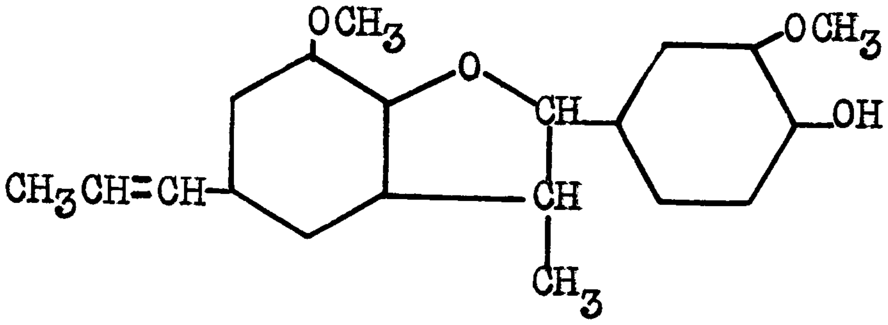
LXXXIII

This acid, (LXXXIII), is obtained by mild oxidation of methylated dehydrodiisoeugenol (LXXXIV).

Isoeugenol (LXXXV), under the influence of bacterial enzymes or ferric chloride (58) forms a dehydrogenated dimer considered by Erdtman (82,83) to have the structure (LXXXIV).



LXXXV



LXXXIV

This is based on the following evidence: The methylated dimer contains only three methoxyl groups; nitric acid cleavage of the methylated product yields 60 per cent of the theoretical quantity of trinitroveratrole calculated on the structure shown; p-nitrobenzoylation gives only a mono p-nitrobenzoate derivative (determination of nitrogen); oxidation of the methyl ether does not yield diveratric acid, hence eliminating a dimer of the type of dehydrodivanillin; ozonolysis yields acetaldehyde in amount proportional to one C_3 side chain only; and, dehydrodiisoeugenol absorbs only one molecule of hydrogen during reduction.

Erdtman (83) prepared the acid (LXXXIII) from dehydrodiisoeugenol (LXXXIV) by mild oxidation with cold potassium permanganate solution. Freudenberg considered the acid (LXXXIII) to be the best model substance for the spruce lignin polymer.

Such a structure (LXXXIII) should yield isohemipinic acid upon oxidation and Freudenberg (11) confirmed this by successive alkali degradation, methylation and permanganate oxidation. Isohemipinic and veratric acids were found in yields of 5 and 21 per cent respectively although the theoretical yields are 66 and 53 per cent.

By a similar treatment of an extracted spruce lignin Freudenberg (12) obtained isohemipinic and veratric acids in yields of 4 and 14 per cent respectively, thus this was evidence supporting his proposed lignin structure (II). More recently (84) he has modified his views and now assumes that only half or even less of the lignin molecules in spruce are of the type which could yield isohemipinic acid. The high yields of vanillin (23) and syringaldehyde (22,85), obtained by the oxidation of wood with alkaline nitrobenzene, necessitated this modification. The cleavage of terminal groups alone from relatively large molecules could not account for the high yields of aldehydes obtained.

The remarkable, and assuredly significant, analogies between the reactions of dehydrodiisoeugenol and lignin have led Erdtman (56) to the conclusion that lignin is in all probability a relatively low molecular weight substance. Thus he suggests that it probably consists of dimers related to the lignans. This possibility is in agreement with many of the experimental facts, but Haworth (57), referring to the absence of free phenolic groups in isolated lignins, suggests that the Erdtman dimeric structure cannot be reconciled with this important characteristic.

This objection is not so important if a broader view is taken of the nature of protolignin. Although the existence of a lignin-carbohydrate complex has not been established definitely, Erdtman's theory (56) may be modified by the assumption that protolignin consists of a dimeric type structure which is combined in some manner with carbohydrates, probably glycosidic, thus blocking the phenolic groups and preventing the ready removal of lignin from wood. The lignin-carbohydrate complex, if present, would cleave under the conditions of the ethanolysis reaction and subsequent cleavage of the resulting dimeric product would yield a highly labile monomer, possibly RCH_2COCH_2OH (XXIX). The latter product can readily undergo allylic rearrangement and dismutation changes (including ethylation) to yield the several relatively stable monomers isolated from the "ethanolysis oils" (page 12).

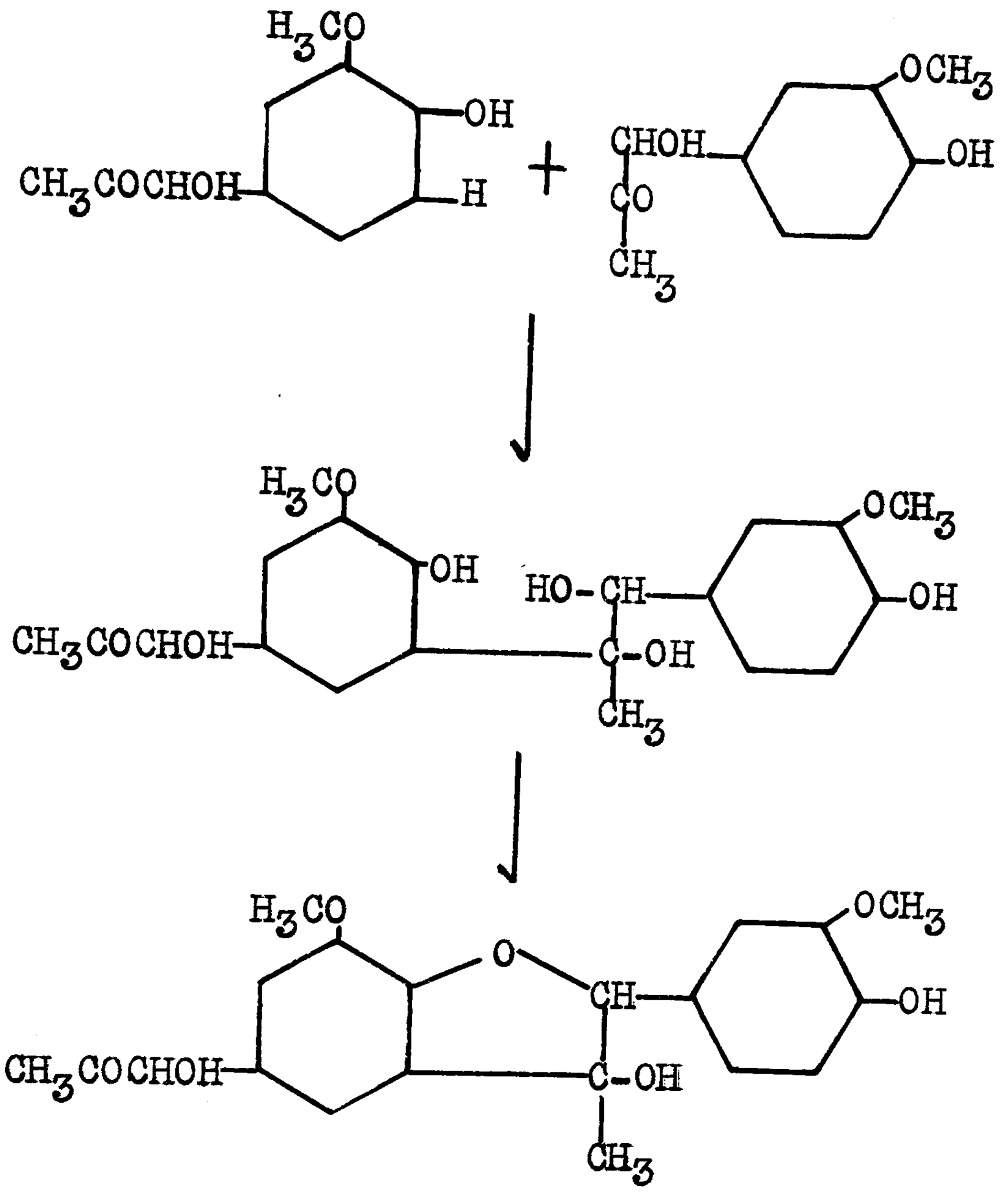
Hibbert (51), elaborating on Erdtman's views, suggests that protolignin is not a simple dimer, but consists of trimers, tetramers, pentamers, etc. Thus the dimer type is one of the simpler forms of lignin and the existence of either highly complex structures or of the lignin-carbohydrate complex, or both, accounts for the difficulty in the isolation of protolignin from the woodmeal.

Michael (86), early, showed that phenols react with carbonyl groups under mild conditions to yield condensation-type polymers. This investigation later became the basis of the new plastics industry, in the preparation of Bakelite (87).

Hibbert suggests on the basis of Michael's investigations that the monomers,

$R\text{-}CO\text{-}CO\text{-}CH_3$	$RCHOHCOCH_3$	RCH_2COCH_3
XXXII	XXX	XVIII

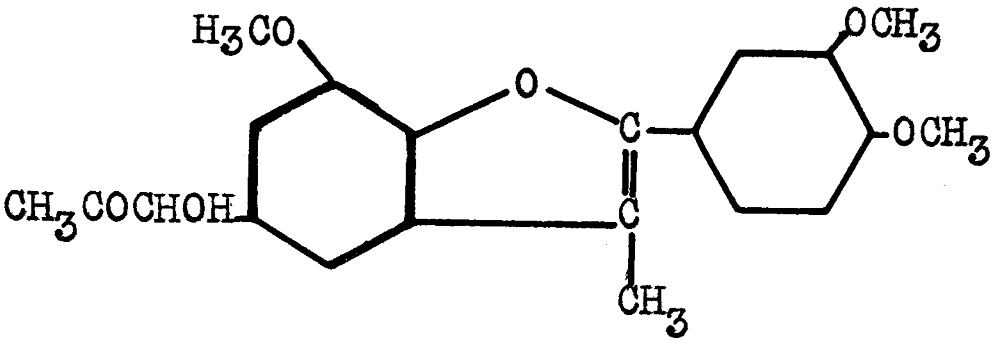
each containing a phenol and a carbonyl group, could undergo para or ortho nuclear condensations to yield condensation-type polymers. For example, this condensation type of polymer formation may arise from (XXX).



XXXIII

II

This reaction mechanism differs from that assumed by Freudenberg in the formation of dimer (II) only in the order in which the first two steps occur. Upon loss of water this dimer (II) forms the benzofuran (LXXXVI). The occurrence of benzofurans in coal tar (88,89,90 page 585-6), beechwood tar (89,91) and many plant tissues (92) indicates

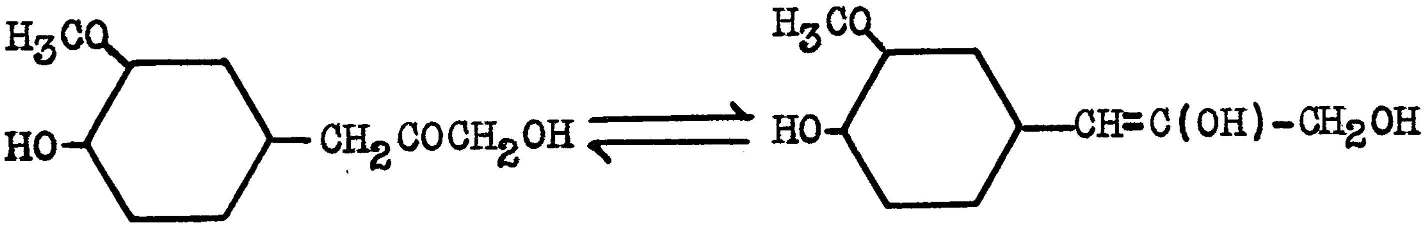


LXXXVI

that the structure (LXXXVI) may arise biochemically. Wright (93) has suggested that lignin has a coumarin type structure since diazomethane reacts in a similar manner with coumarin and with acetic acid lignin. Absorption spectra (94) on an extracted spruce lignin (95) show the presence of a strongly resonating structure and this evidence is in harmony with a benzofuran type. This is supporting evidence for the presence of the benzofuran nucleus in at least part of the lignin molecule as postulated by Hibbert (51) and Freudenberg (14).

MacGregor (30), using the chromic acid oxidation technique, has shown that there are no end-methyl groups in native lignin, therefore it seems highly improbable that lignin dimers arise through the inter-molecular condensation of (XXXII), (XXX) and (XVIII), as in each case dimers would be formed containing one end-methyl group. Hibbert, in his most recent review (51) suggests that three types of dimers (LXXXVIII), (XC) and (XCII) can occur in lignin, each arising from RCH_2COCH_2OH (XXIX) or its dismutation isomer oxyconiferyl alcohol, $R\text{-}CH{=}C(OH)CH_2OH$ (LXXXVII). Two of these dimers (LXXXVIII) and (XC) are formed by a dehydrodiisoeugenol type coupling while the third dimer (XCII) arises through a different mechanism. Hibbert points out that it is not necessary to assume that the coupling stops at the dimer stage, but may continue on into the trimer, tetramer, pentamer, etc. stages.

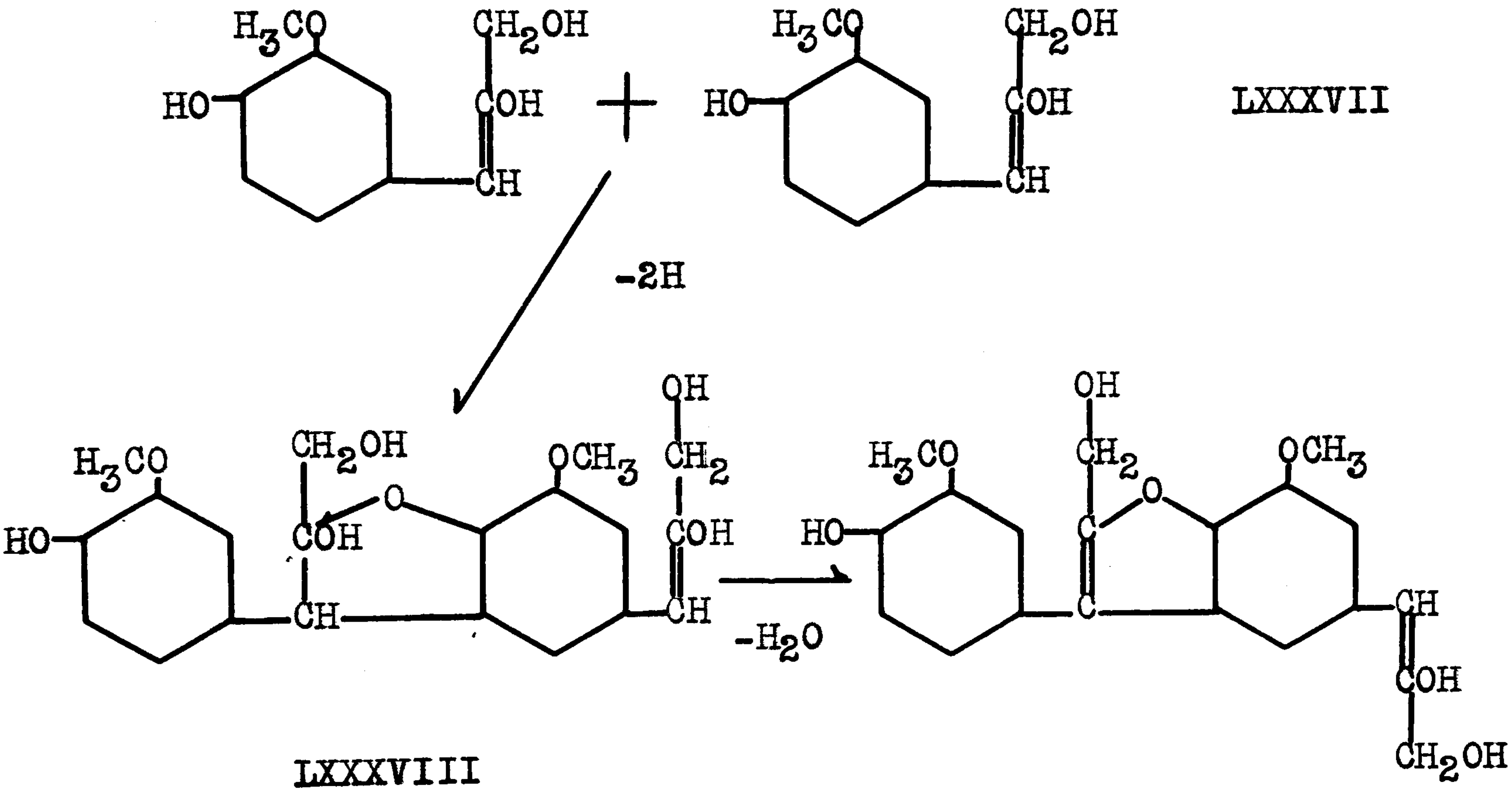
The mechanisms through which the three dimers can arise are indicated below.



XXIX

LXXXVII

(i) First dimer formation mechanism



LXXXVII

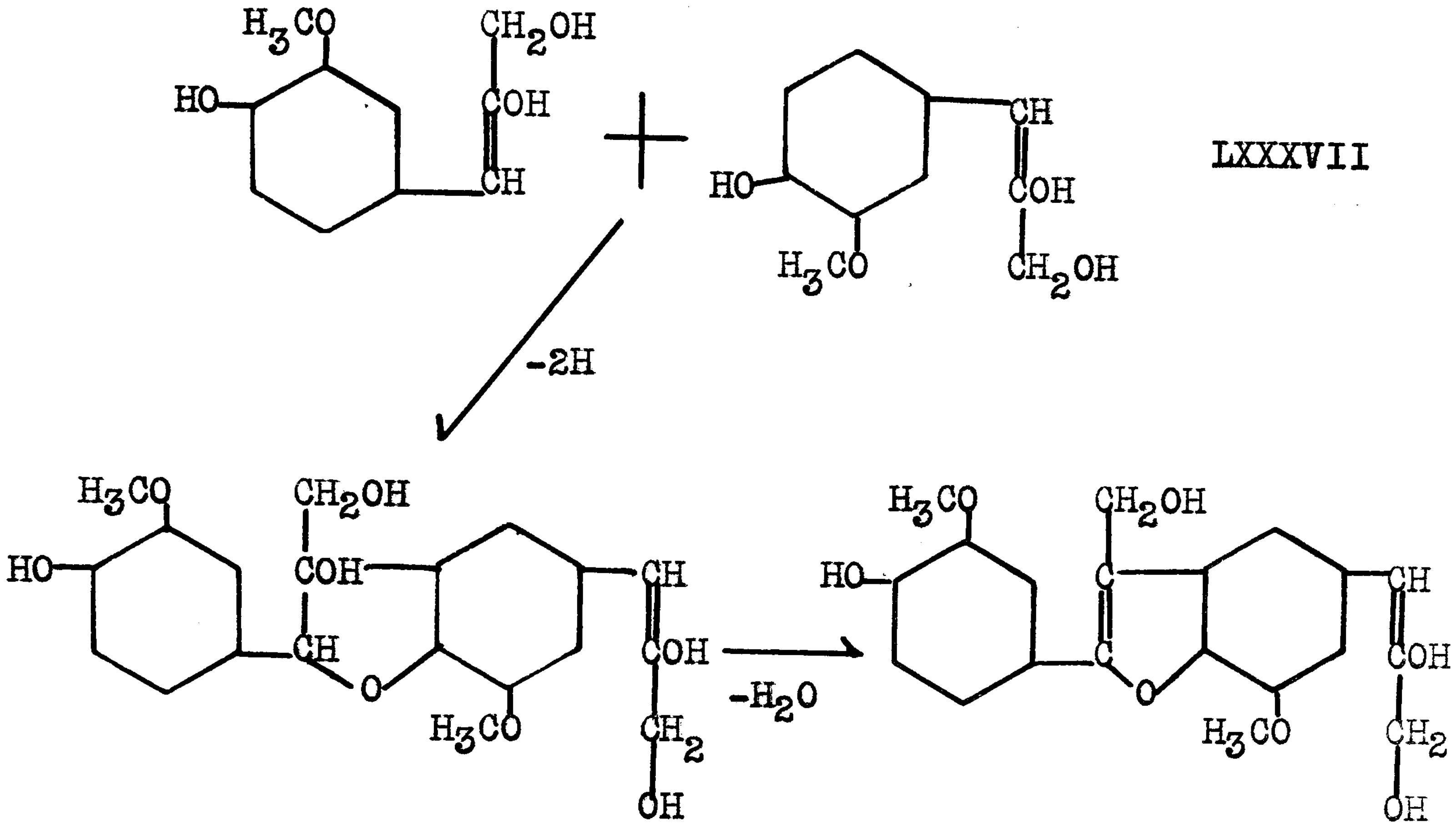
LXXXVIII

LXXXIX

Dimer (LXXXVIII) could lose water to form the benzofuran (LXXXIX).

(ii) Second dimer formation mechanism

The second dimer (XC) arises through the same dehydrogenative type of coupling.



LXXXVII

XC

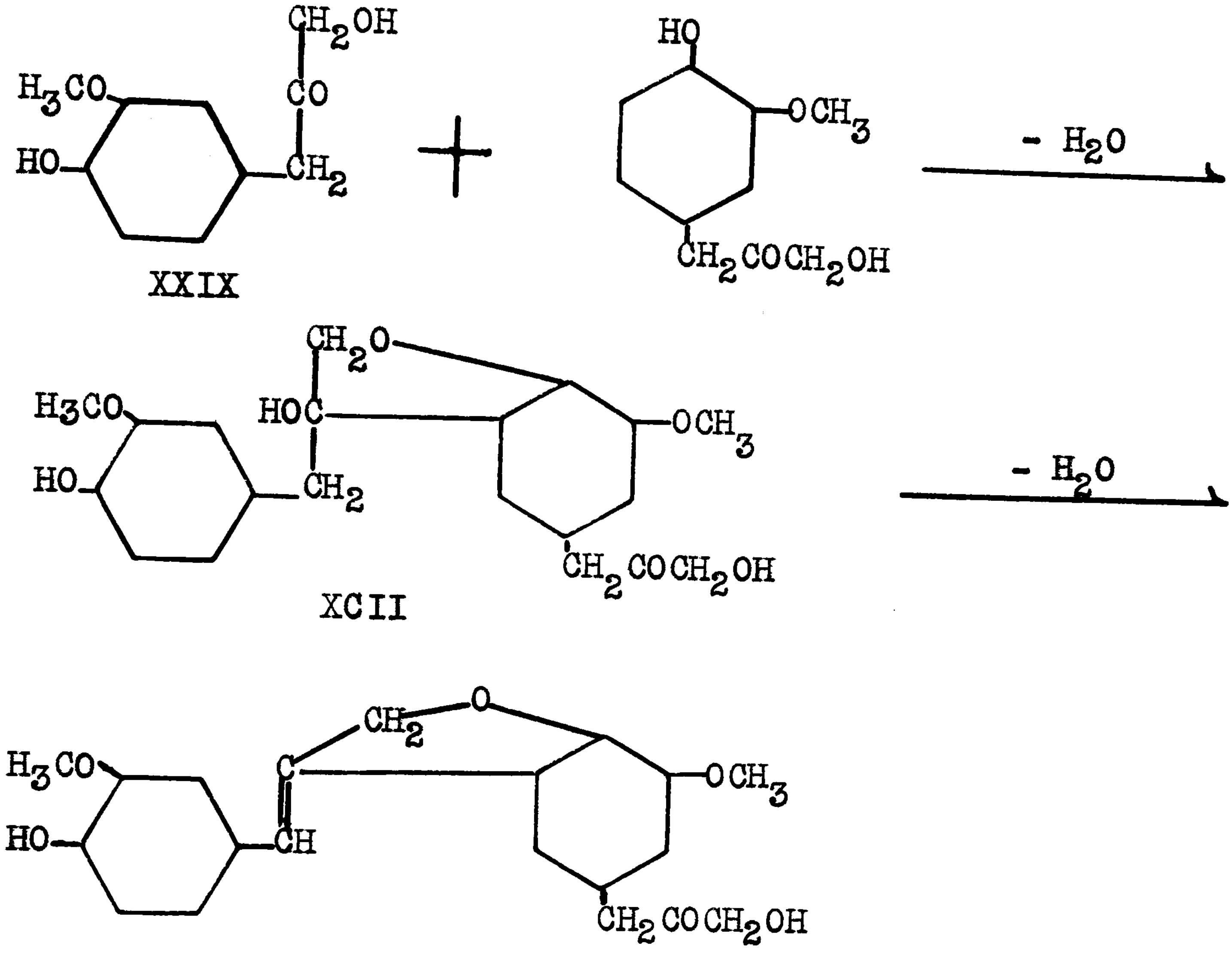
XCI

Dimer (XC) could lose water to form the benzofuran (XCI).

Both (XC) and (LXXXVIII) may be seen to arise through a similar dehydrogenative mechanism, which may be further extended to produce the more highly polymerized lignin.

(iii) Third dimer formation mechanism

The third dimer (XCII) could arise from the ketone (XXIX) through a dehydration reaction, and as in mechanisms (i) and (ii), the nuclear hydrogen, ortho to the phenolic hydroxyl, being very active, tends to add to the carbonyl oxygen as follows:



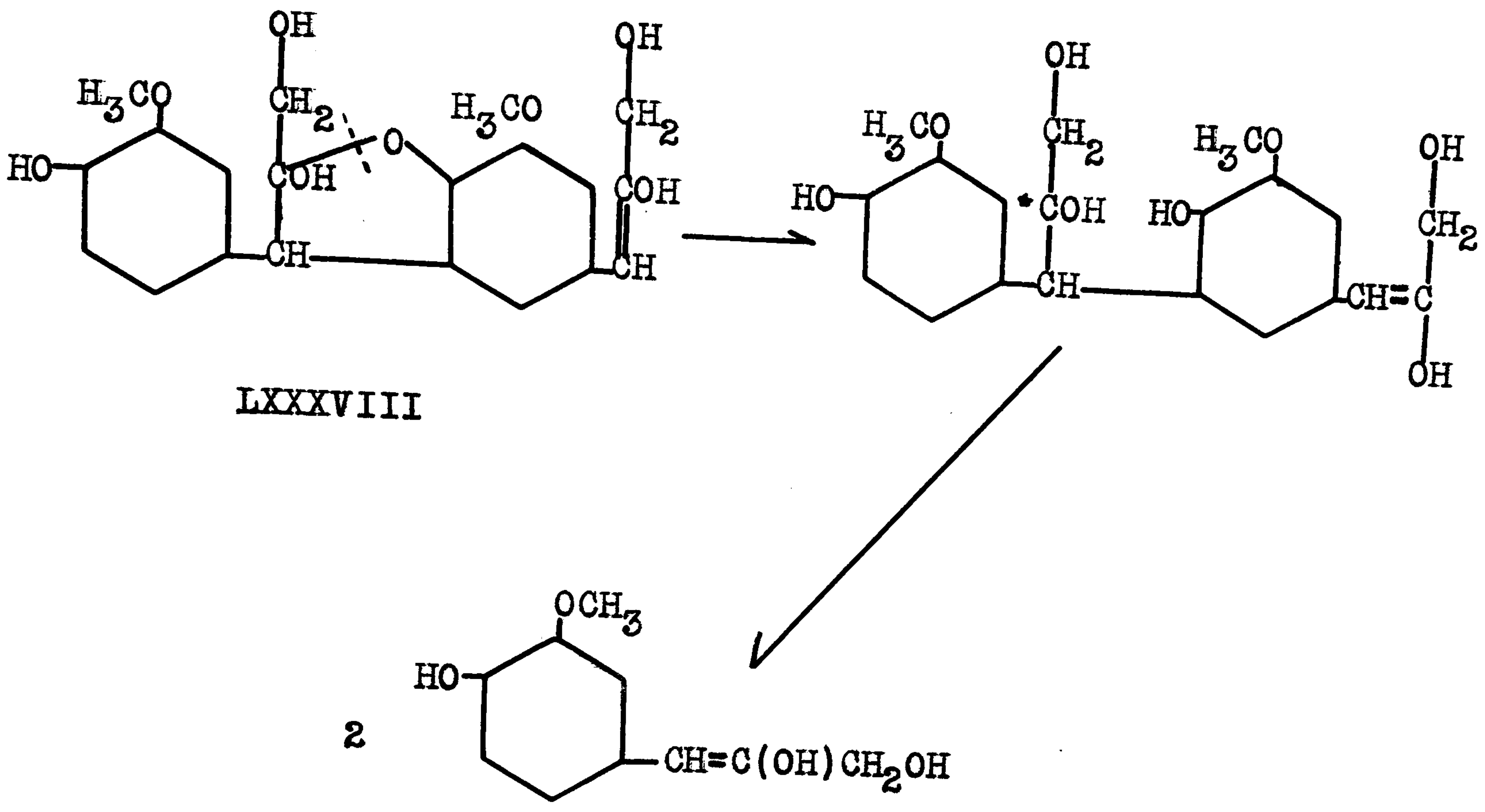
XXIX

XCII

XCIII

Dimer (XCIII) could be formed from (XCII) through a further dehydration reaction.

Since (LXXXVIII), (XC) and (XCII) are possibly "reversible" type polymers, the cleavage discussed on page 29 may occur and give rise to the presence of the monomers (XIV), (XVI), (XVIII) and (XX) formed during the ethanolysis reaction. The dimers postulated above could cleave theoretically, according to the following scheme:



LXXXVIII

LXXXVII

The members of the dismutation series could also arise through the cleavage of ketosidic, acetal and glycosidic linkages. Oxyconiferyl alcohol (LXXXVII), one of the dismutation series, could then undergo immediate intra-molecular rearrangements, dismutation and dehydrogenation to give the relatively stable structures (XVIII), (XXX), (XXXII) and (XXXIII). Etherification of these monomers, catalyzed by the hydrogen ions, could form the ethylated monomers (XX) and (XV).

The same cleavage mechanism, applied to the remaining Hibbert dimers (XC) and (XCII) could yield the same products (XVIII), (XXX), (XXXII) and (XXXIII).

(b) Polymers of the Syringyl and/or Guaiacyl Types

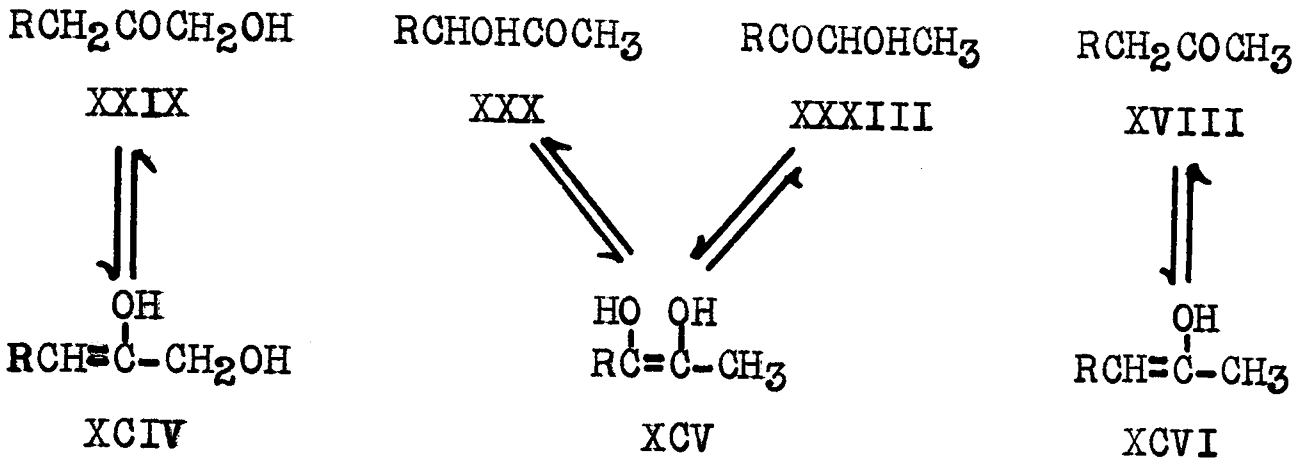
Polymers of the dehydrodiisoeugenol type (LXXXIV) and of the type represented by (XCII) cannot be postulated as arising from monomers containing the syringyl nucleus as both positions ortho to the phenolic hydroxyl group are blocked by methoxyl groups. However, it is possible to suggest different polymeric types and Hibbert, in his most recent review (51), suggests several dimer types and mechanisms. These mechanisms may be applied to the guaiacyl nucleus as well as the syringyl nucleus.

(i) Ether Type Polymers

Cinnamyl alcohol and its derivatives, in the presence of dilute acids, not only undergo an allylic rearrangement, but also form dicinnamyl ethers (96) in high yields. Coniferyl, oxyconiferyl, syringyl and oxysyringyl alcohols may be regarded as substituted cinnamyl alcohols and therefore it is possible that the syringyl units may exist as ethers in the woody tissue. This may account for their greater ease of extraction in the isolation of syringyl-containing compounds from the ethanolysis of wood.

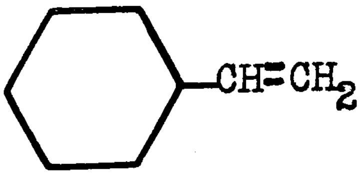
(ii) Styrene Type Polymers

The lignin building units (XXIX), (XXX), (XVIII) and (XXXIII) may function as styrene derivatives through the simple enol forms (XCIV), (XCV) and (XCVI).



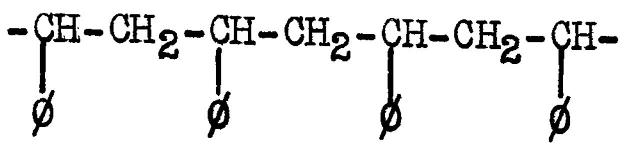
Styrene and its derivatives polymerize under the influence of light, heat, air and various catalysts, such as antimony pentachloride, sulfuric acid, stannic chloride and hydrochloric acid (97) to form simple or more complex polymers, depending upon the reaction conditions.

It is evident, from an examination of the styrene structure (XCVII), that two main types of polymerization



XCVII

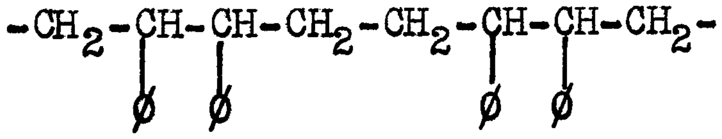
are possible. Staudinger and Steinhofer (98) have suggested that the polystyrenes possess the uniform linear structure (XCVIII), while Midgley and co-workers (99), from studies of



$$-\underset{\phi}{\mathrm{CH}}-\mathrm{CH_2}-\underset{\phi}{\mathrm{CH}}-\mathrm{CH_2}-\underset{\phi}{\mathrm{CH}}-\mathrm{CH_2}-\underset{\phi}{\mathrm{CH}}-$$

XCVIII

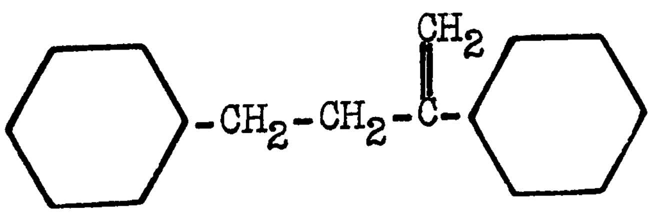
the elastic properties and thermal depolymerization products of the polystyrenes, have suggested that the polystyrenes possess the irregular structure (XCIX).



$$-\mathrm{CH_2}-\underset{\phi}{\mathrm{CH}}-\underset{\phi}{\mathrm{CH}}-\mathrm{CH_2}-\mathrm{CH_2}-\underset{\phi}{\mathrm{CH}}-\underset{\phi}{\mathrm{CH}}-\mathrm{CH_2}-$$

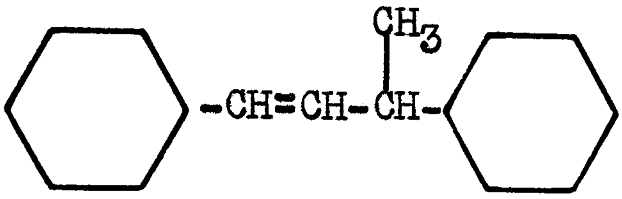
XCIX

Dimeric styrenes have been prepared with additional types of linkages between phenyl groups. These dimers are of both saturated and unsaturated types. The unsaturated dimer (C) was isolated by Staudinger and Steinhofer (98)



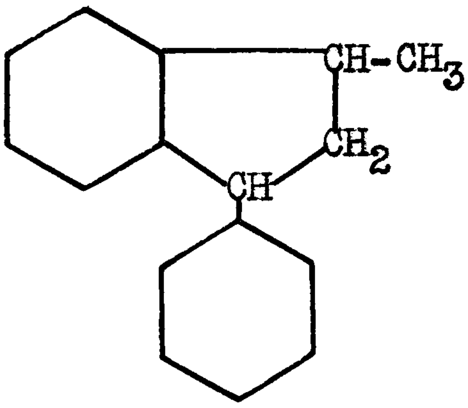
C

from the thermal depolymerization products of a polystyrene. A second dimer (CI) was prepared by Fittig and Erdmann (100) and later studied by Stobbe and Posnjak (101).



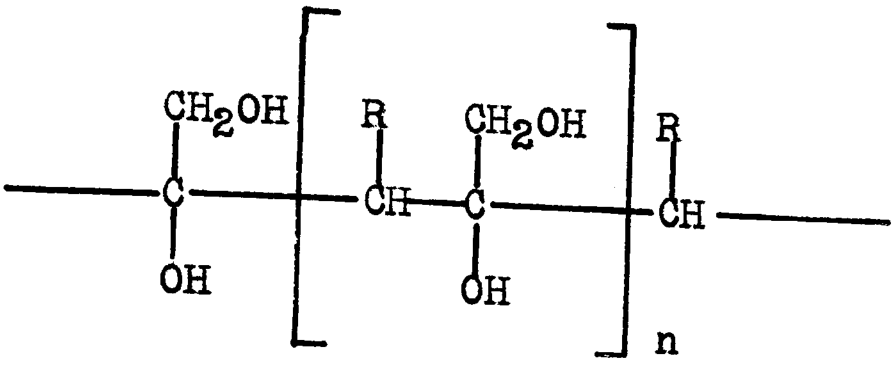
CI

A third dimer (CII) was reported by Stoermer and Kootz (102). The last-mentioned dimer has a cyclic structure and was prepared by ring closure of (CI).



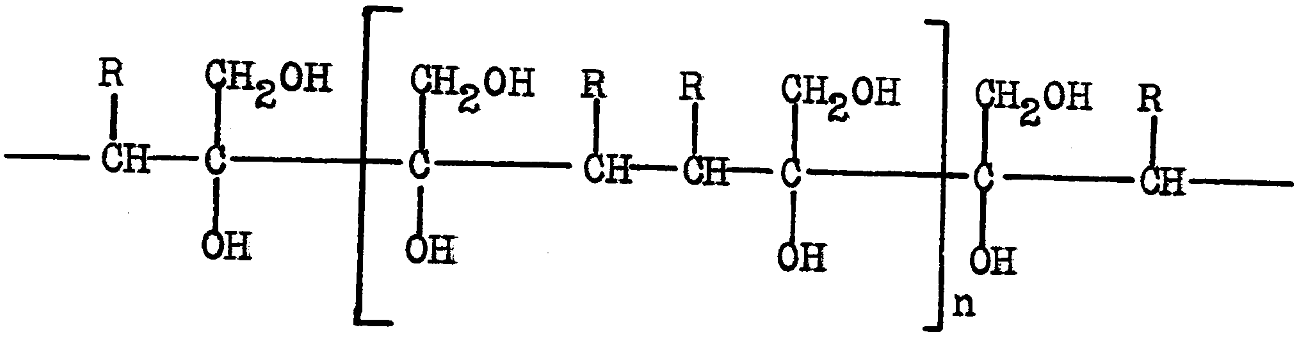
CII

Application of the Staudinger (98) and Midgley (99) polystyrene structures to the enol monomer (XCIV) might conceivably form a long chain linear polymer having the regular structure (98) (CIII) or the irregular structure (99) (CIV).



$-C(CH_2OH)(OH)-[CH(R)-C(CH_2OH)(OH)]_n-CH(R)-$

CIII



$-CH(R)-C(CH_2OH)(OH)-[C(CH_2OH)(OH)-CH(R)-CH(R)-C(CH_2OH)(OH)]_n-C(CH_2OH)(OH)-CH(R)-$

CIV

There is no evidence in favor of the polystyrene type polymer for lignin, indeed, all evidence points to the improbability of this type of structure. Shoruigin and Shoruigina (103,104), in their investigations on the polymerization of substituted styrenes, found that the polymerization was greatly inhibited by substituents in the ethylene side chain as well as in the aromatic nucleus of the molecule.

The polystyrenes may be depolymerized under the influence of heat (99,105), but this is not true of lignin. This is further evidence that the lignin polymer is not of the polystyrene type.

(iii) Lignin Polymers Related to the Phenyltetralin Lignans

As discussed earlier (page 28), l-olivil (LXV), an $\alpha\alpha'$-diphenylfuran, is converted by mild acid treatment into iso-olivil (LXVI), a phenyltetralin (72,73,74). It is interesting to note that a dehydrogenative coupling occurs through the meta position although the position ortho to the phenolic hydroxyl group is presumably more active. Therefore the possible formation of syringyl type polymers through dehydrogenative coupling of this meta position should not be overlooked. Such a polymer might arise as a result of closure to a ring system of minimum strain. Unfortunately there is no experimental evidence for the formation of this type of structure from syringyl units.

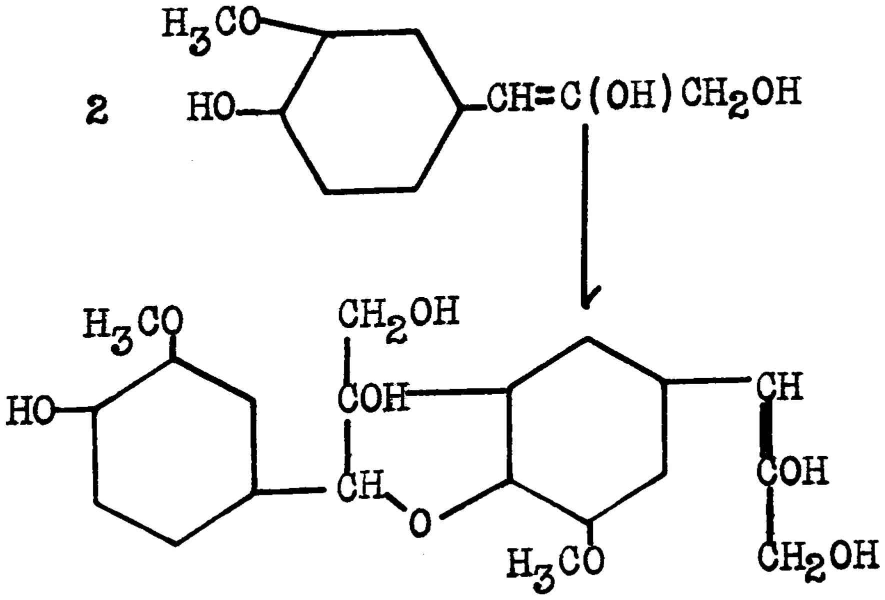
Summary

Several mechanisms of lignin polymer formation have been suggested to explain the formation of lignin, containing the guaiacyl nucleus only. The theories discussed on the proposed syringyl types have as yet no experimental support. Obviously the plant resins, lignin and dehydrodiisoeugenol are closely related types. Of greatest significance is the fact that many, if not most, of the natural phenols, are C_6-C_3 compounds. These may combine under varying conditions depending upon the nature of the plant, its environment, and the presence of enzymes, metallic ions, etc. to yield dimeric structures, including the lignans and lignin. There is also the possibility that the plant forms C_6-C_3 monomers that act as respiratory catalysts during active stages of plant growth, but, under postmortal conditions, these condense to form the lignans and/or lignins.

DISCUSSION OF EXPERIMENTAL RESULTS

A considerable number of previous researches carried out in these laboratories have given clear experimental support to Hibbert's assumption that spruce protolignin consists of a mixture of different substances derived from relatively simple propylphenol units. Although considerable uncertainty still exists regarding the nature of the propyl side chain and the mode of its linkage in the complex protolignin structure, several experimental facts have been established. The aromatic portion of spruce protolignin is always the guaiacyl nucleus, the side chain is an oxygenated radical without terminal methyl groups and it contains primary hydroxyl groups.

According to Hibbert the experimental results seem to indicate that a large portion of native lignin consists of a polymer or polymers of the dehydrodiisoeugenol type in which the isoeugenol unit is replaced by oxyconiferyl alcohol (LXXXVII).

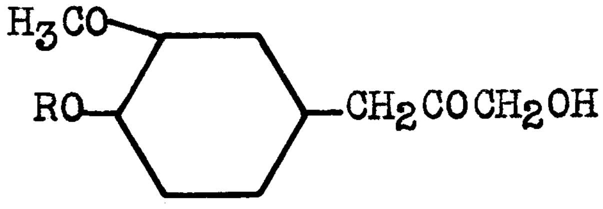


LXXXVII

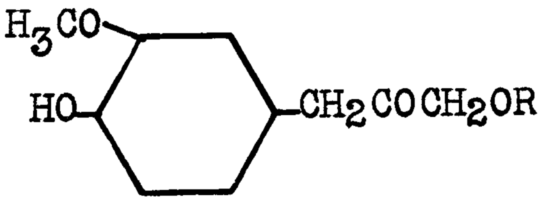
XC

Union through the β carbon atom is highly probable since this has been shown by Erdtman (56) and also by Haworth (57) to be typical of the dimeric resins (lignans).

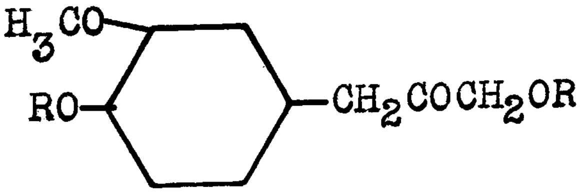
Inasmuch as the ethanolysis reaction indicates that some of the native lignin is present in a much less complex form than the remainder, it has been suggested that the ethanolysis products result from the decomposition of this less complex form. Hibbert suggests three general types that could yield the ethanolysis products. These are assumed to be glycosides, ketals, and ethers. The glycosides (CV), (CVI) and (CVII), the ketals (CVIII) and (CIX), and/or the ether (CX)



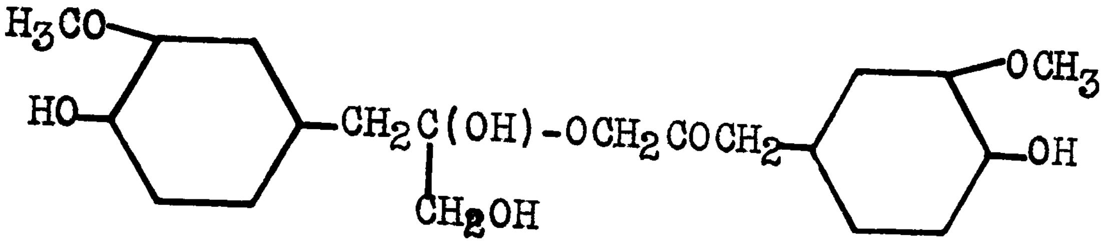
CV



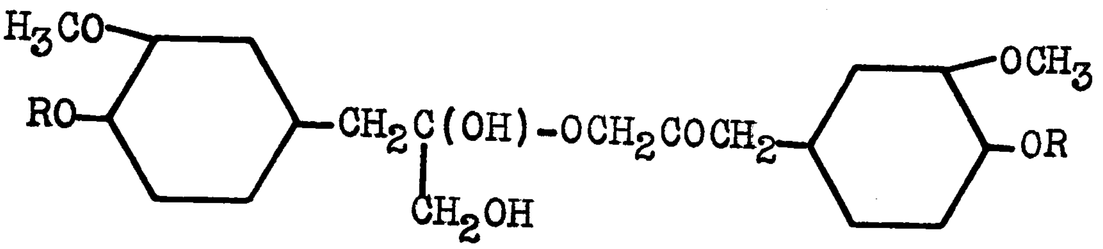
CVI



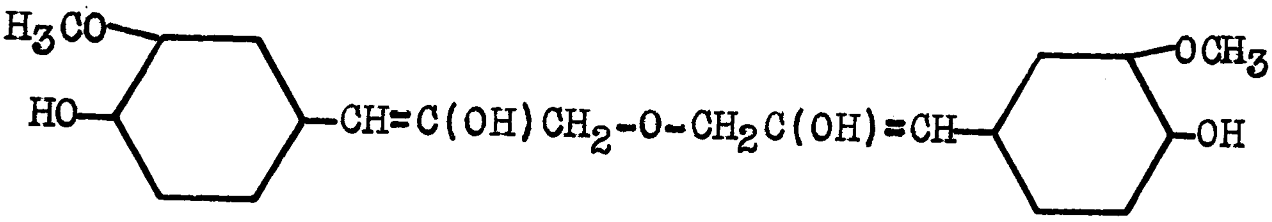
CVII



CVIII



CIX



CX

R = Carbohydrate

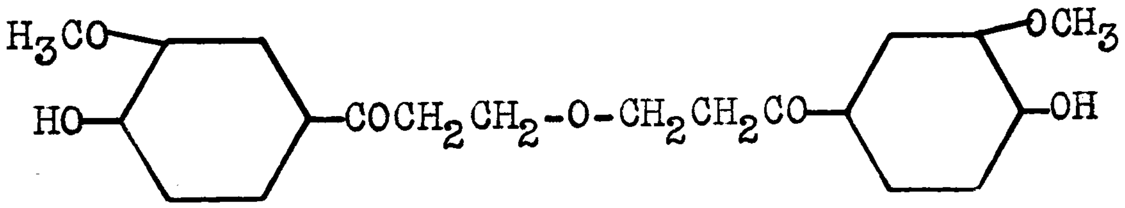
could yield oxyconiferyl alcohol on ethanolysis and this latter could then undergo dismutation and rearrangement to yield the ethanolysis products, discussed earlier on page 7.

The evidence supporting this point of view is to be found in the fact that the ethanolysis products have now been shown, experimentally, to be stabilized end products arising from oxyconiferyl alcohol.

The problem assigned to the writer was a threefold one: (a) Synthesis of ether-linked dimers, possibly closely related to the less complex portion of native lignin, and carbon-to-carbon linked dimer believed to be related to the more complex portion; (b) ethanolysis of same in order to provide evidence as to their ease of conversion, or otherwise, into the monomolecular wood ethanolysis products; and (c) to obtain definite information as to the ease of reduction of carbonyl groups in the propyl side chains of these model dimers and of the ease of fission of the ether-oxygen and carbon-to-carbon linkages.

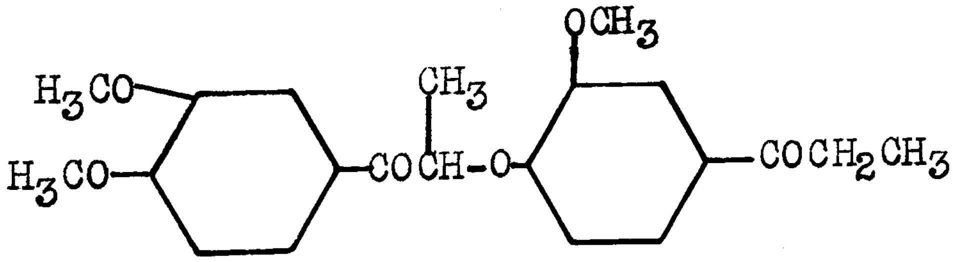
Up to the last two years very little was known regarding the manner in which the building units are combined in native lignin, indeed all knowledge was purely speculative. No information was available to show whether dimers and/or polymers arising from oxy- or dioxy-coniferyl alcohols represent the balance of the protolignin. All evidence to date indicates, however, that they are relatively simple polymeric molecular aggregates but no definite proof on this final phase has been supplied by the studies on ethanolysis.

Recent work carried out by Brewer, Pepper, Mead, Neish, and Hibbert, in these laboratories, on the hydrogenation of spruce and maple woods has thrown new light on the final phase of this problem and their results indicate clearly the methods of investigation to be followed for its solution. Due to the fact that these researches are part of a war problem, they cannot be discussed at the present time. However for the true evaluation of their results and for the solution of the problem relating to the nature of the polymeric linkages present in native lignin polymers it was first necessary to synthesize model dimeric substances, regarded as closely related to the true lignin building unit or units and then to submit them to (a) acid and alkali hydrolysis, (b) ethanolysis and (c) high pressure hydrogenation. Five dimeric substances called for consideration:



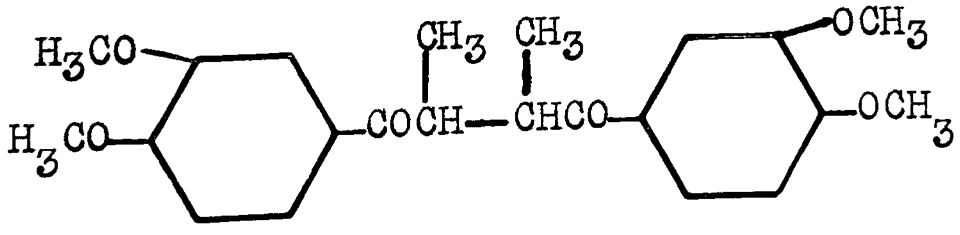
CXI

2,2'-Divanilloyl Diethyl Ether



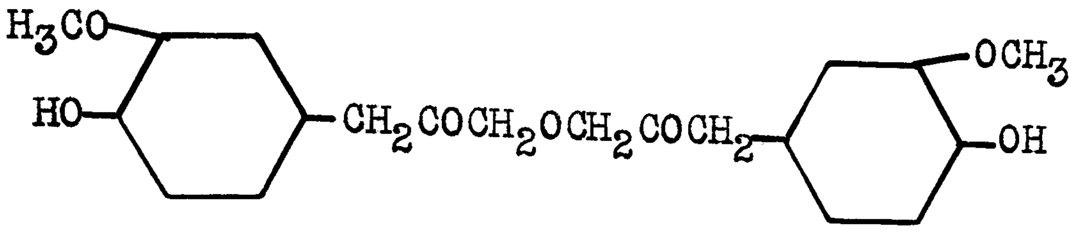
CXII

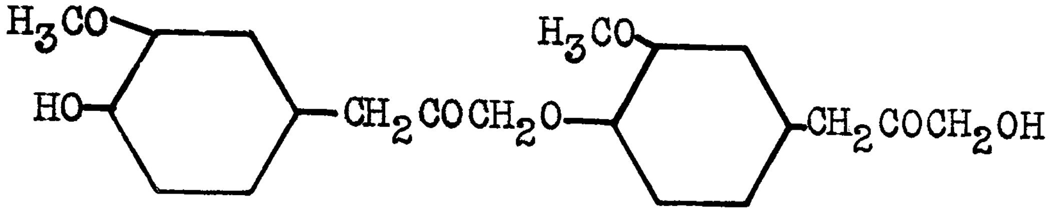
1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone



CXIII

1,4-Diveratryl-2,3-dimethyl-1,4-butanedione


CXIV


CXV

Due to lack of time, caused by experimental difficulties, only (CXI), (CXII) and (CXIII) were synthesized and submitted to acid and alkali hydrolysis, ethanolysis and hydrogenation.

The first dimer (CXI) is characterized by the presence of a dialkyl-oxygen union between the two propylphenol units, each of the latter having a carbonyl group adjacent to the ring and in the γ position to the ether oxygen linkage.

The second dimer (CXII) differs from the first dimer (CXI) in that it contains (a) an alkyl-aryl ether linkage and (b) a carbonyl group adjacent to the ring but in the β position to the ether linkage.

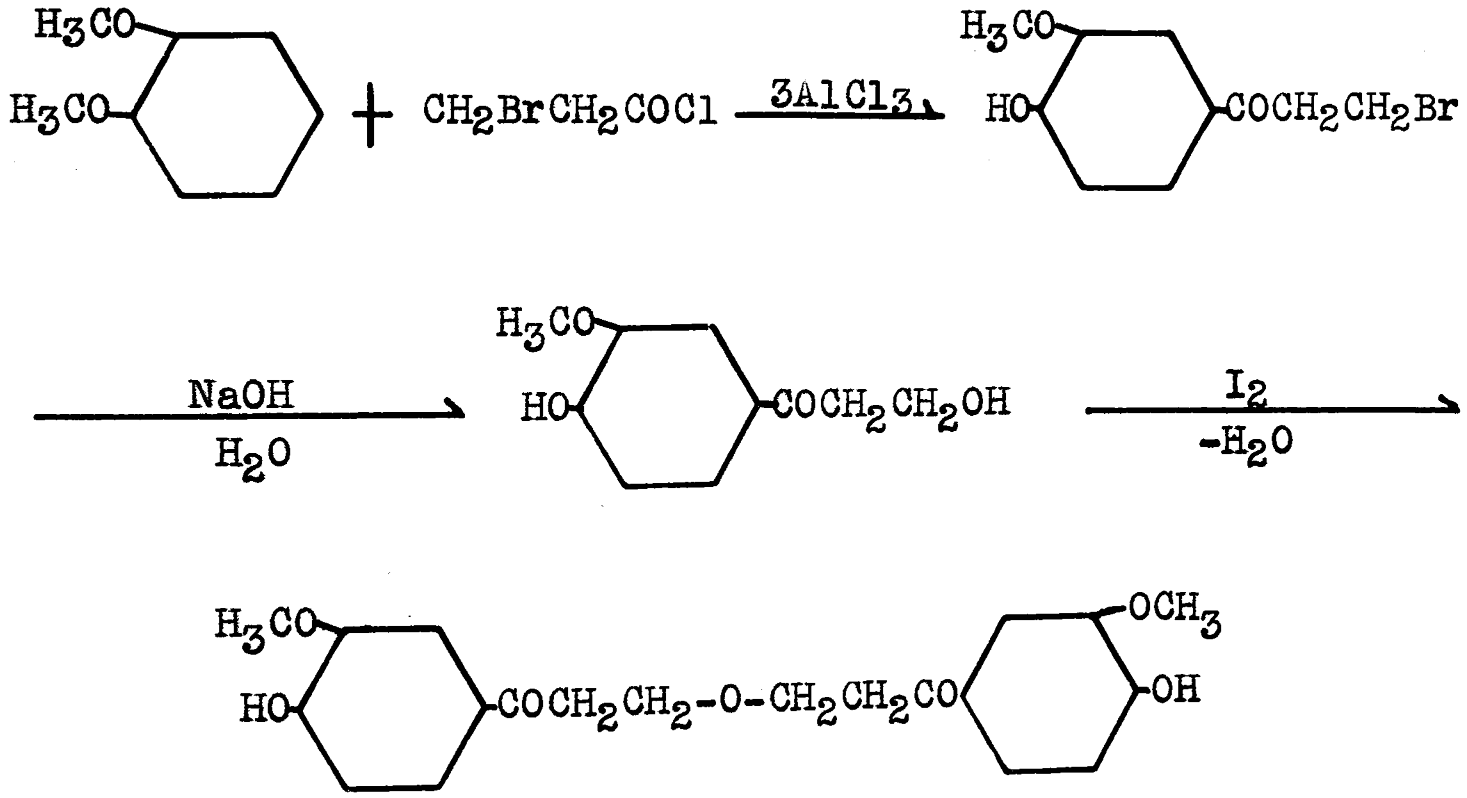
The third dimer (CXIII) is characterized by (a) a carbon-to-carbon union on the β carbon atoms and (b) carbonyl groups adjacent to the rings.

Dimers (CXIV) and (CXV) represent dialkyl and alkyl-aryl ether dimers respectively derived from oxyconiferyl alcohol in which the carbonyl groups are in the β position in the propyl side chains.

The synthesis of dimers (CXI), (CXII) and (CXIII) involved the preparation of hitherto unknown intermediates and the condensation of the C_6-C_3 units by new methods.

Synthesis of 2,2'-Divanilloyl Diethyl Ether

2,2'-Divanilloyl diethyl ether was obtained by the following series of reactions:



CXI

Preparation of 3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone

In 1892 Hartmann and Gattermann (106) found that dealkylation occurred in the Friedel-Crafts condensation of various phenolic ethers with acyl halides when more than one mole of anhydrous aluminium chloride was used as the condensation catalyst. They found also that a higher reaction temperature was more effective than room temperature. Fernholz and Finkelstein (107) continuing this work, many years later, showed that dealkylation was a general phenomenon, but the experimental conditions remained empirical. Thus the present author found after considerable experimentation that the best yield (60 per cent) of 3-bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone was obtained when three moles of anhydrous aluminium chloride was used.

Veratrole was condensed with β- bromopropionyl chloride (108) in the presence of three moles of anhydrous aluminium chloride, yielding 3-bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone. The product was characterized by analyses and by conversion into 3-acetoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone and 3-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone, the latter being prepared by a new method (page 89)

The bromide was converted into 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone by means of direct hydrolysis with one per cent aqueous alkali. After a number of experiments had been carried out to determine the maximum conditions, the yield obtained was 88 per cent.

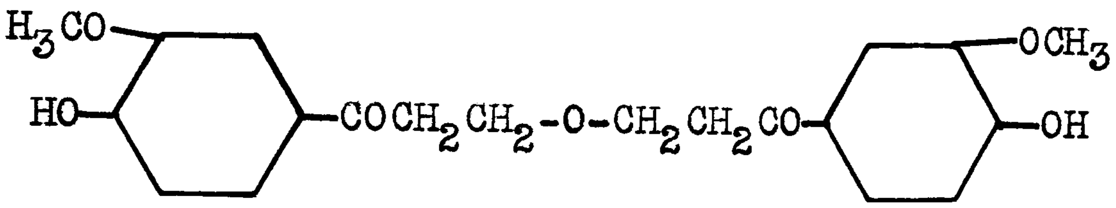
The product, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone, was converted into 2,2'-divanilloyl diethyl ether, by means of an iodine dehydration reaction. Two methods were employed, one using iodine without, the other, with a solvent. The latter method resulted in better yields (36 per cent) than the former (21 per cent), due probably to the dilution factor introduced by the solvent.

Hibbert (109), in 1915, showed that the iodine dehydration was an intramolecular reaction, while the reaction through which 2,2'-divanilloyl diethyl ether was prepared was obviously intermolecular. Therefore dilution of the reactant, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone would result in a certain amount of intermolecular action.

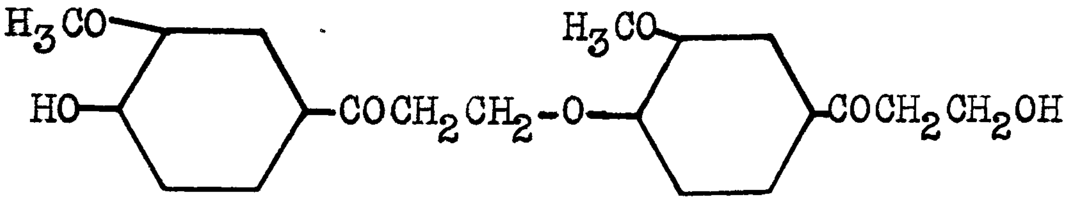
The dimer was characterized by analyses, hydrazone formation, methylation with diazomethane and preparation of the methylated dimer, 2,2'-diveratroyl diethyl ether, from 3-hydroxy-1-(3,4-dimethoxyphenyl)-1-propanone, by means of an iodine dehydration reaction without solvent. The latter compound was prepared by the alkaline hydrolysis of 3-bromo-1-(3,4-dimethoxyphenyl)-1-propanone, which was prepared, in turn, by the Friedel-Crafts condensation of veratrole, β-bromopropionyl chloride and 1.5 moles of anhydrous aluminium chloride. Oxidation of the methylated dimer, 2,2'-diveratroyl diethyl ether, resulted in a 77 per cent yield of veratric acid, indicating the presence of two veratryl nuclei.

Since 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-

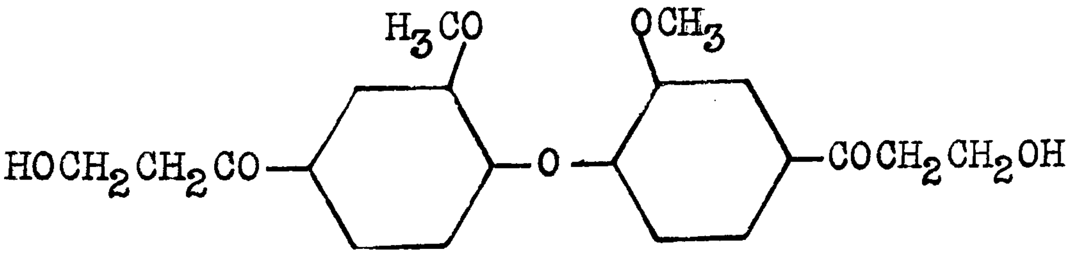
propanone contains two hydroxyl groups, one being phenolic and the other aliphatic, the question arose as to the manner in which the two propylphenol units were linked. This problem was solved by diazomethane methylation. The reaction, through which the dimer was synthesized was an intermolecular dehydration, thus three structures were possible as indicated by (CXI), (CXVI) and (CXVII).



CXI

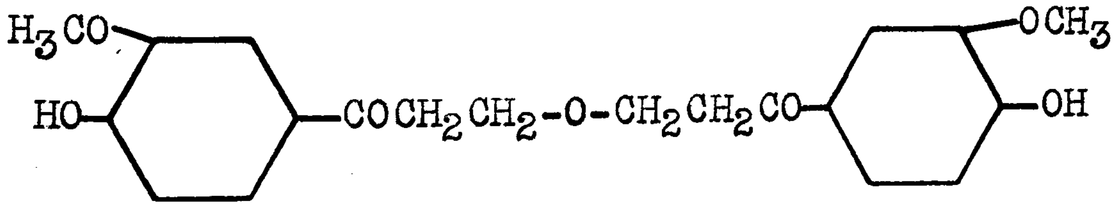


CXVI



CXVII

Structures (CXI) and (CXVI) containing phenolic hydroxyl groups would react with methanolic ferric chloride, while (CXVII) would not. Thus when methanolic ferric chloride solution was added to several crystals of the dimer, the solution immediately changed color from yellow to a deep green, indicating that the structure was either (CXI) or (CXVI). Structures (CXI), (CXVI) and (CXVII) and their respective hydrazones have the same empirical formulae and so could not be distinguished from each other by methoxyl analysis. However, diazomethane methylation (methylation of the phenolic hydroxyl groups only) and subsequent methoxyl analyses would serve to distinguish between the two probable (CXI), (CXVI) and one possible (CXVII) structures, since the methylated products should indicate four, three and two methoxyl groups per molecule respectively. Analysis of the methylated dimer indicated four methoxyl groups per molecule, thus (CXI) was the structure of the dimer.

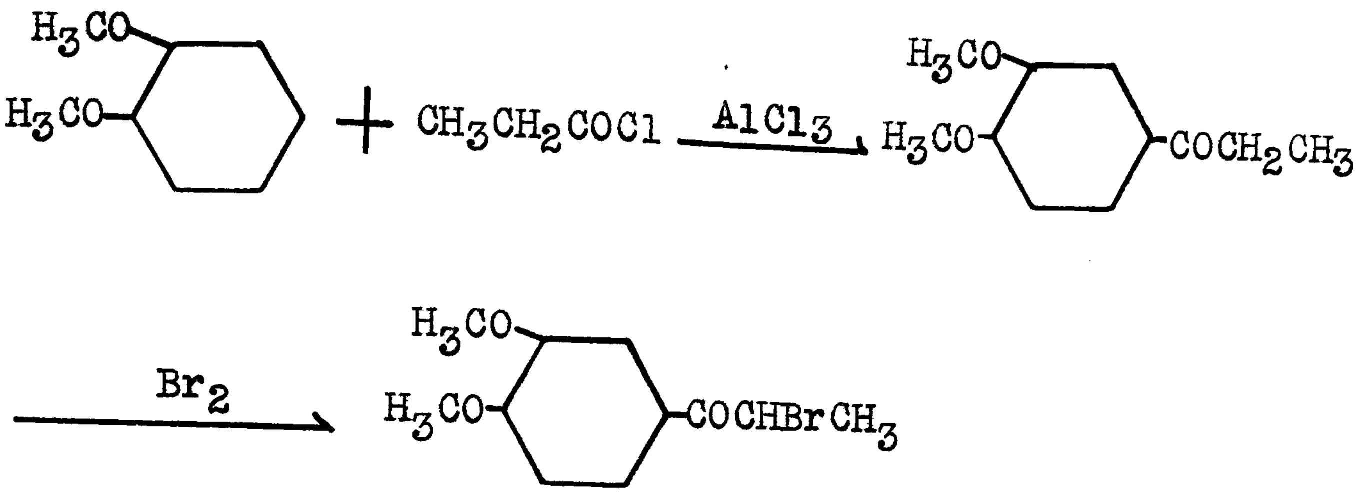


CXI

Synthesis of the Second Dimer - 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone

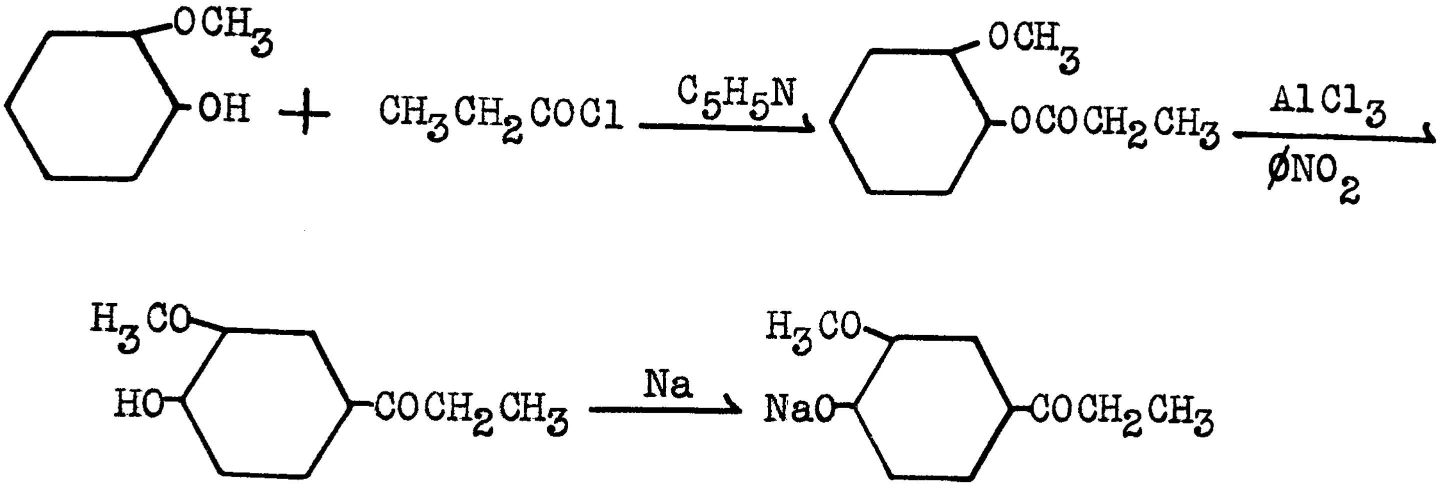
The following scheme indicates the reactions employed in the synthesis of 1-veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone:

A.



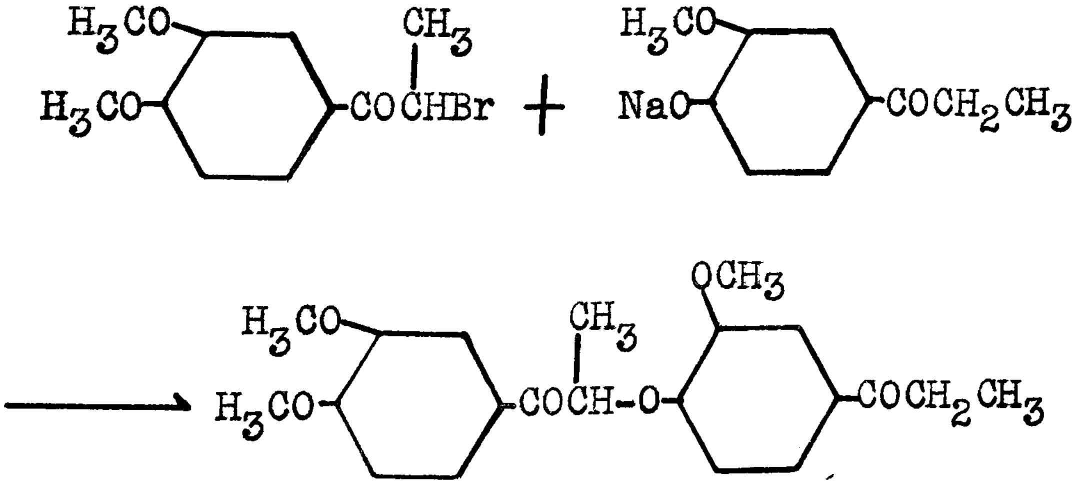
H_3CO
H_3CO
CH_3CH_2COCl
$AlCl_3$
$COCH_2CH_3$
Br_2
$COCHBrCH_3$

B.



OCH_3
OH
CH_3CH_2COCl
C_5H_5N
$OCOCH_2CH_3$
$AlCl_3$
ϕNO_2
H_3CO
HO
$COCH_2CH_3$
Na
NaO

C.



H_3CO
CH_3
COCHBr
NaO
$COCH_2CH_3$
OCH_3
COCH-O

CXII

A. Preparation of 2-Bromo-1-(3,4-dimethoxyphenyl)-1-propanone

This propylphenol unit, required in the synthesis of 1-veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone, was prepared by the Friedel-Crafts condensation of veratrole, propionyl chloride and anhydrous aluminium chloride and subsequent bromination of the Friedel-Crafts reaction product, 1-(3,4-dimethoxyphenyl)-1-propanone. The latter compound was prepared by Cramer (110) in these laboratories in a yield of 55 per cent and the present author was able to increase this to 83 per cent by a modification of Cramer's method. This consisted in decreasing the reaction time from eighteen to four hours and improving the manner of decomposition of the Perrier-aluminium chloride complex. It was found that the decomposition of the latter in ice-hydrochloric acid mixture resulted in a tarry product in yields never exceeding 60 per cent. Addition of chloroform to the well-stirred ice-hydrochloric acid mixture resulted in a yield of 83 per cent. Apparently the Perrier complex, or more correctly the aluminium chloride, caused tar formation when it came into contact with the product, 1-(3,4-dimethoxyphenyl)-1-propanone, but when chloroform was added, the product was dissolved thus removing it from the zone of action of the aluminium chloride.

Bromination of 1-(3,4-dimethoxyphenyl)-1-propanone gave 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone in a yield of 81 per cent.

B. Preparation of 1-(4-Hydroxy-3-methoxyphenyl)-1-propanone

Attempts to prepare 1-(4-hydroxy-3-methoxyphenyl)-1-propanone by means of the Friedel-Crafts dealkylation reaction, similar to that used in the preparation of 3-bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (page 63), using veratrole and propionyl chloride proved unsuccessful, the products being uncharacterizable tars. The synthesis was accomplished successfully by means of the Fries reaction of propionyl-2-methoxyphenolate with a yield of 65 per cent of the required 1-(4-hydroxy-3-methoxyphenyl)-1-propanone.

The Fries rearrangement is a general reaction capable of forming ortho or para substituted phenols. It occurs when a phenolic ester is treated with anhydrous aluminium chloride. Thus this reaction differs from that of the common Friedel-Crafts since the latter represents a condensation of a phenol with an acyl halide while the former is that of a phenolic ester, both reactions being catalyzed by aluminium chloride.

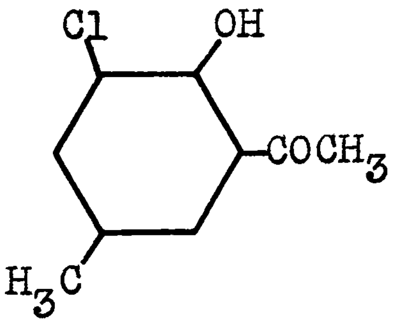
The Fries reaction was first discovered by Fries and Finck (111). Although anhydrous aluminium chloride is the most effective catalyst in carrying this out, anhydrous ferric chloride and especially fused zinc chloride are only slightly less effective (112,113,114,115).

There has been some difference of opinion regarding the mechanism involved. Fries (111,116,117,118), Witt (119), and von Auwers (120) considered the reaction to be a true intramolecular rearrangement. Skraup and Poller (121) suggested the intermediate formation of acetyl chloride in the preparation of o-acetyl-m-cresol from m-tolyl acetate, through decomposition of the ester with zinc chloride, which they used as catalyst, and the subsequent reaction of the zinc chloride-acid radical complex with the cresol to form the ketone. von Auwers and Mauss (122) suggested, that if the reaction were not a molecular rearrangement but a saponification and resubstitution of the two portions of the ester, then a mixture of phenyl acetate and p-tolyl chloroacetate on reacting with aluminium chloride should yield six different ketones, the o-acetyl- and o-chloroacetyl-derivatives of phenol and cresol, as well as p-acetyl- and p-chloroacetyl-phenol. A molecular rearrangement should produce only ortho and para acetyl phenol and 4,2-methylchloroacetyl phenol. The actual product isolated in good yield was ortho acetyl-phenol.

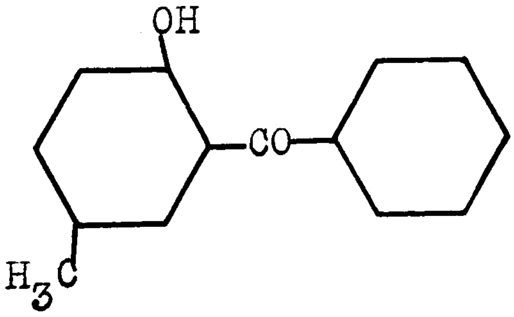
von Auwers (123) also based his suggestion, that the Fries reaction was a true molecular rearrangement, on the fact that Friedel-Crafts condensations of phenols and acyl halides yield, with very few exceptions, para acyl phenols;

the exceptions being meta derivatives. On the other hand only ortho and para and never meta acyl phenols are formed in the Fries reaction, therefore von Auwers considers the change to take place within the molecule, that is, an intramolecular rearrangement.

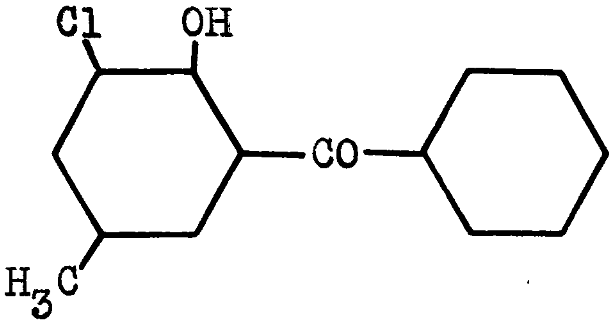
Rosenmund and Schnurr (124) considered the Fries reaction from two viewpoints; (a) a true Friedel-Crafts condensation or (b) an intramolecular rearrangement, suggested by von Auwers. They found that when a mixture of ortho chloro-p-tolyl acetate and p-tolyl benzoate was treated with anhydrous aluminium chloride, four products were obtained These were 2-hydroxy-3-chloro-5-methylacetophenone (CXVIII), 2-hydroxy-5-methylbenzophenone (CXIX), 2-hydroxy-3-chloro-5-methylbenzophenone (CXX), and 2-hydroxy-5-methylacetophenone (CXXI).



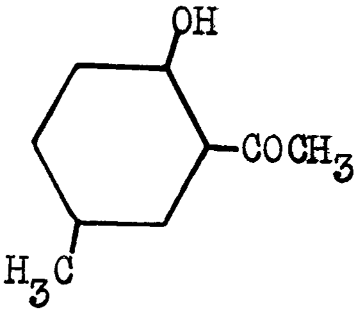
CXVIII



CXIX



CXX

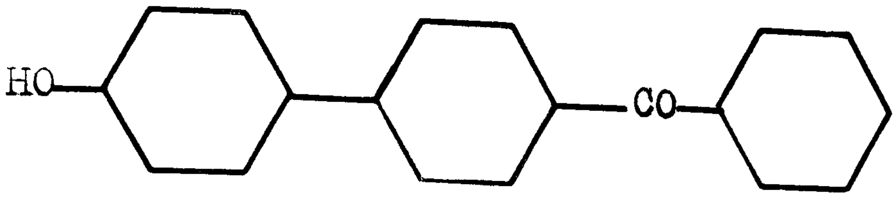


CXXI

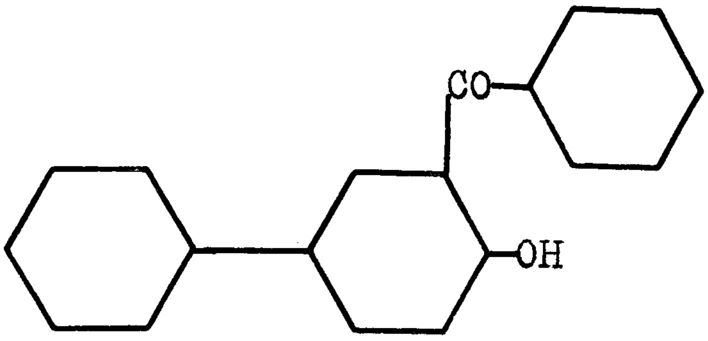
A strictly intramolecular reaction, being monomolecular, should result in the formation of 2-hydroxy-3-chloro-5-methylacetophenone (CXVIII) and 2-hydroxy-5-methylbenzophenone (CXIX), while if the reaction is bimolecular, as is apparently the case in the Friedel-Crafts condensation, then one molecule of the ester would acylate another molecule, by primary cleavage into two components parts. This apparently occurred in the reaction described above, but von Auwers (120) disregards this explanation and postulates an exchange reaction occurring between the reactants in addition to the intramolecular rearrangement. That von Auwers' suggestion may be valid is shown by the Friedel-Crafts reaction of toluene with itself to yield 4,4'-dimethyl diphenyl. In this case a small amount of benzene, o-xylene, and 3,3', 4,4'-tetramethyl diphenyl are formed as well as the expected product. This may be explained by an exchange reaction mechanism between two molecules of toluene, under the influence of aluminium chloride, to yield o-xylene and benzene, the o-xylene yielding the 4,4',3,3'-tetramethyl diphenyl.

The experimental investigations of Cox (125) apparently support the conclusion that the Fries reaction is not intramolecular. When phenolic esters are acted upon by anhydrous aluminium chloride in the presence of diphenyl ether, the free acid chlorides are produced as intermediates which are then introduced into diphenyl ether, yielding ketones. Since a catalyst is necessary before the exchange of free radicals occurs, Cox suggests that the aluminium chloride cleaves the ester linkage, forming a Perrier complex and this in turn is the acylating agent.

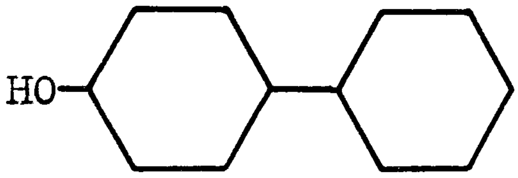
The case for an intermolecular mechanism is again brought out in several instances of heterogeneous migrations of diphenyl esters. Blicke and Weinkauff (126) have obtained 4-hydroxy-4'-benzoyldiphenyl (CXXII) by heating the benzoate of 4-hydroxydiphenyl in tetrachloroethane solution during one hour at 140°. Using the same concentration of reactants and the same reaction conditions, Hey and Jackson (127) obtained 3-benzoyl-4-hydroxydiphenyl (CXXIII) together with some 4-hydroxydiphenyl (CXXIV). Fieser and Bradsher (128) were unable to repeat Hey and Jackson's results, but obtained (CXXII) using carbon disulfide instead of tetrachloroethane, as solvent.



CXXII



CXXIII



CXXIV

The work on diphenyl esters, discussed above, illustrates the abnormality of the Fries reaction and also seems to confirm the possibility of a mechanism involving fission of the ester to the free phenol and subsequent acylation of this, indicating that the reaction is not an intramolecular change but an intermolecular acylation of a portion of the cleaved molecule. The most important conflict between this explanation and the experimental fact that meta-substituted phenolic ketones never occur during the reaction, cannot be reconciled. It is obvious that no satisfactory theory can yet be postulated to explain the experimental results. Probably some reactions do undergo a true intramolecular rearrangement while others take place through a cleavage and substitution mechanism.

Propionyl-2-methoxyphenolate (prepared in 83 and 95 per cent yields by the action of a mixture of thionyl chloride and propionic acid on guaiacol and a mixture of propionyl chloride and pyridine on guaiacol respectively) was treated with a nitrobenzene solution of anhydrous aluminium chloride. It has been found that methoxyl groups tend to form complexes, of the Perrier type, with anhydrous aluminium chloride, therefore more than one mole of aluminium chloride was necessary; namely one mole for the formation of the methoxyl-aluminium chloride complex and an additional mole for the apparent rearrangement. A total of two moles of anhydrous aluminium chloride, dissolved in nitrobenzene, was used resulting in 65 per cent yield of 1-(4-hydroxy-3-methoxyphenyl)-1-propanone. This product was characterized by analyses and by conversion into the known 1-(3,4-dimethoxyphenyl)-1-propanone by means of diazomethane methylation.

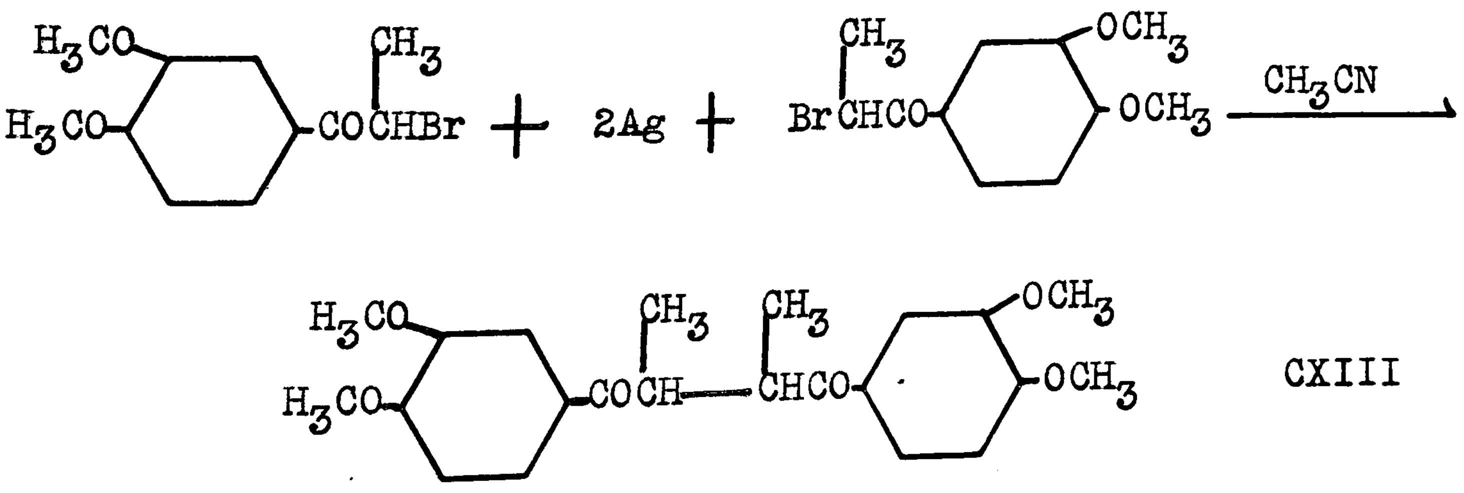
C. Condensation of the Sodium Phenolate of 1-(4-Hydroxy-3-methoxyphenyl)-1-propanone with 2-Bromo-1-(3,4-dimethoxyphenyl)-1-propanone

The sodium phenolate of 1-(4-hydroxy-3-methoxyphenyl)-1-propanone, prepared by the action of ethanolic sodium ethylate, was condensed with 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone by refluxing in absolute ethanol. The resulting product, 1-veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone (CXII), characterized by analyses and hydrazone formation, was used in the subsequent studies of alkyl-aryl ether linkages.

Synthesis of the Third Dimer, 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

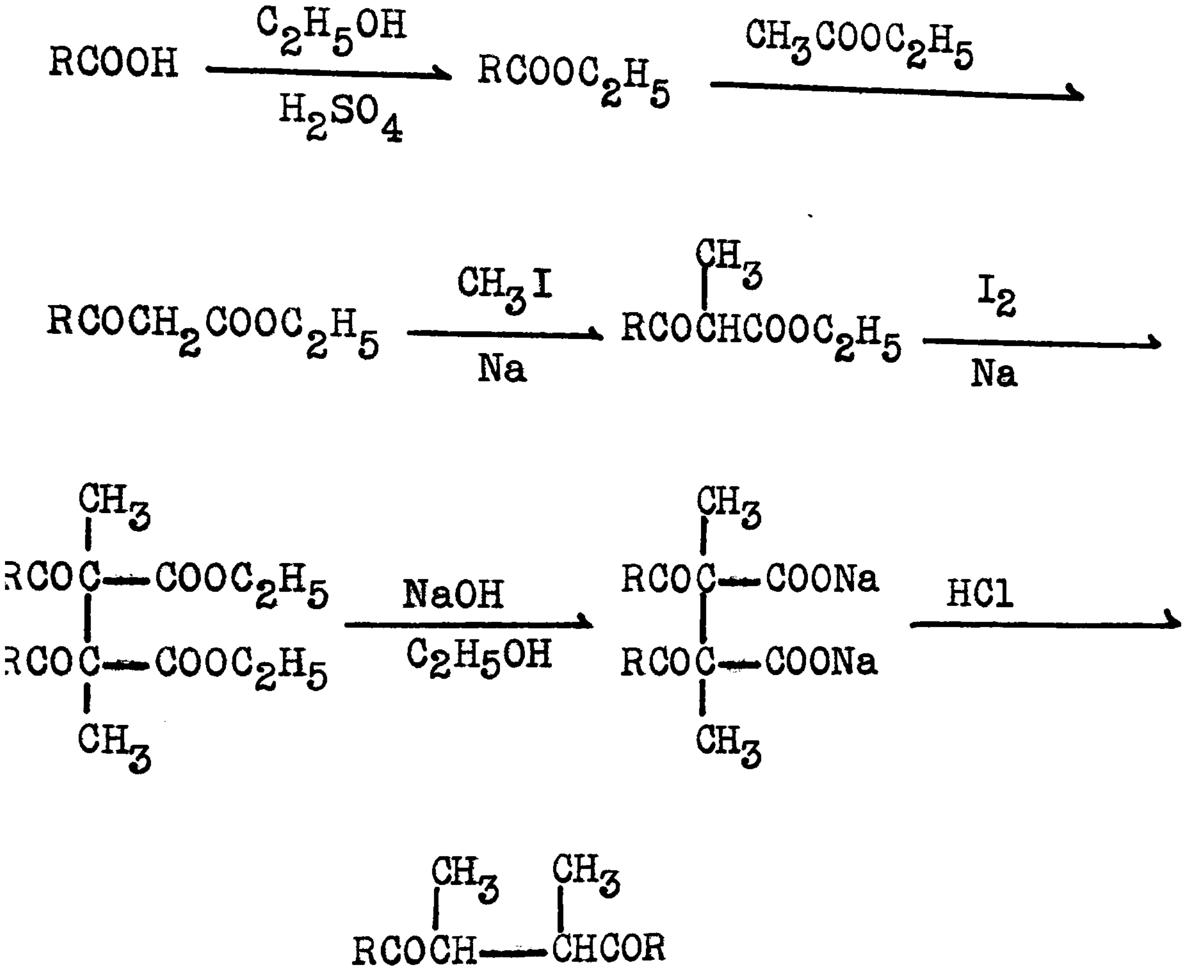
The third dimer, 1,4-diveratryl-2,3-dimethyl-1,4-butanedione, was synthesized by two methods: (a) the action of molecular silver on 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone and (b) the acetoacetic ester synthesis. The reactions involved are outlined below.

(a)

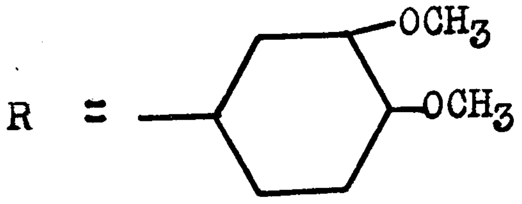


CXIII

(b)



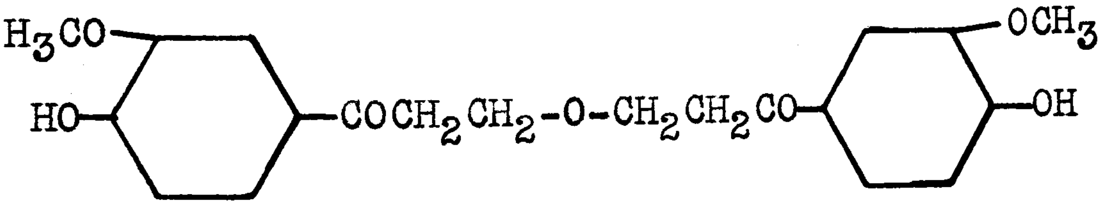
CXIII



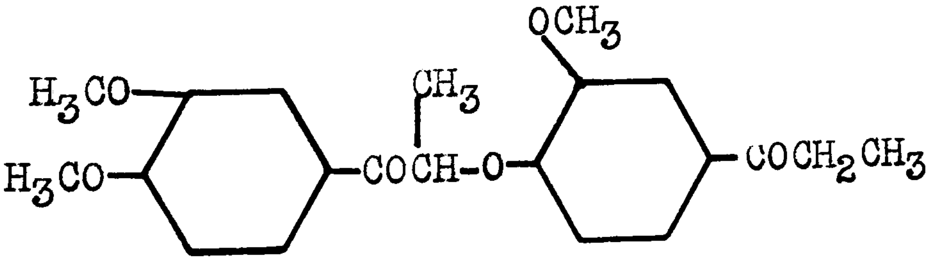
(a) The dimer (CXIII), 1,4-diveratryl-2,3-dimethyl-1,4-butanedione, was prepared by the action of molecular silver on 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone, using a drop of acetonitrile as the condensation catalyst. The yield was very low (11 per cent) and attempts to increase it by using high-boiling solvents and lengthening the time of reaction were unsuccessful. In every case the oil remaining after removal of the dimer (CXIII) and solvent was found to be unchanged 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone. Apparently, the silver lost its reactivity after the initial reaction occurred, probably due to the deposition of silver bromide on the surfaces of the molecular silver.

(b) The acetoacetic ester synthesis of the dimer (CXIII), 1,4-diveratryl-2,3-dimethyl-1,4-butanedione, was successfully carried out as shown in the reaction scheme on page 77 with an over-all yield of 18 per cent.

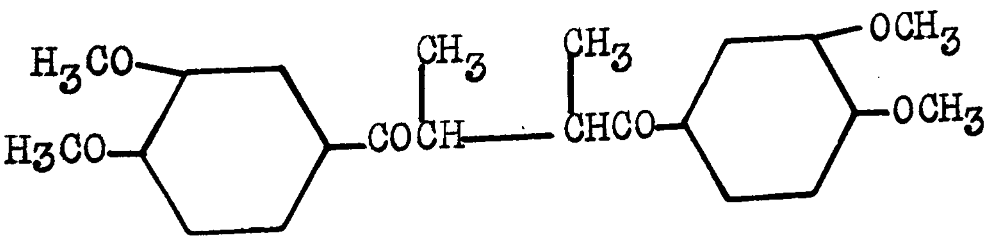
Properties of the Dimers



CXI



CXII

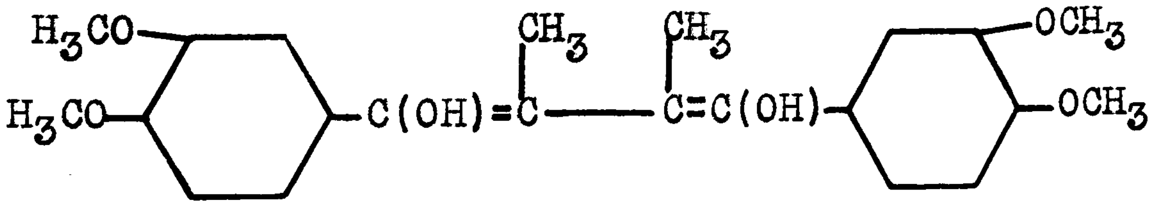


CXIII

I. Behaviour Towards Acids and Alkali

(a) Action of Sulfuric Acid (72 per cent) - Klason Lignin Determination

The second dimer (CXII), 1-veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone, on treatment with 72 per cent sulfuric acid, following the procedure used in a Klason lignin determination, was recovered unchanged. The first dimer (CXI), 2,2'-divanilloyl diethyl ether, yielded an amorphous product to the extent of 20 per cent, while the third dimer (CXIII), 1,4-diveratryl-2,3-dimethyl-1,4-butanedione, was converted to the extent of 70 per cent into an amorphous lignin-like material. In the last case, this change probably occurred as a result of polymerization of a 1,4-conjugated system represented by the dienol (CXXV).



CXXV

(b) Action of Dilute Sulfuric Acid (5 per cent) and Dilute Alkali (1 per cent)

Refluxing each of the dimers (CXI), (CXII) and (CXIII) with either reagent in aqueous solution was without effect; the original product being recovered unchanged.

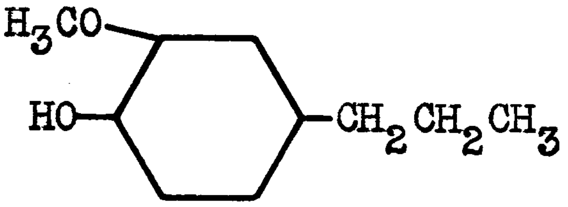
II. Ethanolysis with Ethanolic-Hydrogen Chloride (2 per cent)

Heating with ethanolic-hydrogen chloride (2 per cent) was without effect on the second dimer (CXII), 1-veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone, the ether linkage being quite resistant toward this reagent. Under the same conditions the first dimer (CXI), 2,2'-divanilloyl diethyl ether yielded about 15 per cent of an amorphous lignin-like product; the balance 75-80 per cent being recovered unchanged. Chain fission did not occur as none of the wood ethanolysis products was isolable. The third dimer (CXIII), 1,4-diveratryl-2,3-dimethyl-1,4-butanedione, treated similarly, with ethanolic-hydrogen chloride (2 per cent), gave a high yield (80 per cent) of an amorphous lignin-like product with no indication of chain fission to monomolecular units. Also, in this case, polymer formation was presumably due to the reactivity of the 1,4-conjugated dienol (CXXV).

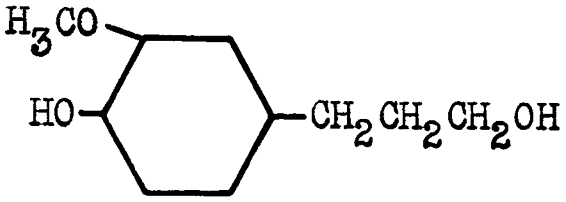
III. Hydrogenation and Hydrogenolysis

(a). Hydrogenation of 2,2'-Divanilloyl Diethyl Ether

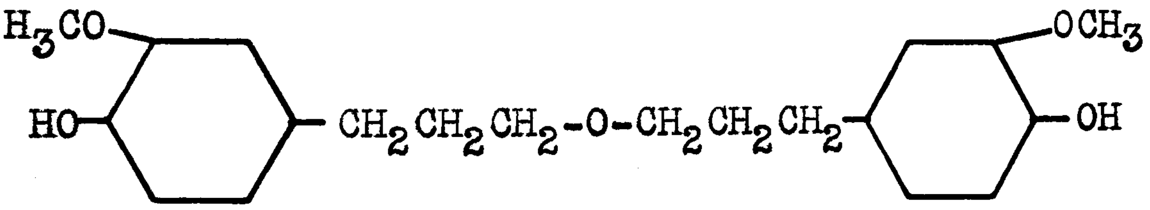
Hydrogenation of the first dimer (CXI), over Raney nickel in aqueous ethanol (1:1) containing 3 per cent alkali for 4 hours at 165°, resulted in hydrogenolysis of the ether union to the extent of 60 per cent. Both carbonyl groups were reduced while the aromatic rings remained intact. The remaining 30 per cent consisted of the original dimer in which the only change taking place was that of a reduction of the carbonyl to methylene groups. The products were identified as 4-hydroxy-3-methoxyphenyl propane (CXXVI), 3-(4-hydroxy-3-methoxyphenyl)-1-propanol (CXXVII) and 3,3'-divanillyl dipropyl ether (CXXVIII), in yields of 30, 30 and 33 per cent respectively.



CXXVI

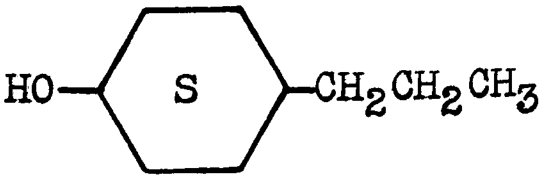


CXXVII

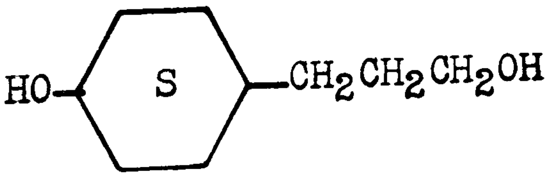


CXXVIII

Hydrogenation with the same catalyst and in the same medium at 185° for 18 hours yielded the following cyclohexane derivatives: 4-n-propylcyclohexanol (CXXIX) and 3-(4-hydroxycyclohexyl)-1-propanol (CXXX), in yields of 46 and 50 per cent respectively. Evidently chain fission



CXXIX



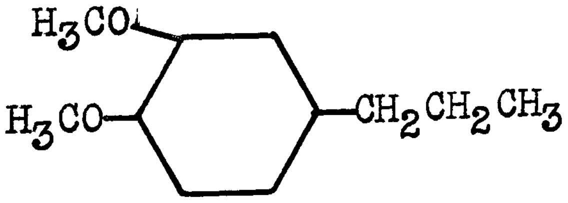
CXXX

occurred at the ether linkage followed by reduction of the aromatic rings. This type of reaction probably occurs in the hydrogenation of native lignin when spruce and maple woods are hydrogenated.

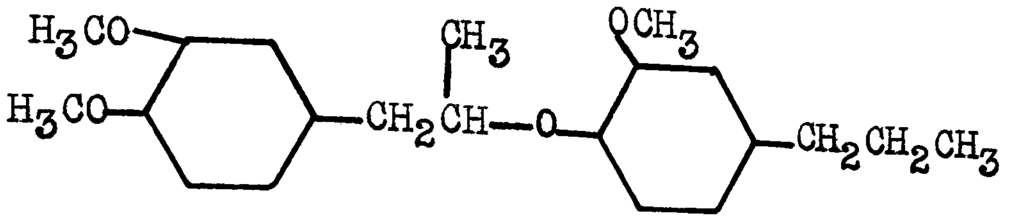
Using copper-chromium oxide as catalyst, hydrogenation of the first dimer (CXI) in aqueous ethanol at 150-160° for one hour, but in the absence of alkali, gave only one product, 3,3'-divanillyl dipropyl ether (CXXVIII) in a yield of 95 per cent. Chain fission did not occur under these conditions.

(b) Hydrogenation of 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone

Treatment of the second dimer (CXII) under the same conditions (Raney nickel, ethanol-water (1:1), alkali (3 per cent) at 165° for 4 hours) brought about cleavage of the ether linkage and also reduction of the carbonyl groups. The products isolated were 4-hydroxy-3-methoxyphenyl propane (CXXVI), 3,4-dimethoxyphenyl propane (CXXXI) and the carbonyl-reduced dimer (CXXXII), in yields of 30 per cent each. The same result was obtained in the absence of alkali.



CXXXI



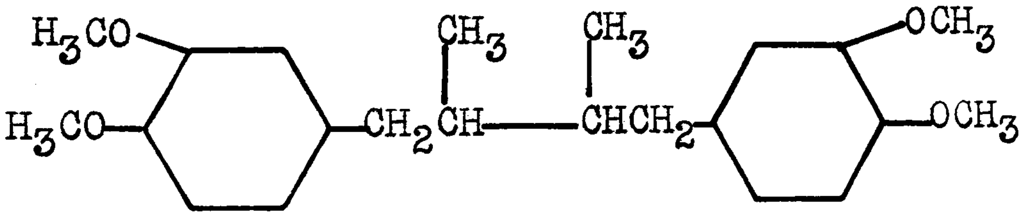
CXXXII

Substitution of copper-chromium oxide for Raney nickel, at 150-160° in ethanol for one hour, yielded the same products (CXXVI), (CXXXI) and (CXXXII) in yields of 40, 40 and 15 per cent respectively. Rehydrogenation of the carbonyl-reduced dimer (CXXXII), under the same conditions with copper-chromium oxide, left the product unchanged. The presence of alkali brought about a partial cleavage, to the extent of 15 per cent, the remainder of the saturated dimer being recovered unchanged. On the other hand, rehydrogenation of the latter (CXXXII) over Raney nickel at 160-165° for 4 hours brought about a cleavage, the reaction products comprising 4-hydroxy-3-methoxyphenyl propane (CXXVI), 3,4-dimethoxyphenyl propane (CXXXI) and unchanged starting material (CXXXII) in yields of 25, 25 and 50 per cent respectively. The presence of the two carbonyl groups exerted a marked effect in the hydrogenation of the dimer over copper-chromium oxide since cleavage did <u>not</u> occur when the saturated dimer (CXXXII) was rehydrogenated, while fission <u>did</u> occur when the unreduced dimer (CXII) was hydrogenated under the same conditions.

When the hydrogenation, over Raney nickel, was carried out at 185° for 18 hours, only one product was obtained, namely 4-n-propylcyclohexanol (CXXIX) in a yield of 90 per cent. Under these conditions both ether cleavage and reduction of the aromatic rings occurred.

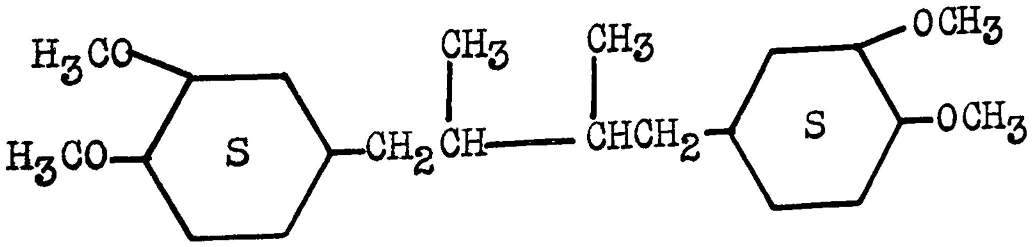
(c) Hydrogenation of 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

Using Raney nickel, ethanol-water (1:1), alkali (3 per cent), a temperature of 165° and time of 4 hours, the only reaction product was the uncleaved saturated side chain dimer, namely 1,4-diveratryl-2,3-dimethylbutane (CXXXIII).



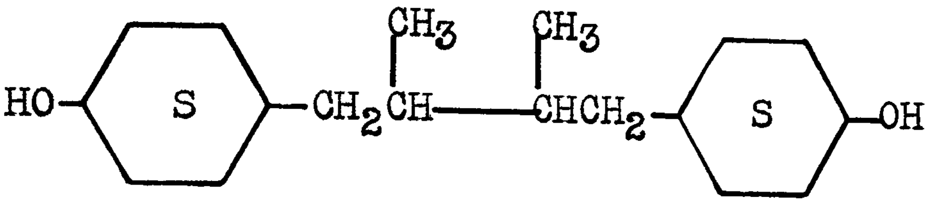
CXXXIII

The same result was obtained using copper-chromium oxide at 150-160° for one hour. This hydrogenated dimer (CXXXIII) when rehydrogenated with the latter catalyst at 185-190° for 12 hours underwent reduction of the aromatic rings, but no fission occurred. The product isolated was (CXXXIV).



CXXXIV

Substitution of the copper-chromium oxide in the last reduction by Raney nickel gave, under the same conditions, only the one product (CXXXV) namely 1,4-bis-(4-hydroxycyclohexyl)-2,3-dimethylbutane. The latter on rehydrogenation at 225-230° with Raney nickel and at 260° and 280°



CXXXV

with copper-chromium oxide was recovered unchanged with gasification of 10, 20 and 38 per cent respectively.

CONCLUSIONS

The experimental results indicate that:

(1) The ethanolysis products from wood are evidently not derived from dimers of the type (CXI), (CXII), (CXIII) and point to the probability of their formation from glycosides or ketals of monomolecular building units.

(2) Hydrogenation of dimers (CXI) and (CXII) show the marked ease of hydrogenolysis of the ether linkages of the type used.

(3) Under the mild conditions of hydrogenation employed side chain carbonyl groups undergo ready reduction to methylene groups, the aromatic rings remaining intact.

(4) In a dimeric unit joined by a carbon-to-carbon linkage

and containing carbonyl groups adjacent to the rings, the carbonyl groups undergo ready primary reduction to methylene groups without chain fission. This latter finding is of marked importance in connection with hydrogenation studies on the structure of lignin since it indicates that dimers and other polymers isolated by high-pressure hydrogenation are present as such in native lignin and are not formed by a hydrogenolysis reaction from more complex polymers.

EXPERIMENTAL

I. Synthesis of 2,2'-Divanilloyl Diethyl Ether

(a) Preparation of 3-Bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone

Powdered anhydrous aluminium chloride (10 g.) was suspended in anhydrous carbon disulfide (40 cc.) in a three-necked flask equipped with a mercury-sealed stirrer, a reflux condenser with drying tube, and a dropping funnel. The reaction flask was cooled by immersion into ice-water and β bromopropionyl chloride (13.0 g.) added rapidly to the well-stirred suspension. Veratrole (10.0 g.) was added gradually during one hour with vigorous stirring and then two more portions of aluminium chloride were added; the second portion (10 g.), fifteen minutes after the first. The reaction mixture was heated at 50° for one hour, allowed to stand overnight at room temperature and the carbon disulfide decanted. The Perrier complex was decomposed in a mixture of ice (500 g.) and hydrochloric acid (50 cc.). The product was filtered, washed on the filter with 10 per cent hydrochloric acid and finally with water. The crude, dried product was dissolved in ether and decolorizing charcoal added. The solution was heated under reflux for one hour, filtered and petroleum ether (30-50°) added until a permanent turbidity was formed. A crystalline product separated from the cooled solution and was recrystallized from ether-petroleum ether (30-50°) (1:1).

Yield : 11.1 g. (60%)

m.p. : 103-104°

Analysis : Calculated for $C_{10}H_{11}O_3Br$; OCH_3:11.9%; Br:30.9%
Found; OCH_3:11.8%; Br:30.7%

(i) Conversion of 3-Bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone to 3-Acetoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone

A mixture of 3-bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (11.0 g.), freshly fused potassium acetate (20 g.) and glacial acetic acid (90 cc.) was heated on the steam bath with continuous stirring during sixteen hours. The reaction mixture was cooled and added, in a fine stream, to ice-water (250 cc.). A thick precipitate which separated was filtered and washed with three portions of distilled water (50 cc.). The product was dried and recrystallized twice from chloroform-petroleum ether (30-50°) (3:1).

Yield : 6.4 g. (60%)

m.p. : 80-81°

A mixed melting point determination with an authentic sample of 3-acetoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone showed no depression.

(ii) Conversion of 3-Bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone to 3-Ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone

3-Bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (2.0 g.) was added to a 2 per cent ethanolic sodium ethylate solution (25 cc.) in a round-bottomed flask equipped with a reflux condenser. The solution was heated on the steam bath during three hours, added to 2 per cent hydrochloric acid (150 cc.) and the acidic solution extracted with chloroform (75 cc.). The chloroform solution was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The resulting oil crystallized on sustained scratching, was recrystallized from anhydrous ether and dried in a vacuum desiccator.

Yield : 1.2 g. (71%)

m.p. : 36-37°

A mixed melting point determination with an authentic sample of 3-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone showed no depression.

(iii) Conversion of 3-Bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone to 3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone

Aqueous sodium hydroxide solution (1%) (100 cc.) was added to 3-bromo-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (2 g.)

in a round-bottomed flask. The reaction mixture was heated at 50° during four hours, cooled, then acidified with dilute hydrochloric acid. The acidified solution was extracted with eight portions of chloroform (60 cc.) and the combined chloroform solutions were dried over anhydrous sodium sulfate. The solvent was removed and the product crystallized on sustained scratching with a soft-glass rod. The product was recrystallized twice from hot benzene (30 cc.).

Yield : 1.32 g. (88%)

m.p. : 109-110°

A mixed melting point determination with an authentic sample of 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone showed no depression.

(b) Preparation of 2,2'-Divanilloyl Diethyl Ether

(i) Dehydration of 3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone with Iodine in the Absence of Solvent

3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (3.0 g.) and resublimed iodine (0.1 g.) were thoroughly mixed in a small Claisen flask which was connected to a high-vacuum pump, through a safety flask. The mixture was heated at 120°/0.75 mm. during thirty minutes, cooled to room temperature (20°) and then extracted twice with hot (70°) benzene (50 cc.). The solvent was removed under reduced pressure, the resulting oil dissolved in hot methanol and the solution cooled. A white crystalline product separated from the solution and was recrystallized from methanol.

Yield : 0.55 g. (21%)

m.p. : 153-154°

Analysis : Calculated for $C_{20}H_{22}O_7$; C:64.17%; H:5.88%;
OCH_3:16.6%; Rast M.W.:374
Found; C:64.19%; H:5.9%; OCH_3:16.6%; Rast M.W.:380

(ii) Dehydration of 3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone with Iodine in the Presence of Solvent

3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (3.0 g.) was dissolved in hot anhydrous benzene (25 cc.) in a small Claisen flask fitted with a reflux condenser. A portion of the benzene (10 cc.) was distilled to remove absorbed water and resublimed iodine (0.05 g.) added. The solution was refluxed for one hour on the steam bath and the benzene removed by distillation at atmospheric pressure. The resulting product, a viscous oil, was dissolved in hot methanol (5 cc.), the solution cooled and an immediate separation of a crystalline substance occurred. The crude product was recrystallized from anhydrous methanol.

Yield : 1.0 g. (36%)

m.p. : 153-154°

A mixed melting point determination with a sample, obtained above (pages 90, 91), showed no depression.

(iii) Preparation of Bis-2,4-Dinitrophenylhydrazone of 2,2'-Divanilloyl Diethyl Ether

A small sample (0.2 g.) of 2,2'-divanilloyl diethyl ether was dissolved in hot ethanol (25 cc.) and a hydrochloric acid (7%) solution of 2,4-dinitrophenylhydrazine-hydrochloride (75 cc.) was added. The reaction mixture was heated at 80° during one hour, then allowed to stand overnight at room temperature. The mixture was filtered and the product washed with 30 per cent aqueous ethanol solution. The hydrazone was dried in a vacuum desiccator prior to two recrystallizations from benzene.

Yield : 0.28 g. (76%)

m.p. : 176-177°

Analysis : Calculated for $C_{32}H_{30}O_{13}N_8$; C:52.31%; H:4.08%; OCH_3:8.4%

Found; C:52.37%; H:4.14%; OCH_3:8.4%

(iv) Diazomethane Methylation of 2,2'-Divanilloyl Diethyl Ether

2,2'-Divanilloyl diethyl ether (0.16 g.) was dissolved in a benzene solution of diazomethane (6 equiv.) (250 cc.) and allowed to stand overnight at 0°. The solvent and excess diazomethane were removed at room temperature under reduced pressure and the resulting oil re-methylated with diazomethane (3 equiv.) in benzene. The oil, after removal of the solvent and excess diazomethane, was dissolved in benzene. The benzene solution was washed once with 2 per cent aqueous sodium hydroxide to remove unchanged 2,2'-divanilloyl diethyl ether and then dried over anhydrous sodium sulfate. Petroleum ether (30-50°) (10 cc.) was added and a crystalline product separated immediately from solution and was recrystallized once from ethanol.

Yield : 0.15 g. (89%)

m.p. : 139-140°

Analysis : Calculated for $C_{22}H_{26}O_7$; C:65.69%; H:6.47%;
OCH_3:30.8%; Rast M.W.:402
Found; C:65.62%; H:6.6%; OCH_3:30.6%; Rast M.W.:395

II. Synthesis of 2,2'-Diveratroyl Diethyl Ether

(a) Preparation of 3-Bromo-1-(3,4-dimethoxyphenyl)-1-propanone

Powdered anhydrous aluminium chloride (30 g.) was suspended in anhydrous carbon disulfide in a three-necked round-bottomed flask, equipped with a mercury-sealed stirrer, a reflux condenser with a drying tube, and a dropping funnel. The reaction flask was cooled in an ice-water bath and β bromopropionyl chloride (25.1 g.) added rapidly to the well-stirred suspension. Veratrole (20.0 g.) was added gradually with stirring during one hour and the reaction mixture heated for thirty minutes in a water bath at 50°. The layer of carbon disulfide was decanted and the oily Perrier complex decomposed in ice (500 g.)-hydrochloric acid (50 cc.) mixture with stirring for two hours. The tan colored product was filtered, washed on the filter with 10 per cent hydrochloric acid (200 cc.) and finally with three portions of distilled water (100 cc.). The crude product was dissolved in chloroform (150 cc.), charcoal added, and the solution refluxed gently during one hour. The solution was filtered and the product recrystallized twice from methanol-ether (4:1).

Yield : 22 g. (55%)

m.p. : 107-108°

Analysis : Calculated for $C_{11}H_{13}O_3Br$; C:48.35%; H:4.76%; OCH_3:22.7%; Br:29.3%

Found; C:48.29%; H:4.81%; OCH_3:22.7%; Br:29.1%

(i) Proof of the Veratryl Nucleus - Potassium Permanganate Oxidation

The assumed 3-bromo-1-(3,4-dimethoxyphenyl)-1-propanone (0.5 g.) was suspended in 3 per cent aqueous sodium hydroxide (100 cc.) in a three-necked flask fitted with a reflux condenser, stirrer and a dropping funnel. A 9 per cent aqueous solution of potassium permanganate (25 cc.) was added dropwise to the hot (100°) alkaline mixture during three hours. The precipitated manganese dioxide was removed by filtration and the filtrate acidified with dilute hydrochloric acid.

A crystalline product which separated was recrystallized from methanol-water (3:1).

Yield : 0.17 g. (50%)

m.p. : 180-181°

A mixed melting point determination with an authentic sample of veratric acid showed no depression.

(ii) Conversion of 3-Bromo-1-(3,4-dimethoxyphenyl)-1-propanone to 3-Acetoxy-1-(3,4-dimethoxyphenyl)-1-propanone

A mixture of 3-bromo-1-(3,4-dimethoxyphenyl)-1-propanone (5.0 g.), freshly fused potassium acetate (15 g.) and glacial acetic acid (30 cc.) was heated on the steam bath during sixteen hours with continuous stirring. The reaction mixture was cooled and added in a fine stream to ice-water (150 cc.). A crystalline precipitate which separated out of solution was recrystallized twice from chloroform-petroleum ether (30-50°) (2:1).

Yield : 3.4 g. (74%)

m.p. : 100-101°

A mixed melting point determination with an authentic sample of 3-acetoxy-1-(3,4-dimethoxyphenyl)-1-propanone showed no depression.

The solution was heated at 50° with stirring during four hours, cooled, extracted with five portions of chloroform (25 cc.) and the chloroform solution dried over anhydrous sodium sulfate. The solvent was removed and the product recrystallized twice from ether-petroleum ether (4:1).
Yield : 2.4 g. (80%)
m.p. : 83-84°
A mixed melting point determination with an authentic sample of 3-hydroxy-1-(3,4-dimethoxyphenyl)-1-propanone showed no depression.

(b) Preparation of 2,2'-Diveratroyl Diethyl Ether

3-Hydroxy-1-(3,4-dimethoxyphenyl)-1-propanone (3.0 g.) and resublimed iodine (0.1 g.) were mixed in a small Claisen flask, connected to a high-vacuum pump through a safety flask. The mixture was heated at 100°/0.75 mm. during thirty minutes, cooled to room temperature and then extracted with two portions of hot (65°) benzene (50 cc.). The solvent was removed under reduced pressure, the resulting light-colored oil dissolved in hot ethanol and the ethanol solution cooled. A crystalline product which separated out of solution was recrystallized from ethanol.
Yield : 0.9 g. (32%)
m.p. : 139-140°
A mixed melting point determination with the crystalline

product obtained from the methylation of 2,2'-divanilloyl diethyl ether (pages 92, 93) showed no depression.

(i) Potassium Permanganate Oxidation of 2,2'-Diveratroyl Diethyl Ether

2,2'-Diveratroyl diethyl ether (0.13 g.) was suspended in 3 per cent aqueous sodium hydroxide solution (50 cc.) in a three-necked flask fitted with a reflux condenser, stirrer and a dropping funnel. A 9 per cent aqueous potassium permanganate solution (25 cc.) was added dropwise to the hot (100°) alkaline solution during one hour. The precipitated manganese dioxide was removed by filtration and the filtrate acidified with dilute hydrochloric acid. A crystalline product which separated was recrystallized from methanol-water (3:1).

Yield : 0.09 g. (77%)

m.p. : 180-181°

A mixed melting point determination with an authentic sample of veratric acid showed no depression.

III. Synthesis of 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone

(a) Preparation of 2-Bromo-1-(3,4-dimethoxyphenyl)-1-propanone

(i) Preparation of 1-(3,4-Dimethoxyphenyl)-1-propanone

Powdered anhydrous aluminium chloride (40 g.) was suspended in anhydrous carbon disulfide (40 cc.) in a three-necked round-bottomed flask, equipped with a mercury-sealed stirrer, a reflux condenser with a drying tube, and a dropping funnel. The reaction flask was cooled by immersion into ice-water and propionyl chloride (33.0 g.) added slowly with vigorous stirring. Veratrole (40.0 g.) was added dropwise and stirring continued during one hour. The reaction temperature was raised to 20° and stirring continued during three hours. The carbon disulfide layer was decanted and the oily Perrier complex decomposed very rapidly in ice (500 g.)-hydrochloric acid (75 cc.) containing a layer of chloroform (100 cc), with vigorous stirring. The chloroform solution was separated, dried over anhydrous sodium sulfate and heated under reflux with activated charcoal. The solution was filtered and the solvent removed under reduced pressure. An oil which resulted was dissolved in anhydrous ether (50 cc.) and petroleum ether (30-50°) added until a permanent turbidity occurred. The solution was cooled (0°) for two hours, during which time crystals of the required product separated.

Yield : 46 g. (83%)

m.p. : 61-62°

A mixed melting point determination with an authentic sample of 1-(3,4-dimethoxyphenyl)-1-propanone showed no depression.

(ii) Bromination of 1-(3,4-Dimethoxyphenyl)-1-propanone

A solution, consisting of 1-(3,4-dimethoxyphenyl)-1-propanone (22.0 g.) and anhydrous chloroform (50 cc.), was added to a three-necked round-bottomed flask, equipped with a mercury-sealed stirrer, a reflux condenser and drying tube, and a dropping funnel. The solution was well-cooled by immersion of the reaction flask into ice-water, and pure bromine (19.0 g.), dissolved in anhydrous chloroform (100 cc.), was added slowly with vigorous stirring. The reaction temperature was permitted to rise to 20° after the addition of bromine was complete and stirring continued during three hours. The mixture was washed with three portions of water (25 cc.), two portions of aqueous sodium bicarbonate (2%) (200 cc.) and once more with water (100 cc.). The chloroform solution was dried over anhydrous sodium sulfate, heated with charcoal for one hour, filtered, and the solvent removed under reduced pressure. The resulting oil was dissolved in ether (100 cc.) and petroleum ether (30-50°) added dropwise until a permanent turbidity occurred. Gleaming white crystals of the required product separated from the cooled solution.

Yield : 25 g. (81%)

m.p. : 85-86°

A mixed melting point determination with an authentic sample of 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone showed no depression.

(b) Preparation of 1-(4-Hydroxy-3-methoxyphenyl)-1-propanone

(i) Preparation of Propionyl-2-methoxyphenolate

First Method: A solution of guaiacol (124 g.) and anhydrous propionic acid (74 g.) was heated at 80° in a three-necked round-bottomed flask, equipped with a mercury-sealed stirrer, a reflux condenser and drying tube, and a dropping funnel. The solution was stirred vigorously while thionyl chloride (125 cc.) was added dropwise during three hours. The reaction mixture was cooled, washed twice with water (100 cc.), once with sodium bicarbonate (2%) (250 cc.) and again with water (100 cc.). The product was dried over anhydrous magnesium sulfate and then distilled at 140-142°/ 20 mm.

Yield : 150 g. (83%)

Analysis : Calculated for $C_{10}H_{12}O_3$; C:66.67%; H:6.67%; OCH_3:17.2%

Found; C:66.61%; H:6.8%; OCH_3:17.1%

Second Method: A solution of guaiacol (25 g.), pyridine (20 g.) and propionyl chloride (19 g.) was heated on the steam bath during one hour. The reaction mixture was cooled and filtered from the pyridinium chloride. The resulting oil was distilled from a Claisen flask at 140-143°/20 mm. Yield : 34.5 g. (95%)

Analysis : Calculated for $C_{10}H_{12}O_3$; C:66.67%; H:6.67%; OCH_3:17.2%

Found; C:66.63%; H:6.9%; OCH_3:17.0%

(ii) Fries Rearrangement of Propionyl-2-methoxyphenolate

Powdered anhydrous aluminium chloride (30 g.) was dissolved in anhydrous nitrobenzene (75 cc.) by heating at 100°. The solution was cooled and added to a three-necked round-bottomed flask, equipped with a mercury-sealed stirrer, a reflux condenser and drying tube, and a thermometer. Stirring was commenced and propionyl-2-methoxyphenolate (20 g.) was added rapidly. The reaction mixture was heated on a water bath at 60° with stirring during one hour and then allowed to stand overnight at room temperature (20°). The mixture was filtered with the exclusion of air and moisture, effected by the addition of petroleum ether (30-50°) to the filter. The Perrier complex was washed on the filter with two portions of anhydrous benzene (100 cc.) and five portions of petroleum ether (30-50°) (100 cc.). The washed aluminium chloride complex was decomposed cautiously, with stirring, in ice (300 g.)-hydrochloric acid (45 cc.) containing chloroform (150 cc.). The chloroform solution was dried over anhydrous sodium sulfate, refluxed for one hour with activated charcoal and the solvent removed under reduced pressure. The light colored oil was dissolved in ether (100 cc.) and petroleum ether (30-50°) added dropwise until a permanent turbidity occurred. White crystals separated from the cooled solution.

Yield : 13 g. (65%)

m.p. : 62-63°

Analysis : Calculated for $C_{10}H_{12}O_3$; C:66.67%; H:6.67%; OCH_3:17.2%

Found; C:66.6%; H:6.9%; OCH_3:17.2%

(iii) Diazomethane Methylation of 1-(4-Hydroxy-3-methoxyphenyl)-1-propanone

The assumed 1-(4-hydroxy-3-methoxyphenyl)-1-propanone (0.25 g.) was dissolved in an ethereal solution of diazomethane (4 equiv.) (200 cc.). After standing for twenty-four hours at 0°, the excess diazomethane and solvent were removed under reduced pressure. The residue was dissolved in ether (100 cc.) and the solution washed with aqueous sodium hydroxide (2%) to remove the unchanged phenol. The ethereal solution was dried over anhydrous sodium sulfate and then concentrated to 40 cc. The addition of petroleum ether (30-50°) (10 cc.) caused the immediate separation of white crystals.

Yield : 0.25 g. (92%)

m.p. : 61-62°

A mixed melting point determination with an authentic sample of 1-(3,4-dimethoxyphenyl)-1-propanone showed no depression.

(c) Preparation of the Sodium Phenolate of 1-(4-Hydroxy-3-methoxyphenyl)-1-propanone

Sodium (2.0 g.) was cautiously dissolved in absolute ethanol (150 cc.) and 1-(4-hydroxy-3-methoxyphenyl)-1-propanone (15 g.) added to the sodium ethylate solution. The sodium phenolate of 1-(4-hydroxy-3-methoxyphenyl)-1-propanone separated immediately and the mixture was allowed to stand overnight at 0° to complete the separation. The mixture was filtered with the exclusion of air and moisture and the sodium phenolate washed once with anhydrous ether.

Yield : 16.8 g. (100%)

Analysis : Calculated for $C_{10}H_{11}O_3Na$; Na:11.38%

Found; Na:11.4%

(d) Condensation of the Sodium Phenolate of 1-(4-Hydroxy-3-methoxyphenyl)-1-propanone with 2-Bromo-1-(3,4-dimethoxyphenyl)-1-propanone

The sodium phenolate of 1-(4-hydroxy-3-methoxyphenyl)-1-propanone (16.5 g.) was added to an anhydrous ethanol (300 cc.) solution of 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone in a round-bottomed ground-glass flask equipped with a reflux condenser with a drying tube. The solution was heated under reflux during four hours, then added while hot, to cold distilled water (1 L.). A white microcrystalline precipitate which separated was removed by filtration and dried. The product was recrystallized twice from methanol.

Yield : 23.8 g. (78%)

m.p. : 148-149°

Analysis : Calculated for $C_{21}H_{24}O_6$; C:67.74%; H:6.45%;
OCH_3:25.0%; Rast M.W.:372
Found; C:67.66%; H:6.48%; OCH_3:24.9%; Rast M.W.:387

(e) Preparation of Bis-2,4-Dinitrophenylhydrazone of 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone

1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone (0.3 g.) was dissolved in hot ethanol (25 cc.) and a solution of 2,4-dinitrophenylhydrazine-hydrochloride (150 cc.) added. The reaction mixture was heated at 80° during one hour, then cooled and allowed to stand overnight at room temperature to complete the reaction. The mixture was filtered; the product washed with aqueous ethanol (30%), dried overnight in a vacuum desiccator and then recrystallized twice from anhydrous benzene.

Yield : 0.37 g. (63%)

m.p. : 219-221°

Analysis : Calculated for $C_{33}H_{32}O_{12}N_8$; C:54.09%; H:4.37%;
OCH_3:12.7%; Rast M.W.:732

Found; C:54.0%; H:4.4%; OCH_3:12.6%; Rast M.W.:724

IV. Synthesis of 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

(a) Preparation of 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione by the Action of Molecular Silver on 2-Bromo-1-(3,4-dimethoxyphenyl)-1-propanone

Molecular silver (1.0 g.), 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone (1.0 g.), acetonitrile (0.01 g.) and xylene (15 cc.) were added to a round-bottomed flask equipped with a ground-glass reflux condenser. The mixture was refluxed gently for forty-eight hours and filtered while hot. The solvent was removed under reduced pressure and the resulting oil dissolved in boiling ether (35 cc.). The ethereal solution was cooled (-15°) for forty-eight hours, during which time white crystals separated. The product was recrystallized from hot methanol.

Yield : 0.08 g. (11%)

m.p. : 189-190°

(b) Preparation of 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione by the Acetoacetic Ester Synthesis

(i) Preparation of Ethyl Veratrate

Veratric acid (80 g.) was dissolved in hot anhydrous ethanol (500 cc.) containing concentrated sulfuric acid (50 cc.). The solution was refluxed gently for four hours, the solvent removed by distillation and the resulting oil precipitated into cold water (500 cc.). The aqueous solution was neutralized by the cautious addition of sodium bicarbonate and extracted with two portions of ether (200 cc.). The ethereal solution was dried over anhydrous sodium sulfate, the solvent removed and the product distilled under reduced pressure. The fraction boiling at 110-115°/0.01 mm. was dissolved in ether and petroleum ether (30-50°) added dropwise until a permanent turbidity occurred. The solution was cooled and a white crystalline product separated.

Yield : 82 g. (89%)

m.p. : 43.5-44.5°

Analysis : Calculated for $C_{11}H_{14}O_4$; OCH_3:44.3%

Found; OCH_3:43.9%

(ii) Preparation of Ethyl Veratroyl Acetate

Ethyl veratrate (50 g.) was added to a three-necked flask equipped with a reflux condenser, a dropping funnel and a sealed-stirrer. Granulated sodium (4 g.) was added, the stirrer started and the mixture heated at 80°. A pasty mass was obtained to which ethyl acetate (15 g.) was added dropwise, and the temperature raised to 90°. An additional quantity of sodium (4 g.) and ethyl acetate (15 g.) was added to the reaction mixture. This addition of sodium and ethyl acetate was continued until a total of 20 g. sodium and 75 g. ethyl acetate were added. Stirring and heating were continued for sixteen hours. The mixture was cooled, added with stirring to ice (500 g.)-hydrochloric acid (100 cc.) and the acidic solution extracted with three portions of ether (250 cc.). The ethereal solution was dried over anhydrous sodium sulfate and the solvent removed. The resulting oil was distilled under diminished pressure. The first fraction, boiling up to 120°/0.01 mm., consisting of ethyl acetoacetate and ethyl veratrate was discarded. The required product distilled as a viscous oil at 150-160°/ 0.01 mm.

Yield : 24.1 g. (40%)

Methoxyl Analysis : Calculated for $C_{13}H_{16}O_5$; 36.9%

Found; 37.3%

(iii) Preparation of Methyl(Ethyl Veratroyl Acetate)

The ethyl veratroyl acetate (24 g.) was dissolved in anhydrous benzene (150 cc.) in a three-necked flask equipped with a condenser, dropping funnel and a sealed-stirrer. Granulated sodium (2.2 g.) was added in small portions during four hours and the mixture heated, with stirring during twelve hours. Methyl iodide (15 g.), dissolved in anhydrous benzene (200 cc.), was added drop-wise to the cooled mixture. Stirring was continued until the reaction mixture became transparent. The mixture was heated on the steam bath during one hour, then cooled and added in a fine stream to cold water (500 cc.). The benzene layer was decanted and the aqueous solution extracted with ether (100 cc.). The combined benzene and ether solutions were dried over sodium sulfate and the solvents removed under reduced pressure. The resulting oil was distilled and the fraction boiling at 155-167°/0.01 mm. used in the subsequent experiment.

Yield : 25 g. (98%)

Methoxyl Analysis : Calculated for $C_{14}H_{18}O_5$: 34.9%

Found: 34.3%

(iv) Preparation of Bis-(Methyl Ethyl Veratroyl Acetate)

The product (25 g.), obtained above, was dissolved in anhydrous benzene (300 cc.) in a three-necked flask equipped with a dropping funnel, sealed-stirrer and a reflux condenser with a drying tube. The solution was heated on the steam bath and granulated sodium (2.2 g.) added in small portions during two hours, with vigorous stirring. The reaction mixture became very viscous, due to the formation of the sodium enolate, and another portion of anhydrous benzene (300 cc.) was added. Iodine (13 g.), dissolved in anhydrous benzene (250 cc.), was added dropwise to the hot, well-stirred mixture during four hours. Stirring continued for one hour and the solution was added in a fine stream to water (1 L.).

The benzene layer was decanted, washed with aqueous sodium thiosulfate (5%) (100 cc.) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the viscous oil, boiling at 210-216°/0.01 mm., used in the subsequent experiment.

Yield : 23.3 g. (93%)

Methoxyl Analysis : Calculated for $C_{28}H_{34}O_{10}$: 35.1%

Found: 34.6%

(v) Preparation of 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

The product (23 g.), obtained above, was dissolved in anhydrous ethanol (375 cc.) containing sodium hydroxide (8.5 g.) and the mixture allowed to stand at room temperature during twenty-four hours with occasional stirring. The reaction mixture was cooled and concentrated hydrochloric acid added dropwise until the evolution of carbon dioxide ceased. The mixture was immediately added to cold water (450 cc.), the solution filtered, the oily product dissolved in chloroform-ethanol (1:2) (200 cc.) and charcoal added. The mixture was heated under reflux on the steam bath during two hours and filtered while hot. The solvent was removed under reduced pressure and the tan-colored crystalline substance which separated was recrystallized twice from hot methanol.

Yield : 8.4 g. (48%)

m.p. : 189-190°

A mixed melting point determination with the product obtained from the action of molecular silver on 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone (page 106) showed no depression.

Analysis : Calculated for $C_{22}H_{26}O_6$; C:68.39%; H:6.76%; OCH_3:32.1%; Rast M.W.:386; Acetic Acid:31.1%

Found; C:68.3%; H:6.9%; OCH_3:31.9%; Rast M.W.:395; Acetic Acid:30.7%

(c) Potassium Permanganate Oxidation of 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

The dimer, 1,4-diveratryl-2,3-dimethyl-1,4-butanedione (0.25 g.), was suspended in aqueous sodium hydroxide (3%) (100 cc.) in a three-necked flask fitted with a reflux condenser, stirrer and a dropping funnel. Aqueous potassium permanganate solution (10%) (30 cc.) was added dropwise to the hot (100°) mixture during three hours. The precipitated manganese dioxide was removed by filtration and the filtrate acidified with hydrochloric acid. A crystalline product which separated was recrystallized from methanol-water (3:1).

Yield : 0.16 g. (72%)

m.p. : 180-181°

A mixed melting point determination with an authentic sample of veratric acid showed no depression.

(d) Preparation of the Bis-2,4-Dinitrophenylhydrazone of 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

The dimer, 1,4-diveratryl-2,3-dimethyl-1,4-butanedione (0.15 g.) was dissolved in hot ethanol (25 cc.) and a solution of 2,4-dinitrophenylhydrazine-hydrochloride (100 cc.) added. The reaction mixture was heated on the steam bath during one hour, then allowed to stand overnight at room temperature. The product was filtered, washed with aqueous ethanol (30%), then dried at room temperature in a vacuum desiccator. The dried hydrazone was recrystallized twice from benzene.

Yield : 0.16 g. (61%)

m.p. : 241-243°

Methoxyl Analysis : Calculated for $C_{34}H_{34}O_{12}N_8$: 16.6%

Found: 16.6%

PROPERTIES OF THE DIMERS

I. (a) Action of 72% Sulfuric Acid on 2,2'-Divanilloyl Diethyl Ether

2,2'-Divanilloyl diethyl ether (0.2 g.) was treated at room temperature during two hours with sulfuric acid (72%) (2 cc.). The mixture was then diluted to 75 cc. with distilled water, refluxed during four hours, cooled, filtered and the product on the filter added to hot methanol (25 cc.). The hot methanol solution was filtered, leaving a small amount of an amorphous lignin-like residue. The methanol filtrate was cooled, causing the separation of unchanged 2,2'-divanilloyl diethyl ether, as shown by a mixed melting point determination with an authentic sample of 2,2'-divanilloyl diethyl ether.

Yield of unchanged dimer : 0.15 g. (75%)

Yield of amorphous product : 0.04 g. (20%)

(b) Action of 72% Sulfuric Acid on 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone

1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone (0.5 g.) was treated at room temperature during two hours with sulfuric acid (72%) (4 cc.). The mixture was diluted to 150 cc. with distilled water, refluxed during four hours, cooled and filtered. The product was recrystallized from hot methanol.

Yield : 0.49 g. (98%)

m.p. : 148-149°

A mixed melting point determination with an authentic sample of 1-veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone showed no depression.

(c) Action of 72% Sulfuric Acid on 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

1,4-Diveratryl-2,3-dimethyl-1,4-butanedione (0.5 g.) was treated at room temperature during two hours with sulfuric acid (72%) (4 cc.). The mixture was diluted to 150 cc. with distilled water and refluxed during four hours. The mixture was cooled and filtered, leaving an amorphous lignin-like residue.

Yield : 0.35 g. (70%)

Methoxyl Analysis : 36.2%

II. (a) Action of 5% Sulfuric Acid on 2,2'-Divanilloyl Diethyl Ether

2,2'-Divanilloyl diethyl ether (0.1 g.) was refluxed during twenty-four hours with aqueous sulfuric acid (5%) (10 cc.). The mixture was cooled, filtered and the product recrystallized from methanol.

Yield : 0.085 g. (85%)

m.p. : 153-154°

A mixed melting point determination with an authentic sample of 2,2'-divanilloyl diethyl ether showed no depression.

(b) Action of 5% Sulfuric Acid on 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone

1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone

(0.100 g.) was refluxed during twenty-four hours with aqueous sulfuric acid (5%) (10 cc.). The mixture was cooled, filtered and the product recrystallized from methanol.

Yield : 0.088 g. (88%)

m.p. : 148-149°

A mixed melting point determination with an authentic sample of 1-veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone showed no depression.

(c) Action of 5% Sulfuric Acid on 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

1,4-Diveratryl-2,3-dimethyl-1,4-butanedione (0.100 g.) was refluxed during twenty-four hours with aqueous sulfuric acid (5%) (10 cc.). The mixture was cooled, filtered and the product recrystallized from methanol.

Yield : 0.083 g. (83%)

m.p. : 189-190°

A mixed melting point determination with an authentic sample of 1,4-diveratryl-2,3-dimethyl-1,4-butanedione showed no depression.

III. (a) Action of 1% Sodium Hydroxide on 2,2'-Divanilloyl Diethyl Ether

2,2'-Divanilloyl diethyl ether (0.100 g.) was refluxed during twenty-four hours with aqueous sodium hydroxide

(1%) (15 cc.). The reaction mixture was cooled, acidified with dilute hydrochloric acid and filtered. The product was recrystallized from methanol.

Yield : 0.08 g. (80%)

m.p. : 153-154°

A mixed melting point determination with an authentic sample of 2,2'-divanilloyl diethyl ether showed no depression.

(b) Action of 1% Sodium Hydroxide on 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone

1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone (0.100 g.) was refluxed during twenty-four hours with aqueous sodium hydroxide (1%) (15 cc.). The reaction mixture was cooled and filtered. The product on the filter was well-washed with water and recrystallized from methanol.

Yield : 0.086 g. (86%)

m.p. : 148-149°

A mixed melting point determination with an authentic sample of 1-veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone showed no depression.

(c) Action of 1% Sodium Hydroxide on 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

1,4-Diveratryl-2,3-dimethyl-1,4-butanedione (0.100 g.) was refluxed during twenty-four hours with aqueous sodium hydroxide (1%) (15 cc.). The reaction mixture was acidified with dilute hydrochloric acid and filtered. The product was recrystallized from methanol.

Yield : 0.084 g. (84%)

m.p. : 189-190°

A mixed melting point determination with an authentic sample of 1,4-diveratryl-2,3-dimethyl-1,4-butanedione showed no depression.

IV. (a) Action of 2% Ethanolic Hydrogen Chloride on 2,2'-Divanilloyl Diethyl Ether

2,2'-Divanilloyl diethyl ether (1.000 g.) was heated under reflux with 2 per cent ethanolic hydrogen chloride (50 cc.) during forty-eight hours in an atmosphere of carbon dioxide. A small amount of an amorphous lignin-like substance which separated was removed by filtration.

Yield : 0.15 g. (15%)

Methoxyl Analysis : 19.6%

The filtrate was neutralized with sodium ethylate and the precipitated sodium chloride removed by filtration. The solvent was removed under reduced pressure and the product recrystallized from methanol.

Yield : 0.75 g. (75%)

m.p. : 153-154°

A mixed melting point determination with an authentic sample of 2,2'-divanilloyl diethyl ether showed no depression.

(b) Action of 2% Ethanolic Hydrogen Chloride on 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone

1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone (1.000 g.) was refluxed with 2 per cent ethanolic hydrogen chloride (50 cc.) during forty-eight hours in an atmosphere of carbon dioxide. The reaction mixture was cooled, neutralized with sodium ethylate and the precipitated sodium chloride removed by filtration. The solvent was removed under reduced pressure and the residue dissolved in hot methanol (25 cc.). The methanol solution was cooled resulting in the separation of a crystalline substance.

Yield : 0.91 g. (91%)

m.p. : 148-149°

A mixed melting point determination with an authentic sample of 1-veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone showed no depression.

(c) Action of 2% Ethanolic Hydrogen Chloride on 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

1,4-Diveratryl-2,3-dimethyl-1,4-butanedione (1.000 g.) was refluxed with 2 per cent ethanolic hydrogen chloride

(50 cc.) during forty-eight hours in an atmosphere of carbon dioxide. The color of the reaction mixture turned dark and an insoluble amorphous substance separated. The hot reaction mixture was filtered and the residue dried.

Yield : 0.79 g. (79%)

Methoxyl Analysis : 36.4%

The filtrate was neutralized with sodium ethylate and the precipitated sodium chloride removed by filtration. The solvent was removed under reduced pressure, yielding a very small amount (0.01 g.) of an amorphous substance which was the same as that above, shown by a methoxyl determination.

V. (a) Hydrogenation of 2,2'-Divanilloyl Diethyl Ether

2,2'-Divanilloyl diethyl ether was hydrogenated in a small hydrogenation bomb under the various conditions indicated in Table I.(page 124).

The product (A), obtained in the first hydrogenation, was dissolved in ethereal diazomethane solution (200 cc.) and the solution allowed to stand overnight at 0°. The solvent and excess diazomethane were removed under reduced pressure and the resulting product re-methylated to completion, as shown by a negative ferric chloride-phenol test. This methylated product was distilled under reduced pressure yielding two fractions, (i) and (ii).

(i) Low-boiling Fraction

Bath Temperature : 80-90°/0.1 mm.

Yield : 0.51 g.

The oil was analysed to determine whether cleavage of the dialkyl ether linkage occurred. The methods used were methoxyl determination and Smith-Bryant (129) hydroxyl determination.

Analysis : Calculated for cleavage mixture; OH:4.54%; OCH_3:32.9%

Found; OH:4.5%; OCH_3:32.8%

(ii) High-boiling Fraction

Bath Temperature : 150-153°/0.01 mm.

Yield : 0.28 g.

Methoxyl Analysis : Calculated for $C_{22}H_{30}O_5$; 33.1%

Found; 33.1%

The product (B) from the second hydrogenation of 2,2'-divanilloyl diethyl ether was distilled under reduced pressure, resulting in two fractions, (i) and (ii).

(i) Bath Temperature : 115-119°/15 mm.

Yield : 0.31 g.

The phenyl urethan was prepared (m.p. : 127-128°) and a mixed melting point determination with the phenyl urethan of 4-*n*-propyl cyclohexanol showed no depression.

(ii) Bath Temperature : 119-123°/0.1 mm.

Yield : 0.35 g.

The product (0.35 g.) was dissolved in a mixture containing chromic oxide (1.1 g.), glacial acetic acid (10 cc.), water (5.5 cc.) and benzene (20 cc.) in a small Erlenmeyer flask. The reaction mixture was shaken at room temperature during 18 hours, the benzene layer removed and the dark-green acid mixture extracted with three portions of benzene (10 cc.). The combined benzene solutions were washed once with water (15 cc.) to remove suspended chromic acid, then extracted with four portions of sodium carbonate (10%) (10 cc.). The carbonate solution was cautiously acidified with dilute hydrochloric acid and the milky solution extracted with five portions of benzene (10 cc.). The combined benzene solutions were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The yield of the resulting oil was 0.17 g.

This oil (0.17 g.) was dissolved in aqueous ethanol (50%) (1 cc.) and added to a solution consisting of semicarbazide-hydrochloride (0.2 g.), potassium acetate (0.25 g.) and water (5 cc.). The solution was heated at 60° during ten minutes and the crystalline product which separated was removed by filtration and recrystallized twice from hot water. Yield : 0.09 g.

m.p. : 200-202°

A mixed melting point determination with an authentic sample of the semicarbazone of 3-(4-cyclohexanone)-1-propanoic acid showed no depression, thereby indicating that the original product, prior to the chromic acid oxidation, was 3-(4-hydroxycyclohexyl)-1-propanol.

The copper-chromium oxide hydrogenation of 2,2'-divanilloyl diethyl ether (1.0 g.) resulted in a product (C), after complete methylation with diazomethane, which boiled at a bath temperature of 150-154°/0.01 mm.

Yield : 0.88 g.

Methoxyl Analysis : Calculated for $C_{22}H_{30}O_5$: 33.1%

Found: 33.0%

(b) Hydrogenation of 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone

1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone was hydrogenated under the various conditions indicated in Table II (page 125). The resulting products were isolated by alkaline separation into phenolic and non-phenolic fractions and distillation under reduced pressure and identified by analysis. In each case the low-boiling phenolic fractions were found to be 4-hydroxy-3-methoxyphenyl propane by the formation of the para nitrobenzoate.

m.p. : 73.5-74.5°
A mixed melting point determination with an authentic sample of the para nitrobenzoate of 4-hydroxy-3-methoxyphenyl propane showed no depression.

The final hydrogenation, with Raney nickel, resulted in one product only, 4-n-propyl cyclohexanol. The phenyl urethan (m.p. : 127-128°) was prepared from phenyl isocyanate and a mixed melting point determination with an authentic sample of the phenyl urethan of 4-n-propyl cyclohexanol showed no depression.

(c) Hydrogenation of 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

The third dimer, 1,4-diveratryl-2,3-dimethyl-1,4-butanedione, was hydrogenated and rehydrogenated under the various conditions indicated in Table III (page 126). Examination of the products indicated reduction of the carbonyl groups, demethylation, demethoxylation and/or ring reduction. However, cleavage of the carbon-to-carbon linkage in the side chain did not occur even at 280°.

TABLE I

Weight	Solvent	Catalyst	Alkali	Time Hours	Temp. °C	Pressure lbs/in.^{2}	Products
1.0g.	EtOH-H_2O 1:1, 100cc.	RaNi 1.0g.	3.0g.	4	165	3020	0.85g. A.
1.0g.	ditto	ditto	ditto	18	185	3000	0.71g. B.
1.0g.	ditto	CuCrO 0.5g.	-	1	150-160	2980	0.88g. C.

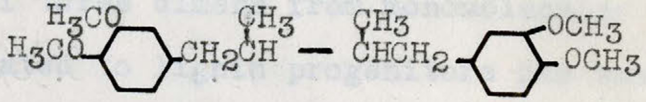
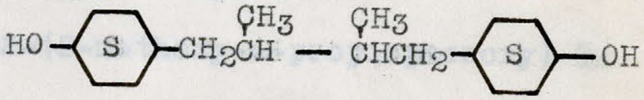
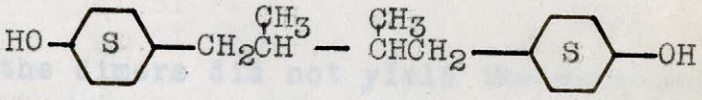
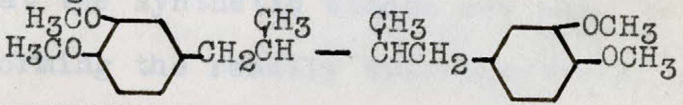
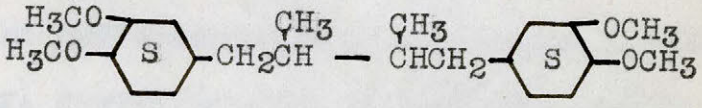
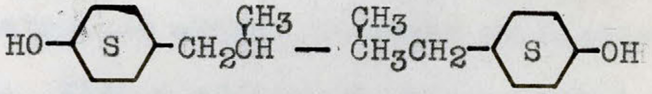
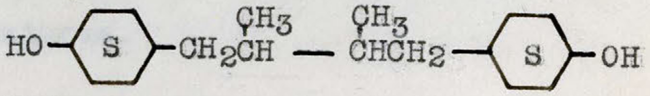
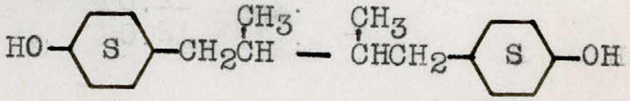
TABLE II

Charge						Pressure lbs/in.^{2}	Tempr.	Time Hours	Products			
Dimer	Sat. Dimer	Solvent	RaNi	CuCrO	NaOH				Total Weight	Sat. Dimer	$RCH_2CH_2CH_3$	$R^1CH_2CH_2CH_3$
4.0g.	-	EtOH-H_2O 1:1, 100cc.	3.5g.	-	3g.	3030	160-165°	4	3.6g.	1.1g. B.P.170-3°/0.015mm.	1.1g. B.P.70-72°/0.01mm.	1.2g. 82-85°/0.01mm.
8.2g.	-	EtOH 150cc.	-	4g.	-	2910	150-160°	1	7.3g.	1.1g. 171-3°/0.01mm.	2.9g. 70-73°/0.01mm.	3.0g. 83-85°/0.01mm.
-	1.0g.	EtOH 75cc.	-	0.5g.	-	2950	150-160°	1	0.96g.	0.96g. 170-2°/0.01mm.	-	-
-	0.96g.	EtOH-H_2O 1:1, 100cc.	1.0g.	-	3.0g.	2950	160-165°	4	0.88g.	0.42g. 171-3°/0.01mm.	0.23g. 70-71°/0.01mm.	0.21g. 84-86°/0.015mm.
1.0g.	-	EtOH-H_2O 1:1, 100cc.	1.0g.	-	-	3020	160-165°	4	0.86g.	0.40g. 172-3°/0.01mm.	0.21g. 70-73°/0.01mm.	0.23g. 81-83°/0.01mm.
1.0g.	-	EtOH-H_2O 1:1, 100cc.	1.0g.	-	-	3020	160-165°	1	0.91g.	0.59g. 170-2°/0.01mm.	0.12g. 70-73°/0.01mm.	0.10g. 82-84°/0.01mm.
1.0g.	-	H_2O 100cc.	1.0g.	-	-	2980	155-165°	4	0.92g.	0.40g. 170-3°/0.01mm.	0.23g. 70-71°/0.01mm.	0.21g. 83-84°/0.01mm.
-	1.0g.	EtOH-H_2O 1:1, 100cc.	-	0.5g.	3.0g.	2950	150-160°	1	0.92g.	0.74g. 171-4°/0.01mm.	0.08g. 70-71°/0.01mm.	0.07g. 82-83°/0.01mm.
1.0g.	-	EtOH-H_2O 1:1, 100cc.	1.0g.	-	3.0g.	2980	185°	18	0.65g. 117-20°/15mm.	Identified as 4-n-propyl-cyclohexanol		

R = Veratryl

R^1 = Guaiacyl

TABLE III

Weight	Solvent	Catalyst	Alkali	Time Hours	Tempr.	Pressure lbs/in.^{2}	Products
5.0g. Dimer CXIII	EtOH-H_2O 1:1, 150cc. 1	RaNi 5g. 	4.5g.	4	165°	2950	4.2g. (91%) distilled[1] at 211-213°/0.01mm. Crystallized from ether; m.p. 77-78° (3.7g.) OCH_3: 34.6%; C: 73.88 H: 8.45% - Found OCH_3: 34.7%; C: 73.74 H: 8.38% - Calculated
1 3.7g.	EtOH-H_2O 1:1, 150cc. 2	RaNi 3.7g. 	4.5g.	12	185°	2950	2.4g. (83%) distilled[2] at 185-188°/0.01mm. OCH_3: 0.3%; OH: 11.8% - Found OCH_3: 0.0%; OH: 12.0% - Calculated
2 2.0g.	EtOH-H_2O 1:1, 150cc. 3	RaNi 2.0g. 	3.0g.	12	225-230°	2450	1.8g. (90%) distilled[3] at 190-194°/0.025mm. OH: 11.6%; C :76.1 H:12.1%; - Found OH: 12.0%; C :76.5 H:12.0%; - Calculated
5.0g. Dimer CXIII	EtOH 150cc. 4	CuCrO 2.5g. 	-	1	150-160°	2950	4.3g. (93%) recrystallized[4] from ether (3.8g.) m.p. 77-78°; mixed m.p. with 1 no depression OCH_3: 34.6%; - Found OCH_3: 34.6%; - Calculated
4 3.8g.	EtOH 150cc. 5	CuCro 1.9g. 	-	12	185-190°	3000	3.3g. (87%) distilled[5] at 200-205°/0.01mm. OCH_3: 33.6%; - Found OCH_3: 33.6%; - Calculated
5 3.3g.	EtOH 100cc. 6	CuCrO 1.6g. 	-	12	225-30°	2420	2.3g. (92%) distilled[6] at 180-184°/0.01mm. OCH_3: 0.2%; OH: 11.3%; C:76.4; H:12.1% - Found OCH_3: 0.0%; OH: 12.0%; C:76.5; H;12.0% - Calculated
6 2.0g.	EtOH 100cc. 7	CuCrO 1.0g. 	-	12	260°	1800	1.6g. (80%) distilled[7] at 180-186°/0.01mm. OH: 11.6% - Found OH: 12.0% - Calculated
7 1.3g.	Dioxane 100cc. 8	CuCrO 0.65g. 	-	12	280°	1650	0.8g. (62%) distilled[8] at 194-199°/0.03mm. OH: 11.7%; C:76.7; H:12.0% - Found OH: 12.0%; C:76.5; H:12.0% - Calculated

SUMMARY

I. The synthesis of three dimers from monomolecular propylphenol units related to lignin progenitors has been carried out. These are:

(a) 2,2'-Divanilloyl Diethyl Ether
(b) 1-Veratryl-2-(3-methoxy-4-propiophenoxy)-1-propanone
(c) 1,4-Diveratryl-2,3-dimethyl-1,4-butanedione

II. Ethanolysis of the dimers did not yield the customary monomolecular fission products, obtained in the ethanolysis of wood, indicating that the synthetic dimers are not identical with those forming the readily hydrolyzable portion of native lignin.

III. Hydrogenation and hydrogenolysis of the three dimers showed that any carbonyl groups present in the side chains of the propylphenol units in native lignin would readily undergo reduction to methylene groups followed by fission of the ether-oxygen union. With a carbon-to-carbon linked dimer fission would not occur under the same conditions, even at relatively high temperatures.

BIBLIOGRAPHY

1. Klason, Svensk. Kem. Tid., 9, 133 (1897)
2. Heuser and Winsvold, Ber., 56, 902 (1923)
3. Czapek, Biochemie der Pflanzen (G. Fischer, Jena, 1921) Vol. 3, p. 464
4. Klason, Ber., 69, 676 (1936)
5. Klason, Cellulosechem., 4, 81 (1923)
6. Willstätter and Zechmeister, Ber., 46, 2401 (1913)
7. Urban, Cellulosechem., 7, 73 (1926)
8. Hilpert and Hellwage, Ber., 68, 380 (1934)
9. Hibbert, Paper Trade J., 113, No. 4, 35 (1941)
10. Freudenberg, Tannin, Cellulose, Lignin (Springer, Berlin, 1933)
11. Freudenberg, Janson, Knopf and Haag, Ber., 69, 1415 (1936)
12. Freudenberg, Meister and Flickinger, Ber., 70, 500 (1937)
13. Freudenberg, Klink, Flickinger and Sobek, Ber., 72, 217 (1939)
14. Freudenberg, Ann. Rev. Biochem., 8, 88 (1939)
15. Erdtman, Ann., 503, 283 (1933)
16. Tomlinson and Hibbert, J. Am. Chem. Soc., 58, 345 (1936)
17. Buckland, Tomlinson and Hibbert, J. Am. Chem. Soc., 59, 597 (1937)
18. Leger and Hibbert, Can. J. Research, 16, 68 (1938)

19. Bell, Hawkins, Wright and Hibbert, J. Am. Chem. Soc., 59, 598 (1937)

20. Leger and Hibbert, J. Am. Chem. Soc., 60, 565 (1938)

21. Tomlinson, Ph.D. Thesis, McGill University, Montreal (1935)

22. Creighton, McCarthy and Hibbert, J. Am. Chem. Soc., 63, 312 (1941)

23. Freudenberg, Lautsch and Engler, Ber., 73, 167 (1940)

24. Lautsch and Piazolo, Ber., 73, 317 (1940)

25. Godard, McCarthy and Hibbert, J. Am. Chem. Soc., 63, 3061 (1941)

26. Bower, Ph.D.Thesis, McGill University, Montreal (1943)

27. Cooke, McCarthy and Hibbert, J. Am. Chem. Soc., 63, 3056 (1941)

28. Harris, D'Ianni and Adkins, J. Am. Chem. Soc., 60, 1467 (1938)

29. Harris and Adkins, Paper Trade J., 107, No. 20, 38 (1938)

30. McGregor, Ph.D. Thesis, McGill University, Montreal (1943)

31. Cramer, Hunter and Hibbert, J. Am. Chem. Soc., 61, 509 (1939)

32. Pyle, Brickman and Hibbert, J. Am. Chem. Soc., 61, 2198 (1939)

33. Same as 31

34. Hunter, Cramer and Hibbert, J. Am. Chem. Soc., 61, 516 (1939)

35. Brickman, Hawkins and Hibbert, J. Am. Chem. Soc., 62, 2149 (1940)

36. Kulka, Hawkins and Hibbert, J. Am. Chem. Soc., 63, 2371 (1941)

37. Kulka, Ph.D. Thesis, McGill University, Montreal, (1942)

38. West E., Ph.D. Thesis, McGill University, Montreal (1942)

39. Hall, Chem. Rev., 20, 305 (1937)

40. Robinson, "The Molecular Architecture of Some Plant Products", International Congress of Pure and Applied Chemistry, Bermejo, Madrid (1934)

41. Hibbert, Address to Cell. Division, Am. Chem. Soc., Chapel Hill, N.C. (1937)

42. Kobel and Scheuer, Biochem. Z., 216, 216 (1929)

43. Oppenheimer and Stern, "Biological Oxidation", Nordemann, New York (1939)

44. Hibbert, Address to Cell. Division, Am. Chem. Soc., Cincinnati, Ohio (1940)

45. Bradley and Eaton, J. C. S., 1913 (1937)

46. Szent-Györgyi and Co-workers, Z. Physiol. Chem., 254, 147 (1938)

47. Banga and Szent-Györgyi, ibid., 255, 57 (1938); ibid., 258, 147 (1939)

48. Idem., J. Biol. Chem., 90, 385 (1931)

49. Szent-Györgyi, Ber., 72, 53 (1939)

50. Krebs, Lancet, 233, 736 (1937)
51. Hibbert, Biochem. Rev. XI, 183 (1942)
52. Oxford and Raistrick, Biochem. J., 27, 634, 1473 (1933)
53. Bistrzycki and Kostanecki St. v., Ber., 18, 1985 (1885)
54. Will, Ber., 18, 1311 (1885)
55. Brunner, Ann., 351, 313 (1907)
56. Erdtman, Svensk. Papperstidn., 44, 243 (1941) translation Pulp and Paper Magazine of Canada, Feb. 1942
57. Haworth, Nature, 147, 255 (1941)
58. Cousin and Herissey, Compt. rend., 146, 1413 (1907)
59. Schroeter and Co-workers, Ber., 51, 1587 (1918)
60. Haworth, J. C. S., 448 (1942)
61. Easterfield and Bee, J. C. S., 97, 1028 (1910)
62. Shinoda and Kawagoe, J. Pharm. Soc. Japan, 49, 565, 1165 (1929)
63. Yoshiki and Ishiguro, ibid., 53, 11 (1933)
64. Mameli, Gazzetta, 37, II, 483 (1907)
65. Tollens and Lindsay, Ann., 267, 353 (1892)
66. Kawamura, Bull. Imp. Forestry Exp. Stat. Tokyo, 31, 73 (1932)
67. Emde and Schartner, Naturwiss., 22, 743 (1934)
68. Haworth, Richardson and Sheldrick, J. C. S., 1576 (1935)
69. Borsche, Ann., 494, 126 (1932)
70. Späth, Ber., 65, 1526 (1932)

71. Korner and Carnelutti, Rend. R. Ist. Lomb. Sci., 15, II, 654 (1882)

72. Briggs and Freiberg, J. C. S., 271 (1937)

73. Vanzetti, Monatsh., 52, 163 (1929)

74. Price, Chem. Rev., 29, 37 (1941)

75. Erdtman, Ann., 516, 162 (1935)

76. Haworth and Richardson, J. C. S., 633 (1935)

77. Holmberg, Ann. Acad. Sci. Fennicae, 29, No. 6, (1927)

78. Erdtman, Ann., 513, 229 (1934)

79. Haworth and Sheldrick, J. C. S., 636 (1935)

80. Späth, Ber., 65, 1536 (1932)

81. Haworth and Kelly, J. C. S., 1645 (1937)

82. Erdtman, Biochem. Z., 258, 192 (1933)

83. Erdtman, Ann., 503, 283 (1933)

84. Freudenberg and Klink, Ber., 73, 1369 (1940)

85. Creighton, McCarthy and Hibbert, J. Am. Chem. Soc., 63, 3049 (1941)

86. Michael A., Am. Chem. J., 5, 349 (1883)

87. Baekeland, J. Ind. Eng. Chem., 1, 149, 158 (1909)

88. Kruber, Oel U. Kohlver Petroleum, 35, 770 (1939)

89. Wacek, Eppinger and Bezard, Ber., 72, 52 (1940)

90. Schmidt, "Textbook of Organic Chemistry", English Trans., Gurney and Jackson, London (1932)

91. Wacek and Nitter, Cellulosechem., 18, 29 (1940)

92. Horner and White, Sci. Agr., 23, 85 (1941)

93. Spencer and Wright, J. Am. Chem. Soc., 63, 2017 (1941)

94. Glading, Paper Trade J., 11, No. 25, 32 (1940)

95. Brauns, Paper Trade J., 11, No. 14, 33 (1940)

96. Meisenheimer and Link, Ann., 479, 211 (1930)

97. Mark and Raff, "High Polymeric Reactions", Interscience Publishers Inc., New York (1941)

98. Staudinger and Steinhofer, Ann., 517, 35 (1935)

99. Midgley, Henne and Leicester, J. Am. Chem. Soc., 58, 1961 (1936)

100. Fittig and Erdmann, Ann., 216, 179 (1883)

101. Stobbe and Posnjak, Ann., 371, 387 (1909)

102. Stoermer and Kootz, Ber., 61, 2330 (1928)

103. Shoruigin and Shoruigina, J. Gen. Chem. U.S.S.R., 5, 555 (1935)

104. Shoruigin and Shoruigina, ibid., 9, 845 (1939)

105. Staudinger, Frey, Garbsch and Wehrli, Ber., 62, 2916 (1929)

106. Hartmann and Gattermann, Ber., 25, 3531 (1892)

107. Fernholz and Finkelstein, J. Am. Chem. Soc., 60, 2402 (1938)

108. Org. Syntheses, Collective Vol. I, 131 (1941)

109. Hibbert, J. Am. Chem. Soc., 37, 1748 (1915)

110. Cramer, Ph.D. Thesis, McGill University, Montreal (1939)

111. Fries and Finck, Ber., 41, 4271 (1908)

112. Eijkman, Chem. Weekblad., 1, 453 (1904)

113. Heller, Ber., 42, 2736 (1909)

114. Heller, Ber., 45, 418 (1912)

115. Heller, Ber., 45, 2389 (1912)

116. Fries and Pfaffendorf, Ber., 43, 212 (1910)

117. Fries and Frellstedt, Ber., 54, 715 (1921)

118. Fries and Ehlers, Ber., 56, 1304 (1923)

119. Witt and Braun, Ber., 47, 3216 (1914)

120. Auwers and Mauss, Ann., 464, 293 (1928)

121. Skraup and Poller, Ber., 57, 2033 (1924)

122. Auwers and Mauss, Ber., 61, 416 (1928)

123. Auwers and Mauss, Ber., 61, 1495 (1928)

124. Rosenmund and Schnurr, Ann., 460, 56 (1928)

125. Cox, J. Am. Chem. Soc., 52, 352 (1930)

126. Blicke and Weinkauff, J. Am. Chem. Soc., 54, 330 (1932)

127. Hey and Jackson, J. C. S., 802 (1936)

128. Fieser and Bradsher, J. Am. Chem. Soc., 58, 2337 (1937)

129. Smith and Bryant, J. Am. Chem. Soc., 57, 61 (1935)