"STUDIES ON LIGNIN PROGENITORS"

BY

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SUMMARY

(1) A number of new compounds have been synthesized. They include, among others, eugenol acetate oxide and its chlorhydrin; 1-hydroxy-1-(3,4 dimethoxyphenyl)-propanone-2; 1-(3,4 dimethoxyphenyl)-propanedione-1,2, and probably 3-chlor-1-(4-acetoxy-3 methoxyphenyl)-propanone-2.

(2) Several interesting intramolecular rearrangements of aromatic halogenated and hydroxylated ketones of the types, $R\text{-}CH_2\text{-}CO\text{-}CH_2Cl$, $R\text{-}CHOH\text{-}CO\text{-}CH_3$ and $R\text{-}CHBr\text{-}CO\text{-}CH_3$ (where R = 3,4 dimethoxyphenyl) have been demonstrated and their bearing on the structure of lignin pointed out.

CLAIM TO ORIGINAL RESEARCH

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I N D E X

Introduction

The study of lignin has been a subject of interest to the chemist for many years because of its obvious scientific value, both chemical and biological and because of its important practical aspects. In the processes by which millions of tons of wood pulp are produced annually throughout the world, the lignin is extracted from the wood and in most cases is discarded. Since this lignin forms 28% of the dry weight of the wood, it represents an enormous loss of a potential raw material, a loss which cannot be prevented without a thorough knowledge of the structure and properties of the lignin molecule. It is therefore not surprising to find that a great deal of intensive investigation has been given to this problem since its study was initiated by Klason in 1892. More surprising, unless the peculiar difficulties of the problem are understood, is the fact that, until recently, no really significant progress has been made.

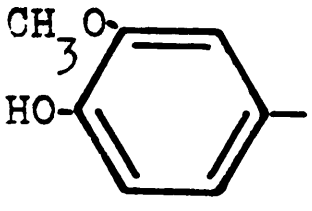
A factor perhaps, in this slow advance, is the difficulty in chemically defining lignin as a constituent of plant materials. The "Klason lignin" determination, which is usually taken as a standard, records as lignin, all that part of the wood which is not soluble in hot dilute sulphuric

acid following a four hour treatment with 72% sulphuric acid at 20°. It is well known however, that the amorphous material thus obtained contains resinified carbohydrates in the form of the carbohydrate humic acids (1) and hence is not a true measure of the lignin content.

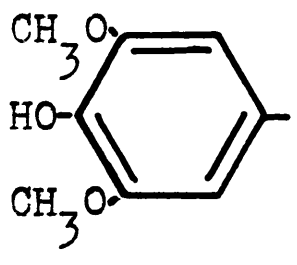
For many purposes lignin can be defined as "the methoxyl containing portion of plant tissues which have been previously extracted to remove fats, resins and tannins". This definition too has its weaknesses, since it cannot be stated definitely that all "lignin" is methoxyl-containing and since it has been shown that a part of the methoxyl content of tissues prepared in this way is attached to carbohydrate (2). However the method has proved of great value when used in conjunction with the less drastic (i.e. non-demethoxylating) methods of isolating lignins and it is a fact that if the chemist can identify all of the methoxylated material in plant tissues he will have gone far towards the final solution of the lignin problem. Unfortunately no direct comparison between methoxyl content and Klason lignin is possible because the treatment with 72% sulphuric acid causes some demethoxylation (2).

The methoxyl contents of solvent pre-extracted woods fall into two groups corresponding taxonomically to the hard and soft woods. The difference is due to the presence in hardwoods of both guaiacyl (I) and syringyl (II) nuclei, and in the soft-

woods, of the guaiacyl only. There appears however, to be a



I



II

more deep-seated difference than methoxyl content in the lignins from the two types of wood, a difference indicated by the consistently greater ease of its isolation from hardwood, as compared to softwood. The first effect of this difference on the development of lignin chemistry, was a retarding one, because it led to confusion, but in more recent work it has perhaps accelerated progress by shifting attention to the hardwoods.

The practical difficulties facing the lignin chemist are in many ways characteristic of the study of plant materials. The lignin material must first be removed from the tissues in an unchanged form, or failing this, in a form such that any changes can be evaluated. However, it is extremely difficult to obtain accurate information on the structure of such materials as they exist in the plant cells and the worker must simply use the mildest available methods of extraction. With many plant products satisfactory results can be obtained by simple solvent extraction, but in the case of lignin, relatively strong chemical action is required before extraction is possible, a fact often taken to indicate a chemical combination between lignin and some

other cell constituent, usually a carbohydrate. As yet no satisfactory method has been developed for the isolation of lignin unchanged from the plant tissue.

The lack of satisfactory extraction methods has been the greatest single retarding factor in the development of lignin chemistry. Similar to proteins, starches and cellulose, lignin is a polymeric substance, but differs from these better known materials in that its building units (monomers), are exceptionally sensitive to the action of relatively mild chemical reagents. Hence in the isolation of lignin from the cell wall, polymerization-condensation reactions of simpler units can occur and at the same time degradation of the polymer followed by degradation or repolymerization of the monomers (3). Since repolymerization need not lead to substances identical with the natural lignin, these products, from a structural standpoint, have but limited experimental value. It is perhaps unfortunate that nature has not supplied, in the form of enzymes, specific hydrolytic agents for lignin as she has for proteins and carbohydrates. True, some living forms are known to decompose lignin but they are not readily adaptable to laboratory requirements.

With this brief summary of a few of the difficulties which face the lignin chemist, it is easy to understand the development of lignin chemistry along three main lines - (a) isolation and study of amorphous lignin preparations; (b) study of degradation products of the lignin polymers and (c) an

effort to relate the reactions of lignin to reactions of well-known organic compounds. The second of these points may be subdivided arbitrarily into two parts (i) the determination of the aromatic nature of lignin and (ii) determination of the lignin building unit. It is with the second of these two subdivisions that this thesis is chiefly concerned.

Before proceeding with a historical review of the development of lignin chemistry it should be mentioned that the slow accumulation of accurate experimental data has permitted a great deal of speculation regarding the structure of the lignin molecule. As a result many theories have been put forward to explain the origin and reactions of lignin and these theories have undergone radical changes or have disappeared altogether as further experimentation made them untenable. At the present time only two or three basically similar views of lignin structure exist and it will be necessary to devote a part of the historical review to them.

Historical Review

Isolation and Study of Amorphous Lignins

The isolation of lignin from wood in a form suitable for study is one of the most important and difficult problems in lignin chemistry. It has received a great deal of attention, particularly from the earlier workers and many methods have been developed for the purpose. Naturally many of the preparations obtained, have in the course of time proved to be of little

value, but others have been found to be of greater value as our knowledge of lignin chemistry has increased. The properties of these isolated lignins vary considerably according to the method of isolation employed. To distinguish them they are usually described according to the reagent used in their isolation but sometimes by the name of the worker who developed them (e.g. "Klason lignin"). They must never be confused with natural lignin, or as it is often called, "protolignin", which is lignin as it exists in plant tissues. For reasons already made clear, the taxonomical source of the lignin must also be stated before a clear definition can be given.

All methods for the extraction of lignin from plant materials depend upon the use, as an extracting medium, of either an acidic or alkaline reagent. The necessity for such a reagent is usually taken to mean that hydrolytic action is required to break some type of bond between lignin and other cell constituents. It is of course conceivable that the lignin polymer is mechanically so distributed throughout the cell-wall that it can be removed only by degradation but there seems to be little evidence for this view. However, the discussion of this point is a subject in itself and the reader, if interested, may refer to the work of Hibbert, Bailey and others (4) for further information.

In two or three cases methods of isolation have been reported which apparently use no hydrolytic agents. The first

of these was the use by Klason (5) of ethanol and water or of ethanol and very dilute acetic acid as described on page 9. More recently, Brauns (6) has claimed to have isolated a simple lignin preparation, his so-called "native lignin" by simple methanol extraction. However since the product represents only 2 - 3% of the Klason lignin, it cannot be said to possess great significance.

A number of organic solvents were examined by Aronovsky and Gortner (4c) for their ability to extract lignin from wood under 10 atmospheres pressure and high temperatures. They found aqueous butanol (1:1) to be particularly effective under these conditions. Bailey (4b) extended this work in his studies on pulping with butanol-water and butanol-water-alkali mixtures, and after comparative studies of lignin removal from aspen and jackpine woods, concluded that a portion of the lignin in soft-woods, but not in hardwoods, is chemically bound to cellulose. However, no satisfactory control of pH is possible under such conditions of temperature (185°) and pressure and the possibility of hydrolytic action cannot be eliminated.

In a few instances lignin preparations have been obtained by dissolving away the other cell constituents. Typical are "Klason lignin" obtained by treating wood at 20°C. with 72% sulphuric acid and "Willstätter lignin" obtained similarly by use of 42% hydrochloric acid at 0°C. Although still employed to some extent, these methods do not meet with much favor

as they are altogether too drastic for use with so sensitive a material as "natural lignin". Furthermore, strong acids are known to resinify carbohydrate materials and these resins remain incorporated with the lignin. Indeed, it was this fact that led Hilpert (7) to believe that isolated lignins are actually derived from cell carbohydrates, a point of view since shown to be quite untenable.

A better mode of lignin isolation, using the same principle of solvation of the non-lignin constituents of the plant tissues, is the "cuproxam lignin" extraction procedure developed by Freudenberg (8). It consists in extracting the wood alternately with copper-ammonium hydroxide and hot aqueous sulphuric acid (1%). The method is relatively mild and the amount of polymerization-condensation products formed is much less than when stronger acids or alkalis are used.

The greater part of the laboratory methods for isolating lignins and all the commercial pulping processes are associated with the removal of the lignin from the cellulose. One of the first developments of this type was the well-known sulphite process brought out by Tilghman (9) in 1867 and now the basis of a huge industry because it causes little degradation of the cellulose. In this process the lignin is extracted by cooking the wood under pressure at 140°C. with an aqueous solution of calcium bisulphite and sulphur dioxide. The lignin goes into solution as the water soluble calcium salts of the so-called

"lignin sulphonic acids". Both the acids themselves and the reactions by which they are formed, are extremely complex and, although their study has received a great deal of attention, the results obtained thus far have not contributed greatly to our knowledge of lignin structure. From this point of view their chief interest arises from their degradation to aromatic materials by alkaline oxidation (see pg. 17).

Of commercial value but of little scientific importance are the methods employing aqueous alkalis to extract the lignin. The soda process for the preparation of wood pulp requires 7 - 10% aqueous sodium hydroxide at 170° to remove the lignin. The extraction probably depends upon the release of phenolic hydroxyls which, by interaction with the alkali, result in a solubilisation of the lignin.

The most recent advance in lignin extraction has been the development of methods in which the addition of, or condensation with, the extractant and lignin takes place. The most important of these methods are alcoholysis and hydrogenolysis, but extractions have also been carried out in acylating, (particularly acetylating) media. The alcoholysis reactions have been developed from the observation of Klason (10) in 1893 that a part of the lignin is dissolved when spruce wood is cooked with methanol-hydrogen chloride. Many alcohols, glycols and similar reagents have since been tried, but the most important results have been obtained by Hibbert and co-workers using an-

hydrous ethanol-hydrogen chloride. Their results will require further discussion later but a brief resume is possible here.

These workers have found that refluxing wood meal (previously extracted to remove fats, resins and tannins) for 48 hours with anhydrous ethanol containing 2% hydrogen chloride will remove about 40 - 60% of the Klason lignin. Of the extracted lignin, about half is the typical brown amorphous type of lignin preparation, but the remainder is obtained in the form of low boiling, water-soluble oils, the so-called "ethanolysis oils". From these oils a number of monomeric compounds have been isolated and identified, and since these compounds are of exceptional importance in connection with the nature of the lignin building unit, their discussion will be reserved for a later section.

From the many other alcoholysis studies, the work of Holmberg and others using thioglycolic acid (11) as extraction medium may be mentioned. This reagent seems to behave in a somewhat similar manner to bisulphite, but as yet no very significant results have been obtained with it. Most important are the experiments in which thioglycolic acid was allowed to react with known organic compounds in an effort to relate their structure to lignin (see pg. 28).

The use of high pressure hydrogenation as a means of removing lignin from wood is a new and important development. The first reports on the method came from the laboratory of Prof. Adkins in 1938 (12). With his student and co-worker,

D'Ianni, and Harris, he studied the hydrogenation of aspen methanol lignin. Hibbert and co-workers shortly thereafter extended the method to wood meal and succeeded in obtaining complete liquefaction of the wood (13). Much experimental work has since been done by both groups (14, 15), but unfortunately the later results of Harris and co-workers have been found somewhat unreliable. Freudenberg and Adam (16) have recently developed a technique for the simultaneous dry distillation and catalytic hydrogenation of isolated lignins on which various metallic catalysts were precipitated. Little data has yet appeared however, regarding the nature of the products. Freudenberg (17), following earlier work by Bobrov and Kolotova (18) has also applied hydrogenation to lignin sulphonic acids but has obtained no important information.

Just as with ethanolysis the application of hydrogenolysis is important chiefly because of the relatively high yields of low molecular weight lignin derivatives so obtainable. These derivatives will be discussed in connection with the nature of the lignin building unit.

The brown, amorphous lignin preparations obtained by various methods of extraction, have been widely studied in an effort to characterize them and to relate them to natural lignin. In the absence of satisfactory criteria of purity and homogenity, however, little progress could be made and the structure of these isolated lignins is still completely unknown.

In spite of many attempts to determine the molecular weights of these materials, no satisfactory results have ever been obtained. Perhaps the most careful studies are those of Loughborough and Stamm (19) in which lignins from various sources were purified as far as possible and their molecular weights determined by a variety of methods. A fairly uniform value of about 3900 was found. Other workers however, report values ranging from 250 - 10,000 and it is probable that, depending upon the source and upon the method of isolation, wide deviation occurs.

Analyses of the isolated lignins show them to have fairly uniform carbon and hydrogen content. A number of alkali lignins from various sources were analysed by Powell and Whittaker (20) and found to have carbon and hydrogen contents of 63.2 - 64.0% and 5.2 - 5.8% respectively, values which may be taken as fairly representative of lignins. The remaining percentage is represented by oxygen. The methoxyl content, as mentioned earlier, varies considerably between hardwoods and softwoods but 21 - 22% and 15% respectively are fairly representative figures.

The nature of the individual groups present in these isolated lignins is still very obscure despite intensive study. The presence of a number of free hydroxyl groups in many of these preparations was quickly established, and a number of investigations, involving acylation and methylation, were undertaken in an attempt to characterize them as phenolic, enolic,

primary, secondary or tertiary. In reviewing these investigations, Erdtmann (21) states that it has been shown that 11% of spruce lignin is represented by hydroxyl groups distributed as follows: 6 - 7% secondary, about 2% tertiary and about 2% phenolic. Such conclusions however, seem questionable because no completely satisfactory differentiation between types of hydroxyl groups is possible by these methods, even with pure organic compounds.

A number of workers, notably Brauns (6) claim to have demonstrated the presence of aldehyde or ketone carbonyl groups in lignins, but no adequate proof has ever been obtained. No carboxyl groups are present. Erdtmann states (21) that all non-hydroxylic oxygen is obviously ether linked, a conclusion probably justified.

On the basis of these analytical results a number of empirical formulae were proposed for lignin. In view of the amorphous nature of the material however, these formulae mean little and are of interest only in that they express an approximate relationship between groups. Typical is that of Brauns and Hibbert (22) for spruce lignin viz. $C_{42}H_{32}O_6(OCH_3)_5(OH)_5$ Hibbert soon rejected this view (23), but recently Brauns (6) assigned the formula, $C_{42}H_{31}O_6(OCH_3)_7(OH)_3$ to his "native lignin".

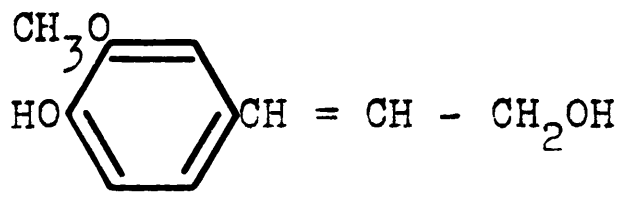
Of some interest are the results obtained on oxidizing lignins with chromic acid. In model substances all methyl groups bound to carbon appear as acetic acid and Erdtmann, in his review,

claims (21) that application of this method to extracted lignin has shown the presence of 2.7% of such methyl groups. He finds significance in the fact that this value agrees closely with the tertiary hydroxyl content and believes it indicates the presence of a = C(OH) - CH_3 grouping in lignin. However, application of this method by McGregor and Hibbert (25) to spruce and maple woods has proven that natural lignin contains no terminal methyl groups in the three-carbon side chain attached to the aromatic nucleus from which lignin is derived.

No mention will be made here of the many sulphonation, chlorination and nitration studies which have been reported because they have contributed little to our knowledge of lignin structure.

The Aromatic Character of Lignin

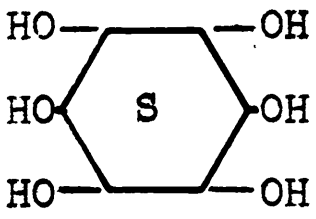
Since 1897 when Klason (26) first suggested that lignin was derived from coniferyl alcohol (III) and hence was an aromatic



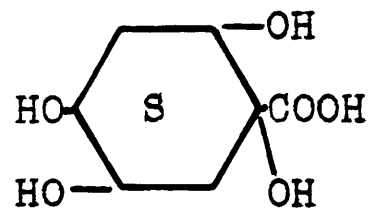
III

substance, chemists have sought to determine the extent to which aromatic nuclei occur in lignin. Through the intervening years steadily increasing amounts of syringyl and guaiacyl derivatives have been isolated and at the present time it is generally

accepted by workers in the field that lignin is indeed an aromatic substance. An opposing view has been taken by Hilpert (7) who, as already mentioned, believes isolated lignins to be carbohydrate derivatives. In the following review however, the evidence for aromatic character will be presented and will show that Hilpert's view is untenable. The suggestion by Erdtmann (21) that isolated lignins might derive their aromatic nuclei through dehydration of hydroaromatic substances (e.g. inositol (IV) and quinic acid (V)) in the cells does not seem very reasonable.



IV

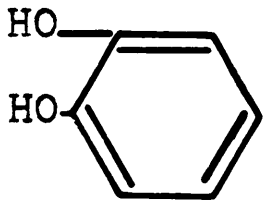


(S = saturated)

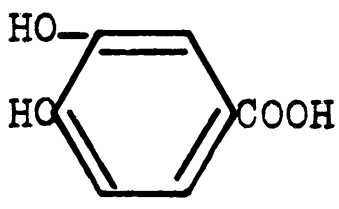
V

Odinzow (27) after comparative studies of the reactivities of woods, isolated lignins, and humic acids, concluded that lignin exists pre-formed in the wood. Herzog (28) in absorption spectrum studies, found that alkali lignins closely resembled coniferyl alcohol polymers.

The demonstration of the aromatic character of lignin has shown steady progress. In 1926, following earlier experiments by Heuser and Winsvold (29), Freudenberg and his coworkers (8, 30) showed that various spruce lignins on fusion with alkali, gave catechol (VI) and protocatechuic acid (VII) in yields of about 5% of the Klason lignin. Later by methylating

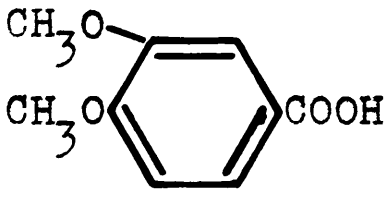


VI

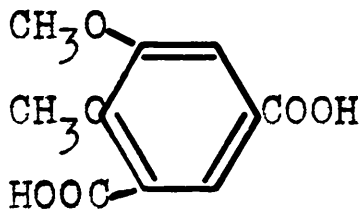


VII

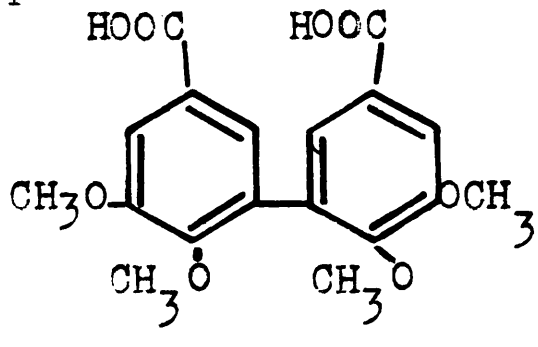
and oxidizing spruce "cuproxam lignin" he was able to isolate veratric (VIII), isohemipinic (IX) and dehydrodiveratric (X) acids in yields of 10 - 14%, 2 - 4% and 3% respectively (31). These compounds are interesting, and lend support to the de-



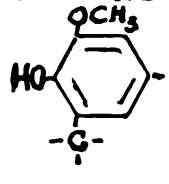
VIII



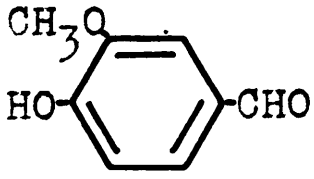
IX



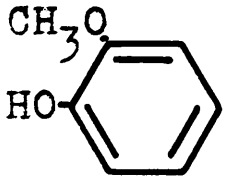
X

hydrodiisoeugenol theory (pg. 35) of lignin structure but the drastic conditions under which they are formed (70% KOH at 170°, followed by methylation and permanganate oxidation) detracts considerably from their significance, because of the possibility of secondary condensations. Freudenberg however believes them to be true lignin degradation products and from them has derived a theory of lignin structure in which the linkage  is postulated. Recently (32) he has revised this theory and now states that "half or more" of the units in spruce lignin are of this type.

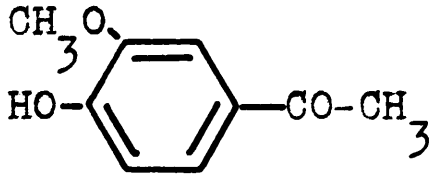
The guaiacyl group (I) was definitely established as a part of the lignin molecule by Hibbert and co-workers (33). Following earlier experiments by Grafe (34), Kürschner (35), Pauly and Fuerstein (36), and Hönig and Ruziczka (37), they subjected carefully purified spruce lignin sulphonic acids to alkaline oxidation. From the reaction mixture they were able to isolate vanillin (XI), in 6 - 7% yields, together with small amounts of guaiacol (XII) and acetovanillone (XIII). Maple lignin sulphonic acid on similar treatment, gave these three compounds together with the corresponding syringyl derivatives, syringaldehyde (XIV), pyrogallol-1:3-dimethyl ether (XV) and acetosyringone (XVI). This work served to demonstrate



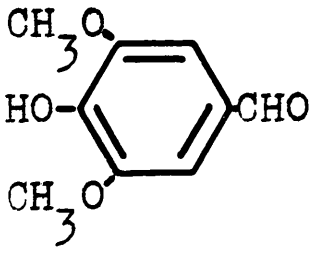
XI



XII



XIII



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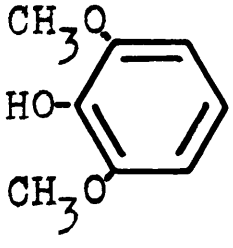

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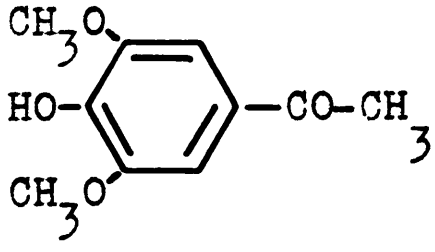


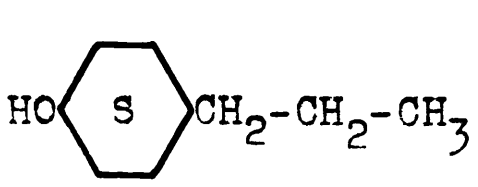
XVI

the essential difference in the "natural lignin" present in gymnosperms and angiosperms.

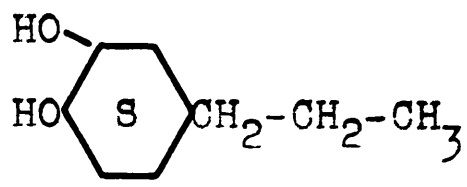
These experiments by Hibbert, Freudenberg and their co-workers, which were completed about 1937, showed that the guaiacyl and syringyl nuclei constituted at least 10 - 15% of the Klason lignin. At about the same time, these results were confirmed but not greatly extended by the ethanolysis studies of Hibbert and co-workers (38). More recently, however, the yield of ethanolysis oils from maple wood has been considerably increased with the isolation of a number of hitherto unknown products (39) (see pg.22). The most recent advances in the proof of the aromatic nature of lignin have resulted from the application of hydrogenation and of nitrobenzene oxidation methods to woods and lignins.

The hydrogenation of woods and lignins gives rise to propyl cyclohexane derivatives which are assumed to be derived from aromatic nuclei. Since the presence of aromatic substances in lignin has already been established and since the conditions of hydrogenation are such that any benzenoid types would be completely saturated, the assumption is quite justifiable.

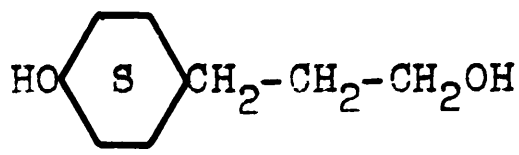
Harris, D'Ianni and Adkins (12) in 1938 hydrogenated methanol aspen lignin and obtained 4-n-propyl-cyclohexanol-1 (XVII), 4-n-propyl-cyclohexane diol-1,2 (XVIII), and 3-(4-hydroxy-cyclohexyl)propanol-1 (XIX). The yields reported by them in this paper, in which they neglect to evaluate the water formed in the reaction, require marked correction and the same remarks apply to their subsequent investigations (15).



XVII



XVIII



XIX

The combined yields reported by them (30-35%) have been shown in these laboratories to be considerably too high. Based on their assumed value, the cyclohexane nuclei when calculated as guaiacyl and syringyl groups indicated that 20 - 25% of the lignin was aromatic.

Following the initial experiments of these workers, Hibbert and co-workers (14) hydrogenated maple ethanol lignin under the same conditions. They identified the same products (XVII, XVIII, and XIX) but found that the yields were considerably lower (ca. 15%) a difference which they could not account for except by assuming a fundamental difference in maple and aspen lignin. They then successfully applied the hydrogenation technique to the isolation of lignin from wood (13). Complete conversion of the wood to dioxane-soluble products was effected and, after separation of the carbohydrate derivatives, the three cyclohexane derivatives were obtained in yields which on a carbon basis (allowing for loss of methoxyl) represented 36% of the Klason lignin. On calculation as syringyl and guaiacyl nuclei, these results raise the aromatic content of lignin to almost 30%.

Recently Harris and co-workers (15c,d) have claimed that 70% of the Klason lignin can be removed from the wood as identifiable hydroaromatic substances but, as neither the methods used nor the identity of the products has been disclosed, these claims do not call for serious consideration.

The recent development of a method for the oxidation of wood and lignins with alkaline nitrobenzene has extended still further the evidence for the aromatic character of lignin. This method, reported first by Freudenberg and co-workers (40), was found by them to give vanillin from spruce "cuproxam lignin" and from spruce woods in yields of 22% and 25% respectively. The results were confirmed by Hibbert and co-workers (41) who then applied the method to a wide range of plants. Their most startling results were obtained with maple, aspen and other dicotyledons which were shown to yield mixtures of vanillin and syringaldehyde in amounts varying from 37 to 45% of the Klason lignin. Monocotyledons (rye, corn and bamboo) gave only 20 - 30% and the ratio of vanillin to syringaldehyde was about 1:1 in contrast to the approximate ratio of 1 : 3 found in the dicotyledons.

From these experiments it is obvious that lignin is highly aromatic. The establishment of this point is of the utmost importance, especially in view of the marked significance it gives to the phenyl propane type of degradation product. The structural significance of these phenyl propane units is of

wider interest than that of syringaldehyde or vanillin, but the yields are much smaller. If however, it is assumed that these aldehydes arise from phenyl propane types, then they represent over 60% of the Klason lignin. That the assumption may not be unjustified will be seen from the following discussion of the nature of the lignin building unit.

The Nature of the Lignin Building Unit

All of the important experimental data concerning the nature of the lignin building unit have been obtained in the past four years and have been derived from ethanolysis and hydrogenolysis reactions of lignin. These two methods are, as yet, the only ones to give the C_6-C_3 (phenyl propane) type of lignin degradation product. As has been mentioned, the first aromatic nuclei with more than one carbon in the side chains were acetovanillone (XIII) and acetosyringone (XVI) discovered by Hibbert and co-workers in the alkaline oxidation products of lignin sulphonic acids (33). Since that time a number of degradation products, having three carbon side chains, have been isolated by them in yields which seem sufficient to warrant the belief that in their carbon skeleton these compounds are identical with lignin building units.

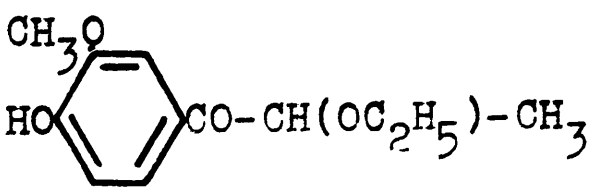
The first reported isolation of phenyl propane type lignin degradation products came from Klason (26) in 1892. By

extracting spruce wood alternately with ethanol and very dilute acetic acid, he was able to isolate two amorphous products which he claimed, on the basis of his analyses, to have the formulae $(C_{10}H_{12}O_3)_2$ and $(C_{10}H_{12}O_4)_2$. The first of these he regarded without proof as a dimer of coniferyl alcohol; to the other he assigned no structure but designated it as "oxy-coniferyl alcohol". It was not until 1938 when Hunter, Cramer and Hibbert (38a) published the results of the first ethanolysis studies, that further evidence was presented for the presence of propyl phenols in lignin, a rather remarkable fact in view of the almost general acceptance of such a unit in all theoretical considerations of lignin structure prior to this discovery.

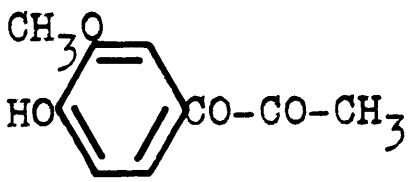
It has already been mentioned (pg. 10) that when lignin is extracted from the wood with 2% ethanolic hydrogen chloride, a part of the lignin is removed as low boiling, methoxyl-containing, "ethanolysis oils". In an extensive series of investigations Hibbert and co-workers have succeeded in separating and identifying a large part of these oils. The compounds identified so far, are: vanillin (XI;38c), 2-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-propanone-1 (XX;38a), 1-(4-hydroxy-3-methoxyphenyl)-propanedione-1,2 (XXI;38d) from spruce, and these as well as the corresponding syringyl derivatives, syringaldehyde (XIV;38c), 2-ethoxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-propanone-1 (XXII;38a), and 1-(4-hydroxy-3,5-dimethoxyphenyl)-propanedione-1,2 (XXIII;38d) from maple. From maple, 1-(4-hydroxy-3-methoxyphenyl)-propanone-2 (XXIV) and 1-(4-hydroxy-3,5-dimethoxyphenyl)-propanone-2 (XXV) were also obtained (39a); from spruce, 1-ethoxy-1-(4-hydroxy-3-

- methoxyphenyl)-propanone-2 (XXVI;39b) has very recently been isolated. It was also shown that re-ethanolysis of amorphous ethanol lignin resulted in its partial degradation to these monomeric units, an important finding since it shows that these monomers are indeed lignin degradation products. The ethoxyl groups found on some of the units are assumed to be derived from the extractant since no such groups have ever been observed in lignins isolated in the absence of ethanol.

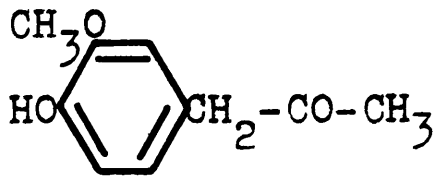
The significance of these products is obvious. They are the largest single units ever isolated from lignin and they can be definitely associated with lignin. Furthermore, it is well known that many derivatives of phenyl propane occur in nature (coniferyl (III) and syringyl (XXVII) alcohols, eugenol (XXVIII) safrol (XXIX), etc.). There is therefore good reason to believe



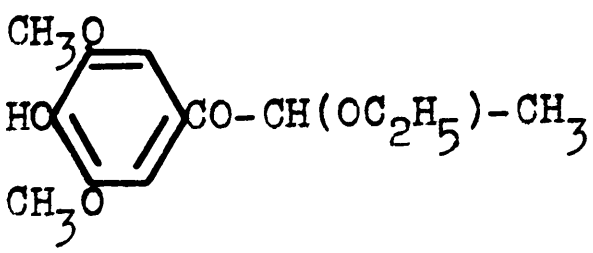
XX



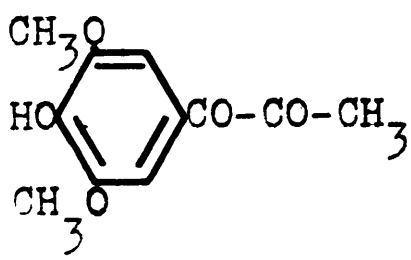
XXI



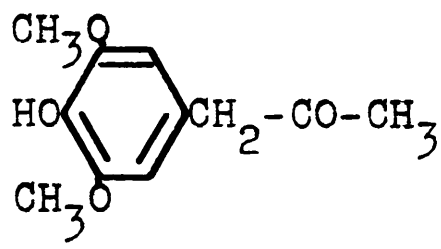
XXIV



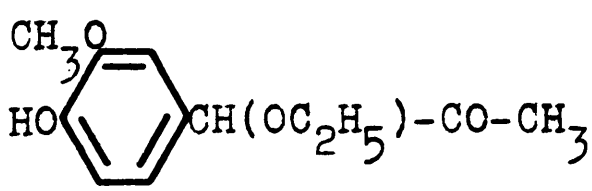
XXII



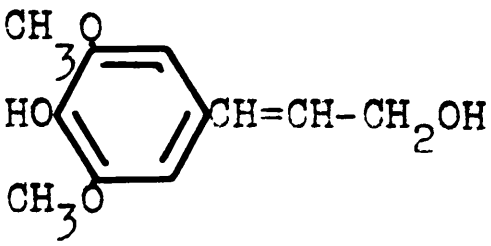
XXIII



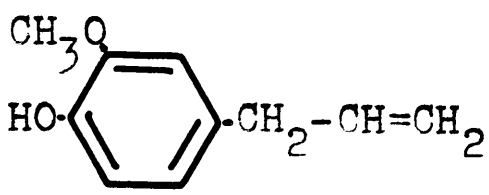
XXV



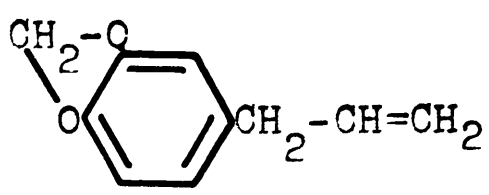
XXVI



XXVII



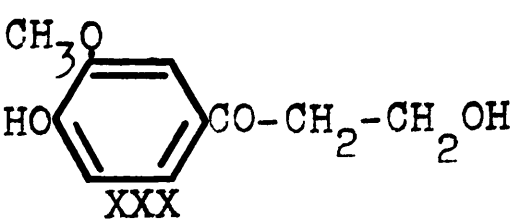
XXVIII



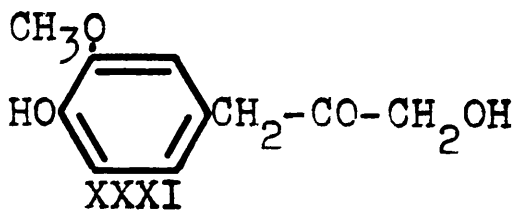
XXIX

that the ethanolysis products are indeed closely associated with the lignin building units.

However, in spite of the fact that a number of these products have oxygen atoms located on the α- and β- carbon atoms, it cannot be assumed that the grouping $R-\dot{C}(-O)-\dot{C}(-O)-CH_3$ actually occurs in lignin. It is well known that hydroxy-ketones are very susceptible to rearrangement, as for example in the well known Lobry de Bruyn transformations, and hence, as Erdtmann has pointed out (21), the ethanolysis products are not necessarily the true lignin building units, but may be stabilized forms of them. This possibility had already been recognized by Hibbert and to clarify the problem, the synthesis and characterization of the two compounds, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propanone-1 (XXX) and 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propanone-2 (XXXI) were undertaken in his laboratories.



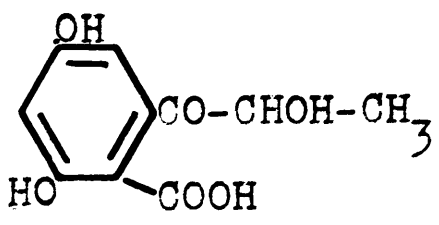
XXX



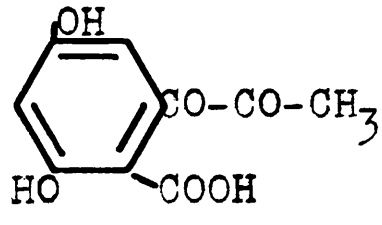
XXXI

The properties of the first of these (XXX) have already been reported (42). This compound was found to polymerize readily to lignin-like materials but showed no tendency to undergo intramolecular rearrangements. The attempted synthesis of the second of these compounds (XXXI), together with evidence to show that this compound can undoubtedly rearrange readily on treatment with ethanol-HCl to give the ethanolysis products XX and XXVI, will be presented in this thesis. In view of the importance of rearrangements of this type in any discussion of the problem, a review of the known rearrangements of hydroxyketones will be given following this historical review of the development of lignin chemistry.

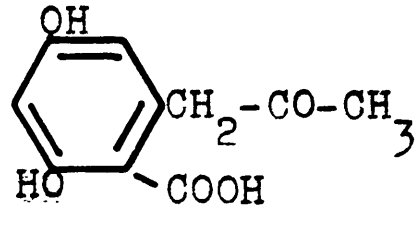
Of considerable interest in connection with these ethanolysis products are the researches of Oxford and Raistrick (43) on Penicillium brevi-compactum. This mold, when grown on an acid (pH 4-5) glucose medium produced the following products (XXXII, XXXIII, XXXIV), whose similarity to the ethanolysis



XXXII



XXXIII



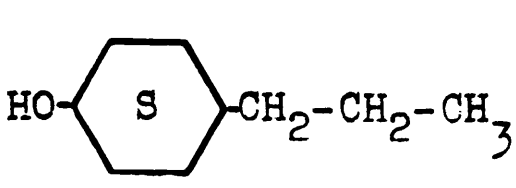
XXXIV

products is obvious. The fact that they are isolated by simple

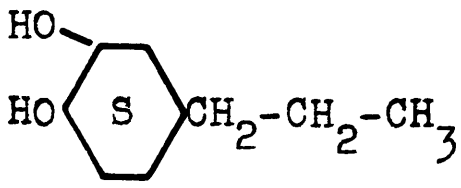
solvent extraction without the use of chemical reagents seems to eliminate any possibility of rearrangement subsequent to isolation.

Hibbert suggests (44) that these products may arise from a phloroglucinol intermediate by a process of plant synthesis such as that which he has put forward to explain the formation of the corresponding guaiacyl derivatives (see pg.37). He points out that the introduction of a carboxyl group is not surprising since resorcinol and phloroglucinol are carboxylated by warming at 70° - 100° with aqueous bicarbonate (45). Carboxylation can even be obtained at room temperature by passing CO_2 into an aqueous solution of phloroglucinol and sodium bicarbonate (46) and Hällström (47) found that by using this same technique at 50°, he obtained an equilibrium mixture of phloroglucinol and phloroglucinol carboxylic acid regardless of which of the two compounds he started with. The fundamental importance of this latter reaction in plant synthesis is emphasized by Ruben (48) in his very recent paper on "Plant Photosynthesis and Phosphorylation".

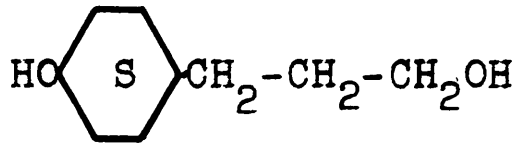
The ethanolysis evidence for the phenyl propane type of lignin building unit has been confirmed by hydrogenolysis studies which have resulted in the isolation of a number of propyl cyclohexane derivatives, viz:



XVII



XVIII



XIX

On a carbon basis, after allowing for loss of methoxyl, these compounds represent 36% of the Klason lignin, a very substantial fraction. The presence of a primary hydroxyl group on one of these compounds (XIX) is of particular importance in view of the already mentioned possibility of rearrangements during ethanolysis. The possibility of such rearrangements during hydrogenation is considerably smaller since all carbonyl groups would be reduced as soon as formed.

The above products are obtained both from lignins and from wood itself. Hibbert and co-workers (14) have compared the effects of ethanolysis and hydrogenolysis on a series of ethanol lignins. As already discussed, ethanolysis of wood yields both ethanolysis oils and amorphous ethanol lignins (38). Re-ethanolysis of the amorphous material gives a further small amount of the oils but the amounts decrease as ethanolysis is repeated apparently indicating a conversion of the amorphous material to a more stable product (49). Hydrogenation of these lignin preparations showed that the yields of C_6-C_3 units decreased as the number of ethanolyses

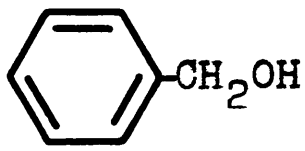
increased. In other words, the increased stability to ethanolysis is paralleled by increased stability to hydrogenation (14). These results are taken to indicate a conversion of ether linkages to carbon-carbon linkages during ethanolysis. It is taken as evidence for the presence of an irreversible polymerization together with a reversible degradation-polymerization reaction during the ethanolysis (see pg.43), a view confirmed by studies on the mechanism of the ethanolysis reaction (49).

Of the many studies which have been made in an effort to relate known organic compounds to groupings in the lignin molecule, only a few will be mentioned here and they only briefly. In general this approach has not contributed a great deal to our knowledge.

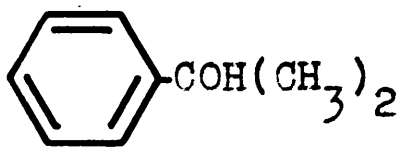
The reactions of wood and lignins with mercaptans, particularly thioglycolic acid, have been extensively investigated by Holmberg, Richtzenhain and others (11) and are of some interest in connection with the theories of lignin structure. Mercaptans, in the presence of acids, react with lignins in much the same way as do alcohols. If ethanol lignin is treated with thioglycolic acid, the ethoxyl groups are replaced by the $-S-CH_2-COOH$ radical (11b), and this in turn can take up more thioglycolic acid to give a lignin of high sulphur content. By treating wood with thio-

glycolic acid, Holmberg (11a) was able to obtain lignins of even higher thioglycolic acid content, a portion of which was ester linked.

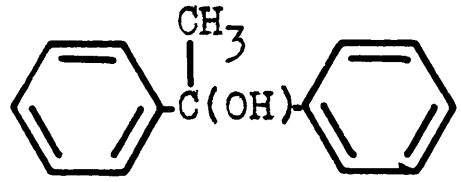
Phenyl substituted alcohols and ethers were examined by Holmberg (11a,b,c) and found to react in various ways. Addition, with or without ether cleavage, was found to occur with benzyl alcohol (XXXV), phenyl dimethyl carbinol (XXXVI), benzhydrol (XXXVII), diphenyl glycolic acid (XXXVIII), styrene (XXXIX), benzyl ethyl ether (XL), α-phenyl diethyl ether (XLI) and ethyl triphenyl-methyl ether (XLII). No addition occurred with 3-phenyl-propanol-1 (XLIII), phenyl glycolic acid (XLIV) and β-phenyl ethyl alcohol (XLV).



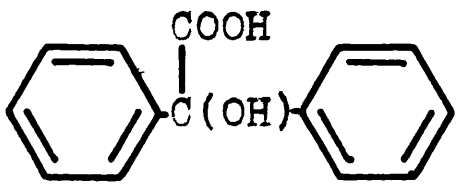
XXXV



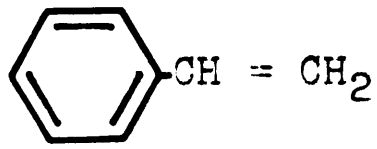
XXXVI



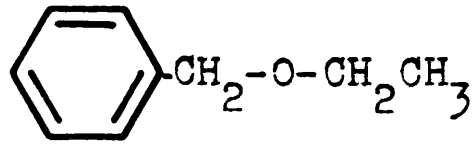
XXXVII



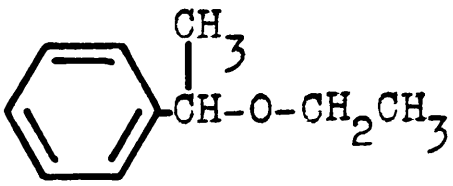
XXXVIII



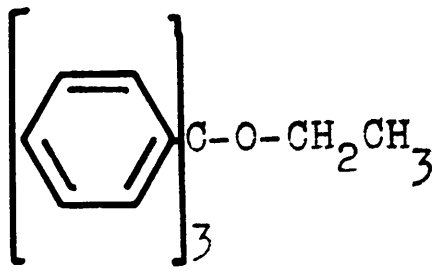
XXXIX



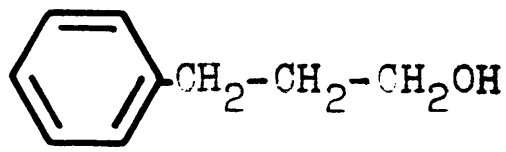
XL



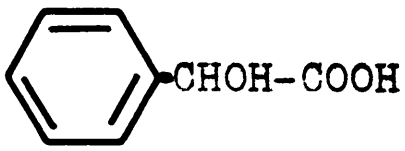
XLI



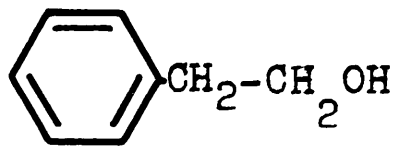
XLII



XLIII



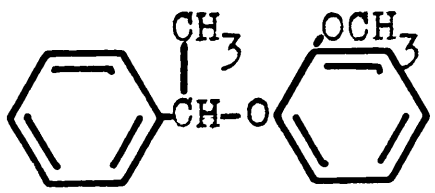
XLIV



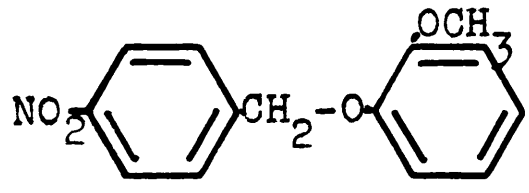
XLV

In related experiments, Hellström and Lauritzson(11g) found that while tertiary butyl alcohol reacts with thioglycolic acid, propyl, and normal and secondary butyl alcohols do not.

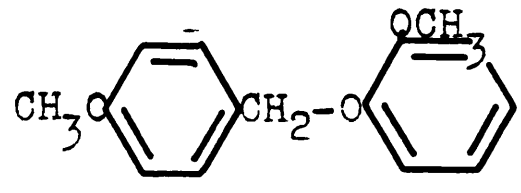
Richtzenhain (11f) studied the effect of thioglycolic acid on a series of guaiacyl ethers. In the presence of 2N HCl, thioglycolic acid was found to give 22% cleavage of α-methyl benzyl guaiacyl ether (XLVI) but no reaction with p-nitro-benzyl-(XLVII), and p-methoxy-benzyl-(XLVIII), guaiacyl ethers. He also studied (11f) a number of cyclic compounds



XLVI



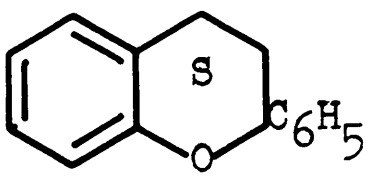
XLVII



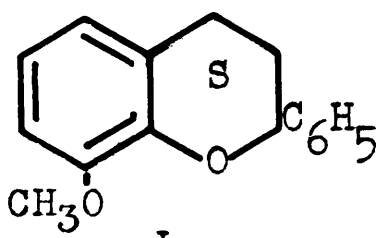
XLVIII

which presumably could be related to lignin. He found that flavan (XLIX), 9-methoxy-flavan (L), 2-methyl coumarane (LI), 2-methyl-3-phenyl-coumarane (LII) and 2-phenyl coumarone (LIII), did not react with thioglycolic acid, but that introduction

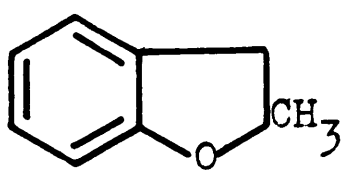
of a carbonyl group, as in flavone (LIV) brought about partial cleavage. In contrast however, Freudenberg (11d) claims to obtain cleavage in the absence of carbonyl activation (LV → LVI). There is however, considerable uncertainty attached to his results.



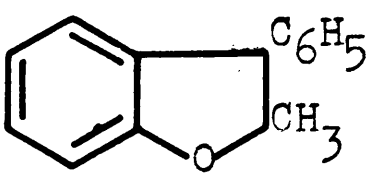
XLIX



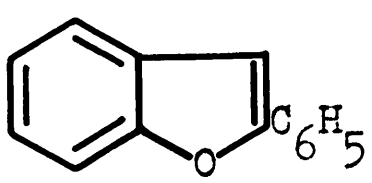
L



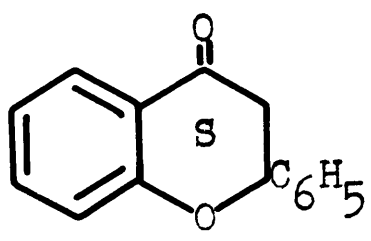
LI



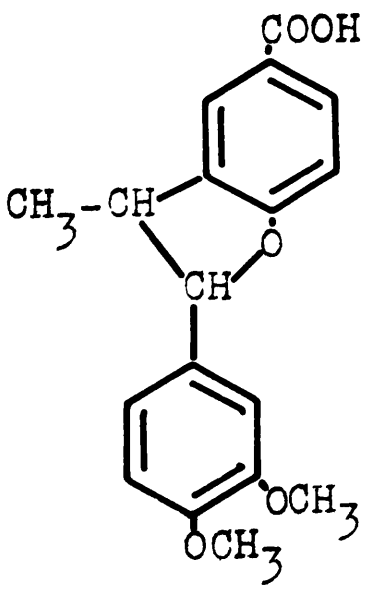
LII



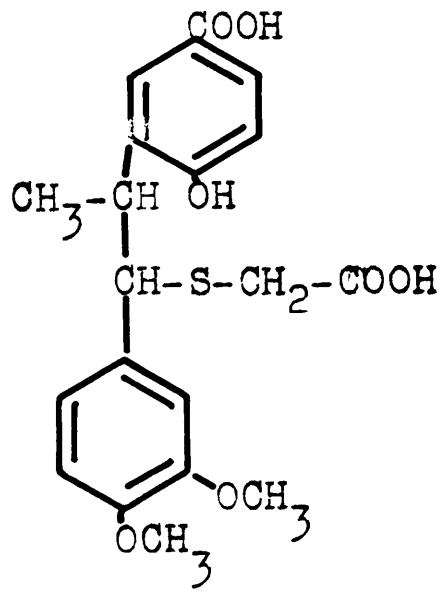
LIII



LIV



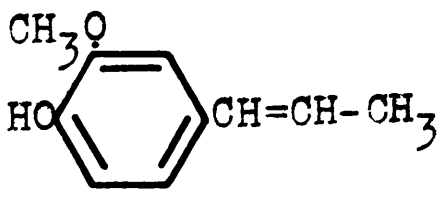
LV



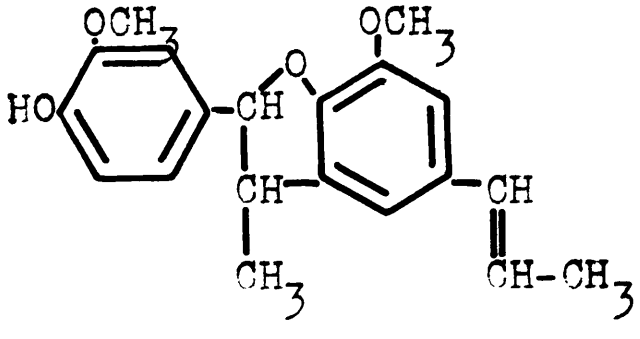
LVI

From these various studies, it would appear that reactivity towards thioglycolic acid is characteristic of benzyl and benzyl substituted alcohols, but not, except in the presence of carbonyls, of flavan and coumarane compounds. Most theories of lignin structure accept the first of these points, but not the second. However, far more information on the reaction of organic compounds with thioglycolic acid would be required before any reasonable conclusions could be drawn on the structure of lignin.

Among the other experiments on model substances one of the most interesting is the dimerization of isoeugenol. By enzymatic or ferric chloride dehydrogenation, isoeugenol (LVII) is converted to dehydrodiisoeugenol (LVIII). Erdtmann (21) believes that this type of condensation may have significance in the formation of lignin in the plant. He points out that whenever phenyl propane units condense in nature, the side chain, if involved in the reaction, always reacts through the central or β-carbon atom.



LVII



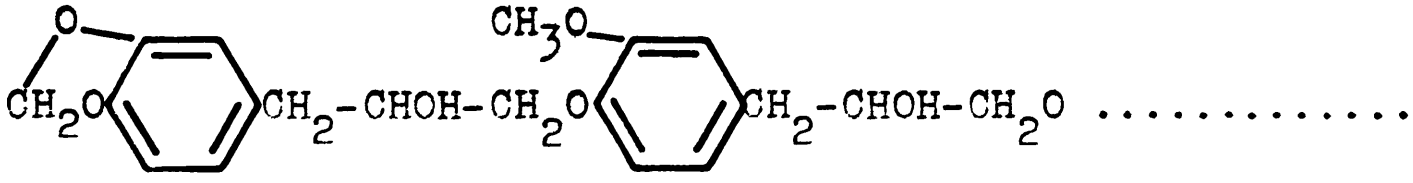
LVIII

With the foregoing brief review of the experimental results obtained in the investigation of lignin, some discussion of the various theories of lignin structure and origin is possible. It may be said that at the present time three views, those of Freudenberg, Erdtmann and Hibbert respectively, warrant consideration. All three postulate a propyl phenol type of lignin building unit with modifications in the mode of linkage of the three carbon side chain.. As has already been indicated, the theory of Hibbert is probably based on the best experimental evidence since, in contrast to other workers, he and his co-workers have been successful in actually isolating not only C_6-C but also C_6 C-C and C_6 C-C-C lignin degradation products. Freudenberg and his co-workers however, have done a great deal of excellent work and have many years of experience in the field so serious attention must be given to their views.

No discussion of the theories of lignin structure would be complete without reference to the work of Klason. This remarkable investigator, the pioneer of lignin chemistry, on the basis of a minimum of experimental evidence, drew some extraordinarily shrewd conclusions as to the nature of lignin. To quote Erdtmann (21), "As early as 1897, P. Klason emphasized that lignin, in all probability was related to coniferyl alcohol and therefore was an aromatic substance. During the

past decades, that timely speculation has been of considerable value and in many respects has appeared to be quite valid. Without exaggerating one can say that almost all investigators who have seriously considered the lignin problem, have been forced to follow similar lines of thought."

Freudenberg's theory of lignin structure has undergone considerable change over the past ten years. His earliest view postulated (50) a long chain, ether-linked polymer of the form -



LIX

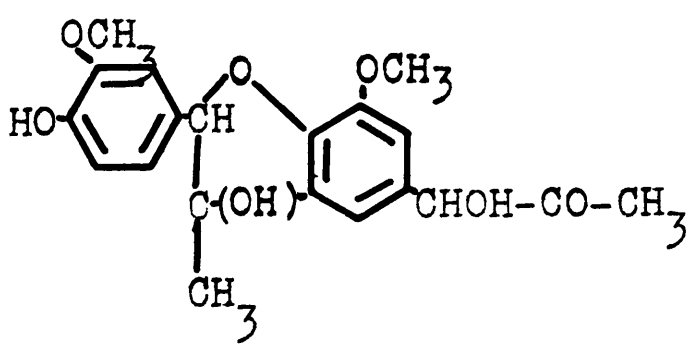
This structure was based on analyses of isolated lignins and on the presence of catechol, protocatechuic acid and formaldehyde in the degradation products of spruce-hydrochloric acid lignin. From these results he concluded that lignin was aromatic in type, had no free phenolic groups, contained aliphatic hydroxyl groups and had methoxyl groups attached to the aromatic nuclei. On the basis of these conclusions he assumed a phenyl propane type of unit (8,30).

This theory was open to a number of serious objections. A long chain polymer of this type should readily undergo

degradation to its monomeric units, a property not characteristic of lignin. Furthermore the structure does not lend itself to secondary transformations which might explain the stability (50).

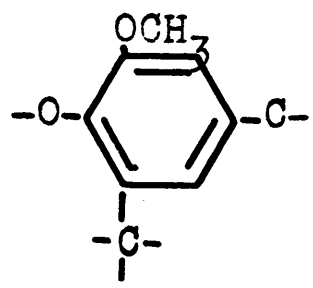
The presence of piperonylic nuclei is characteristic of all Freudenberg theories and is based on the presence of small amounts of formaldehyde (1 - 2%) in the lignin degradation products (52). Hibbert (51) has pointed out that formaldehyde is also a carbohydrate degradation product and could easily arise from impurities. A more serious objection, however, is that no piperonylic nuclei have ever been isolated from lignin. In this early theory the dioxymethylene groups were, of necessity, located terminally, but in later theories, in which the straight chain structure was abandoned, they were located throughout the polymer.

In 1933 Erdtmann suggested, consequent on his studies on dehydrodiisoeugenol, that lignin might consist of propyl phenol units polymerized in a similar manner. Freudenberg accepted this view (53) and postulated the structure



LX

As further evidence for this view he presented his experiments showing the formation of isohemipinic acid from "cuproxam lignin". The objections to this evidence have already been noted (pg.16). Recently however he has modified his views somewhat (54), and now believes that only somewhat over half of the nuclei in spruce lignin are of the type

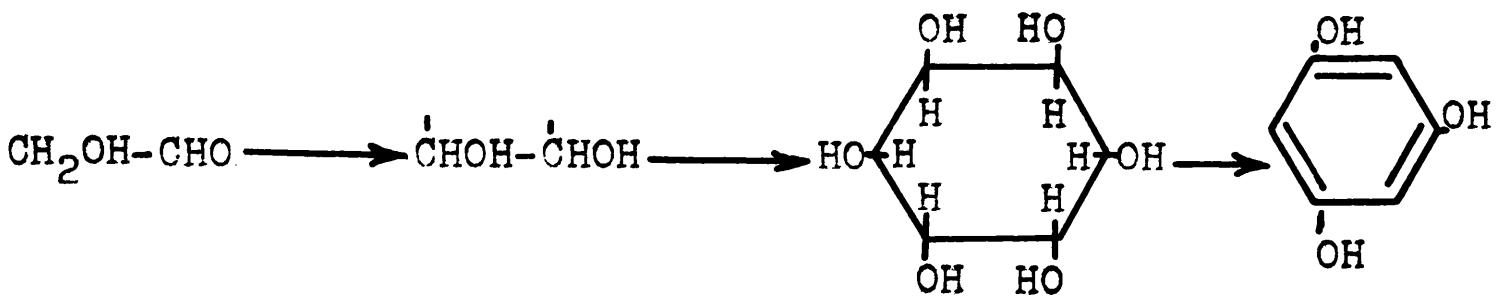


Opposed to this view of Erdtmann, Haworth believes (55) that the absence of free phenolic groups in lignin indicates a different type of linkage to that present in the majority of plant resins.

Hibbert's theory of lignin structure embraces both the biological synthesis and polymerization of the monomers. It is based primarily on the ethanolysis degradation products but is supported by evidence obtained from hydrogenolysis and hydrogenation studies on lignin and wood and from various researches on model substances.

In contrast to various theories (56) suggesting that the aromatic nuclei arise through rearrangement of hexoses, Hibbert (44) has put forward the idea that these

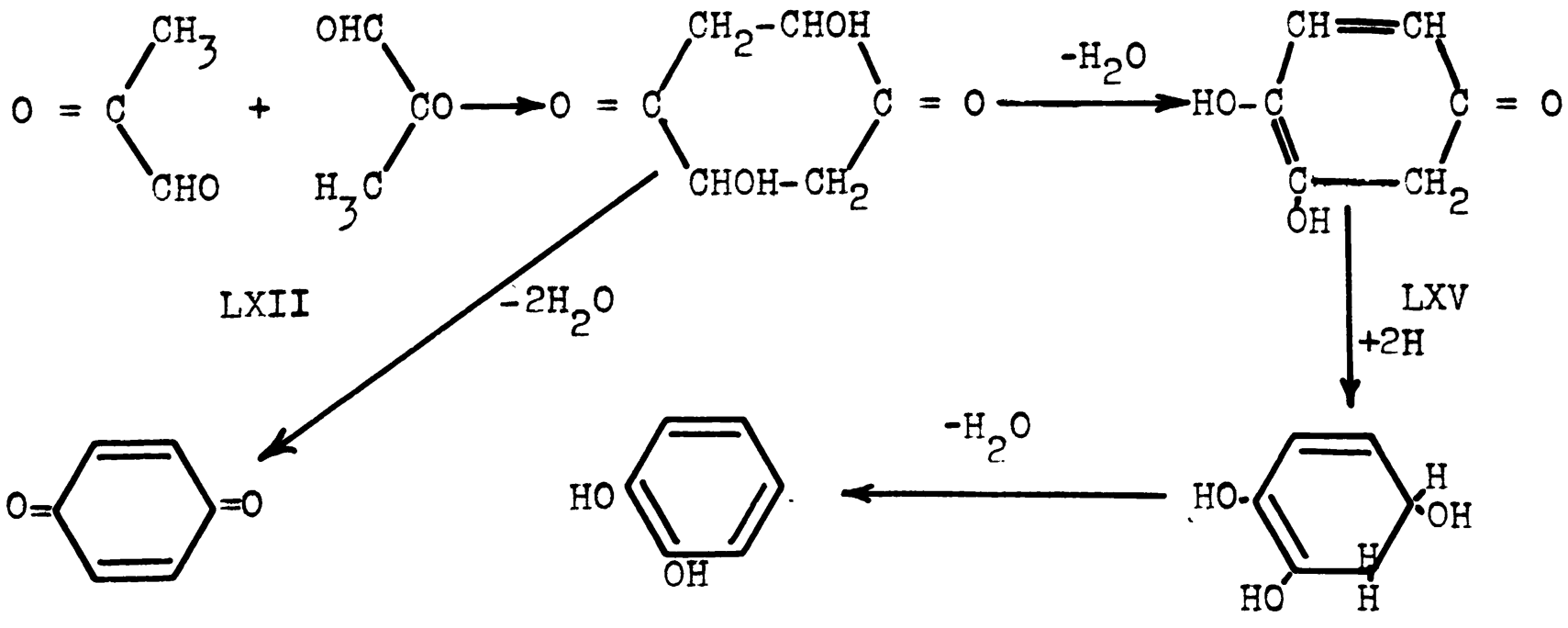
nuclei may arise directly from photosynthetic and/or respiratory products. In his earlier view he postulated the formation of hydroxylated cyclohexanes from the "enolic free radicals" of formic acid, glycolic aldehyde and acetaldehyde, e.g.



IV LXI

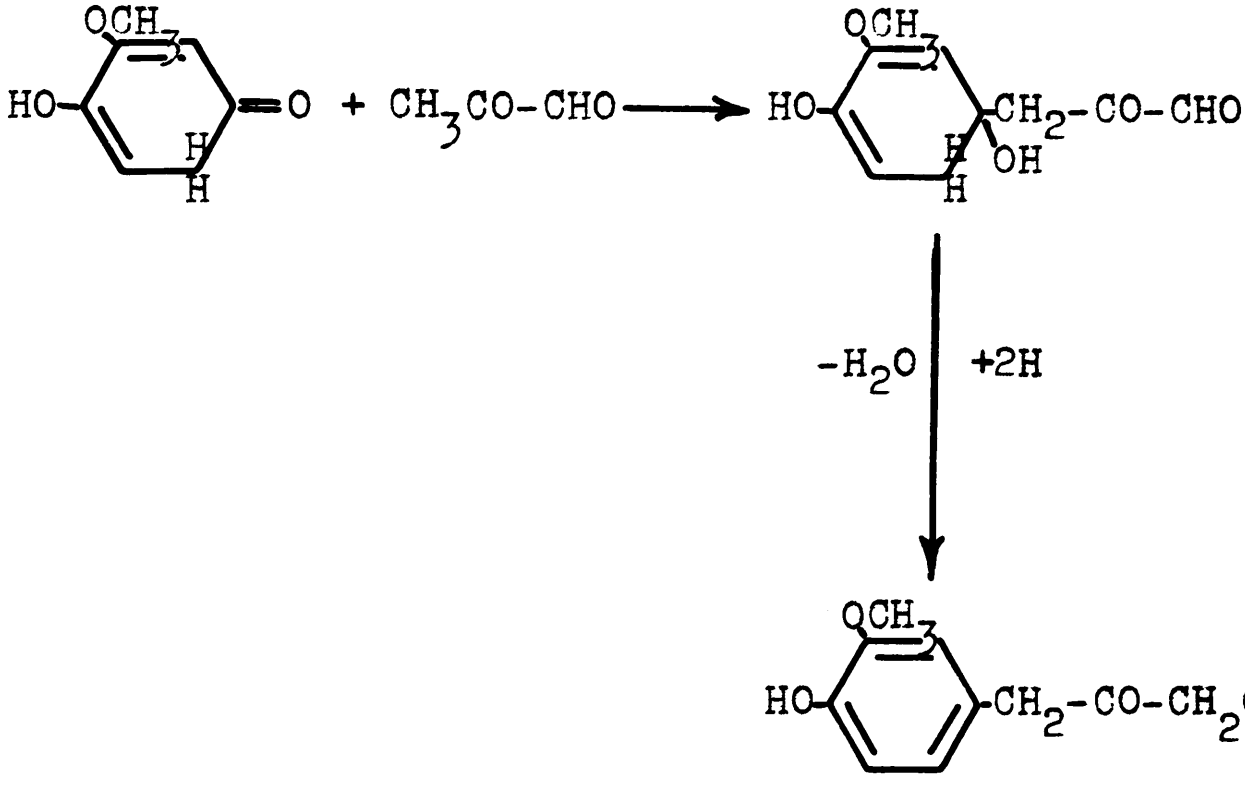
Here the condensation of three molecules of glycolic aldehyde could give inosito1 (IV) which on dehydration could give phloroglucinol (LXI).

More recently (44b) he has suggested that the phenols may arise from an intermediate plant respiratory product, namely, methyl glyoxal (LXII) as follows:



LXIII VI

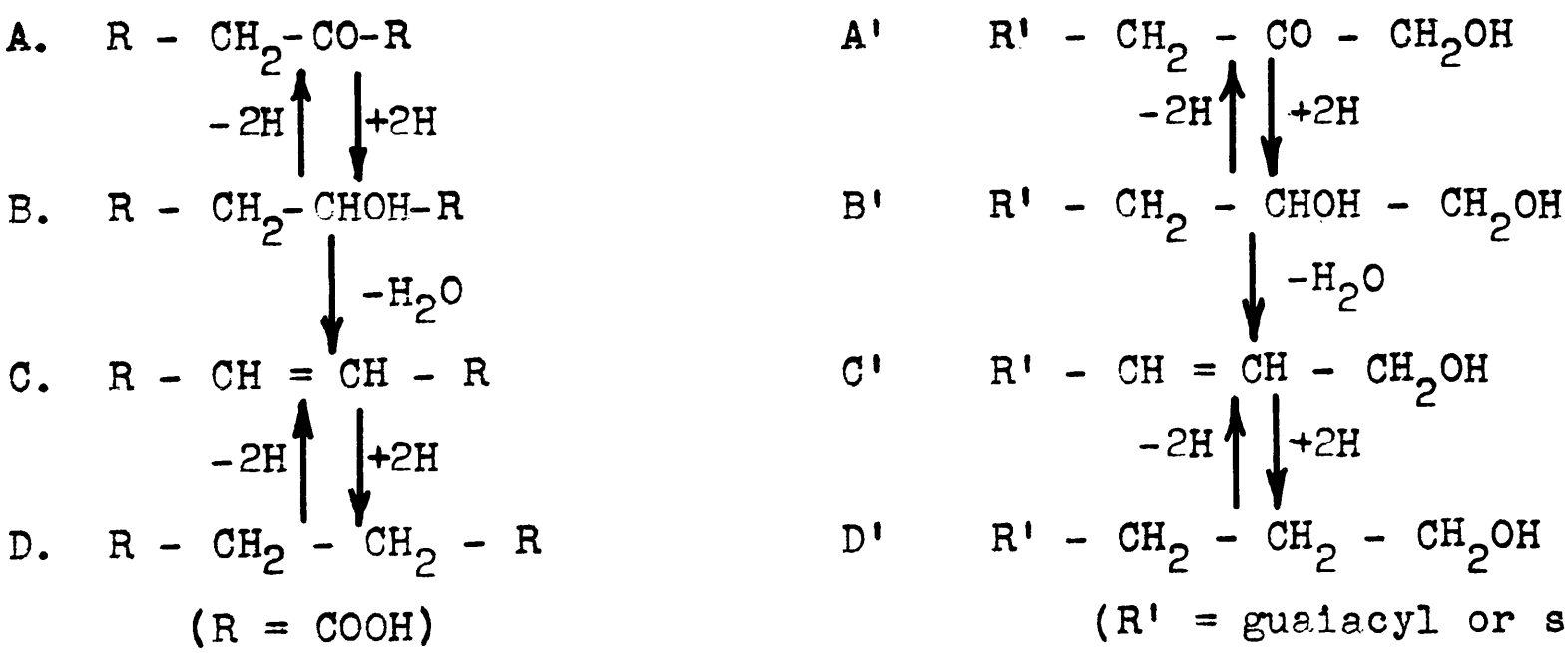
In this way the formation of quinones (LXIII) and catechol (VI) in plants could be explained. The propyl phenols, as will be seen, are derived from the intermediate LXV. Syringyl analogues it is suggested, may arise by oxidation of guaiacyl nuclei just as catechol may be obtained from phenol (57). The question of methoxylation of the phenols has not been touched, but, assuming that it has occurred, the syntheses of the propyl phenols are brought about by the addition of another molecule of methyl glyoxal to "methoxylated" LXV:



XXXI

This product, XXXI, is assumed to be the key substance from which all related products are derived. Hibbert believes that the ethanolysis products are stabilized forms of a series

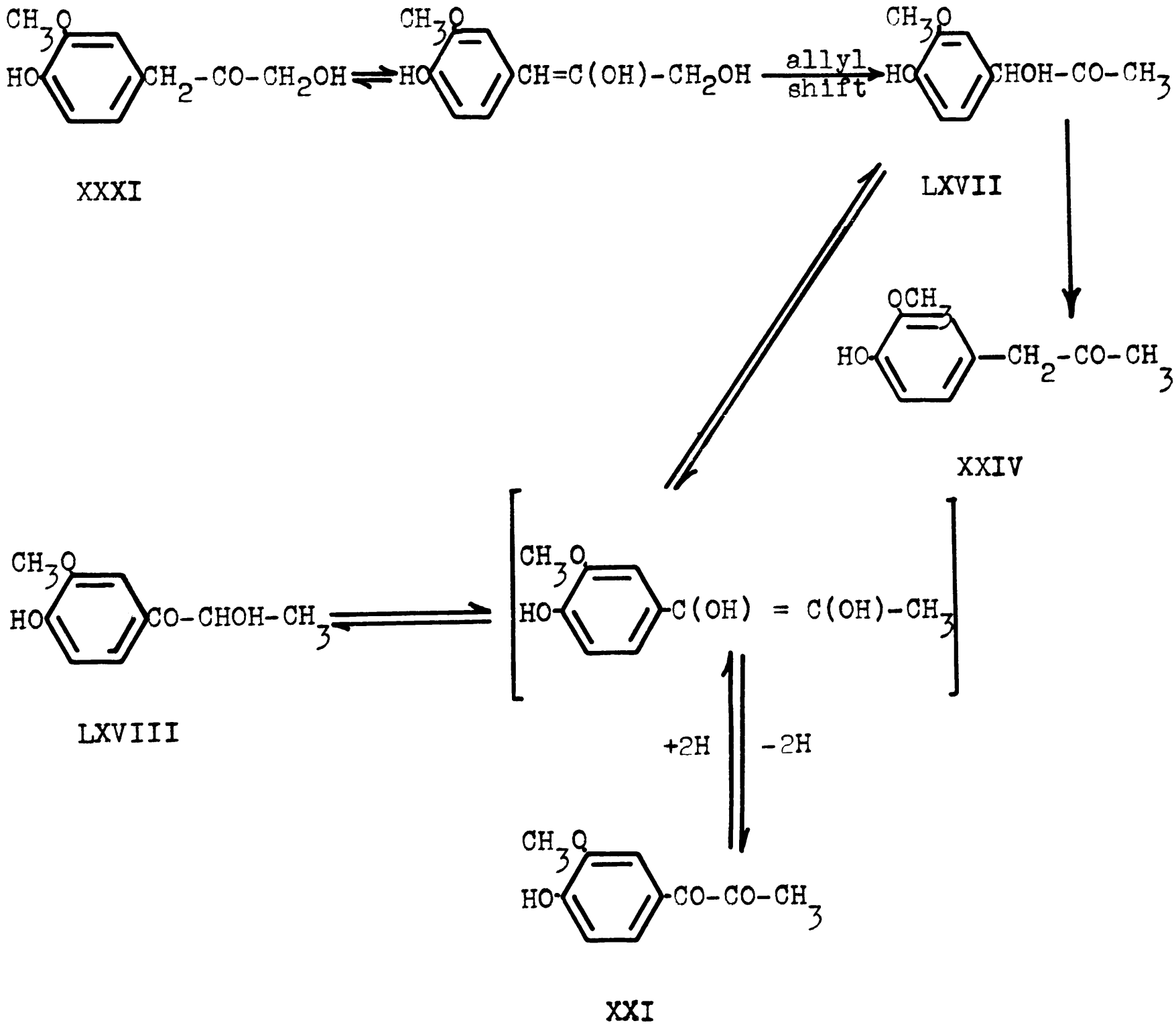
of plant products, which constitute a system of plant respiratory catalysts. He has pointed out the similarity between such a system and the C_4 aliphatic.dicarboxylic acid system of animal cell respiratory catalysts postulated by Szent-Gyorgi (58). In the plant system the two carboxyl groups are replaced by an aromatic (guaiacyl or syringyl), and a primary alcohol group:



The first member (A') of the series is the product (XXXI) obtained by condensation of three molecules of methyl glyoxal, and corresponds to oxalacetic acid (A) in the Szent-Gyorgi system. The third member, (C') analogous to fumaric acid (C) would be coniferyl alcohol which is well known and very widely distributed in the plant kingdom. It is possible that A' and the isomeric R' - CO - CH_2 - CH_2OH (XXX) may function similarly in such a system but investigation of the

latter compound has shown it to be rather more stable than one might expect. (42).

The derivation of the ethanolysis products from these primary products is assumed to occur as follows:

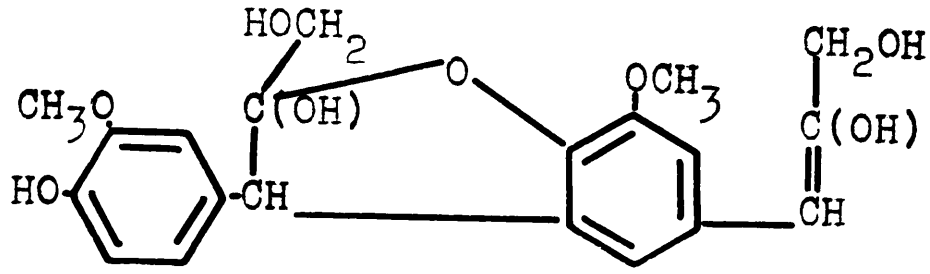


XXI, XXIV and, as ethyl ethers, LXVIII and LXVII have all now

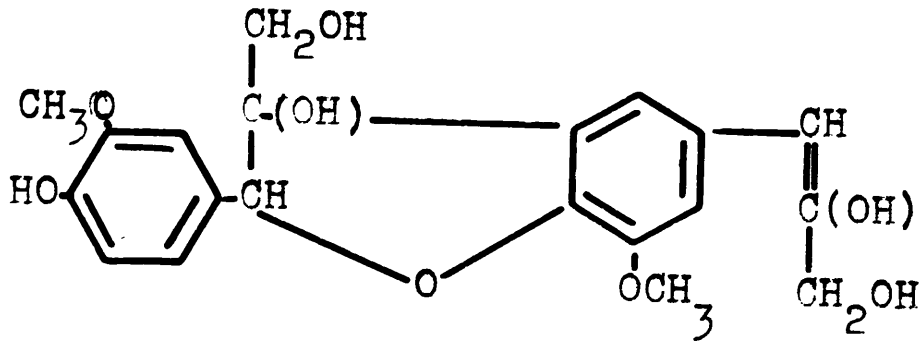
been identified among the ethanolysis products, leaving only the starting material, XXXI to be located. In the experimental section of this thesis, however, strong evidence will be presented to show that this compound, if formed, probably undergoes immediate rearrangement to other members of this series, especially LXVII and LXVIII.

The recognition of the possible existence of such a series of completely interconvertible phenyl propanes naturally makes it difficult to single out any one of them as the fundamental lignin building unit. The presence of primary hydroxyl groups in the hydrogenolysis products leads Hibbert to believe that, compound XXXI is probably present, but may be associated with isomeric hydroxy-ketones (LXVII and LXVIII) p.40 in a series of polymers.

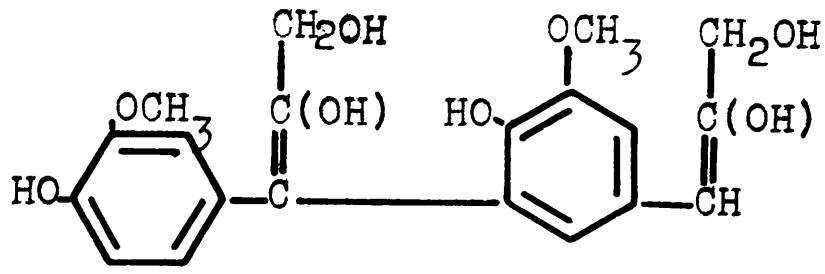
He believes, with Erdtmann and Freudenberg, that the dehydrodiisoeugenol type of polymerization is a distinct possibility. Dimers of the type LXIX or LXX p.42 would be possible and could to give trimers, tetramers, etc. Such dimers by ring cleavage and allylic shifts could give rise to LXXI and LXXII p.42 from which, on further degradation, the ethoxy ketones (XX and XXVI) could be obtained. The diketone (XXI) could perhaps arise through cleavage as indicated by the dotted line (p.42).



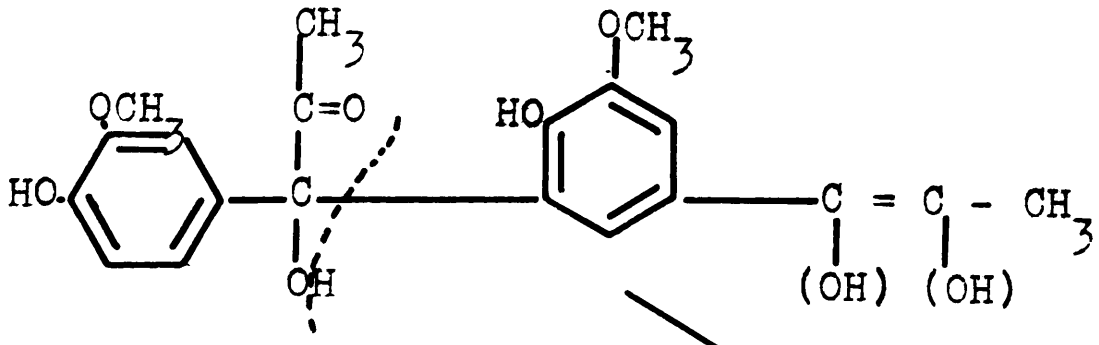
LXIX



LXX



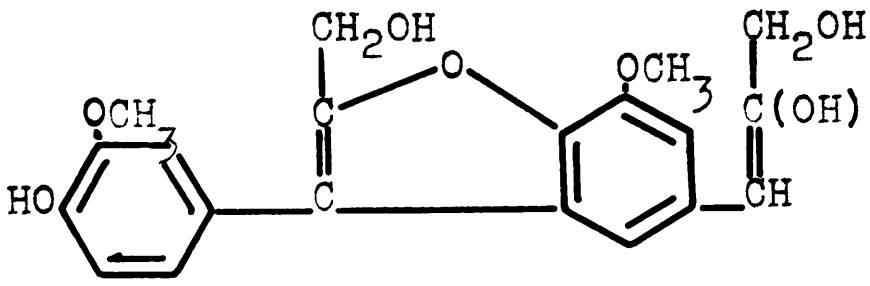
LXXI



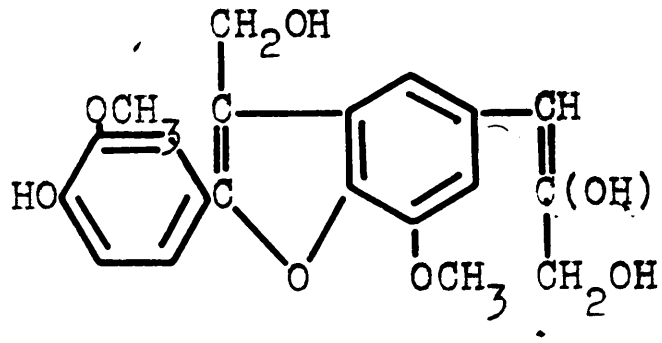
LXXII

LXVII, LXVIII, XXI

Hibbert also suggests that a polymer of this type (LXIX and LXX) through loss of water could go over to the benzofurane types (LXXIII and LXXIV). If such a dehydration should occur during isolation it might explain the greater stability to ethanolysis and hydrogenolysis of isolated lignins as compared to natural lignins.



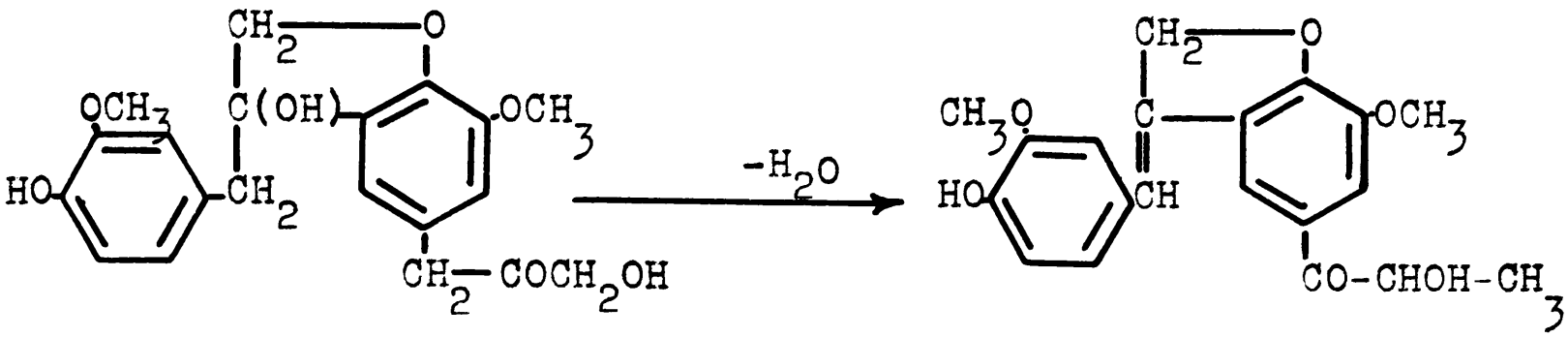
LXXIII



LXXIV

However, as Hibbert points out, the dehydrodiisoeugenol type polymer can only account for gymnosperm lignin, since the presence of syringyl groups is impossible in such a structure. Furthermore a system such as LXXV would explain all lignin reactions but diketone formation*. Also possible are styrene (through ene-diol forms) and aldol types of polymerization but these he believes are less probable.

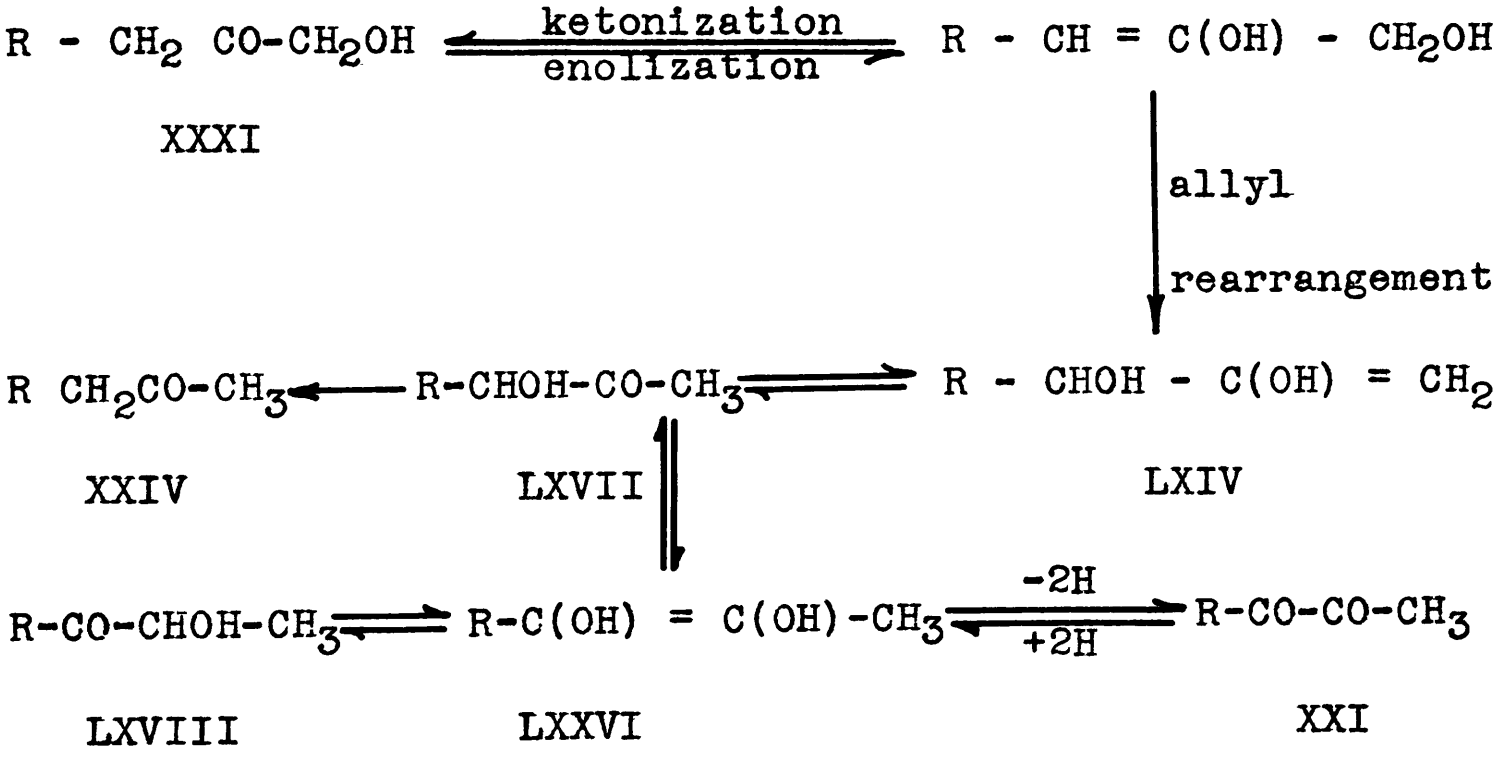
* There is a possibility, as will be seen in the experimental section, that diketone formation is the result of a secondary oxidation reaction.



LXXV

Rearrangement Reactions of Hydroxy-Ketones

It has been pointed out that the lignin degradation products obtained by ethanolysis are not necessarily primary products but may be the stabilized forms of a series of isomeric compounds. The relation between them, according to Hibbert (44) is shown in the series of reactions



R = guaiacyl (I)

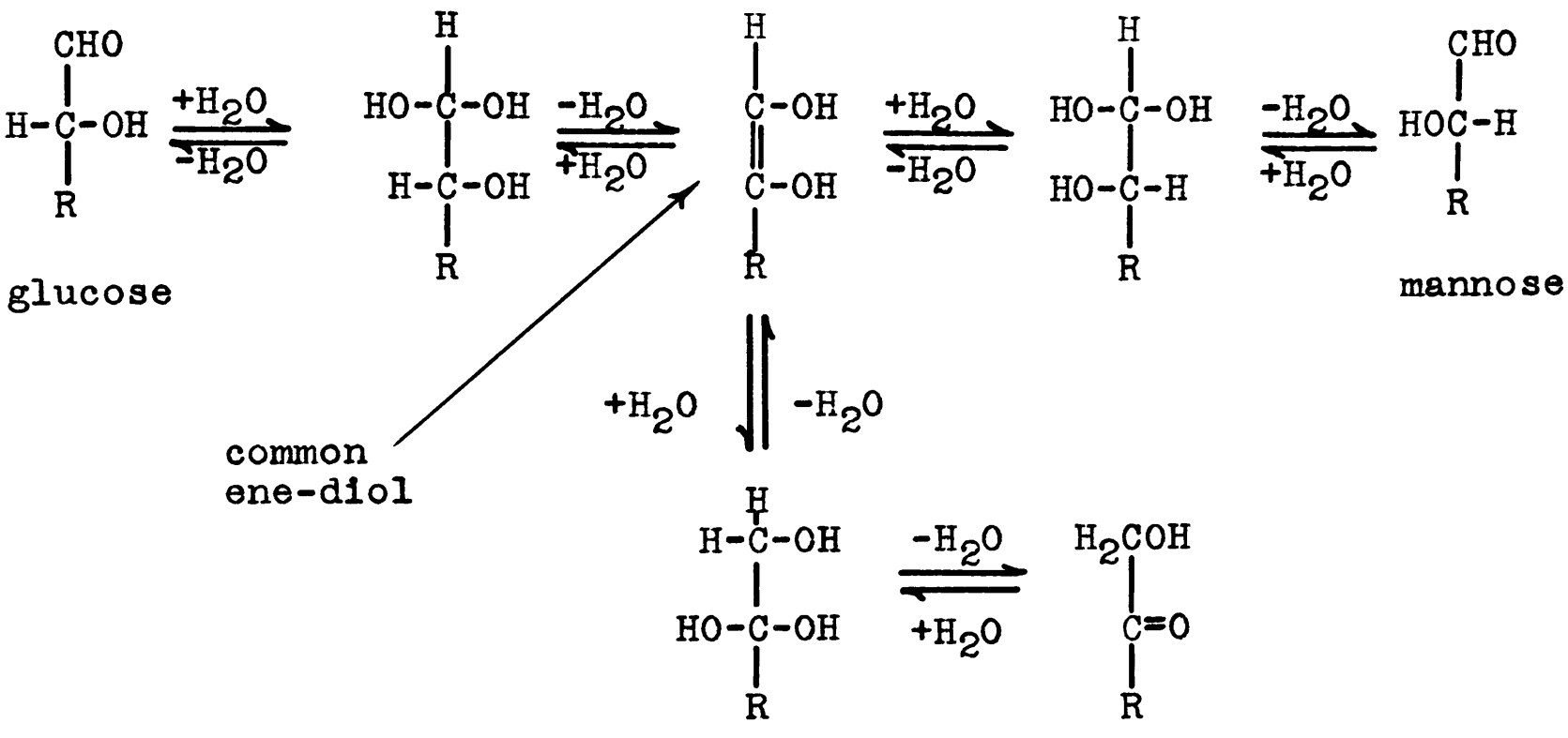
Two types of rearrangements are shown here, the first a dismutation type represented by the interconversion of LXVII and LXVIII through their common ene-diol, LXXVI, and the second an allylic type shown in the transformation of the ketol XXXI to the ene-diol LXIV. The latter rearrangement is rather unusual in that the double bond required for

the shift is obtained by a primary enolization. As will be seen later, only two examples of such a transformation appear to exist in the literature, but further evidence will be found in the experimental section of this thesis.

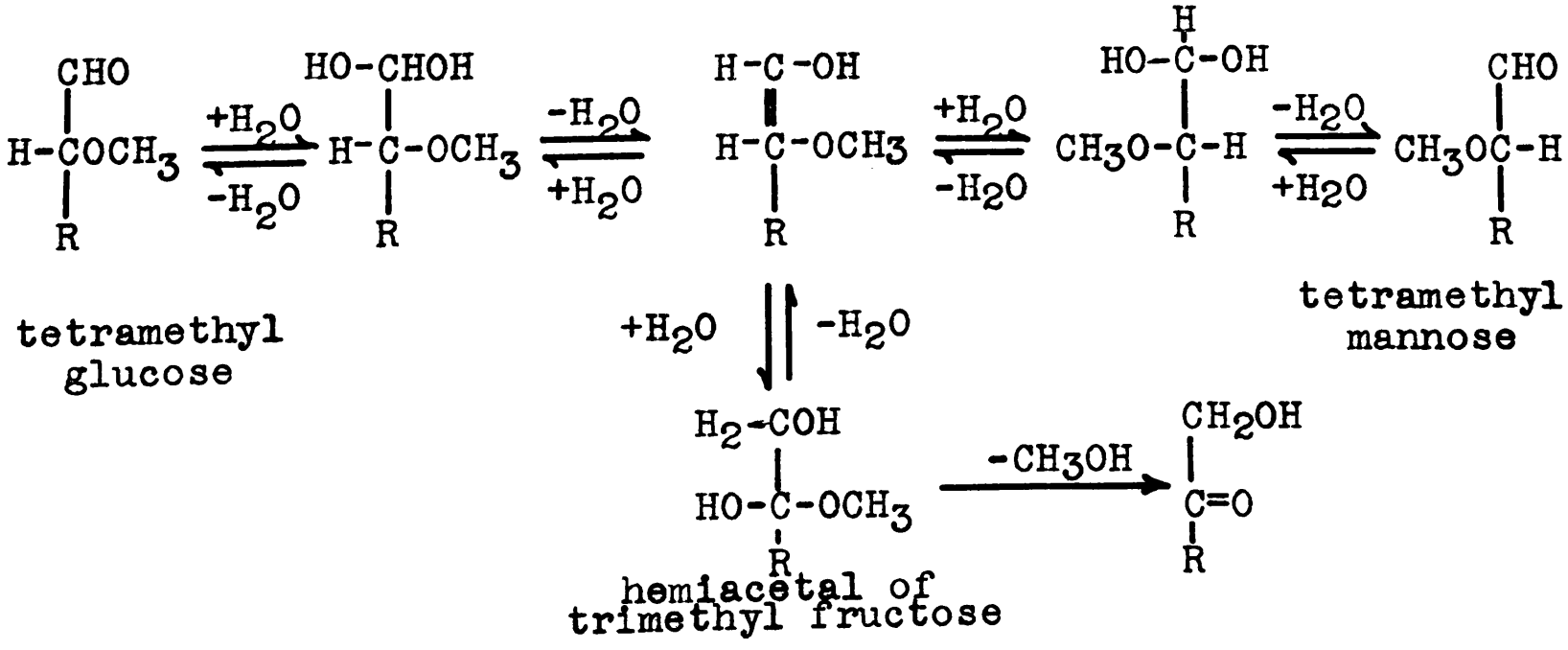
The study of intramolecular rearrangements in organic chemistry is of fairly recent origin. Generally the work requires the separation of mixtures of isomers, a difficult task at best, and hence accurate information is scarce. In reviewing the literature one must be extremely cautious in accepting experimental data particularly those of the earlier workers, and in no case should data be accepted unless the author has stated definitely that he has recognized the possibility of rearrangement and has taken all the necessary precautions to demonstrate its presence or absence in his experiments. Far too much confusion is already extant in the literature because workers failed to realize that the compounds with which they were dealing were members of a system of interconvertible isomers.

The dismutation transformation, represented by the equation $R'\text{-}CO\text{-}CHOH\text{-}R \rightleftharpoons R'\text{-}CHOH\text{-}CO\text{-}R$ is well known and is supported in the literature by a wide variety of examples. Perhaps the best known of these are to be found in the field of carbohydrate chemistry and more particularly, in the Lobry de Bruyn transformations (59) where an equilibrium between glucose, mannose and fructose is established in alkaline

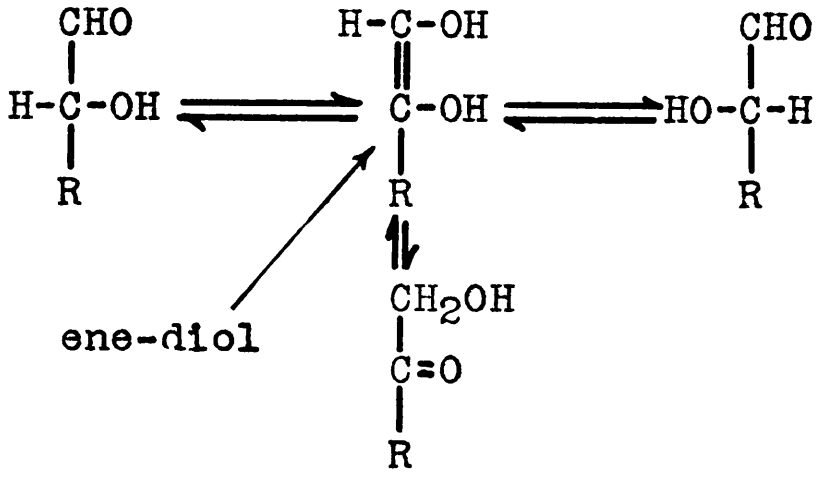
solution. Nef (60) attempted to explain these transformations by addition and elimination of water, as follows



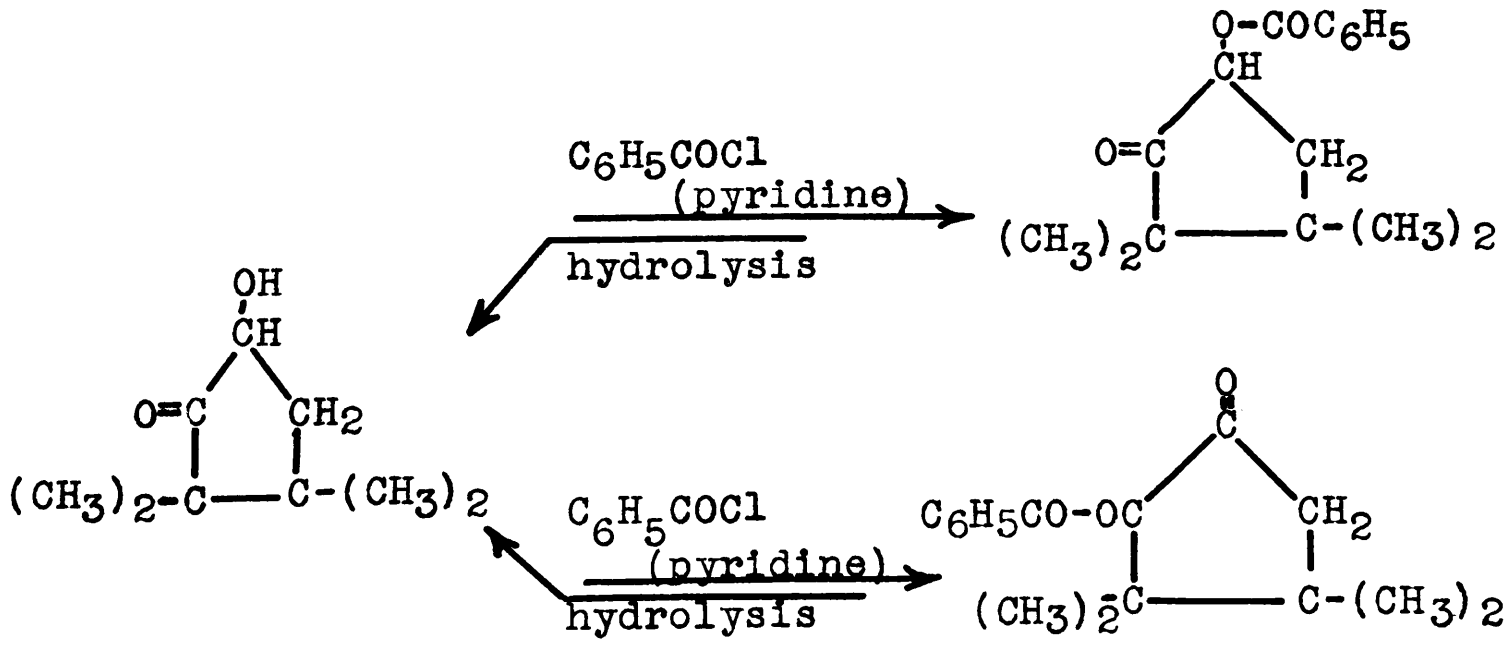
That such a mechanism was improbable was shown by Lewis and co-workers (61) in studies on methylated sugars. If Nef's theory were correct then it should be possible to obtain tetramethyl mannose and trimethyl fructose from tetramethyl glucose (trimethyl fructose would be formed by loss of methanol from the intermediate hemiacetal). The reactions, it is assumed, would occur as follows



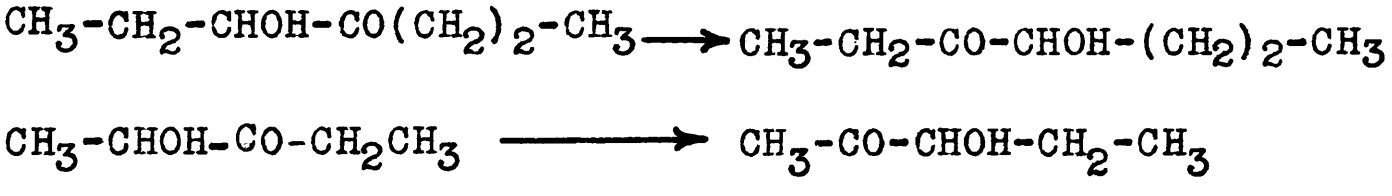
Wolfram and Lewis (61b) showed that no fructose was formed and postulated a new mechanism in which the transformations were attributed to keto-enol shifts, i.e.



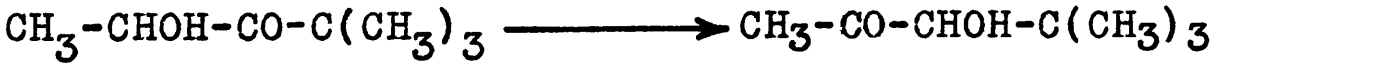
Such an explanation seems quite reasonable and explains similar changes in many other related compounds. Thus Shoppee (62) showed that highly substituted cyclic hydroxy ketones such as 2.2, 3.3, - tetramethyl-5-hydroxy-cyclopentanone undergo dismutation reactions. This compound on benzoylation gives two distinct isomeric benzoates, both of which on hydrolysis give back the original hydroxy-ketone. These results are explained by the following equations:



However, it is now known that even the simplest of ∝-hydroxy - ketones and - aldehydes will undergo such rearrangements. Favorskii (63) has studied a series of aliphatic ∝-hydroxy-ketones and found that their dismutation is effected by heating under pressure at 120° - 130° in dilute alcoholic sulphuric acid. He concludes from these experiments that the carbonyl group tends to move towards the end of the chain. His results may be summarized in the following changes:



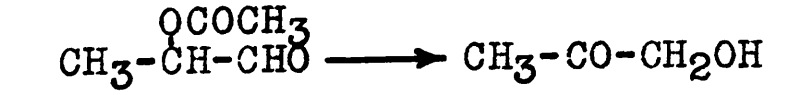
$$CH_3\text{-}CH_2\text{-}CHOH\text{-}CO(CH_2)_2\text{-}CH_3 \longrightarrow CH_3\text{-}CH_2\text{-}CO\text{-}CHOH\text{-}(CH_2)_2\text{-}CH_3$$



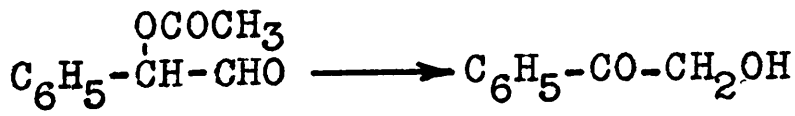
$$CH_3\text{-}CHOH\text{-}CO\text{-}CH_2CH_3 \longrightarrow CH_3\text{-}CO\text{-}CHOH\text{-}CH_2\text{-}CH_3$$

$$CH_3\text{-}CHOH\text{-}CO\text{-}C(CH_3)_3 \longrightarrow CH_3\text{-}CO\text{-}CHOH\text{-}C(CH_3)_3$$

Similar rearrangements are found among hydroxy-aldehydes. Hydrolysis of the acetates of lactic and mandelic aldehydes do not give the corresponding hydroxy aldehydes, but, instead, the isomeric hydroxy-ketones (64). The same is true of the hydrolysis of mandelic aldehyde acetal.



$$CH_3\text{-}\overset{\overset{OCOCH_3}{|}}{CH}\text{-}CHO \longrightarrow CH_3\text{-}CO\text{-}CH_2OH$$



$$C_6H_5\text{-}\overset{\overset{OCOCH_3}{|}}{CH}\text{-}CHO \longrightarrow C_6H_5\text{-}CO\text{-}CH_2OH$$

The two hydroxy aldehydes differ greatly in their stability towards rearrangement. Mandelic aldehyde is converted to benzoyl carbinol in dilute ethanol or water at 0° and even

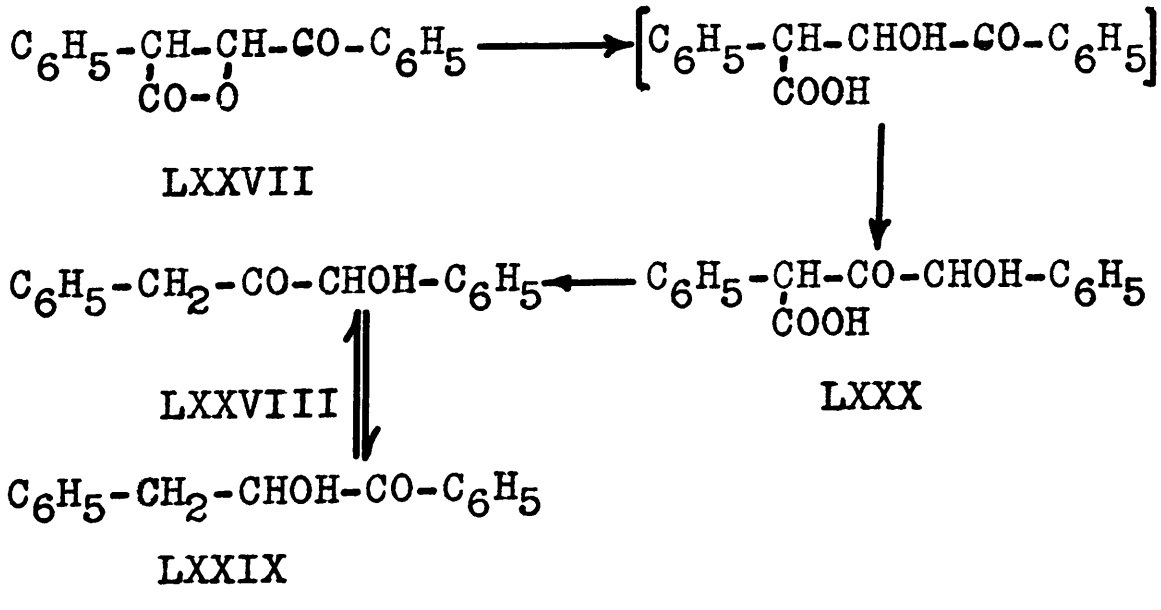
in moist air at room temperature. It is quite stable under anhydrous conditions. Lactic aldehyde on the other hand, requires heating at 100° in aqueous solution for its conversion to acetol.

When heated with 14% ethanolic sulphuric acid, benzyl glycolic aldehyde likewise undergoes rearrangement but yields also some of the corresponding diketone (65). This reaction

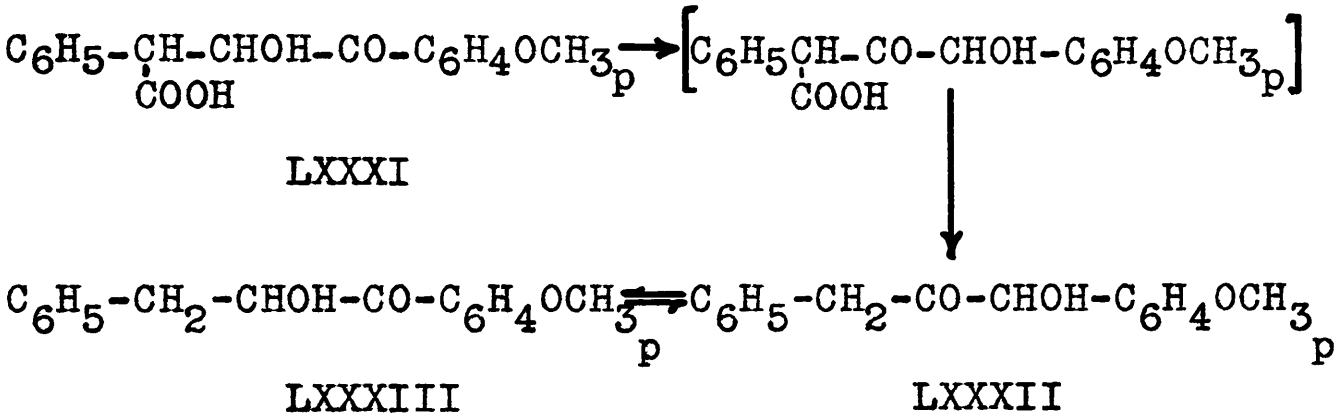
$$C_6H_5\text{-}CH_2\text{-}CHOH\text{-}CHO \longrightarrow C_6H_5\text{-}CHOH\text{-}CO\text{-}CH_3 + C_6H_5\text{-}CO\text{-}CO\text{-}CH_3$$

however requires further consideration in connection with allylic shifts.

The study of the rearrangement of benzoins has given some interesting results. Kohler and Kimball (66a) found that the β-lactone of α-phenyl -β-hydroxy-β-benzoyl-propionic acid (LXXVII) on treatment with 5% aqueous sodium hydroxide lost carbon dioxide and gave a mixture of hydroxy-ketones (LXXVIII and LXXIX). They belived that dismutation occurred immediately upon opening of the lactone ring and was followed by decarboxylation of this new isomeric acid (LXXX). The hydroxy ketone LXXIX was believed to arise from a secondary dismutation change of the isomeric LXXVIII.



Confirmation of these views, they belived, was to be found in the work of Kohler and Leers (66b) on α-phenyl-β-hydroxy-β-anisoyl-propionic acid (LXXXI). In cold dilute alkali this compound undergoes decarboxylation to give the hydroxy ketone, LXXXII. On heating however, this underwent complete dismutation to LXXXIII.



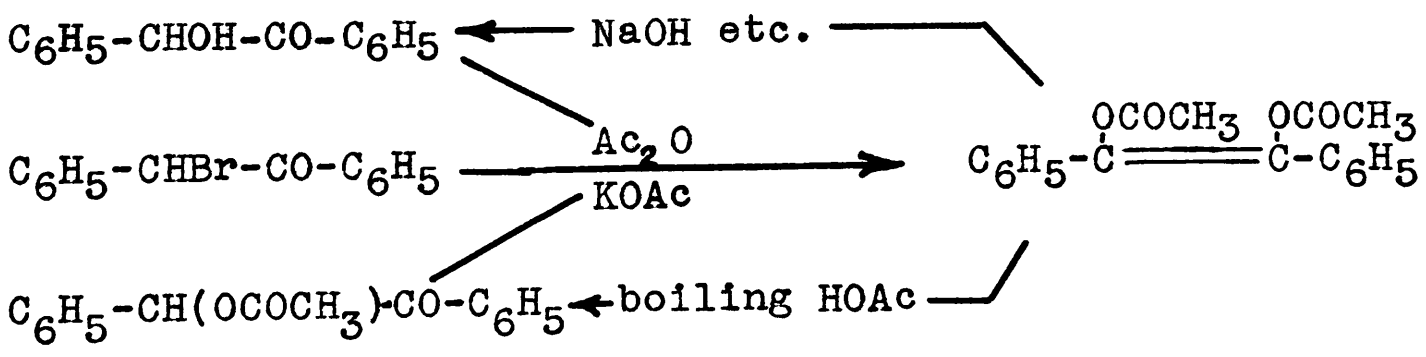
Treatment of the lactone, LXXVII, with methanolic-HBr gave the corresponding ester without rearrangement.

Kohler concluded from these studies that the isomeric hydroxy-ketones are in equilibrium but had no experimental evidence to support this view, for he was never able to demonstrate the reverse shift, $-CH_2-CHOH-CO- \longrightarrow -CH_2-CO-CHOH-$. Evidence for this belief was, however, supplied by Stevens (67) in studies on a monoparachloro-derivative. He showed that treatment of either one of the two isomers, $C_6H_5-CH_2-CHOH-CO-C_6H_4Cl_p$ and $C_6H_5-CH_2-CO-CHOH-C_6H_4-Cl_p$ with sodium carbonate in aqueous alcohol gave rise to the same mixture of the two ketols. He concluded that all 1, 2-hydroxy-ketones probably exist in solution as equilibrium mixtures, and that failure to recognize these equilibria may

be due to peculiar difficulties associated with the isolation of one of the components, or to the presence of one isomer in very high concentration as compared to the other.

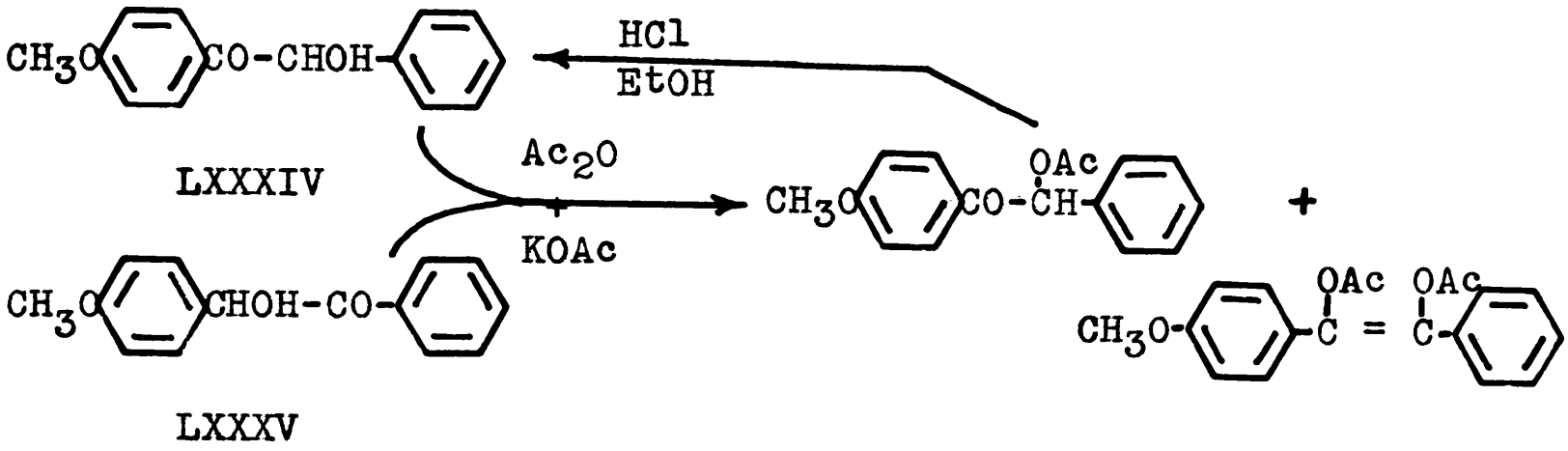
Benzoins and benzoin-like compounds have been studied by Barnes and co-workers (68) particularly with reference to the effect of aromatic substituents on the dismutation. Earlier, Auwers and co-workers (69) had shown that substituents in the aromatic nuclei could completely reverse the normal transition of benzoyl methyl carbinol to phenyl acetyl carbinol (see pg.60).

Barnes and Tulane (68a) in preliminary studies, showed that benzoin, or its corresponding bromide or acetate, is converted by vigorous acetylation to the ene-diol diacetate. By boiling with acetic acid the latter was converted to benzoin acetate, and with aqueous hydrolytic agents to benzoin itself.



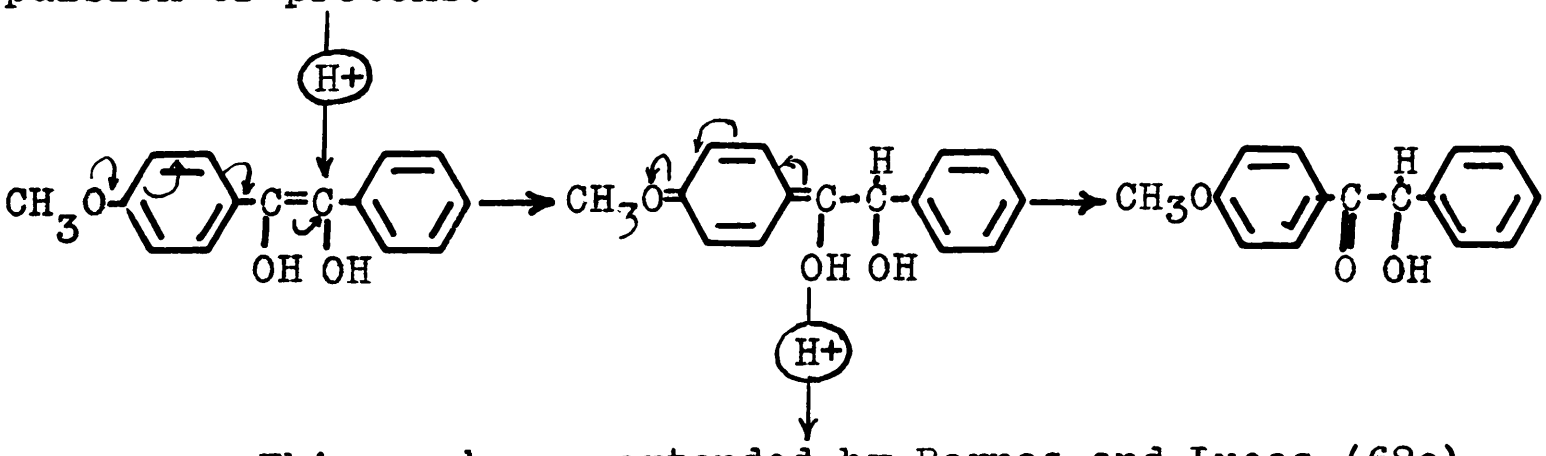
These reactions were then applied to benzanisoin (LXXXIV) and anisbenzoin (LXXXV; 68b). The diacetate was formed with some difficulty but on hydrolysis gave back only benzanisoin.

Similar results



were obtained with the corresponding α-brom compound.

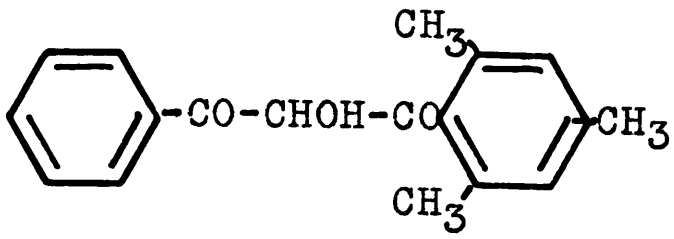
These workers believe that the methoxyl group, due to a strong tendency to electron release, exerts a directing influence upon the ene-diol. A negative charge is developed at the para carbon atom which directs the addition and expulsion of protons.



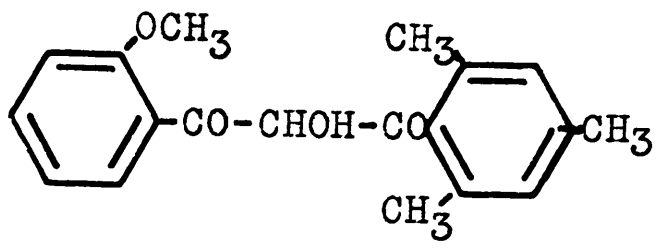
This work was extended by Barnes and Lucas (68c) to benzoins containing methoxyl groups in both aromatic nuclei. In the case of the dipara-methoxy derivative it was found impossible to prepare the ene-diol diacetate directly by acetylation and the diortho-methoxy derivative gave only a very poor yield. However, by catalytic reduction of the

corresponding benzils in acetic anhydride the desired diacetates were obtained. Unlike the unsubstituted benzoins however, they could not be hydrolysed to the normal benzoin acetates with boiling acetic acid. Total hydrolysis with cold concentrated sulphuric acid showed sharp differences in the case of the ortho and para compounds. The former gave benzoin, as expected, but the latter underwent oxidation to the corresponding benzil (anisil). They concluded that para-methoxyl groups had greater stabilizing effects on ene-diols and benzoins than did ortho-methoxyls.

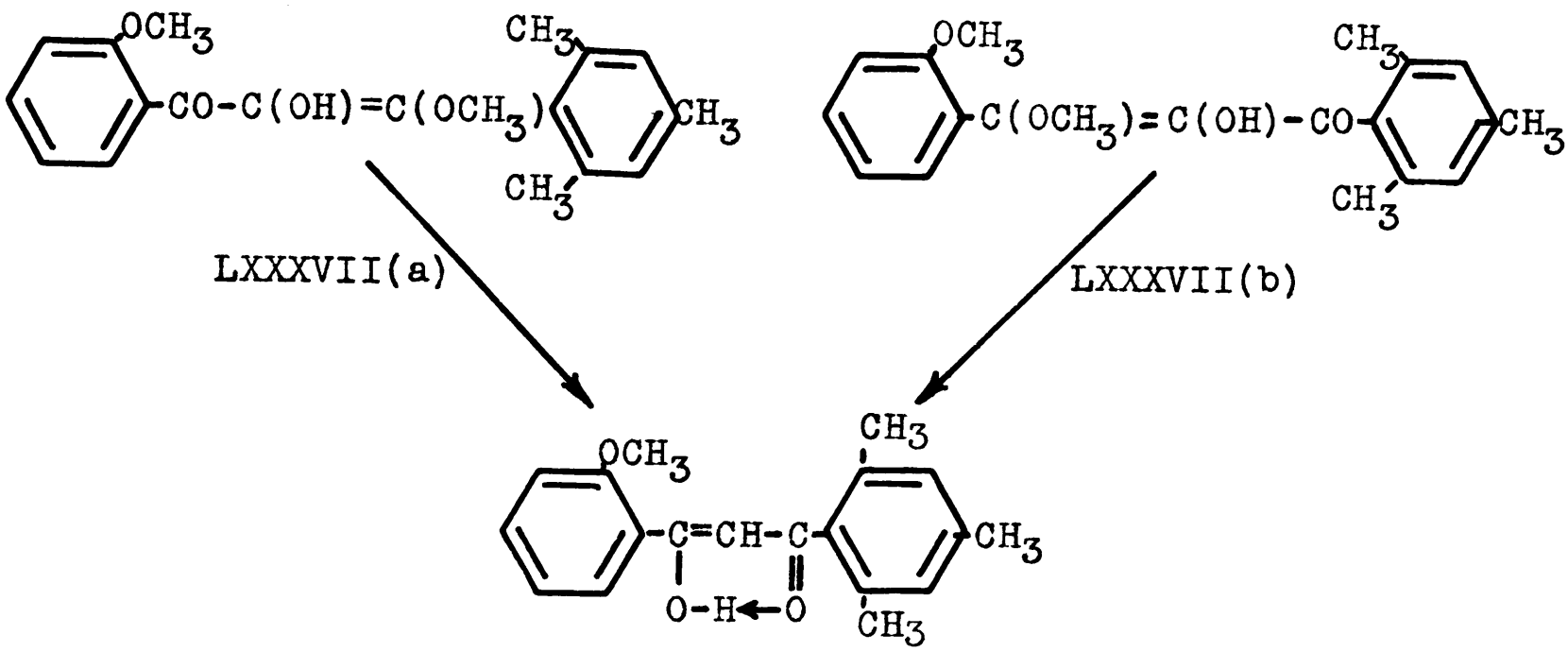
Barnes and co-workers (68c, d) have also investigated compounds of type LXXXVI.(p.55) This derivative itself is only partially enolized but orthosubstitution of a methoxyl group (LXXXVII) renders it completely enolic. They succeeded in preparing the isomeric enol methyl ethers (LXXXVII(a) and LXXXVII(b)) of LXXXVII and found that on hydrolysis of either of these ethers with cold concentrated HCl they obtained the same compound (LXXXVIIc). They believed it to be the chelated form of LXXXVII since it was completely enolic yet not methylatable with diazomethane.



LXXXVI

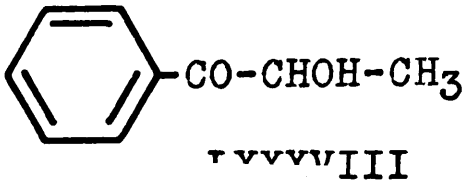


LXXXVII

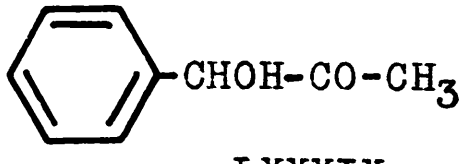


LXXXVII(c)

Of particular interest to lignin chemists are the dismutation reactions of mixed aliphatic aromatic α-ketols, particularly those related to the ethanolysis products isolated from wood by Hibbert and co-workers (44a). Benzoyl methyl carbinol (LXXXVIII) and phenyl acetyl carbinol (LXXXIX) have been investigated by a number of workers but much of the earlier data has since been shown to be unreliable. The recent work of Favorskii, Temnikova, Auwers and others, directed specifically towards the study of dismutation reactions, appears to be quite sound.



LXXXVIII

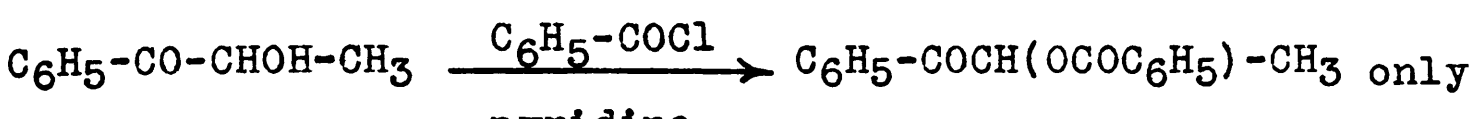


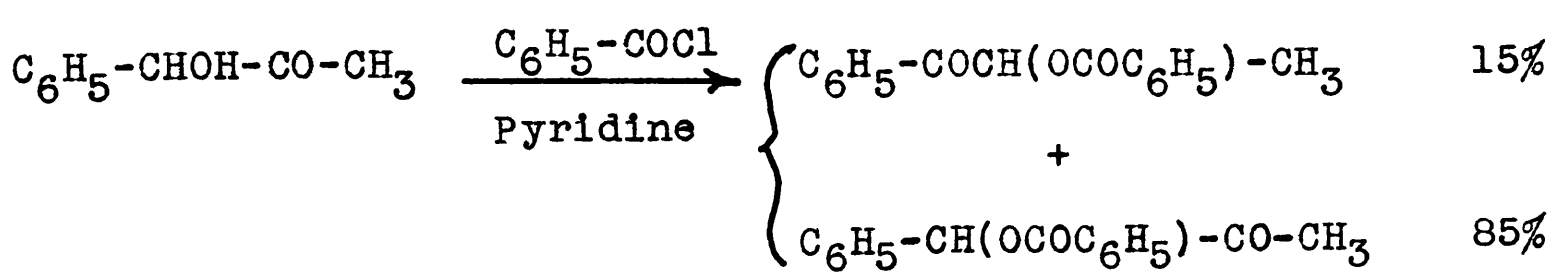
LXXXIX

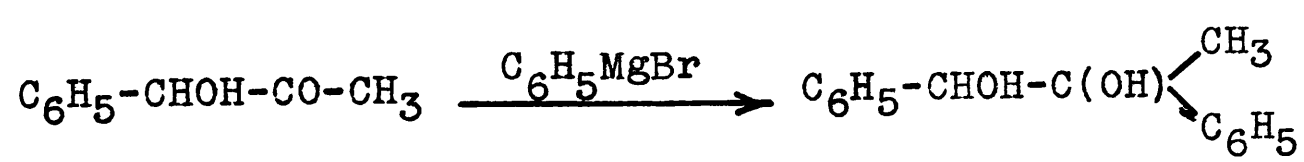
Favorskii (70) predicted that phenyl acetyl carbinol, because it contains the acetyl group, would be the more stable, a prediction substantiated by conversion of LXXXVIII to LXXXIX on heating with dilute alcoholic sulphuric acid. His results have been confirmed by other workers (71,72).

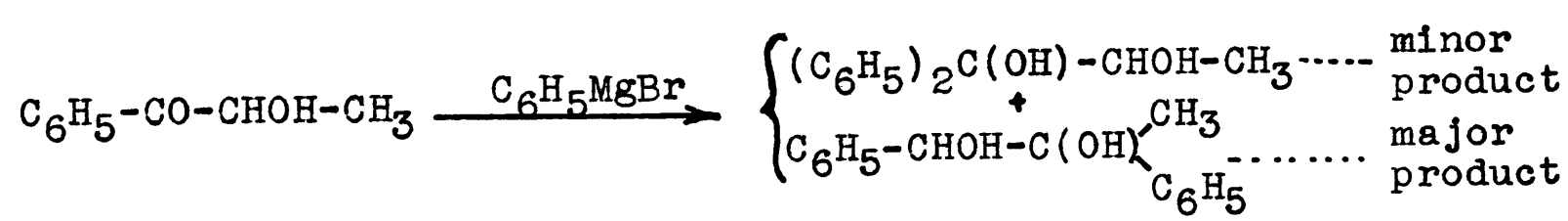
Temnikova and Favorskii (71a) showed that each of these ketols (LXXXVIII, LXXXIX) is stable in the absence of catalysts (acids and bases) but that on treatment with a variety of reagents a tautomeric mixture is obtained. Auwers and co-workers (72) found that aqueous barium hydroxide or ethanolic HCl at reflux temperatures, or sodium ethoxide at 0°, would convert benzoyl methyl carbinol into phenyl acetyl carbinol.

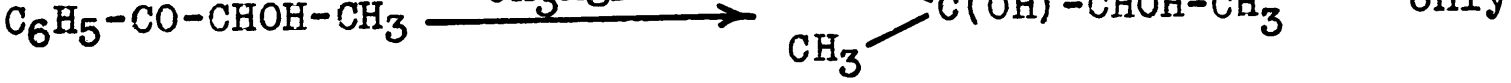
Because of some discrepancies in the earlier work Temnikova (71b) carefully reinvestigated this system and showed that benzoyl methyl carbinol (LXXXVIII) could be converted to phenyl acetyl carbinol (LXXXIX) by acids or alkalis but that the reverse reaction did not occur. In benzoylation or Grignard reactions however both isomers could be obtained. Her results may be summarized as follows -

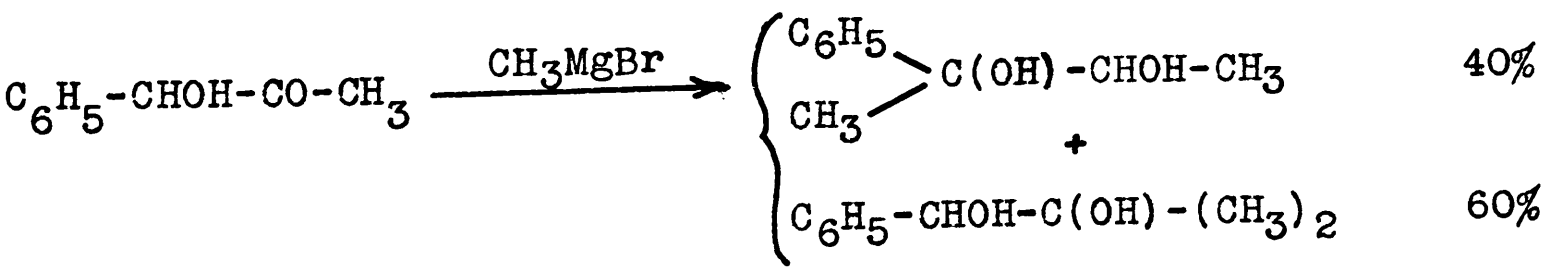












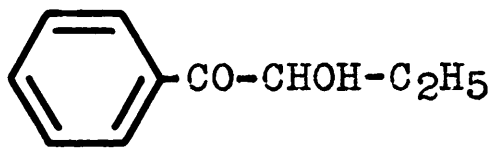
She draws attention to the fact that when the radical present in the Grignard reagent is different to that attached to the carbonyl there seems to be no rearrangement, but that if these two radicals are identical, then rearrangement occurs.

From her studies she attempted to show that no dynamic equilibrium exists between the isomeric ketols and

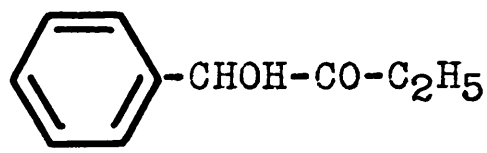
considered that the mixtures obtained were consequent on the relative rates of reaction of the two isomers with any reagent. She suggests that by loss of a proton an intermediate fragment is formed and undergoes rearrangement, i.e. $C_6H_5\text{-}CH\overset{\ominus}{O}\text{-}CO\text{-}CH_3 \rightleftharpoons C_6H_5\text{-}CO\text{-}CH\overset{\ominus}{O}\text{-}CH_3$. The entering radical may then add to one or the other of these fragments. However, although the rates of reaction could undoubtedly be a factor, this does not exclude the possibility of an equilibrium between the fragments or between the parent ketols. Furthermore it is difficult to explain, on this basis, the reactions of methyl magnesium bromide with the two ketols. With this reagent phenyl acetyl carbinol, which has been shown to be the more stable isomer and which, since it is a methyl ketone, should be the most reactive, gives derivatives of both ketols in almost equal amounts. Benzoyl methyl carbinol, on the other hand, undergoes no rearrangement.

Her observation of a possible relationship between rearrangement and the nature of the radicals attached to the Grignard and carbonyl, may be significant since similar results were obtained in an extension of this work to benzoyl ethyl carbinol (XC) and phenyl propionyl carbinol (XCI) (73). The first of these, she found, could be prepared directly from its corresponding bromide by treatment with potassium formate or from the acetate by hydrolysis with barium carbonate. If, however, either of the two isomers were allowed to stand at room temperature with a little ethanolic potassium hydroxide,

a mixture containing 60-65% of XC and 35-40% of XCI was obtained. There seems to be little doubt that an equilibrium exists here, especially since the same mixture is obtained where XCI is heated with dilute ethonolic sulphuric acid.



XC



XCI

The behaviour of these compounds toward the Grignard reagent is shown below:

$$C_6H_5\text{-}CO\text{-}CHOH\text{-}C_2H_5 \xrightarrow{R\text{-}MgBr} C_6H_5\text{-}CR(OH)\text{-}CHOH\text{-}C_2H_5$$

where R = methyl, ethyl & n-propyl

$$C_6H_5\text{-}CO\text{-}CHOH\text{-}C_2H_5 \xrightarrow{C_6H_5MgBr} \begin{cases} (C_6H_5)_2C(OH)\text{-}CHOH\text{-}C_2H_5 & \text{(large)} \\ C_6H_5\text{-}CHOH\text{-}C(OH)(C_2H_5)(C_6H_5) & \text{(small)} \end{cases}$$

$$C_6H_5\text{-}CHOH\text{-}CO\text{-}C_2H_5 \xrightarrow{R\text{-}MgBr} C_6H_5\text{-}CHOH\text{-}C(OH)(R)(C_2H_5)$$

where R = methyl, ethyl or propyl

$$C_6H_5\text{-}CHOH\text{-}CO\text{-}C_2H_5 \xrightarrow{C_2H_5MgBr} \begin{cases} C_6H_5\text{-}CHOH\text{-}C(OH)\cdot(C_2H_5)_2 & \text{(large)} \\ (C_6H_5)(C_2H_5)C(OH)\text{-}CHOH\text{-}C_2H_5 & \text{(small)} \end{cases}$$

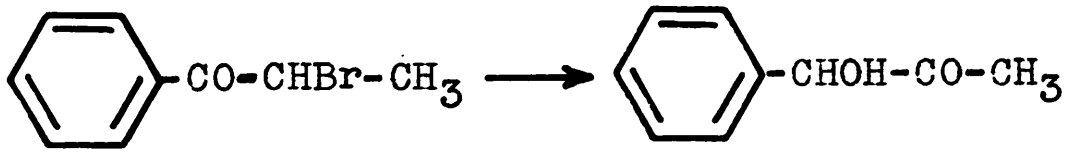
Somewhat earlier Urion and Baum (74) had also studied this system. They found that phenyl propionyl carbinol (XCI) was heat stable whereas its isomer could only be distilled without rearrangement at pressures below 2 - 3 mm. The dismutation was strongly catalysed by hydroxyl ions, but in contrast to Temnikova's studies, these workers were unable to show a reverse rearrangement of phenyl propionyl carbinol to benzoyl ethyl carbinol. It seems improbable however, that replacement of an acetyl group, as in phenyl acetyl carbinol, by a propionyl group should shift the equilibrium completely towards the isomeric ketol.

Further evidence to show that phenyl acetyl carbinol is more stable than the benzoyl methyl carbinol has come from fermentation studies. Neuberg (75) showed that benzaldehyde, when added to an actively fermenting sugar solution, was converted to phenyl acetyl carbinol, a synthesis which he attributed to a condensation of benzaldehyde and acetaldehyde brought about by a yeast enzyme, "carboligase". Favorskii (63) believed that the primary product in this condensation was benzoyl methyl carbinol and by introducing this derivative into the fermentation mixture he was able to show its conversion to the dismutation isomer. His experiments were confirmed by Auwers and Mauss (76).

The effect of aromatic substituents on dismutation changes in the mixed benzoins (acetoins) has not been widely studied. It has been shown above that in the system, benzoyl methyl carbinol (LXXXVIII) - phenyl acetyl carbinol (LXXXIX),

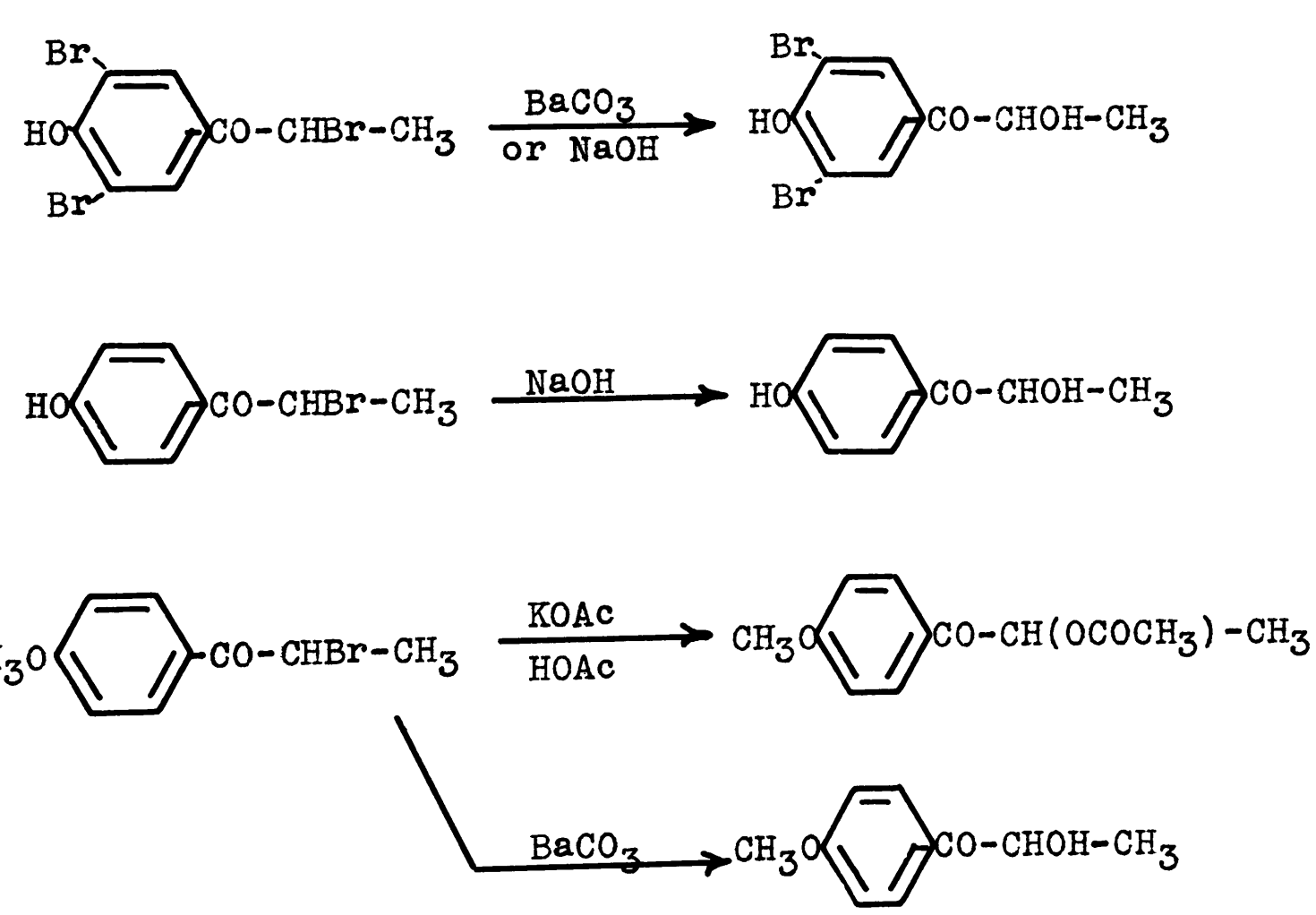
the latter compound is the more stable. Auwers and co-workers (69) however, have shown that the stability towards rearrangement is completely reversed if p-hydroxyl or p-methoxyl groups are substituted in the aromatic ring.

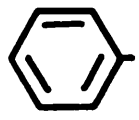
Thus the hydrolysis of α-brom-propiophenone gives phenyl acetyl carbinol, i.e.,



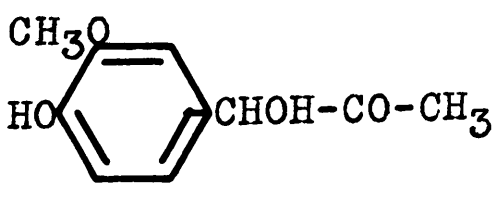
LXXXIX

whereas the substituted α-brom-propiophenones give derivatives of benzoyl methyl carbinol as follows:

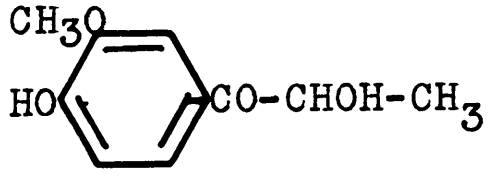


From the dismutation reactions described above it is possible to draw a few general conclusions. It is apparent that ∝-ketols and ∝-hydroxy aldehydes are very labile systems capable of undergoing dismutation rearrangements especially in the presence of acids or alkalis. It is possible, perhaps probable, that an equilibrium exists between the isomeric forms but the point has not yet been adequately proven. In the purely aliphatic ketols the carbonyl group shifts towards the shortest end of the chain, but in mixed aliphatic-aromatic ketols of the type R-CO-CHOH-R' the direction of the shift cannot be predicted with any certainty at the present time. It depends upon the nature of the aliphatic group, but more especially upon the nature of the aromatic group particularly as influenced by substituents in the ring. It has been shown that the presence of para-methoxyl and hydroxyl groups and of ortho-methoxyl groups have a profound stabilizing effect upon the  -CO group.

Although these conclusions are very general they would seem to be of importance to the worker in the field of lignin chemistry. It is apparent that 2-hydroxy-1-(4-hydroxy-3methoxyphenyl)-propanone-1 (LXVIII) should be more stable than the isomeric 1-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propanone-2 (LXVII). It is



LXVII



LXVIII

not therefore surprising to find that in the ethanolysis products, the ethyl ether of LXVIII occurs in much larger amounts than does that of LXVII. It seems highly probable that the ethyl ether of LXVIII is formed from a more labile isomer as a result of rearrangement reactions.

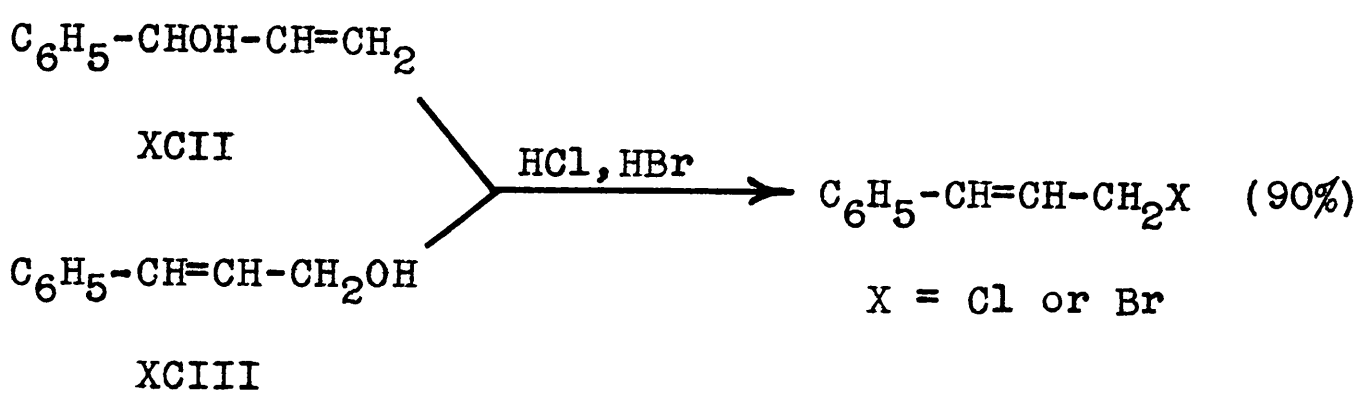
The possibility that allylic shifts may occur in the reactions of α-ketols has been suggested by Hibbert to explain some of the anomalous experimental data in lignin chemistry. It has already been pointed out that the n-propyl cyclohexane derivatives obtained by hydrogenation of lignin contain primary hydroxyl groups while the ethanolysis products have only secondary hydroxyls. To explain these facts Hibbert suggests that all the products may be derived from a building unit having the skeletal structure R-$\dot{C}$-$\dot{C}$(-O)-$\dot{C}$(-O)- and that the first product of the ethanolysis reaction may be the corresponding ketol, R-CH_2CO-CH_2OH. This compound on enolization to R-CH=C(OH)-CH_2OH becomes a substituted allyl alcohol which presumably might be capable of undergoing an allylic shift i.e.,

$$\text{R-CH=C(OH)-CH}_2\text{OH} \rightleftharpoons \text{R-CHOH-C(OH)=CH}_2$$

(R = guaiacyl or syringyl)

The product of this rearrangement is an ene-diol which by hydrogen migration could give the hydroxy-ketone R-CHOH-CO-CH_3. This hydroxy-ketone is the dismutation isomer of R-CO-CHOH-CH_3 and both of these hydroxy ketones, in the form of their ethyl ethers, are isolated from the ethanolysis products of lignin.

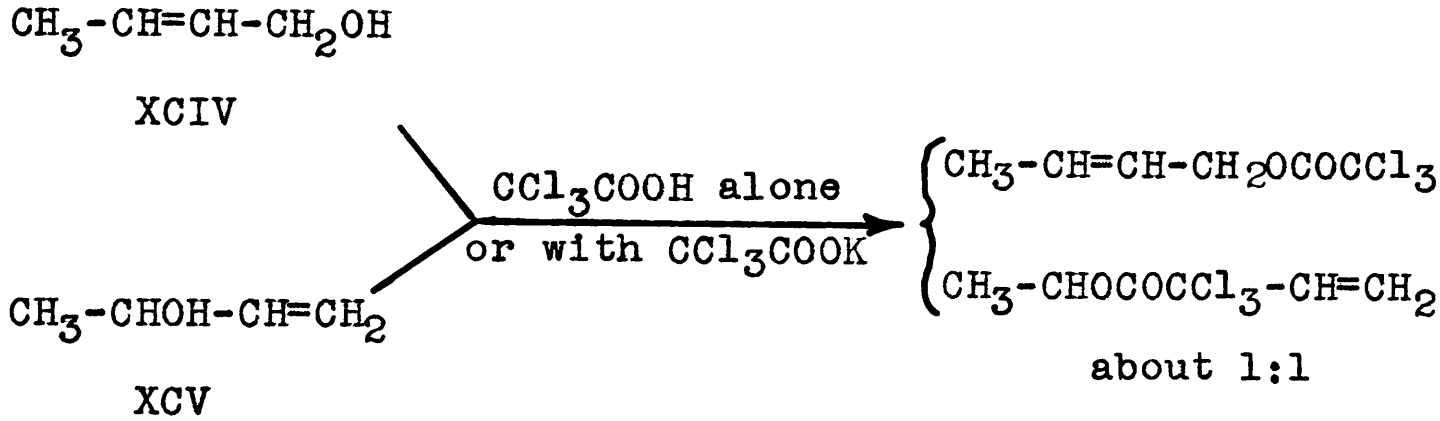
The simple allylic shift is a well recognized, but not a well understood transformation. It is usually observed in replacement reactions, but also occurs by simple isomerization of a molecule. A typical example (77a) of the shift is found in the esterification of phenyl vinyl carbinol (XCII) and cinnamyl alcohol (XCIII) with hydrochloric or hydrobromic acids. Here phenyl



vinyl carbinol undergoes an allylic rearrangement, while with cinnamyl alcohol simple substitution occurs.

About 1930 the allylic shift began to receive considerable attention, notably from Prevost (78), Burton (79) and Meisenheimer (77). Prevost and Burton confined themselves primarily to the esterification of allyl alcohols, principally aliphatic, of the types R-CH=CH-CH_2OH and R-CHOH-CH=CH_2, using acetic and trichloracetic acids and their anhydrides. Prevost found that esterification of either crotyl alcohol (XCIV) or of methyl vinyl carbinol (XCV), with trichloracetic acid gave essentially the same mixture (about 1:1) of acetates. With the anhydride some variation from this mixture was found but Prevost did not

consider the deviation to be very significant. He concluded that an equilibrium existed between the two alcohols and explained it by an ionic mechanism. He believed that loss of the hydroxyl gave rise to the ion $CH_3 - \overset{\oplus}{C} - \overset{\ominus}{C}H - \overset{\oplus}{C}H_2$ from either alcohol and that the composition of the resulting mixture was governed solely by the relative affinity of the acetate ion for the two positive charges.



Burton in his studies (79) found less uniformity in the composition of the mixture and showed also that heating the esters in solvents of high dielectric constant would isomerize them. He concluded that no simple equilibrium existed between the isomers but that the composition of the mixture $R\text{-}CHX\text{-}CH{=}CH_2$ and $R\text{-}CH{=}CH\text{-}CH_2X$ was controlled by three factors (a) some molecular property of the solvent such as the dielectric constant; (b) the mobilizing power of the group R; and (c) the anionic stability of X. With regard to R, Burton found that n-hexyl- and iso-amyl- groups had about the same activating effect as methyl but that aromatic groups gave a much more labile system and exerted a greater

directing influence. The migratory tendency of X, he found, varied as the strength of the acids HX; thus bromide ion was more mobile than the trichloracetate radical, which in turn was more mobile than the p-nitro benzoate.

Meisenheimer and Link (77a) studied a wide variety of reactions of the two systems $C_6H_5-CH=CH-CH_2X \rightleftharpoons C_6H_5-CHX-CH=CH_2$ and $C_2H_5-CH=CH-CH_2X \rightleftharpoons C_2H_5-CHX\ CH=CH_2$. The following changes summarize the most important of their results.

X = Br or Cl

$C_6H_5-CHOH-CH=CH_2$ and $C_6H_5-CH=CH-CH_2OH$ —HCl, HBr with or without solvent→ $C_6H_5-CH=CH-CH_2X$ (90%)

$C_6H_5-CH=CH-CH_2X$ —H_2O or dilute alkali→ mainly……$(C_6H_5-CH=CH-CH_2)_2O$; trace……$C_6H_5-CH=CH-CH_2OH$; occasionally..$C_6H_5-CHOH-CH=CH_2$

$C_6H_5-CH=CH-CH_2OH$ and $C_6H_5-CHOH-CH=CH_2$ —warm dilute acids→ mainly $(C_6H_5-CH=CH-CH_2)_2O$

$C_6H_5-CH=CH-CH_2OH$ —alkali→ no reaction.

$C_6H_5-CHOH-CH=CH_2$ —alkali→ slow formation of $C_6H_5-\overset{\overset{O}{\|}}{C}-CH_2CH_3$

$C_6H_5-CH=CH-CH_2X$ —KCN or $KHCO_3$ - 8% C_2H_5OH / NaOH-70% C_2H_5OH→ $C_6H_5-CH=CH-CH_2OC_2H_5$ (70%); $C_6H_5-CHOC_2H_5-CH=CH_2$ (30%)

$C_6H_5-CH=CH-CH_2X$ —KOH, abs. alcohol→ $C_6H_5-CH=CH-CH_2OC_2H_5$ only

(They found that the ethers of the two alcohols did not undergo rearrangement.)

$C_6H_5-CH=CH-CH_2OH \xrightarrow[\text{pyridine}]{CH_3COCl} C_6H_5-CH=CH-CH_2OCOCH_3$ quantitative

(hydrolysis of the acetate gives no rearrangement)

$C_6H_5-CH=CH-CH_2Cl \xrightarrow[1\text{ hr. at }100^\circ]{\text{glac. } CH_3COOH}$ $C_6H_5-CH=CH-CH_2OCOCH_3$ 55-60%; $C_6H_5-CHOCOCH_3-CH=CH_2$ 40-45%

$C_2H_5-CHOH-CH=CH_2 \xrightarrow[0^\circ]{\text{dry HCl}}$ $C_2H_5-CHCl-CH=CH_2$ 40%; $C_2H_5-CH=CH-CH_2Cl$ 60%

$C_2H_5-CH=CH-CH_2OH \xrightarrow[0^\circ]{\text{dry HCl}}$ $C_2H_5-CHCl-CH=CH_2$ 70%; $C_2H_5-CH=CH-CH_2Cl$ 30%

$C_2H_5-CH=CH-CH_2OH \xrightarrow[(\text{ether})]{SOCl_2} C_2H_5-CHCl-CH=CH_2$ 80%

$C_2H_5-CHOH-CH=CH_2 \xrightarrow[\text{diethyl aniline}]{SOCl_2}$ $C_2H_5-CHCl-CH=CH_2$ 45%; $C_2H_5-CH=CH-CH_2Cl$ 55%

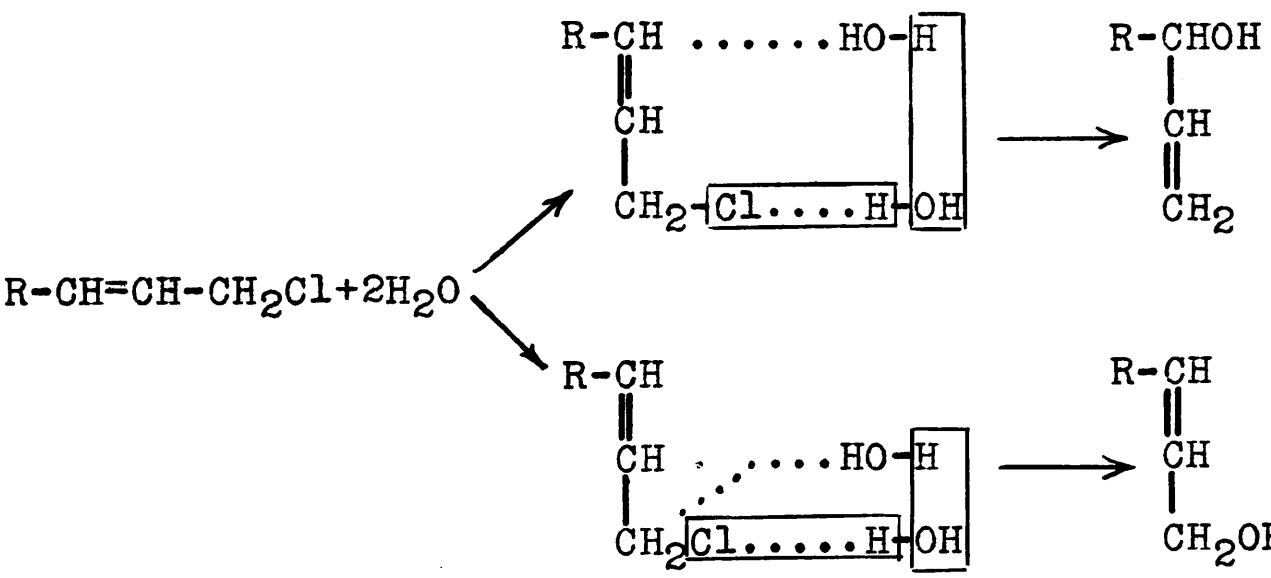
$C_2H_5-CHOH-CH=CH_2$

$C_2H_5-CH=CH-CH_2OH \xrightarrow[\text{pyridine}]{CH_3COCl}$ corresponding acetate in high yields without rearrangement.

$C_2H_5-CH=CH-CH_2Cl \xrightarrow[116^\circ - 4\frac{1}{2}\text{ hrs}]{\text{HOAc-KOAc}}$ $C_2H_5-CH=CH-CH_2OAc$ 90%; $C_2H_5-CHOAc-CH=CH_2$ 7-8%

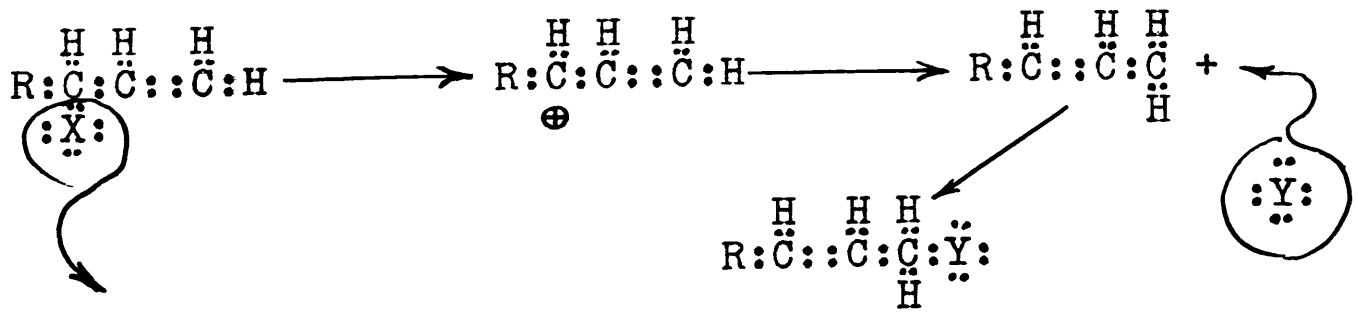
It is apparent from these reactions that the phenyl group exerts a much greater directing influence upon the shift

than does the ethyl group. It is also true that these reactions provide very little support for the assumption of an equilibrium between the two isomers. To explain the isomerizations, Meisenheimer and Link suggested that the reaction might occur through addition and elimination of the reagent; for example,



There is however, little basis for such a view.

In an attempt to explain the allylic rearrangement, Whitmore (80) applied his theory of "open sextets" to the problem, as follows.



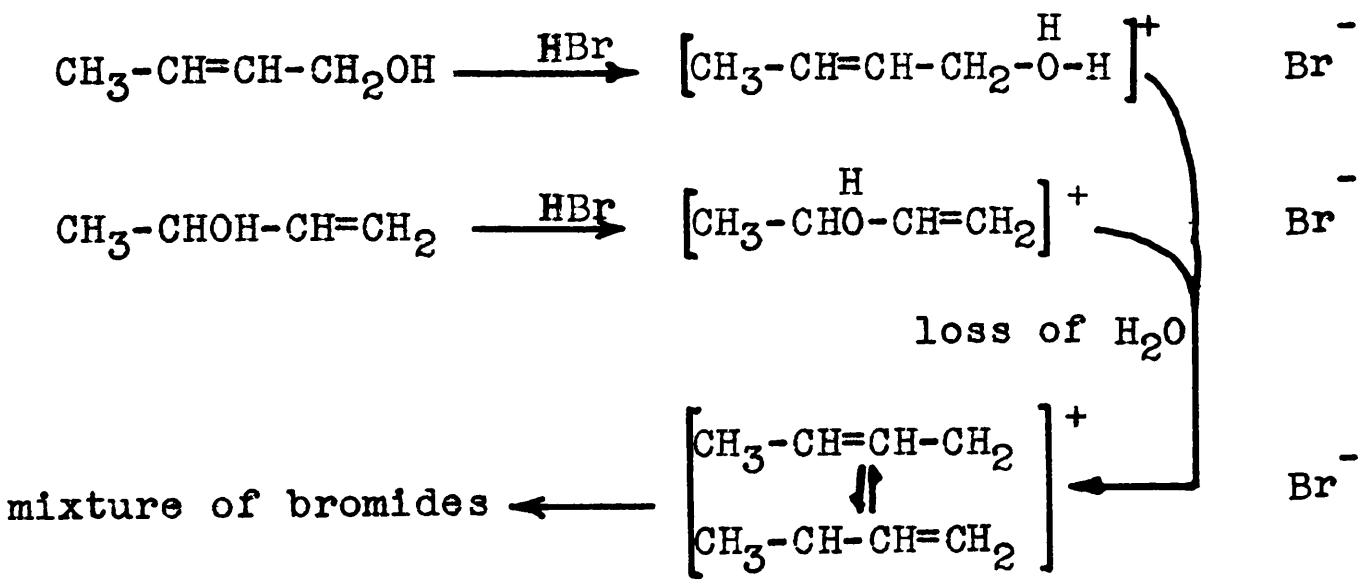
The anion X is eliminated with its electrons and leaves a positively charged fragment. By a shift of one of the electron

pairs from the double bond to the "open sextet" a new fragment is created. The incoming ion, Y, can attach itself to either of the two fragments. It can be seen that this theory is not very different to that of Prevost (78a).

In recent years, Young and co-workers (81) have carried out extensive investigations on the allylic shift as it occurs in the conversion of crotyl alcohol and methyl vinyl carbinol to the corresponding bromides. By using a variety of reagents and by standardizing the conditions in each case, they showed (a) that each alcohol always gave the same mixture of bromides, (b) that the two alcohols, when treated identically, gave slightly but significantly different mixtures, and (c) that the nature of the mixtures obtained varied with the method of esterification.

They concluded that while an equilibrium of some sort was indicated, the ionic mechanism of Prevost was an inadequate explanation, since it failed to account for the slightly different reactions of the isomeric alcohols. They pointed out also that much of the confusion in the work of Burton (79), Prevost (78), and to a lesser extent, in that of Meisenheimer (77), was due to failure of these workers to recognize two distinct types of allylic shift, one completely thermal and the other chemical. By carrying out their reactions at 0°, or lower, where the bromides are quite stable they eliminated the thermal reaction.

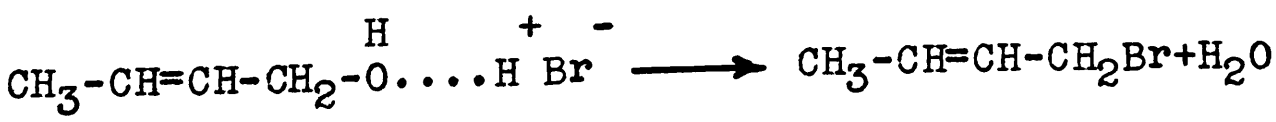
To explain their results they suggested that two mechanisms are involved in these intramolecular changes. The first accounts for the greater part of the reaction and is essentially similar to that of Prevost and others.



resonating system

According to Young, the composition of the mixture of bromides obtained by this system will depend entirely upon the medium (i.e. dielectric constant, etc.) and upon the nature of the resonating system, but not upon the alcohol itself.

The second reaction (shown below) occurs only to a slight extent and serves to explain the small differences in composition of the mixtures of bromides obtained by identical methods from the isomeric alcohols. The oxonium ion is assumed to add bromine and lose water without resonating so that no rearrangement occurs.



The above results found by the various workers were all obtained using normal unsubstituted allylic type compounds and no investigation as yet has been made employing substituted allyl derivatives of the type $R\text{-}CH{=}CY\text{-}CH_2X$. However, if Y were a hydroxyl group, the substance would be an enol corresponding to the ketone $R\text{-}CH_2\text{-}CO\text{-}CH_2X$ and a few examples of allylic shifts in such compounds do actually appear to exist. As already mentioned, Danilov and Danilova (65) found that the hydroxy aldehyde XCVI undergoes re-arrangement and oxidation (intermolecular) to phenyl acetyl carbinol (LXXXIX) and to benzoyl methyl ketone (XCVII).

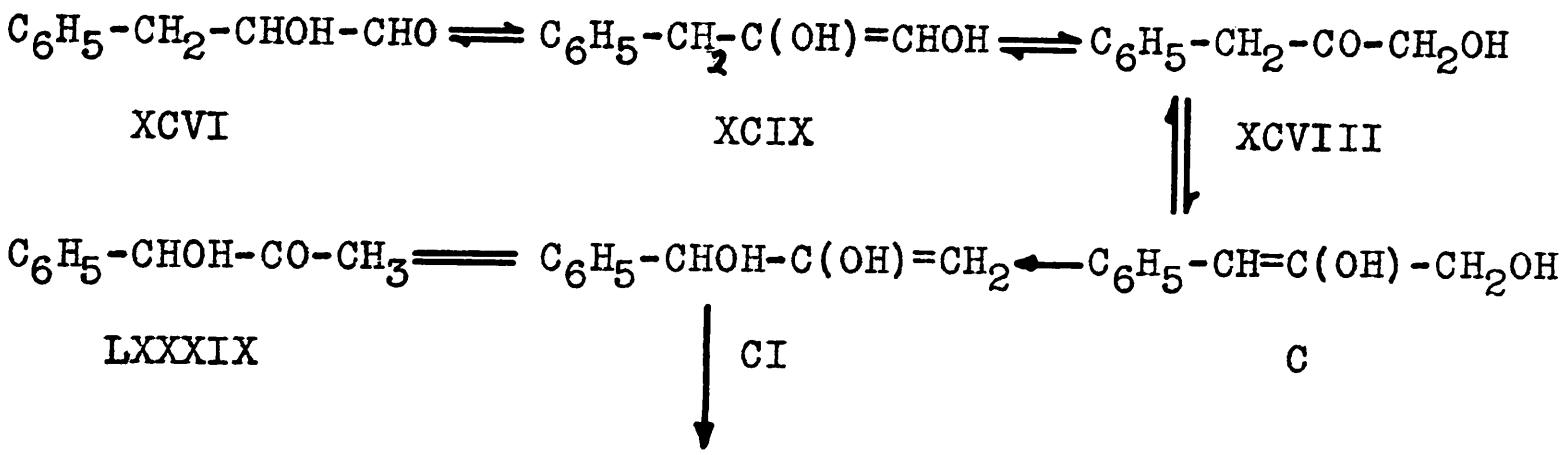
$$C_6H_5\text{-}CH_2\text{-}CHOH\text{-}CHO \longrightarrow C_6H_5\text{-}CHOH\text{-}COCH_3 + C_6H_5CO\text{-}COCH_3$$

XCVI LXXXIX XCVII

They claim that the hydroxy-aldehyde is stable under the experimental conditions required for the hydrolysis of the corresponding α-bromo-aldehyde with aqueous barium carbonate but that it undergoes rearrangement on heating with dilute ethanolic sulphuric acid.

It is apparent from the earlier discussion that the first step in the rearrangement of the hydroxy aldehyde (XCVI) is probably a dismutation to the corresponding hydroxy-ketone (XCVIII) through the ene-diol XCIX. This ketone (XCVIII) has been reported in the literature by a number of workers (82) without mention of any tendency of the product to

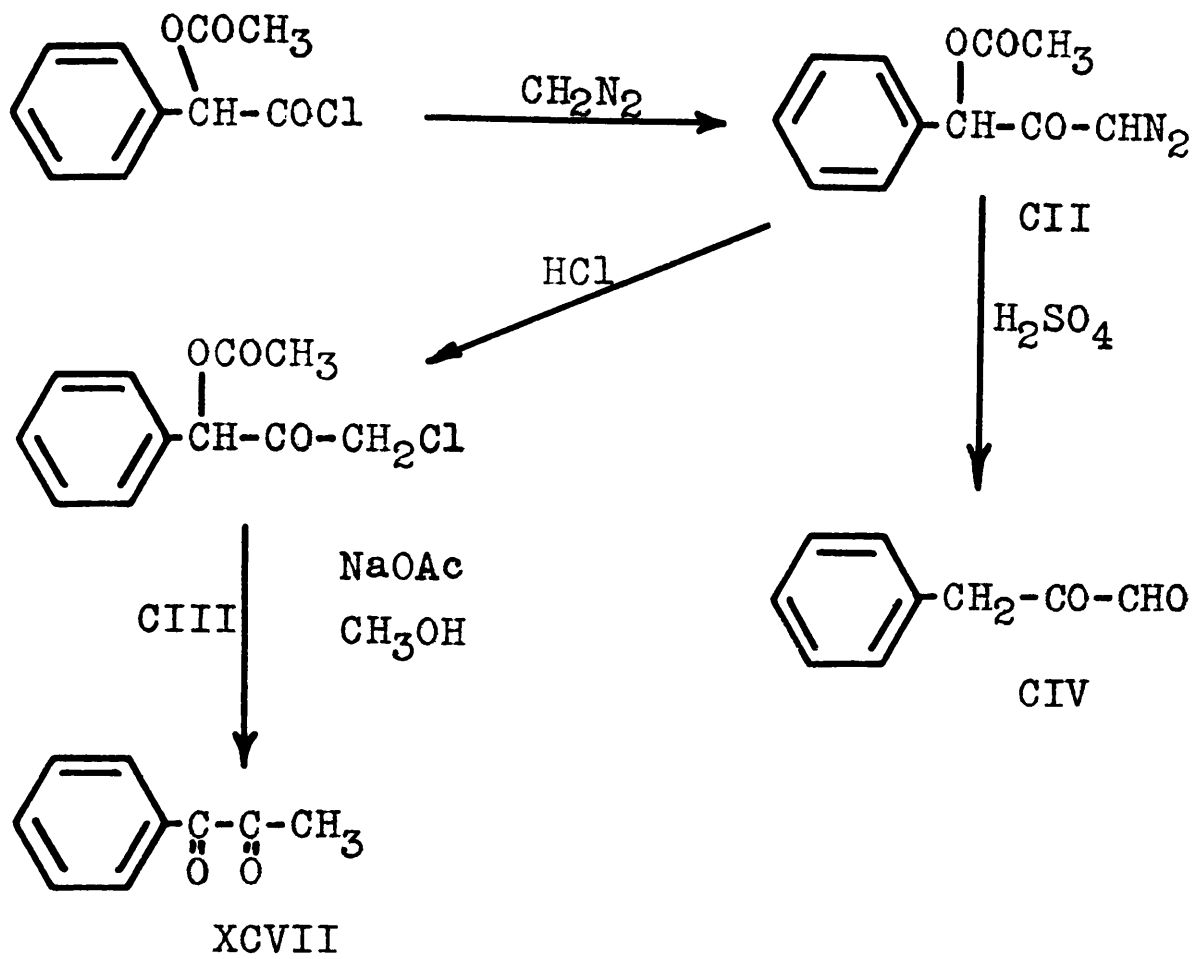
undergo rearrangement. However, since none of them was interested in this aspect, much significance cannot be attached to their results. The second step in the rearrangement is probably a second enolization to C, followed by an allylic shift to give the ene-diol (CI) of phenyl acetyl carbinol (LXXXIX). It has already been shown that the latter hydroxy ketone is stable to dilute acids.



C_6H_5-CO-CO-CH_3

XCVII

Such a mechanism would readily explain this rearrangement. The allylic shift occurs in the opposite direction to that which might be expected from studies of cinnamyl alcohol, but the difference is undoubtedly due to the presence of the additional hydroxyl group and to the formation of a stable product. The following series of reactions, reported by Bradley and Eaton (83) can probably be explained by a similar mechanism and illustrate an allylic shift in both directions.

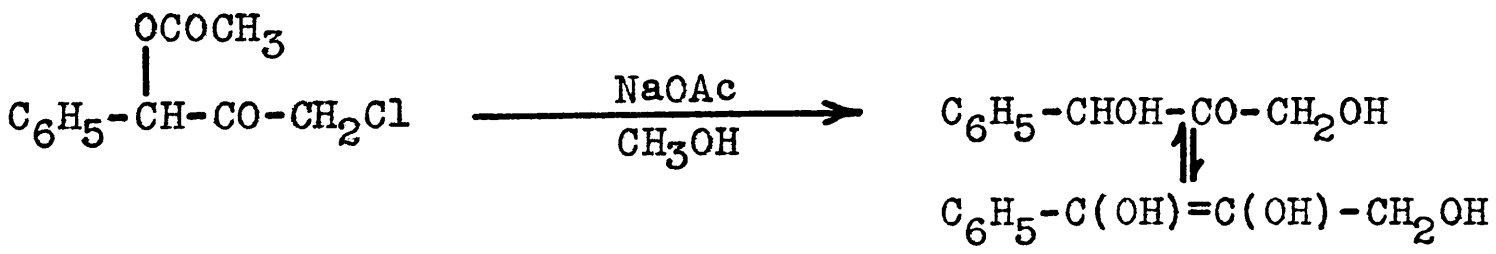


XCVII

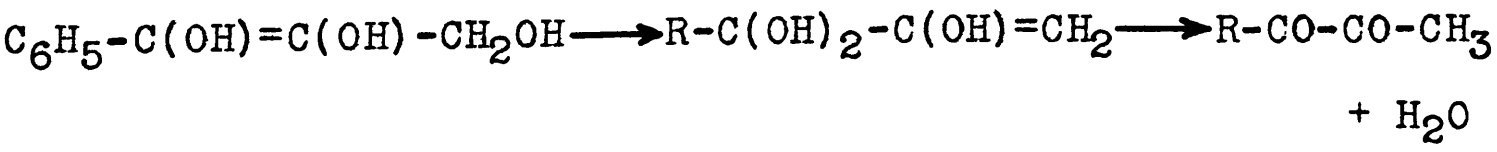
These reactions presumably proceed as follows:

Reaction I - Hydrolysis of the chloro-ketone (CIII)

(a) the chloro-ketone undergoes hydrolysis, followed by enolization:

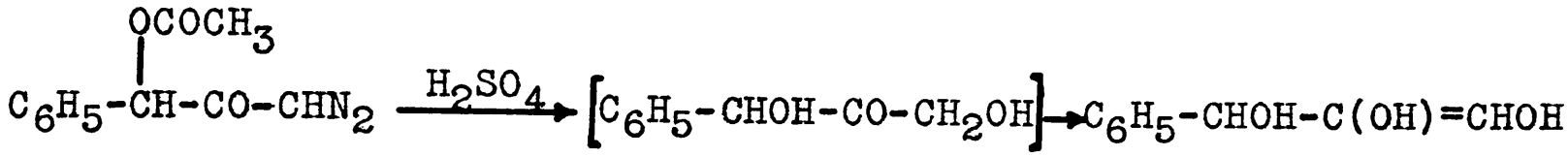


(b) an allyl shift occurs and is followed by loss of water and hydrogen migration

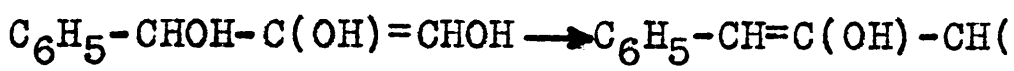


Reaction II - Hydrolysis of the diazomethyl ketone (CII)

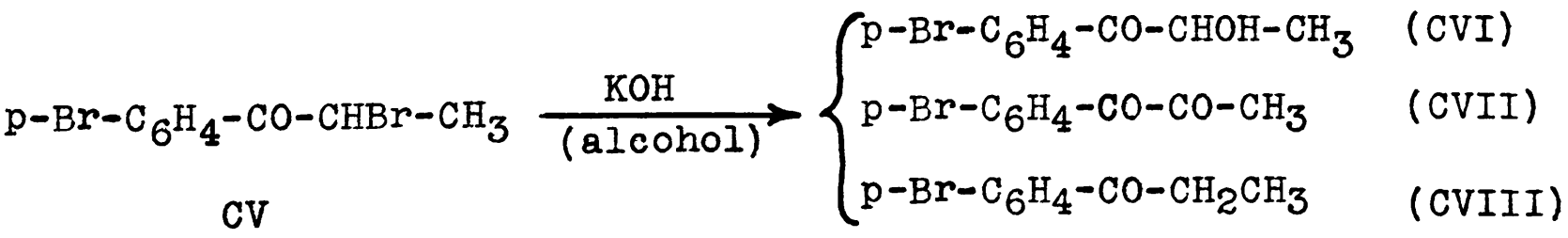
(a) the diazomethyl ketone undergoes hydrolysis, again followed by enolization. In this case, however, the enolization occurs in the opposite direction



(b) an allyl shift, but in the reverse direction to the above, and again followed by loss of water and hydrogen migration.



Also of interest in this connection is the work of Kohler (84) on the reactions of alcoholic potassium hydroxide with a variety of α-bromo-ketones. These ketones were essentially of the alkyl-aryl type, i.e. R-CO-CHBr-CHRR', where R, in general, is aromatic. Three products are formed namely (1) R-CO-CHOH-CHRR'; (2) R-CO-CO-CHRR' and (3) R-CO-CH_2-CHRR'. Thus 2-bromo-1-(4-bromo-phenyl)-propanone-1 (CV) with concentrated alcoholic potash yields CVI, CVII & CVIII,



in yield of 11, 20 and 20% respectively.

These changes only occur when the strong alkali solution is added slowly to the bromo-ketone at room tempera-

ture. If the alkali is added rapidly to a boiling solution of the bromo-ketone, a high yield of benzoin (CVI) is obtained. The diketone (CVII) is formed in quantity only when the solution is alkaline. Kohler also found that the benzoins R-CO-CHOH-CHRR', under the same conditions of alkali treatment do not yield the diketones so presumably they do not represent the intermediates (or sole intermediates) in these transformations. It is possible that the mechanism may be as follows:

(a) $R\text{-}CO\text{-}CHBr\text{-}CHRR' \xrightarrow{KOH} R\text{-}CO\text{-}CHOH\text{-}CHRR' \rightarrow RC(OH)=C(OH)\text{-}CHRR'$

$\downarrow KOH$

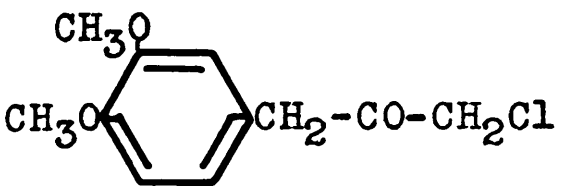
$R\text{-}COH=C(OK)\text{-}CHRR'$

(b) $R\text{-}COH=C(OK)\text{-}CHRR' + R\text{-}CO\text{-}CHBr\text{-}CHRR' \longrightarrow R\text{-}COH\text{-}C(O)\text{-}CHRR' \longrightarrow R\text{-}CO\text{-}CO\text{-}CH\text{-}RR' + R\text{-}CO\text{-}CH_2\text{-}CHRR'$

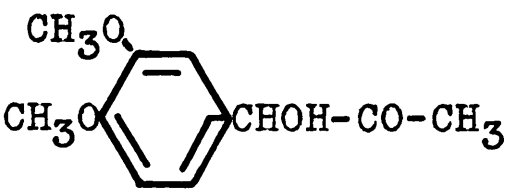
A similar type of reaction may be involved in the ethanolysis of wood whereby the benzoin $R\text{-}CHOH\text{-}CO\text{-}CH_3$ (R = guaiacyl) possibly is converted into $R\text{-}CO\text{-}CO\text{-}CH_3$ and $R\text{-}CH_2\text{-}CO\text{-}CH_3$.

In the experimental section of this thesis further similar reactions of substituted ketones will be discussed. It will be shown that hydrolysis of the chloro-ketone CIX yields

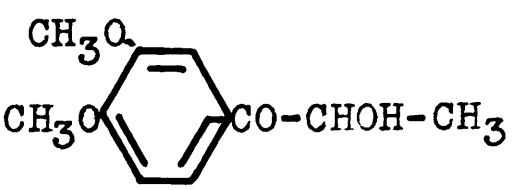
the hydroxy-ketones CXI



CIX



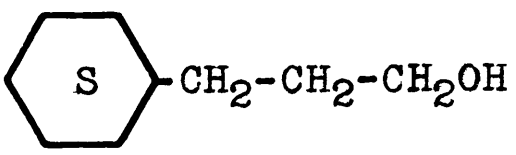
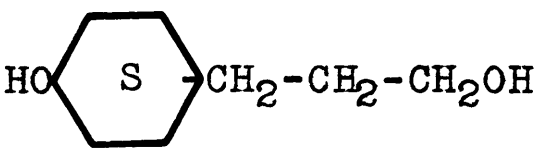
CX

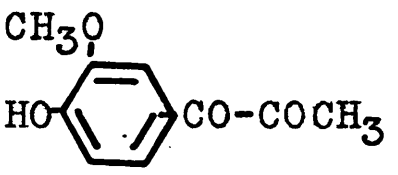


CXI

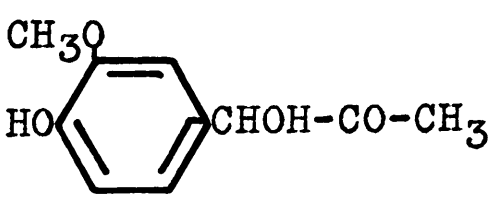
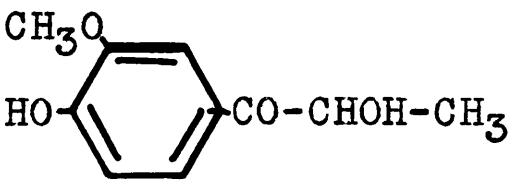
and CXII or derivatives of the latter.

From this discussion of dismutation and allylic rearrangements it is apparent that Hibbert's theory of lignin as a derivative of a series of interrelated ketones is indeed tenable. When it is recalled, in the light of this review, that hydrogenation of lignin leads to the isolation of cyclohexyl derivatives of n-propanol, i.e.

 and 

and that ethanolysis of lignin gives the diketone 

and ethyl ethers of the two hydroxy ketones

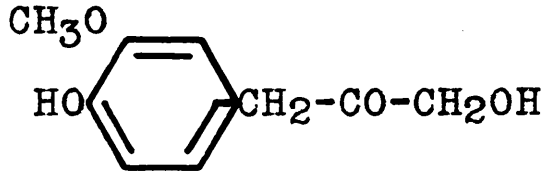
 and 

it is apparent there is good reason to believe that the primary ethanolysis product may be a hydroxy ketone or hydroxy aldehyde of the type

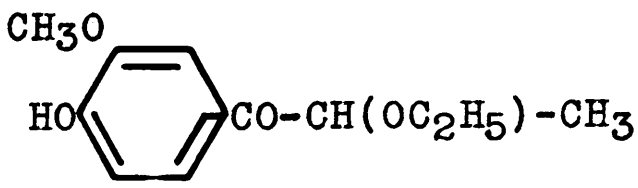
$R\text{-}CH_2\text{-}CO\text{-}CH_2OH$ or $R\text{-}CH_2CHOH\text{-}CHO$

Discussion of Experimental Results

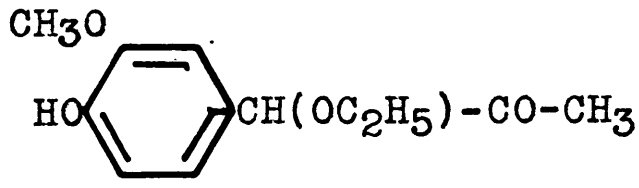
The object of this research was to synthesize 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propanone-2 (XXXI), and to investigate its behaviour towards chemical reagents, particularly with a view to determining any possible relationship between this compound and the spruce wood ethanolysis products XX and XXVI.



XXXI



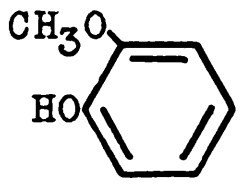
XX



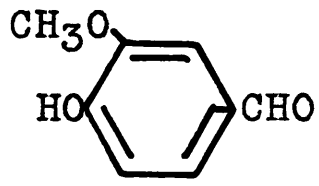
XXVI

The phenyl analogue of XXXI has been synthesized by a number of workers (82) but, as already mentioned, in none of their studies was the synthesis undertaken with a view to ascertaining the possibility of intramolecular rearrangements under the influence of mild reagents. The methods of preparation vary, but none is readily applicable to the guaiacyl analogue since, in order to synthesize the latter the chemist is more or less limited to such readily

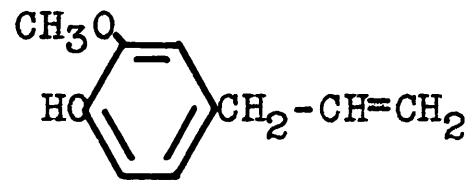
available starting materials as guaiacol (XII), vanillin (XI) and eugenol (XXVIII)



XII

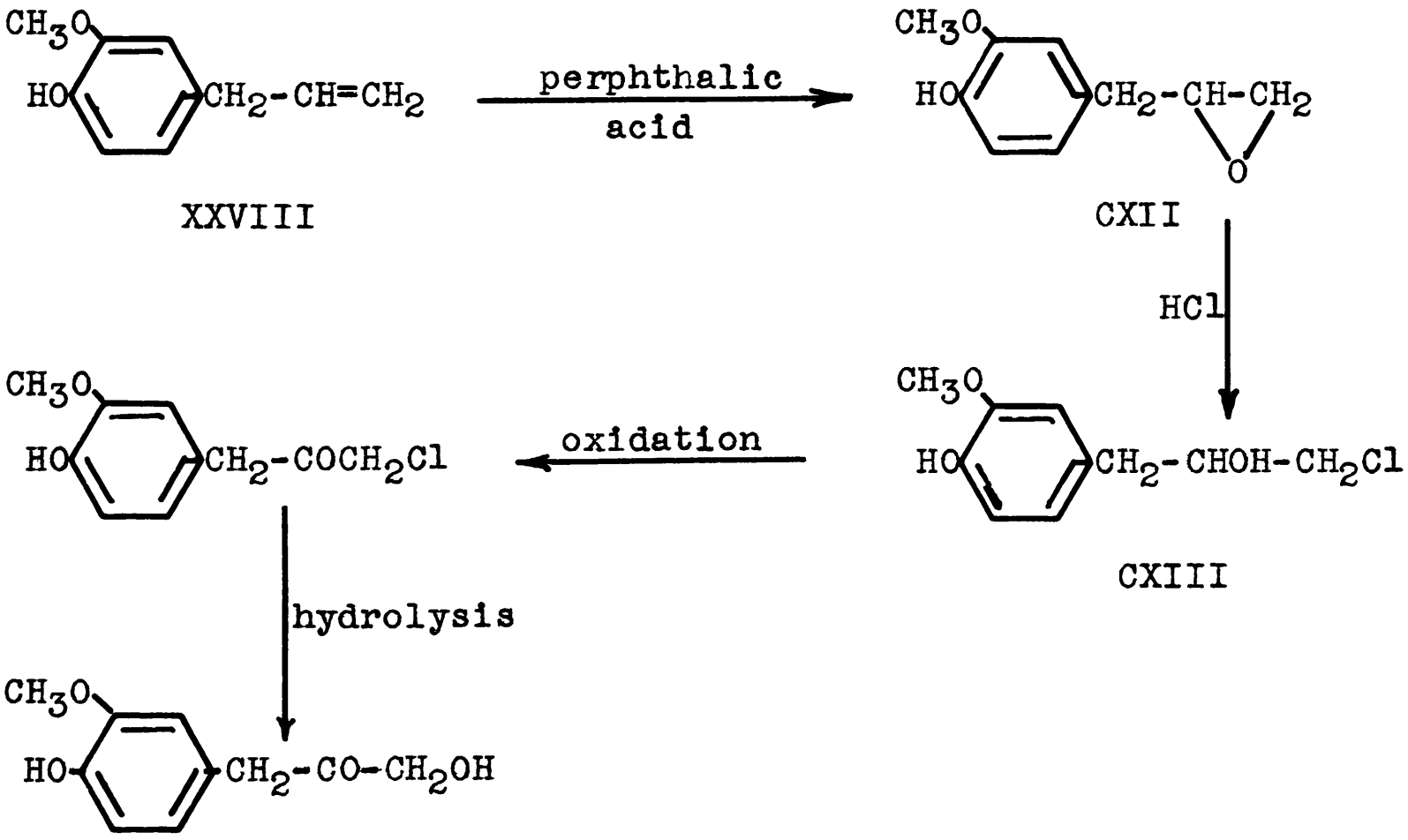


XI



XXVIII

In the first attempted synthesis of XXXI the following series of reactions was investigated:



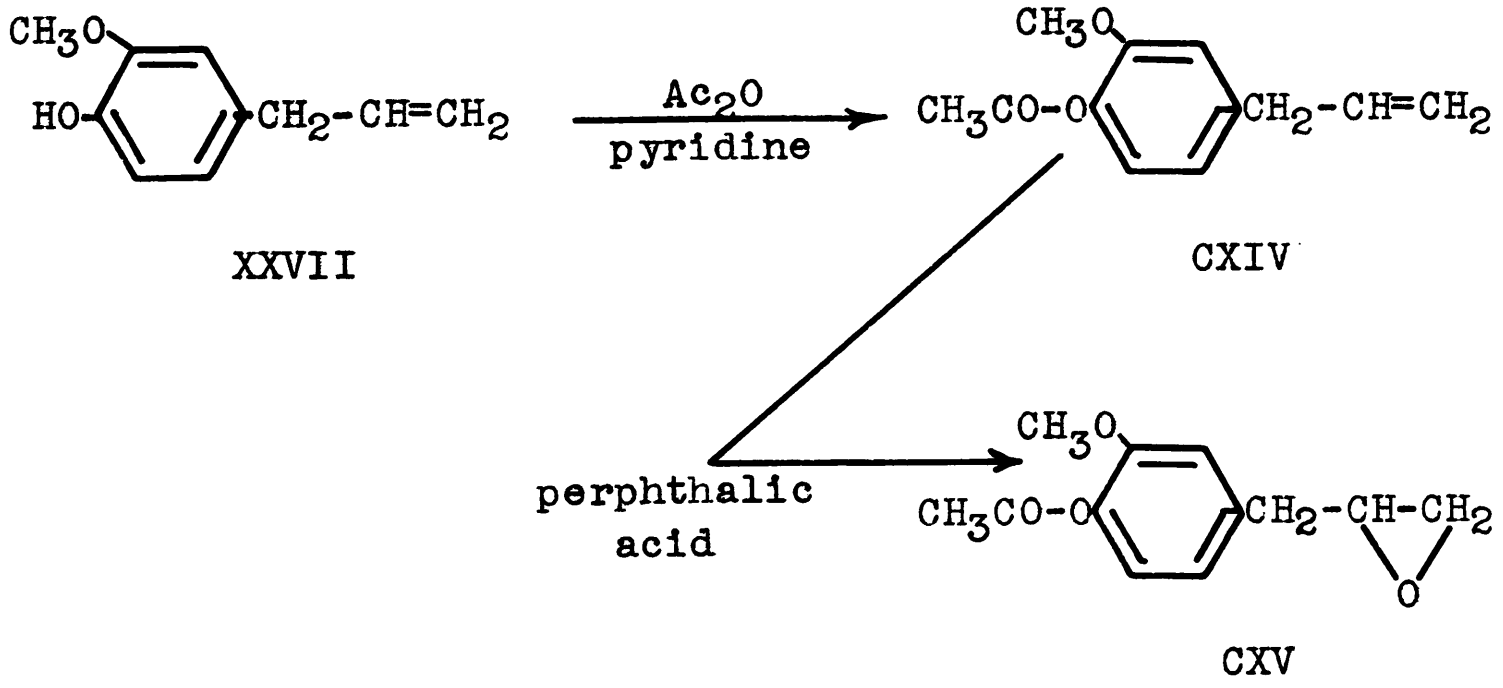
XXVIII

CXII

CXIII

Direct conversion of eugenol (XXVIII) to the chlorhydrin (CXIII) by addition of hypochlorous acid to the ethylenic linkage is not possible because of the strong tendency for the aromatic phenol nucleus to undergo chlorination with this reagent.

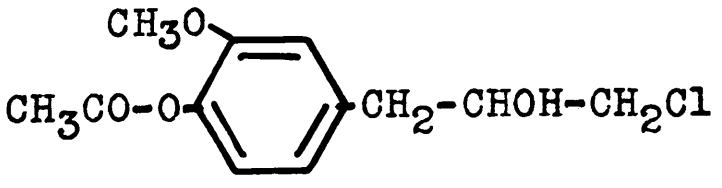
Conversion of eugenol to eugenol oxide (CXII) was not found practical. The reaction does not take place readily and gives an oil, apparently the oxide, in a yield of 8-10%. Similar results are reported by Arbuzov and Mikhailov (85) for the oxidation of eugenol with peracetic acid. This difficulty was overcome by the writer by first acetylating the eugenol. Treatment of the eugenol acetate (CXIV) then gave crystalline eugenol acetate oxide (CXV) in a yield of 50%.



XXVII CXIV CXV

Similar results were reported subsequently by Schopf et al (86).

Conversion of eugenol acetate oxide to the chlorhydrin (CXVI)

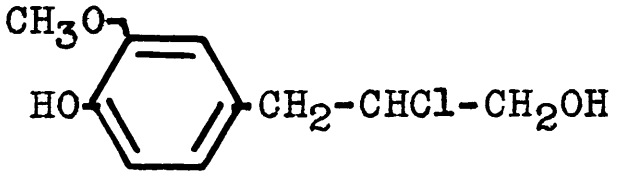


CXVI

was accomplished in good yield but required considerable care in order to avoid deacetylation. The oxide was added slowly at -10° to a dry ethereal solution containing the theoretical amount of hydrogen chloride and complete reaction obtained in 45 minutes. The product, a colorless oil, b.p. 137°/0.06 mm, was isolated by high vacuum distillation in yields of 90% or more. For reasons not known it was found necessary to use freshly prepared ethereal hydrogen chloride for this reaction.

The product formed an α-naphthyl urethane in low yield (45%).

The possible presence of the isomeric chlorhydrin (CXVII)



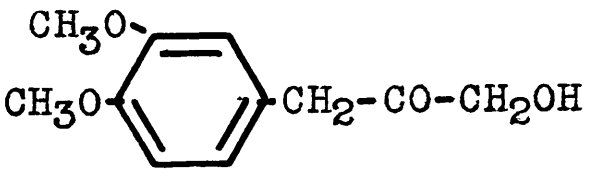
CXVII

cannot be disregarded, but from fractionation results, from Markovnikov's rule, from literature analogies and from the fact that a single urethane is obtained from the product it appears highly probable that CXVI is the main product and that CXVII can only be present in small amounts if at all.

The attempted oxidation of the chlorhydrin to the corresponding chloro-ketone by means of chromic oxide, in a variety of solvents and under various conditions, was unsuccessful. After complete reaction of the theoretical amount

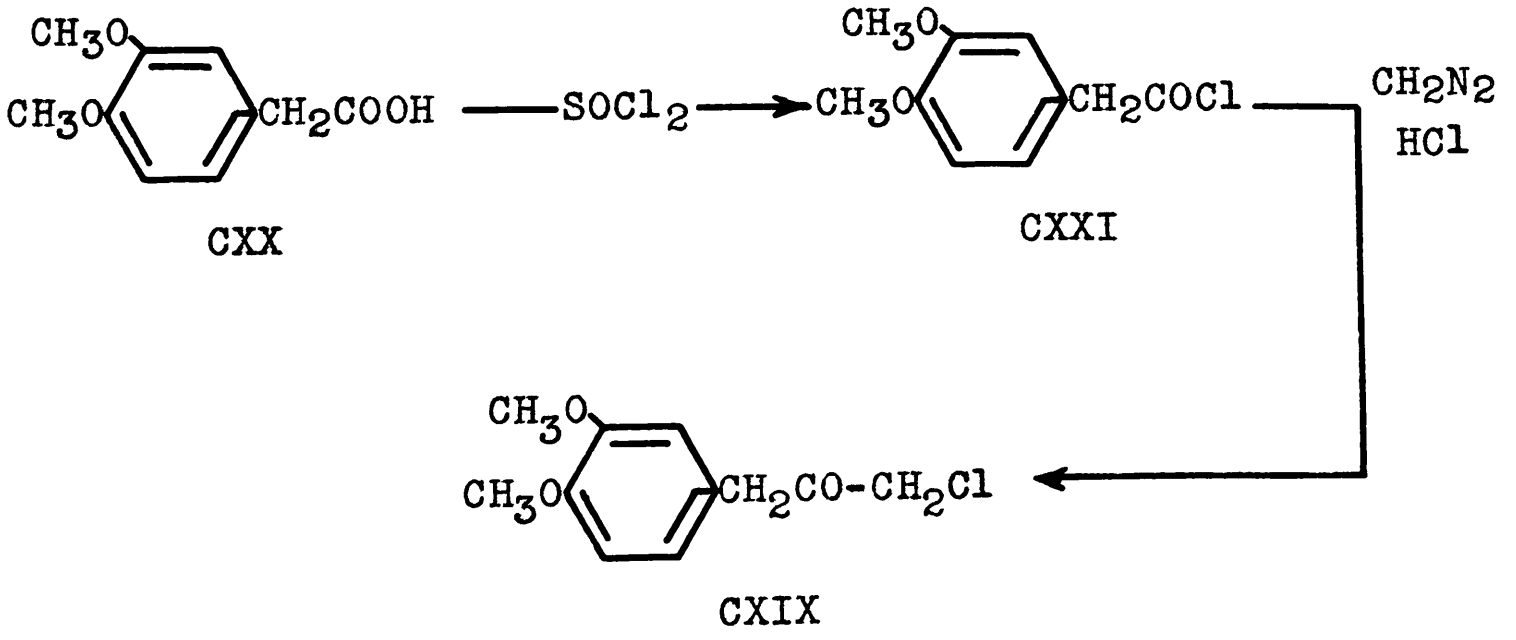
of chromic oxide, the greater part of the chlorhydrin was recovered unchanged indicating that secondary reactions predominated. No products were isolated from the residue although a pronounced odor of vanillin was noted.

Following this first unsuccessful attempt to synthesize the 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propanone-2, it was decided to attempt the synthesis of the corresponding veratryl derivative (CXVIII) by methods which might later be



CXVIII

applicable to the guaiacylic compound. Haworth and Atkinson (87) synthesized the chloro-ketone CXIX by converting homoveratric acid (CXX) with thionyl chloride to its acid chloride (CXXI) and then treating the latter with diazomethane and hydrogen chloride, i.e.



CXX

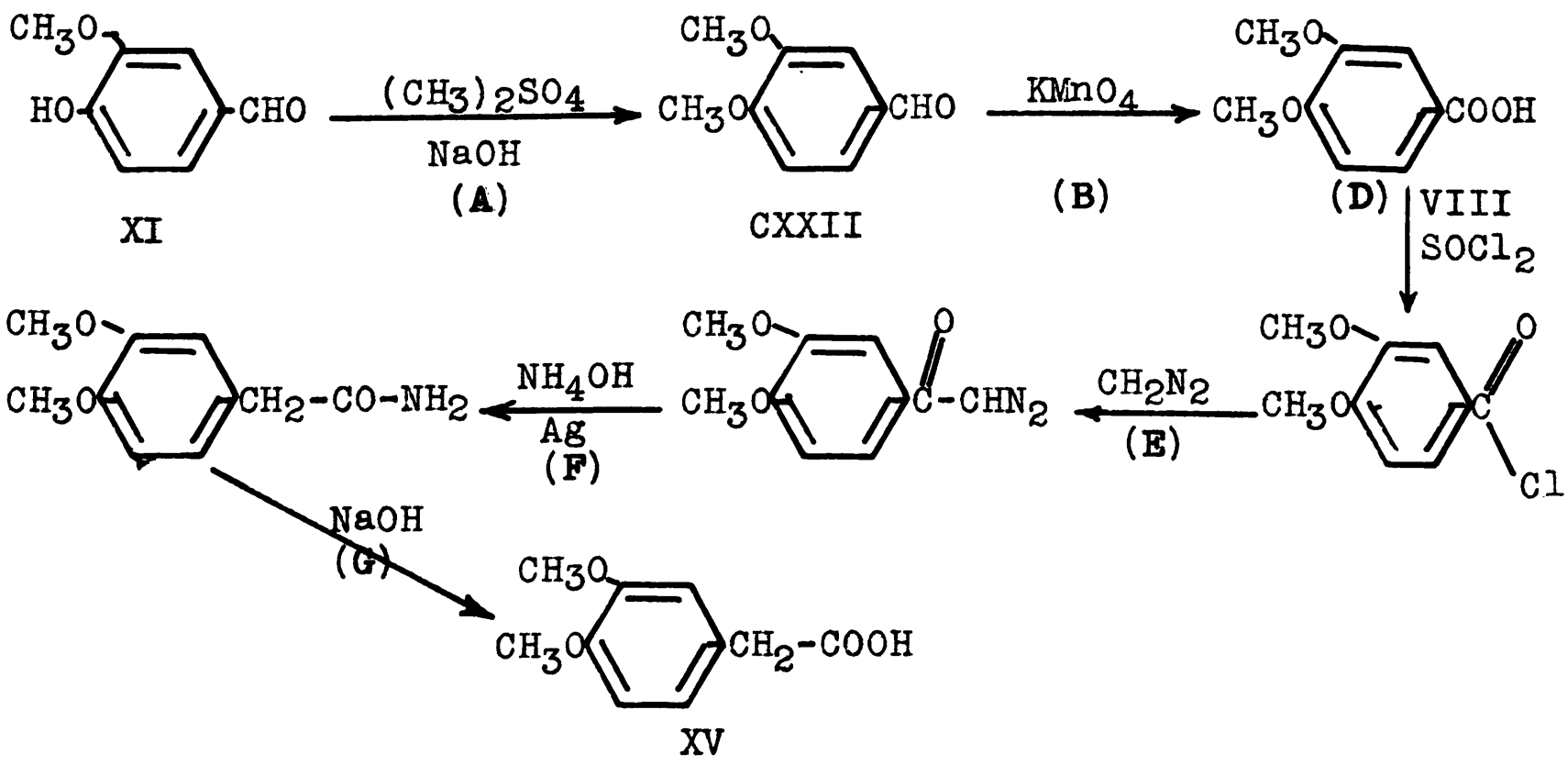
CXXI

CXIX

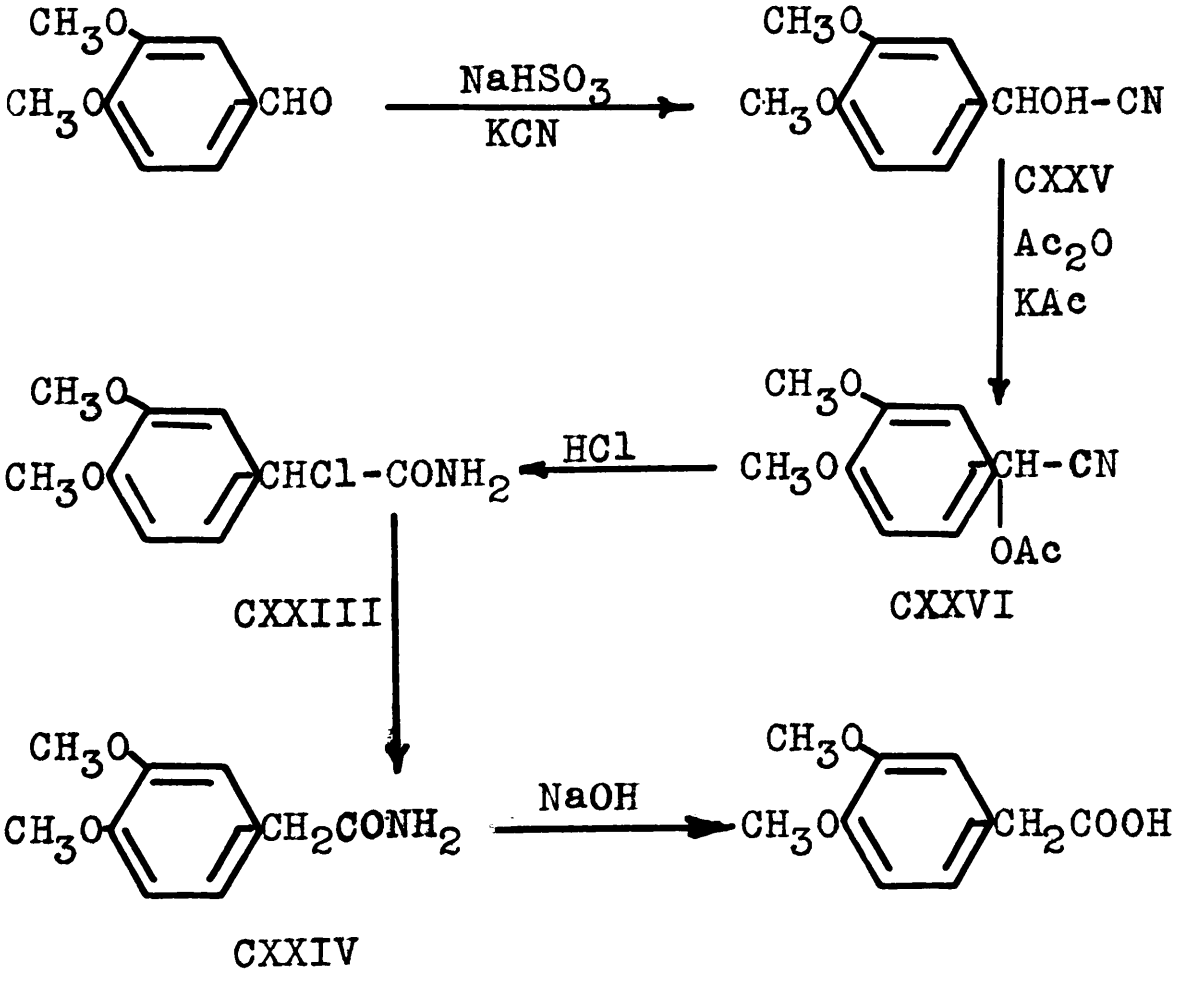
It was felt that these reactions might provide a suitable method of synthesis in spite of the known lack of satisfactory methods for the preparation of homoveratric and homovanillic acids.

The synthesis of substituted phenyl acetic acids has received considerable attention from various workers (88) possibly because of the interest aroused in naphthalene acetic acid and related products as plant growth promoting substances. After examination of the various methods for the synthesis of homoveratric acid, those of Arndt and Eistert (88a) and of Hahn, Stiehl and Schultz (88b) appeared to be the most suitable. The process developed by the former workers was employed in the initial studies but was abandoned later in favor of that of the latter workers which is less expensive, and somewhat more convenient.

The method of Arndt and Eistert is indicated in the following series of reactions:



The conversion (A & B) of vanillin (XI) to veratraldehyde (CXXII) and of the latter to veratric acid (VIII) were carried out by the methods of Buck (89) and of Schriner and Keiderer (90) respectively. Both reactions proceed smoothly and give excellent yields (80-90%). Similarly, conversion of the acid to its chloride (D) with thionyl chloride takes place smoothly with a yield of 85-90%. In the subsequent reactions (E, F and G) good agreement with the results of Arndt and Eistert was obtained, that is, an overall yield of 40-50%. The overall yield for the six steps was of the order of 25%. The method of Hahn, Stiehl and Schultz can be represented as follows:

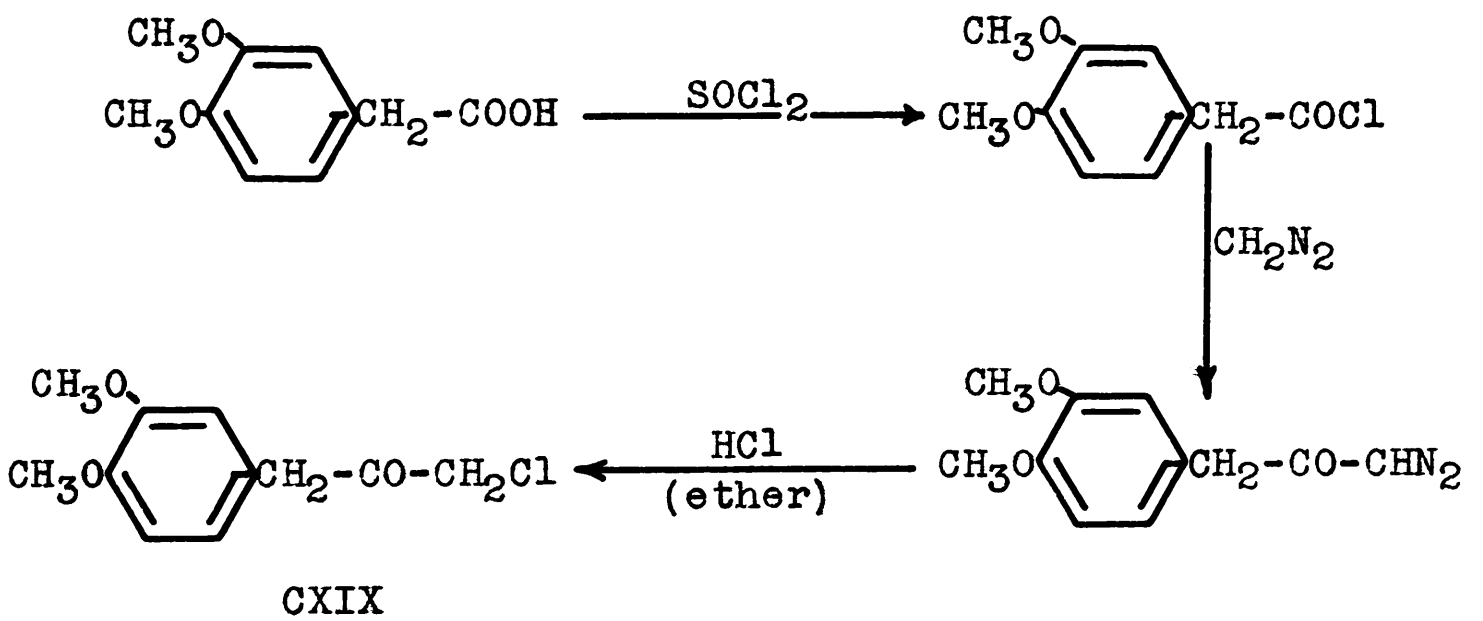


It was modified slightly for the present investigation in that the reduction of the chloro-amide (CXXIII) to homoveratric amide (CXXIV) was carried out with hydriodic acid in place of catalytic hydrogenation over palladium. The yield was slightly lower but the reaction was found to be more convenient, particularly with larger scale operations.

The chief difficulties in the synthesis were encountered in the initial steps. The condensation of veratric aldehyde with HCN gives good yields but the reaction mixture is difficult to handle because it tends to form stiff emulsions which must be broken quickly. Best results were obtained by shaking the emulsions with a mixture of alcohol and ether. To ensure good yields, the oxy-nitrile (CXXV) must be acetylated as soon as it is isolated. In most cases conversion of the acetoxy-nitrile (CXXVI) to the chloro-amide (CXXIII) took place smoothly and gave good yields, but as noted by Hahn, Stiehl and Schultz, poor yields are occasionally obtained with much tar formation. The reason for this is not known.

The chloro-amide can be rapidly reduced to homoveratric amide with hydriodic acid in glacial acetic acid. The product precipitates out as a beautiful crystalline, dark purple precipitate and is freed from iodine with sodium bisulphite. The yield is 75-80%. The amide is quantitatively hydrolysed to the acid by alkali.

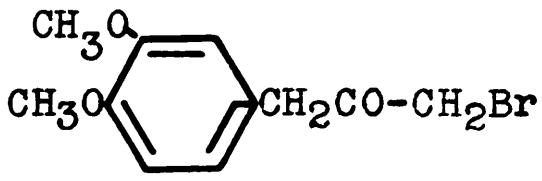
The chloro-methyl ketone, 3-chloro-1-(3, 4-dimethoxy-phenyl)-propanone-2 (CXIX) is obtained smoothly and in excellent yields from homoveratric acid by means of the so-called "Nierenstein reaction" (87,91). For good yields it is essential that the homoveratric acid and more especially,



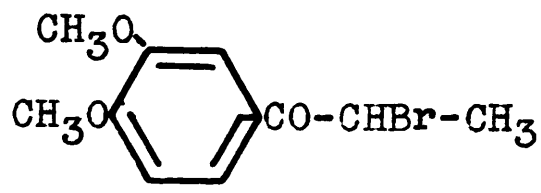
CXIX

the thionyl chloride should be carefully purified before use. Failure to observe this precaution may easily result in complete decomposition of the homoveratric acid. The chloro-ketone is obtained in yields of 90% or better, the crude product melting at 50-51°. Recrystallization failed to raise the melting point above 51°. When pure it will keep for several days but decomposes slowly.

To check the structure of the chloro-ketone, the corresponding bromide (CXXVII) was prepared in exactly the same way and its melting point found to be 44°-45°. The isomeric 2-bromo-1-(3, 4-dimethoxy-phenyl)-propanone-1 (CXXVIII)

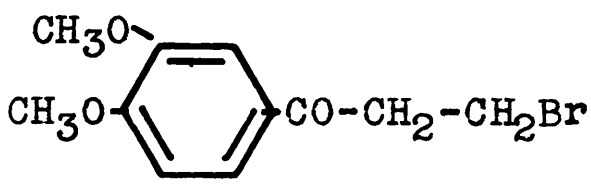


CXXVII

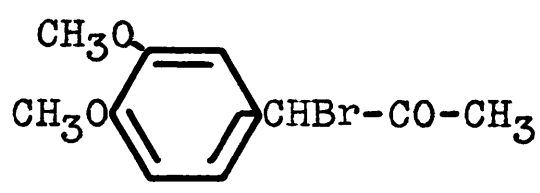


CXXVIII

is known and melts at 89°. The two remaining isomers, CXXIX and CXXX, have been prepared in these laboratories, the former by Mr. S. B. Baker, the latter by Mr. H.E. Fisher, and found to melt at 107-108° and 86-87° respectively. CXXVIII and CXXX



CXXIX

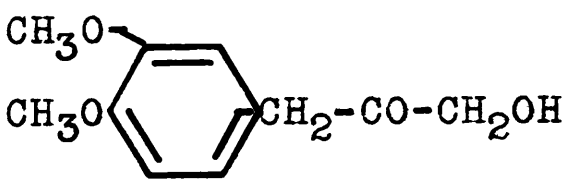


CXXX

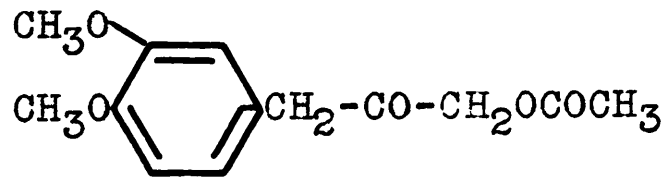
were prepared by direct bromination of the corresponding ketones, while CXXIX was synthesized from β-brom-propionic acid and veratrole by a Friedel-Craft reaction. The chloride corresponding to CXXIX has been reported by Freudenberg and Kentscher (92) and melts at 113°-114°. From these comparisons and since no rearrangements could be detected in the synthesis of these halides, there can be no doubt that they have the structures assigned to them. Furthermore, Bradley and Eaton observed no rearrangement in the preparation of the chloro-ketone, 3-chloro-1-acetoxy-1-phenyl-propanone-2 from the corresponding diazo compound (see pg.72). It seems probable that the conversion of these diazomethyl derivatives to chloro-ketones without rearrangement is due to the fact that the re-

action involves the addition of a molecule of hydrogen chloride rather than the replacement of a group by a chlorine atom or ion.

In all of the writer's experimental work the chloride (CXIX) was used, because the bromide, even when pure, is very unstable. It decomposes completely to a black tar in two days at room temperature.

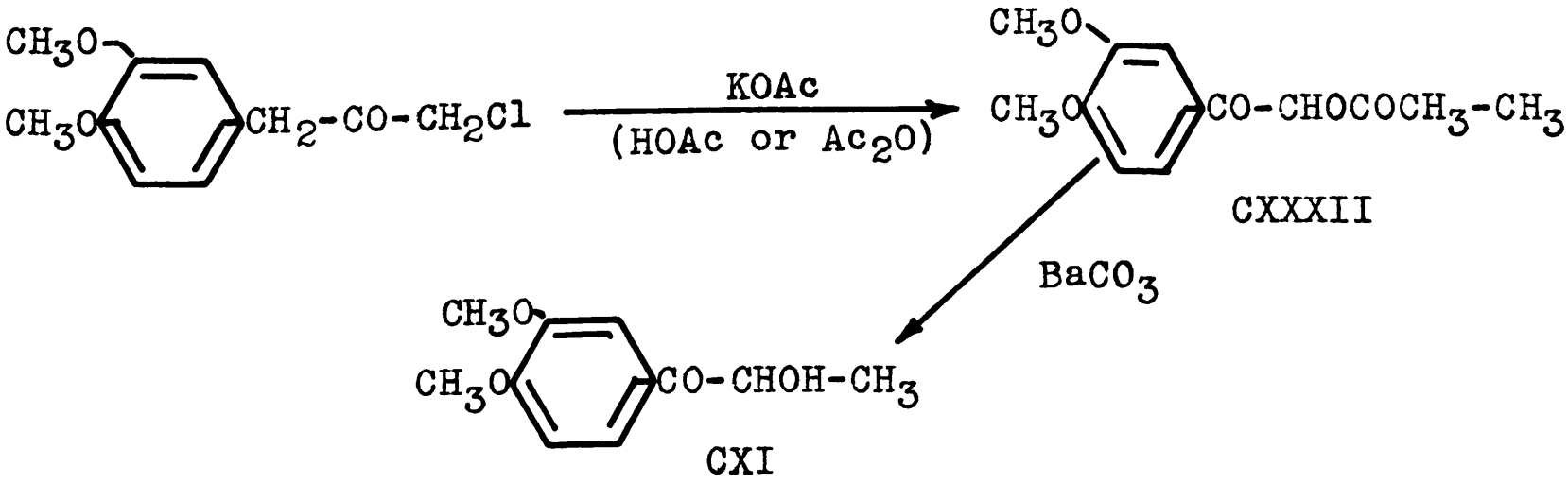


CXVIII



CXXXI

The first plan for the conversion of the chloro-ketone to its corresponding ketol (CXVIII) involved the preparation and hydrolysis of the corresponding acetate (CXXXI). The chloro-ketone was treated with potassium acetate in acetic acid or acetic anhydride and gave a partially crystalline product which proved extremely difficult to isolate. The crystalline component was separated by transferring the mixture to a porous plate and on recrystallization was shown, by mixed melting point determinations to be 2-acetoxy-1-(3, 4-dimethoxy-phenyl)-propanone-1 (CXXXII). Analysis of the

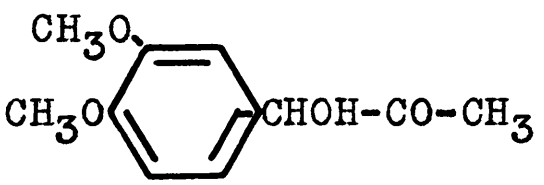


CXXXII

CXI

partially crystalline material indicated that it was probably a mixture of acetates of which CXXXII formed 50%. Hydrolysis of the mixture gave an oil which analysed for the ketols, and which was shown spectroscopically by Dr. R. Patterson of these laboratories, to contain about 92% of 2-hydroxy-1-(3,4 dimethoxy-phenyl)-propanone-1 (CXI). It was therefore apparent that the chloro-ketone had undergone a rearrangement in these reactions.

Hydrolysis of the chloro-ketone with 5% aqueous potassium acetate gave a new ketol (CX) at first believed to

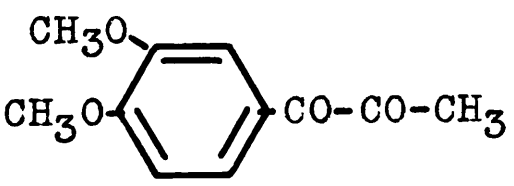


CX

be the desired product (CXVIII). It was separated from the aqueous solution by repeatedly extracting with chloroform, concentrating the extract, and distilling the residue under high vacuum in a carbon dioxide atmosphere. The distillate which set to a sticky crystalline mass, was taken up in ether and the solution (A) cooled to -10°. The ketol crystallized out and was filtered off. It proved to be a water soluble, white crystalline solid, melting at 75°-77°, and readily soluble in all organic solvents except petroleum ether. It could be recrystallized to constant melting point (76-77°) from small volumes of ether or benzene. The yield, about 50%, was decreased

when barium carbonate or silver oxide was substituted for the potassium acetate.

The ethereal residue left after isolating the ketol from A was fractionated in a small but efficient column under a few microns pressure of carbon dioxide. A small amount of a low boiling crystalline solid was isolated, but the remainder of the fractions showed neither constant boiling points nor constant refractive indices. The low boiling crystalline fraction was identified by mixed melting points as the 1,2-diketone, 1-(3,4-dimethoxy-phenyl)-propanedione-1,2. (CXXXIII) and its formation, in view of the precautions taken, could not have been the result of atmospheric oxidation. It is perhaps formed as the result of an intermolecular condensation reaction followed by a hydrogen migration as will be explained later.

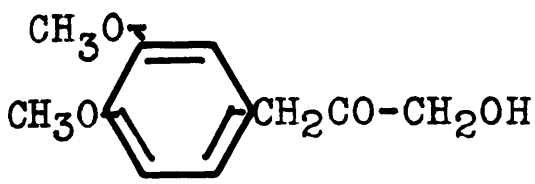


CXXXIII

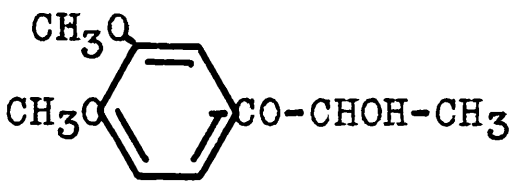
Identification of the New Ketol (CX)

From its method of preparation the new ketol was believed to have the structure CXVIII. The isomeric ketols 2-hydroxy-1-(3,4-dimethoxy-phenyl)-propanone-1 (CXI) and 3-hydroxy-1-(3,4-dimethoxy-phenyl)-propanone-1 (CXXXIV) have

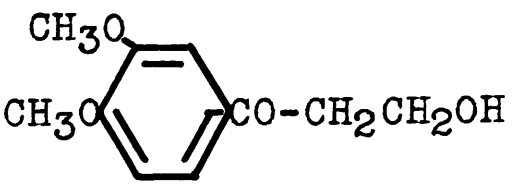
been previously synthesized (42,93) and were shown not to be identical with the new ketol. There remained however, the



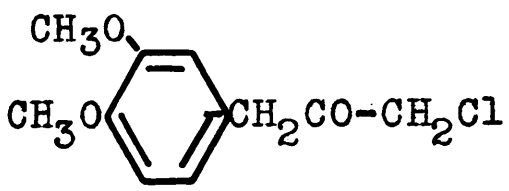
CXVIII



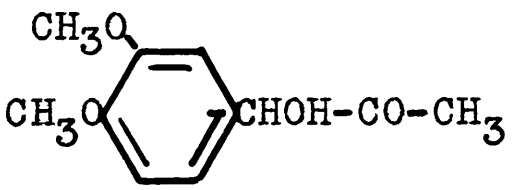
CXI



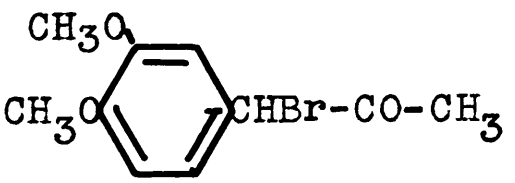
CXXXIV



CXIX



CX



CXXX

possibility that the new derivative might be the fourth isomer (CX) and to check this point the corresponding bromide (CXXX) was hydrolysed with potassium acetate by the same method as employed with the chlor-ketone (CXIX). The same hydroxy-ketone was obtained in a similar yield so that a rearrangement had occurred in one of these reactions and the product was either CXVIII or CX.

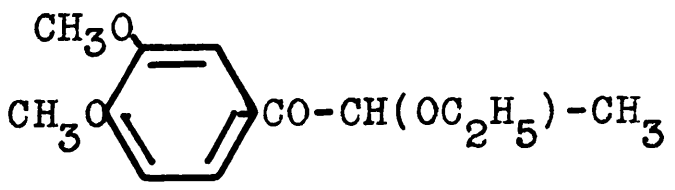
Its structure was definitely established as 1-hydroxy-1-(3,4-dimethoxy-phenyl)-propanone-2 (CX) by oxidation with pyridine and copper sulphate. This reagent has been employed previously (94) for the oxidation of benzoins to benzils and when applied to the new hydroxy-ketone gave 1-(3,4-dimethoxy phenyl)-propanedione-1,2(CXXXIII) identical with that obtained in the same way from 2-hydroxy-1-(3,4-dimethyoxy-phenyl)-propanone-1 (CXI).

The semicarbazone and oxime of the new hydroxy-ketone were prepared. The latter was obtained as a glass and could not be crystallized. It was purified by crystallization as a chloroform addition product from chloroform or chloroform-petroleum ether solution. The addition compound is very unstable and on drying yields the glass-like product from which all chloroform is removable, although with some difficulty.

On oxidation with periodic acid in dilute sulphuric acid the new hydroxy-ketone (CX) gives veratric aldehyde in good yield.

Ethanolysis of 1-hydroxy-1-(3,4-dimethoxy phenyl)-propanone -2(CX)

Ethanolysis with an absolute ethanol-HCl (2%) mixture for 48 hours gave 2-ethoxy-1-(3,4-dimethoxy phenyl)-propanone-1 (CXXXV) in a yield of 50% together with a small amount (5%) of an amorphous, petroleum-ether insoluble material. No other products could be isolated from the residues but the presence, in small quantities, of isomers of CXXXV is not excluded.



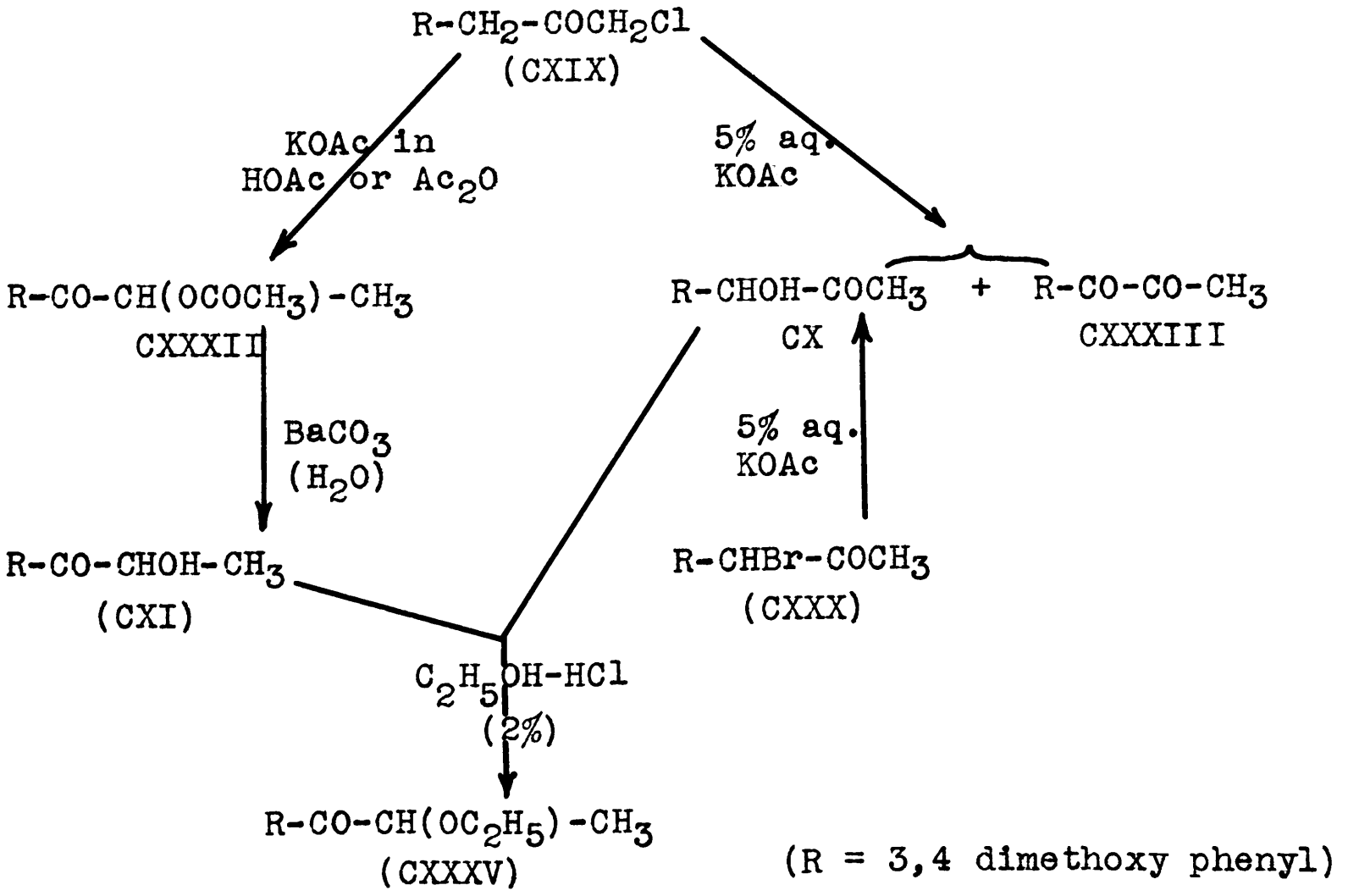
CXXXV

On treatment with 72% sulphuric acid under the conditions of the standard Klason lignin determination, the new

hydroxy ketone (CX) gave a 75% yield of a brown amorphous, lignin-like material. Treatment with aqueous sulphuric acid (5%) at 70°-80° for 4 hours apparently brought about no reaction, 70% of the starting material being recovered unchanged.

To obtain further information regarding these rearrangements, 2-hydroxy-1-(3,4 dimethoxy phenyl)-propanone-1 (CXI) was treated with 5% aqueous potassium acetate but none of the new ketol could be detected in the reaction product. The semicarbazone of the starting material only was obtained and although the yield was low (40%) the purity was quite high. Since the isomer (CX) forms a semicarbazone much more readily than does CXI, this would indicate that no rearrangement had occurred.

The rearrangements reported here are summarized in the following diagram.



(R = 3,4 dimethoxy phenyl)

Mechanism of 1,2-diketone formation by hydrolysis of 3-chloro-1-(3,4-dimethoxy phenyl)-propanone-2 (CXIX)

The formation of the 1,2 diketone, 1-(3,4 dimethoxy phenyl)-propanedione-1,2 (CXXXIII), in the hydrolysis of 3-chloro-1-(3,4-dimethoxy phenyl)-propanone-2 (CXIX) raises again the question of the mechanism whereby the corresponding 1,2-diketone, 1-(4-hydroxy-3-methoxy-phenyl)-propanedione-1,2 (XXI) is formed in the ethanolysis of wood. Perhaps the most interesting work in this connection is that of Kohler (84) already discussed (pg. 74) but which will be briefly reviewed again here.

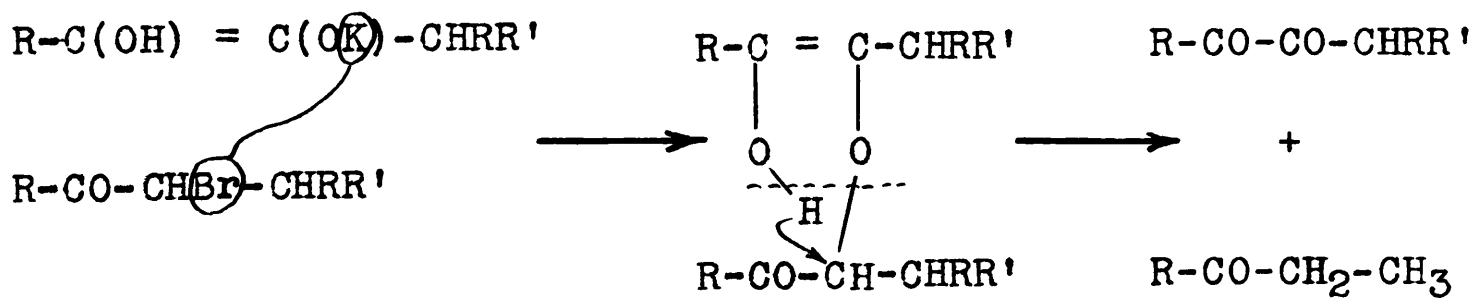
Kohler found that hydrolysis of α-bromo-ketones of the type R-CO-CHBr-CHRR' (where R in general is aromatic) with alcoholic potassium hydroxide gave three products, namely (1) R-CO-CHOH-CHRR', (2) R-CO-CO-CHRR' and (3) $R\text{-}CO\text{-}CH_2\text{-}CHRR'$. Thus 2-bromo-1-(4-bromophenyl)-propanone-1 (CV) gives $p\text{-}Br\text{-}C_6H_4\text{-}CO\text{-}CHOH\text{-}CH_3$(CVI), $p\text{-}Br\text{-}C_6H_4\text{-}CO\text{-}CO\text{-}CH_3$ (CVII) and $p\text{-}Br\text{-}C_6H_4\text{-}CO\text{-}CH_2\text{-}CH_3$ (CVIII), in yields of 11, 20 and 20% respectively. This mixture, however, is only obtained when the strongly alkaline alcoholic solution is added slowly to the bromo-ketone at room temperature. If added rapidly to the boiling solution instantaneous reaction and a high yield of the benzoin (CVI) is obtained. The diketone is formed in high yield only when the solution is alkaline.

Kohler showed further that the benzoins, when subjected to the same treatment with alkali as used with the bromo-ketones, gave no diketones and he concluded from this that the benzoins were presumably not intermediates in the diketone formation.

A possible explanation of these reactions is the following: The primary action of the alkali on the α-bromo-ketone is the formation of the corresponding benzoin which immediately undergoes rearrangement to the ene-diol.

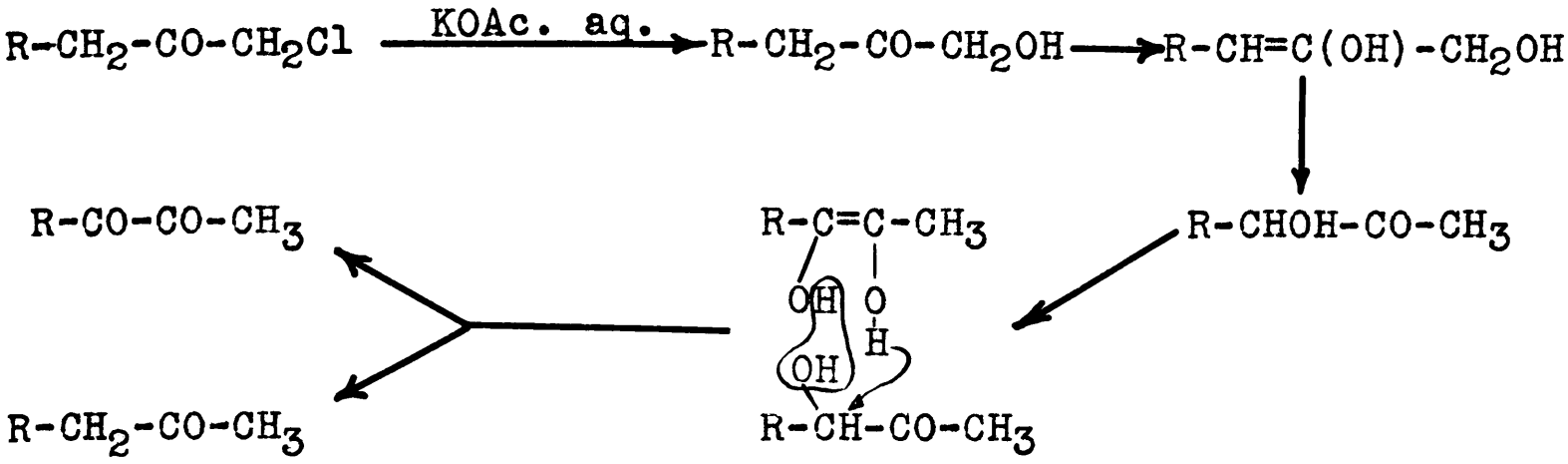
$$R\text{-}CO\text{-}CHBr\text{-}CHRR' \longrightarrow R\text{-}CO\text{-}CHOH\text{-}CHRR' \longrightarrow R\text{-}C(OH) = C(OH)\text{-}CHRR'$$

The acidic ene-diol then forms a mono-potassium salt which reacts with a second molecule of the bromo-ketone. Migration



of the hydrogen atom then occurs, followed by fission of the -C-O-C- linkage to give one mole each of a mono-ketone and a 1,2-diketone.

A similar type of reaction may be involved in the case of 3-chloro-1-(3,4 dimethoxy phenyl)-propanone-2, as shown below:

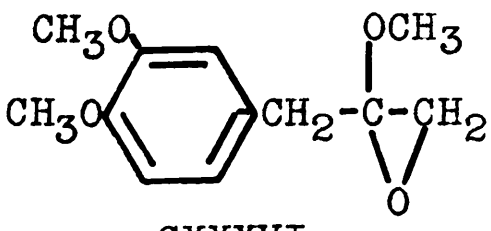


Actually, in the ethanolysis of wood, there is always present the desoxybenzoin in addition to the 1,2 diketone.(See pg. 22)

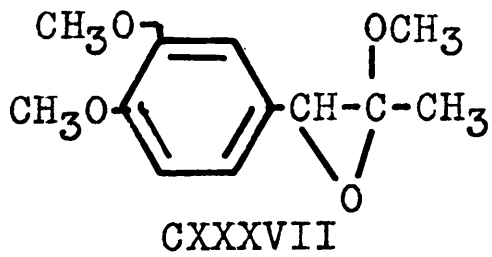
Etherification Experiments.

Various unsuccessful attempts were made to prepare ethers i.e. $R\text{-}CH_2CO\text{-}CH_2OR'$ and $RCHOR'\text{-}CO\text{-}CH_3$, where R = 3,4 dimethoxyphenyl and R' = CH_3 or C_2H_5, from the chloro-ketone CIX and the hydroxy-ketone CX.

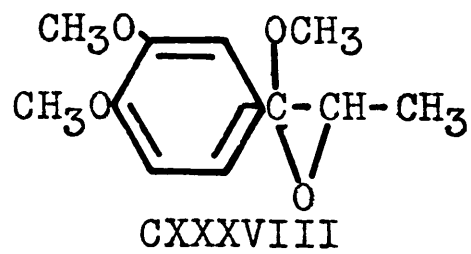
Treatment of the chloro-ketone with one equivalent of potassium hydroxide in methanol or with one equivalent of sodium methylate in methanol gave high yields of an isomer of the methyl ether. The compound was beautifully crystalline (m.p. 40-41°), soluble in petroleum ether and in very dilute alcohol, but showed no carbonyl reaction and was decomposed by dilute acids. It is believed from literature analogies to have structure CXXXVI although the isomeric forms(CXXXVII and CXXXVIII) are also possible.



CXXXVI



CXXXVII



CXXXVIII

Kohler and Addinal (95) studied the effect of sodium alcoholates on α,β-dibromo-benzal-p-bromo-acetophenone (CXXXIX) and similar α,β-dibromo-ketones. They found that when this compound was boiled with excess sodium methylate in methanol, they obtained products corresponding to formulae CXLI and CXLII.

C_6H_5-CHBr-CHBr-CO-C_6H_4Br — CXXXIX

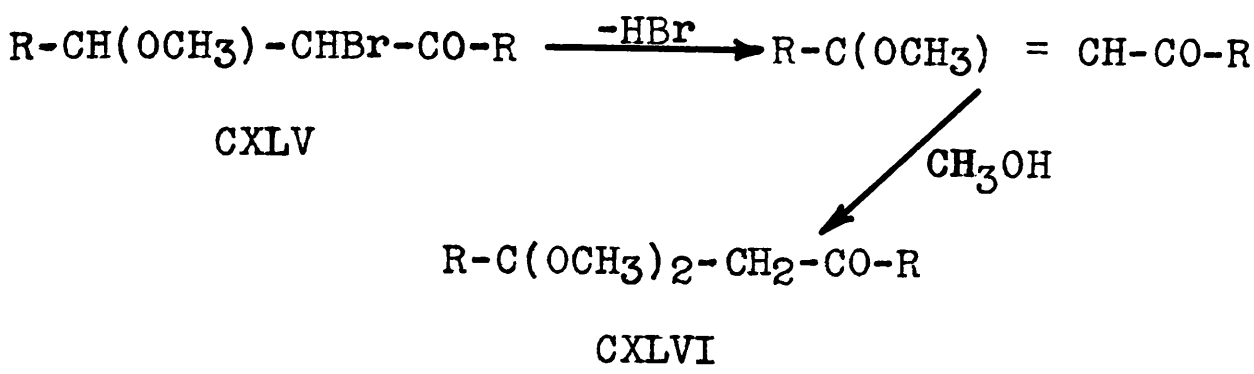
C_6H_5-$C(OC_2H_5)_2$-CH_2-CO-C_6H_4Br — CXLI

C_6H_5-$CH(OC_2H_5)$-CHOH-$C(OC_2H_5)_2$-C_6H_4Br — CXLII

They believed that two different mechanisms were involved in the formation of these products. The first was proposed earlier by Wieland (96) to account for the presence of the diketone acetal (CXLVI). It presumes that the first reaction is loss of a molecule of hydrogen bromide from the dibromide CXLIII to give an unsaturated bromo-ketone (CXLIV) and that this is followed by addition of methanol to the ethylenic link to give a saturated ether (CXLV). According

$$\underset{\text{CXLIII}}{R\text{-}CHBr\text{-}CHBr\text{-}CO\text{-}R} \xrightarrow{-HBr} \underset{\text{CXLIV}}{R\text{-}CH{=}CBr\text{-}CO\text{-}R} \xrightarrow{CH_3OH} \underset{\text{CXLV}}{R\text{-}CH(OCH_3)\text{-}CHBr\text{-}CO\text{-}R}$$

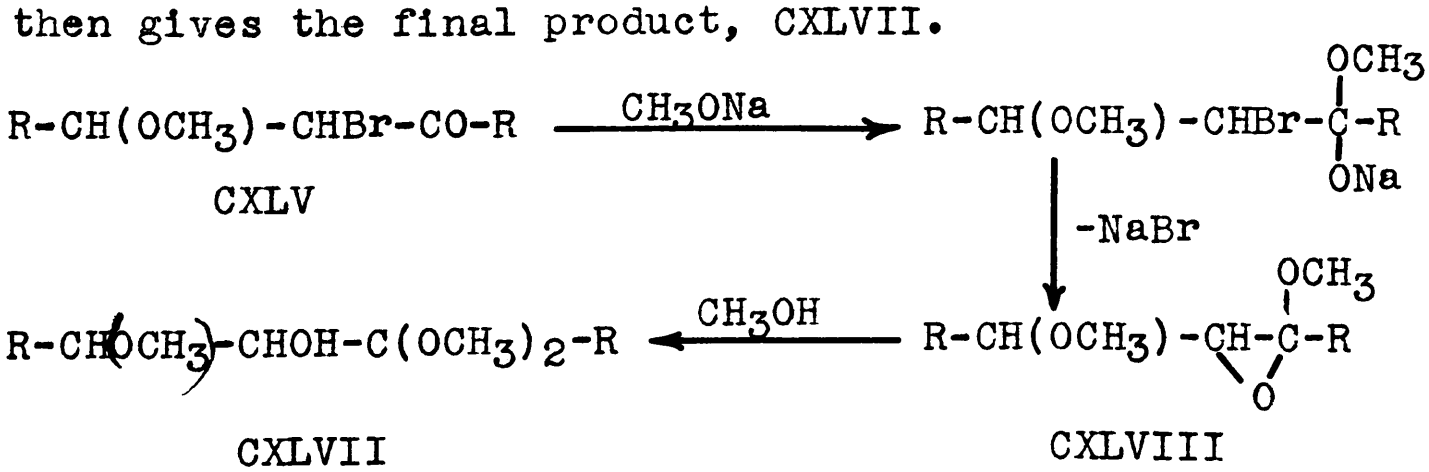
to Wieland the next stage is exactly similar;



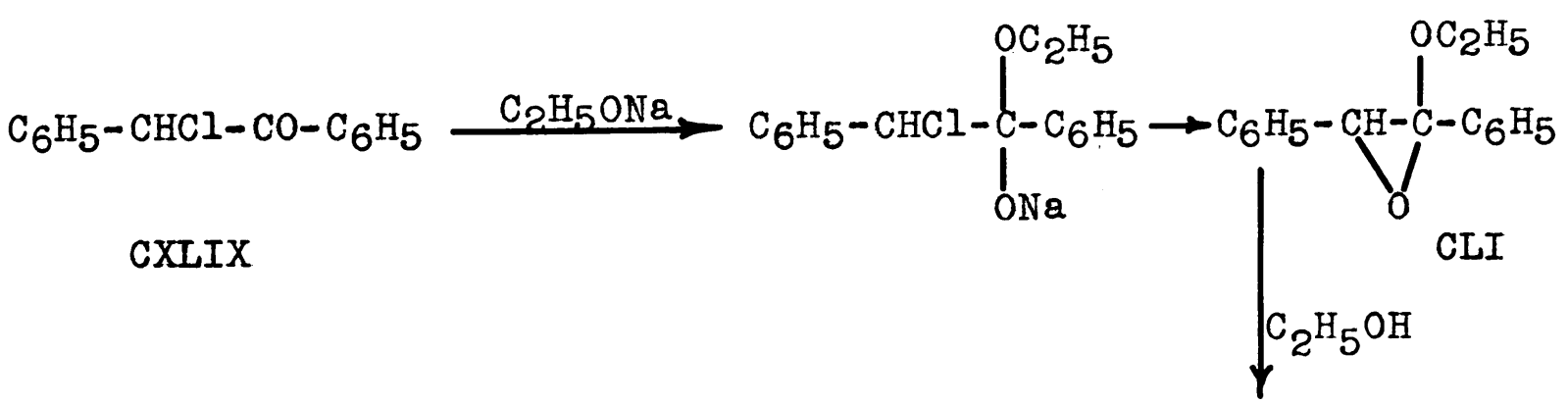
Kohler and Addinal state that in all cases examined by them, some of the dibromide reacted in this manner. Occasionally CXLVI represents the sole product of the reaction but this only occurs when an unusually active hydrogen is present on the β-carbon atom of the dibromide (CXLIII) (96,97).

To explain the formation of the second product, R-CH(OCH$_3$)-CHOH-C(OCH$_3$)$_2$-R (CXLVII), these workers propose a mechanism involving an intermediate oxide ring. The first two steps are identical with those of Wieland's mechanism and give rise to the same bromo-ether (CXLV).

Kohler and Addinal believe, however, that the next step is addition of sodium methylate to the carbonyl group followed by loss of sodium bromide to give an ethylene oxide (CXLVIII). Cleavage of the oxide by the methanolic alkali then gives the final product, CXLVII.



Ward (98) showed that α-chlor-desoxybenzoin (CXLIX), when treated with sodium ethylate, gave benzoin acetal (CL) and like Kohler and Addinal, explained his results by assuming a primary addition of sodium ethylate to the carbonyl group followed by loss of sodium chloride to give an ethylene oxide intermediate (CLI). This intermediate then added a second molecule of methanol to give the acetal.



CXLIX

CLI

C_6H_5-CHOHCH$(OC_2H_5)_2$-C_6H_5

CL

Aston and Greenburg (99) attempted to methylate $(CH_3)_2C(OH)$-CO-CH_3 with dimethyl sulphate in alkali and also with methanolic-HCl but were unsuccessful. They suggested their failure might be due to the ease of hydrolysis of the ether when formed.

From the results of these various workers it appears probable that the new compound is an oxide. If Kohler's theory is correct and addition to the carbonyl is the first reaction, then the compound p. 95 probably has structure CXXXVI. If however, the replacement of the halogen occurs first and is accompanied by an allylic shift then formula CXXXVII is possible. Other isomers are much less probable than these two.

The methyl derivative was studied in the author's experiments because it was crystalline. Substantially similar results were obtained by the use of ethylates and also of potassium acetate in ethanol.

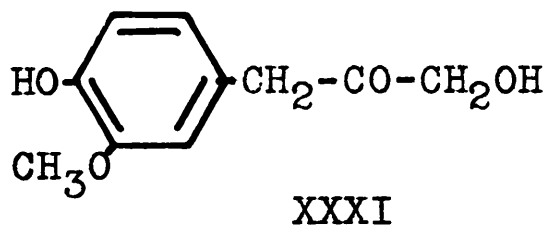
It seemed that etherification in the case of $R\text{-}CH_2\text{-}CO\text{-}CH_2Cl$ (CXIX) might be possible if the carbonyl group were blocked. The ketone could then be regenerated following etherification, since the ether would prevent rearrangement. However, due to condensation reactions between the halogen and the amino group of the carbonyl reagents (2,4-dinitrophenyl hydrazine and semicarbazide) no derivatives could be prepared from the chlor-ketone. No reaction was obtained with hydroxylamine and the chlor-ketone.

The oxime of the hydroxy ketone $R\text{-}CHOH\text{-}COCH_3$ (CX) was treated with diethyl sulphate in 0.2N sodium hydroxide at room temperature, but apparently no ethylation occurred.

The stability of semicarbazone groupings under methylation conditions was investigated in the case of the semicarbazone of 2-ethoxy-1-(3,4 dimethoxy phenyl)-propanone-1 (XX). It was found that on treatment with dilute alkali at room temperature rapid and complete hydrolysis took place so that the product was useless for the object in view.

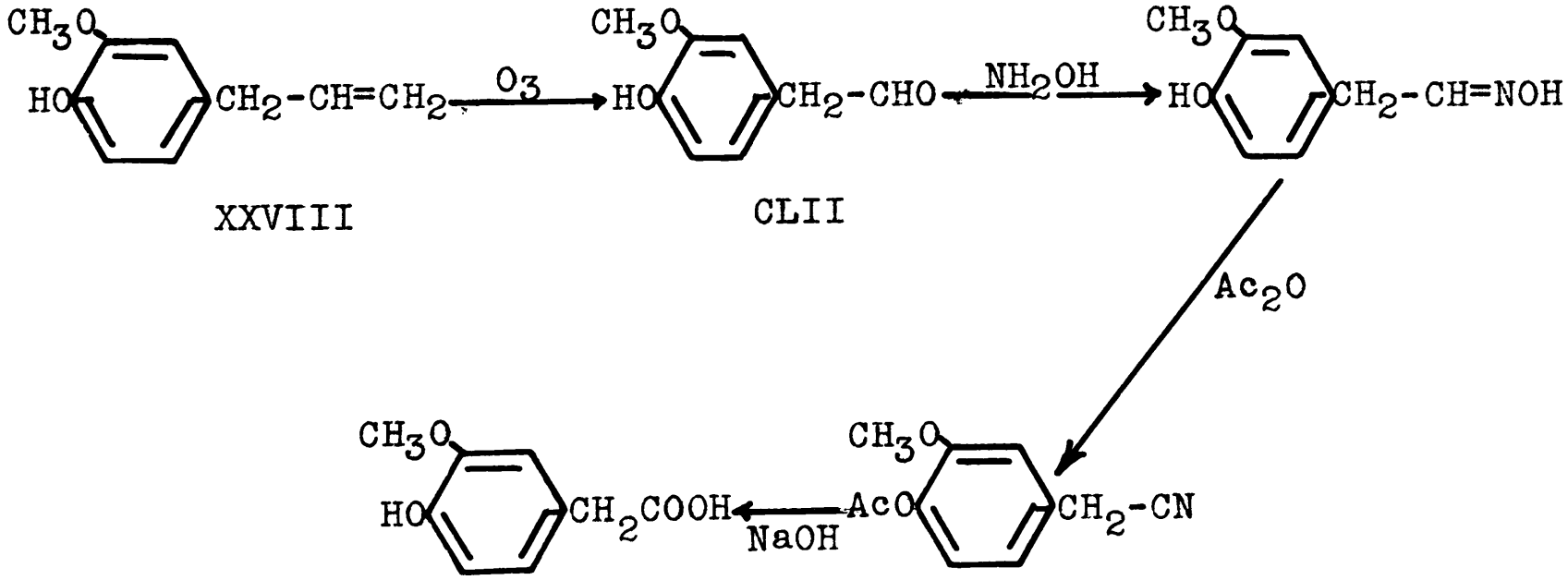
Attempts to obtain etherification of the chlor-ketone (CXIX) with silver oxide in ethanol were unsuccessful because of the strongly oxidizing action of this reagent. Potassium iodide in ethanol likewise gave no ether.

Attempted Synthesis of 3-Hydroxy-1-(4-hydroxy-3-methoxy-phenyl)-propanone-2 (XXXI).



XXXI

Initial studies on the preparation of the non-methylated hydroxy-ketone (XXXI) were carried out on lines roughly paralleling those on the veratryl analogue. For the preparation of homo vanillic acid the method of Hahn and Schales (100) was adopted with slight modification. It is represented in the following scheme:



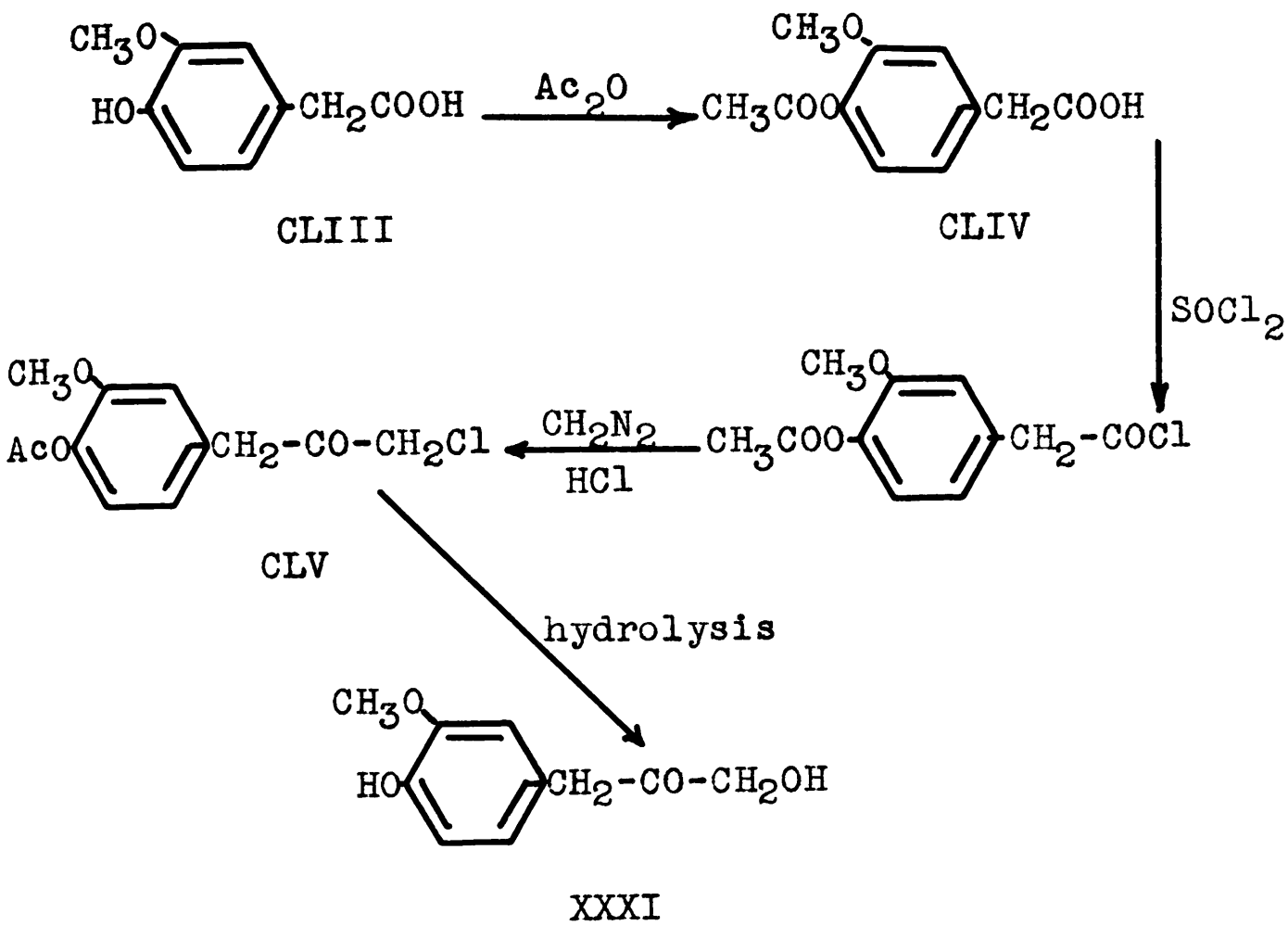
XXVIII CLII CLIII

Ozonization of eugenol (XXVIII) to give homovanillin (CLII) was carried out by Harries and Haarman (101) and by Hahn and Schales (100). Their methods differed only in the mode of decomposition of the ozonide. Harries used zinc in

acetic acid as the reducing agent, while Hahn employed hydrogenation with palladium as catalyst; the latter method gives somewhat better yields. In the writer's work a modification of Harries' procedure was used by which the amount of zinc required was reduced to one third of that employed by Harries. The new method reported by Whitmore (102) for reduction of ozonides, in which Raney nickel alone serves as the reducing agent, was also tried but proved unsuccessful. Homovanillin (CLII) was obtained in yields of about 50% by rapid distillation of the neutral residue from the ozonide reduction. Since some decomposition occurred during this distillation the heating period was made as short as possible. It is conceivable that preparation of an oxime directly from the reaction mixture might give better yields, but this point has not been examined.

The conversion of homovanillin to homovanillic acid (CLIII) presented little difficulty. It was found necessary to add the hydroxylamine hydrochloride to a solution of the homovanillin mixed with potassium acetate to avoid decomposition in the preparation of the oxime. Homovanillin is very sensitive to the action of acid, especially in warm solutions so that the mixtures must be kept slightly alkaline.

It was hoped that the hydroxy-ketone (XXXI) could be obtained from homovanillic acid (CLIII) according to the following scheme:

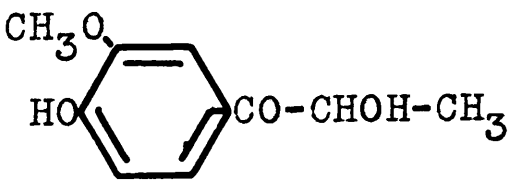


Acetyl homovanillic acid (CLIV) was prepared by direct acetylation of homovanillic acid with acetic anhydride. Its preparation has been reported previously by Tiemann and Nagai (103) who obtained it by fractional crystallization of the permanganate oxidation products from acetyl eugenol. The acetyl homovanillic acid was converted smoothly into its acid chloride by treatment with pure thionyl chloride and the product isolated and purified by high vacuum distillation.

It was added slowly to a solution of diazomethane and after the reaction was complete, ethereal-HCl was added, exactly as in the preparation of the veratryl chlor-ketone (CXIX) from homoveratroyl chloride. The product obtained was a yellow oil which resisted all attempts at crystallization

and which decomposed when low pressure distillation was attempted. It was purified as far as possible by precipitation from ether solution by addition of petroleum ether (30-50°) and then dried under vacuum. The viscous yellow oil thus obtained gave methoxyl and chlorine analyses in good agreement with the theoretical values for the chlor-ketone (CLV). No evidence was found to indicate the possible presence of isomeric chloro-ketones.

Simultaneous hydrolysis of the acetyl and chlorine groups was effected by refluxing the chlor-ketone with an aqueous suspension of lead oxide. The product was a partially crystalline yellow oil. A small amount of the crystalline component was separated by crystallization from ether-petroleum ether and was shown by mixed melting point determinations to be 2-hydroxy-1-(4 -hydroxy-3-methoxy-phenyl)-propanone-1 (LXVIII). The remainder of the material was not identified.



LXVIII

It was apparent that an intramolecular rearrangement had again occurred and from analogy with the veratryl derivatives it would appear that in this case also the rearrangement took place during the hydrolysis of the chloro-ketone rather than in the steps preceding the chloro-ketone

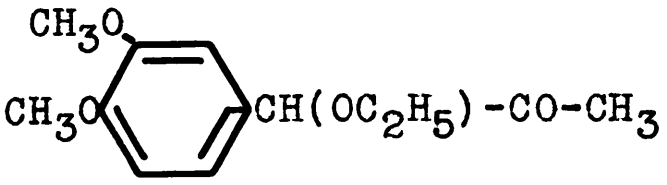
formation. The experiment suggests however, that the free phenolic group may exert a different directing effect on the rearrangement than does the para-methoxyl group since the final hydrolysis product is R-CO-CHOH-CH_3 (LXVIII) rather than R-CHOH-CO-CH_3 (LXVII).

The objects of this research were (a) to synthesize 3-hydroxy-1-(4-hydroxy-3-methoxy-phenyl)-propanone-2 and (b) to investigate relationships between this compound and the water-soluble lignin progenitors isolated in the ethanolysis of wood. Due to the experimental difficulties involved the first of these objects was not achieved, but the second was accomplished, at least in part. It has already been shown in the discussion on allylic rearrangements that substituted allyl alcohols and their halides behave analogously in their intramolecular rearrangement reactions and since it has been shown in this experimental work that the rearrangement represented by the change

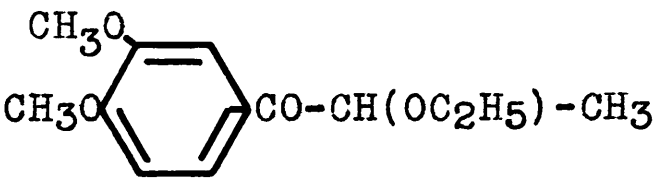
$$R\text{-}CH_2CO\text{-}CH_2Cl \xrightarrow{KOAc(aq)} R\text{-}CHOH\text{-}CO\text{-}CH_3 \quad (R=veratryl)$$

actually occurs, and under very mild conditions, it seems permissible to conclude that a similar rearrangement would also occur with the corresponding hydroxy derivative, $R\text{-}CH_2\text{-}CO\text{-}CH_2OH$. Furthermore, experimental evidence has been provided to show that the hydroxy-ketone R-CHOH-CO-CH_3, on ethanolysis, readily undergoes rearrangement

to R-CO-CH(OC_2H_5)-CH_3 and thus a very definite relationship has been established between (a) the veratryl analogues of the ethanolysis ethoxy-ketones (CXXXV and CLVI),

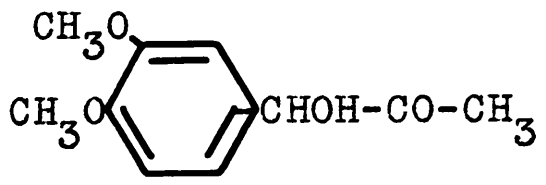


CLVI

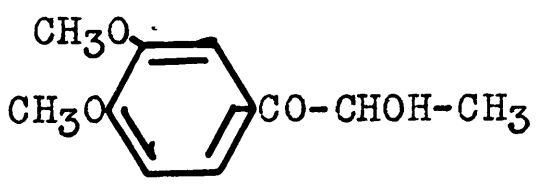


CXXXV

(b) the corresponding ketols (CX and CXI),

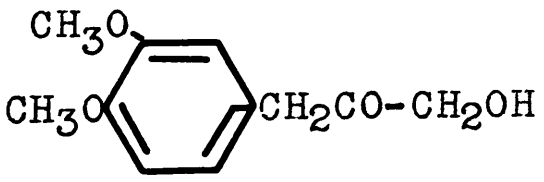


CX



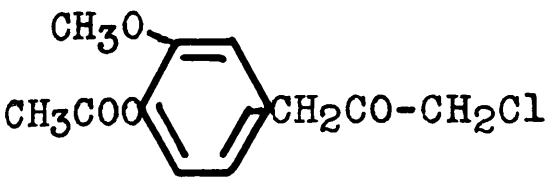
CXI

and (c) their potential precursor (XXXI),

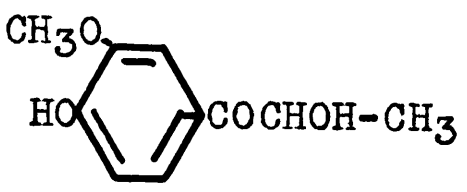


XXXI

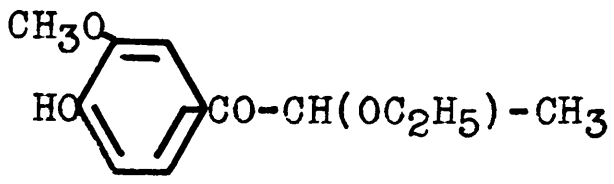
It has been shown also, in preliminary experiments, that the hydrolysis of the corresponding chloro-ketone, 3-chloro-1-(4-acetoxy-3-methoxyphenyl)-propanone-2, (CLV) gives the guaiacylic ketol, 2-hydroxy-1-(4-hydroxy-3 methoxy-phenyl)-propanone-1 (LXVIII) which on ethanolysis is known to give the corresponding ethoxy derivative (XX) in high yields (104).



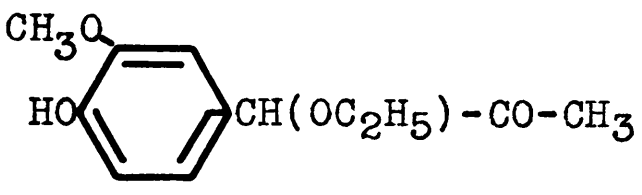
CLV



LXVIII

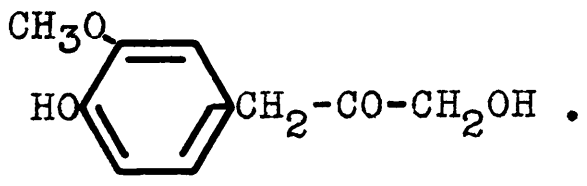


XX



XXVI

This result is in harmony with the experimental findings on the ethanolysis of spruce wood which show a ratio of XX to XXVI of about 4:1. Since hydrogenation of lignin indicates the presence of considerable amounts of primary hydroxyl groups in the three carbon side chain, the first product of the ethanolysis is presumably a hydroxy-ketone of the type



The isomeric form, $R\text{-}CO\text{-}CH_2\text{-}CH_2OH$ is eliminated from consideration since it has been shown (42) to give, under ethanolysis conditions, only the corresponding ethyl ether $R\text{-}CO\text{-}CH_2\text{-}CH_2OC_2H_5$.

As a result of these studies an interesting explanation has been provided to account for the presence of the 1,2-diketone, namely 1-(4-hydroxy-3 methoxyphenyl)-propanedione-1,2 (XXI) found in the ethanolysis products from both spruce

and maple woods. Experimental proof has been provided to show that the veratryl analogue (CXXXIII) of this diketone is formed, in the absence of oxygen, during the hydrolysis of the chloro-ketone, 3-chloro-1-(3,4 dimethoxyphenyl)-propanone-2 (CXIX) and it is suggested that its formation is due to a bimolecular condensation reaction involving loss of a molecule of water and followed in turn by migration of a hydrogen atom (see pg. 93).

Finally, the experimental results provide strong direct and indirect support for the theory that oxy-coniferyl alcohol, in equilibrium with its keto-form forms one of the principal building stones of the natural lignin structure.

EXPERIMENTAL

I. Attempted Synthesis of 3-Hydroxy-1-(4-hydroxy-3-methoxy-phenyl)-propanone-2.

(a) Addition of Oxygen to Eugenol by treatment with Perphthalic Acid.

7 g. of freshly distilled eugenol were added to 9.0 g. of perphthalic acid in 200 cc. of ether. (The perphthalic acid was prepared by the method of Bohme (105)). The solution was allowed to stand at room temperature and aliquots were removed at intervals for perphthalic acid determinations. Reaction was complete in three days.

The ether was distilled off and the residue extracted with 150 cc. of chloroform. The extract was washed with 5% sodium bicarbonate solution, dried over sodium sulphate and concentrated. The residue was distilled at 0.2 mm. pressure and after the removal of unchanged eugenol gave 0.85 g. (10%) of a clear oil which was probably eugenol oxide.

Analyses - Calcd. for $C_{10}H_{12}O_3$: CH_3O, 17.3; Found: CH_3O, 17.2.

(b) Preparation of Eugenol Acetate.

50 g. of freshly distilled eugenol and 50 g. of acetic anhydride were dissolved in sufficient dry pyridine to make 275 cc. of solution, and allowed to stand for two days. The greater part of the solvent was distilled off and 50 cc. of water added. The low boiling materials were re-

moved and the residue distilled in vacuum. Yield 58 g. (93%), m.p. 29-31°.

(Tiemann and Nagai (103) report the melting point to be 30-31°)

(c) Synthesis of Eugenol Acetate Oxide.

50 g. of eugenol acetate were added to 59 g. of perphthalic acid in 700 cc. of ether and the mixture allowed to stand 10 days. The ether was distilled off and the residue thoroughly extracted with chloroform. The extract was washed with 5% sodium bicarbonate solution, then with water, dried and concentrated. The residue was distilled in vacuum and gave 26 g. (48%) of a yellowish oil which solidified in the receiver to a white solid, m.p. 48-50°. Recrystallized from petroleum-ether - m.p. 49-50°.

Analyses - Calcd. for $C_{12}H_{14}O_4$: CH_3O, 13.4; Found: CH_3O, 13.4.

(Schopf and co-workers (86) later reported the melting point of this oxide as 50-52°)

(d) Cleavage of Eugenol Acetate Oxide with Hydrogen Chloride.

22 cc. of ether containing 1.14 g. of dry hydrogen chloride were cooled to -10° and 6 g. of eugenol acetate oxide added slowly. The mixture was allowed to stand at -10°, with occasional stirring, for 45 minutes. The ether and hydrogen chloride were removed under reduced pressure and the residue distilled at 0.06 mm. The product was a clear, colorless oil, boiling almost entirely at 137°. $[n]_D^{25} = 1.5346$; yield 90%.

Analyses - Calcd. for $C_{12}H_{15}O_4Cl$: CH_3O, 12.1; Found: CH_3O, 12.0.

For satisfactory results the above procedure must be followed carefully. Deacetylation occurs readily and reduces the chlorhydrin yield to about 50%. This can be detected by a sharp drop in the refractive index and by the ferric chloride test for phenols. For reasons not known it was found necessary to use freshly prepared ethereal-HCl.

α-Napthyl Urethane of the Chlorhydrin.

0.49 g. of the chlorhydrin and 0.47 g. of α-napthyl isocyanate were warmed at 60°-70° for 18 hours. The reaction mixture was dissolved in 100 cc. of boiling petroleum ether (80°-90°) and filtered. The urethane crystallized out on cooling. Yield 0.36 g. (45%), m.p. 126-129°.

Recrystallization from methanol and from petroleum ether raised the melting point to 130-131°.

Analyses - Calcd. for $C_{24}H_{24}NO_5Cl$: C, 64.2; H, 5.2; CH_3O, 7.2;
Found: C, 65.0; H, 5.4; CH_3O, 7.2;

Schotten-Baumann Reactions with p-nitro-benzoyl chloride and with 3,5-dinitro-benzoyl chloride failed to give crystalline derivatives of the chlorhydrin.

(e) Oxidation of the Chlorhydrin.

Repeated attempts were made, under various conditions of temperature and concentration, to oxidize the chlorhydrin to a chloro-ketone with CrO_3-HAc mixtures. In all cases the greater part of the chlorhydrin was recovered unchanged. The remainder of the material appeared to undergo oxidation to lower molecular weight compounds such as vanillin.

II. Synthesis and Properties of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2.

(a) Synthesis of Homoveratric Acid by the Method of Arndt and Eistert (88a).

(i) Synthesis of Veratric Acid.

200 g. of vanillin were methylated with dimethyl sulphate and alkali by the method of Buck (89). The crude product was washed with water and without further purification, oxidized with potassium permanganate according to the procedure of Schriner and Kleiderer (90). The manganese dioxide formed in the reaction was dissolved by passing SO_2 into the solution and the veratric acid was then precipitated by acidifying and cooling the solution. It was filtered off, washed with water and dried. Yield 196 g. (82% based on vanillin) m.p. 178-181°. The crude product was sufficiently pure for use in the preparation of veratroyl chloride.

(Goldschmiedt (107) gives the melting point of veratric acid as 181°.)

(ii) Synthesis of Veratroyl Chloride.

196 g. of veratric acid, 150 g. of toluene and 150 g. of thionyl chloride were heated at 100° for 90 minutes. Toluene and excess $SOCl_2$ were removed under reduced pressure and the residue distilled at about 1 mm. pressure. Yield 185 g. (85%), m.p. 70-71°.

(The melting point of veratroyl chloride, according to Meyer (108), is 70°.)

(iii) Synthesis of Veratroyl Diazomethane.

25 g. of veratroyl chloride were added to an ethereal solution of diazomethane and allowed to stand two hours and the solution concentrated and cooled. Veratroyl diazomethane precipitated out in yellow, thread-like crystals. Yield 25.5 g. (95%), m.p. 72-74°.

(Arndt and Eistert report the melting point to be 75°.)

(iv) Synthesis of Homoveratric Amide.

15 g. of crude veratroyl diazomethane were treated with aqueous ammonia in the presence of finely divided silver exactly as in the procedure of Arndt and Eistert (88a). Yield 5.1 g. (38%), m.p. 140-142°. Recrystallized from a small volume of methanol; m.p. 145-146°.

(Kaufmann and Müller (109) give 145-147° and Arndt and Eistert give 146° as the melting point of this amide.)

(v) Synthesis of Homoveratric Acid

23 g. of homoveratric amide were hydrolysed to homoveratric acid with aqueous sodium hydroxide, according to the method of Hahn and Schultz (106). The product was recrystallized from a small volume of ethyl acetate. Yield 20.5 g. (90%), m.p. 98-99°.

(Various workers (106, 88) give the melting point of homoveratric acid as 98-99°.)

(b) Synthesis of Homoveratric Acid according to the Method of Hahn, Stiehl and Schultz (88b)

(i) Preparation of Veratraldehyde.

200 g. of vanillin were methylated with dimethyl sulphate and alkali according to the procedure of Buck (89) and the product purified by distillation. Yield 215 g. (97%), m.p. 44-45°.

(The melting point of veratraldehyde according to Buck is 46°.)

(ii) Preparation of α-Chloro-homoveratric Amide.

60 g. of veratraldehyde were converted to the cyanohydrin, and the latter acetylated to give α-acetoxy-homoveratronitrile, according to the procedure of Hahn, Stiehl and Schultz (88b). Yield 55 g. (70% based on vanillin), m.p. 73-75°.

30 g. of this acetoxy-nitrile were treated with dry HCl in an ether-benzene solution according to the procedure of these same workers, to give α-chlorohomoveratric amide. Yield 24 g. (75%), m.p. 139-141°. Recrystallized from benzene; m.p. 143-144°.

(The melting point of this compound according to Hahn, Stiehl and Schultz is 145°.)

(iii) Preparation of Homoveratric Amide.

6 g. of α-chloro-homoveratric amide were dissolved in 20 cc. of glacial acetic acid and 8 cc. of constant boiling hydriodic acid were added. A heavy, beautifully crystalline,

reddish-purple precipitate slowly settled out. After 15 hours at room temperature the precipitate was filtered off, sucked as dry as possible, then placed in a vacuum desiccator over sodium hydroxide. 22 g. of this material, which was apparently chiefly free iodine, were obtained.

50 cc. of a saturated solution of sodium bisulphite were prepared and the above iodine complex was added with vigorous stirring to this solution. The resulting solution was treated with charcoal, filtered and the amide precipitated by addition of ammonium hydroxide.
Yield 4.2 g. (82%), m.p. 141-144°.

An attempt to convert α-acetoxy-homoveratro-nitrile directly to homoveratric amide with hydriodic acid was unsuccessful. Attempted reduction of the chlor-amide with zinc and acetic acid gave a halogen-free product, melting at 146-148°, but which showed a strong depression in a mixed melting point with homoveratric amide. It was not studied further.

(iv) Preparation of Homoveratric Acid.

Hydrolysis of the amide was carried out exactly as before (pg.112).

(c) Synthesis of 3-Chloro-1-(3,4-dimethoxyphenyl)-propanone-2

This compound was prepared exactly according to the procedure of Haworth and Atkinson (87).

7.5 g. of homoveratric acid were warmed for a short time with thionyl chloride, the excess thionyl chloride distilled off and the residue added to a solution of diazomethane. After 2 hours ethereal HCl was added until effervescence ceased, and the solution was then washed, and dried and concentrated to a small volume. The chloro-ketone crystallized out. Yield 6.7 g. (87%), m.p. 50-51°.

(Haworth and Atkinson give the melting point of this compound as 52°.)

It is essential for the success of this preparation that the homoveratric acid and more especially the thionyl chloride, be of a high degree of purity.

(d) Synthesis of 3-Brom-1-(3,4-dimethoxyphenyl)-propanone-2.

The preparation of this compound was carried out exactly as in the case of the chlor-ketone except that a somewhat larger excess of diazomethane was used to ensure complete elimination of all chlorine (in the homoveratroyl chloride) and the diazo-derivative was treated with ethereal HBr instead of with ethereal HCl. A pure product was obtained in 80% yield. Repeated recrystallization from ether-petroleum ether (30-50°) failed to raise the melting point above 44-45°. The product, even when purified, was very unstable.

Analyses - Calcd. for $C_{11}H_{13}O_3Br$: CH_3O, 22.7; Found: CH_3O, 22.5.

(e) Formation of 2-Acetoxy-1-(3,4-dimethoxyphenyl)-propanone-1 from 3-Chloro-1-(3,4-dimethoxyphenyl)-propanone-2.

8 g. of the chloro-ketone were heated for 8 hours at 100° with a mixture of 21 g. of freshly fused potassium acetate and 35 cc. of glacial acetic acid. The reaction product was poured into a solution of 35 g. of sodium carbonate in 300 cc. of water and the mixture extracted with chloroform. The extract was dried over sodium sulphate, the solvent removed and the residual oil distilled in high vacuum.

Fraction	Vapor Temp.	Pressure	Yield	$[n]_D^{25}$
1	below 115°	0.15 mm.	0.43 g.	1.5450
2	115°-135°	0.15 "	1.62	1.5392
3	121°-123°	0.02 "	2.41	1.5374
4	123°-140°	0.02-0.05 "	1.02	1.5383
			5.48 g.	

Analyses - Calcd. for $C_{13}H_{16}O_5$: CH_3O, 24.6; Found: for fractions 2 and 3, CH_3O, 24.6.

Each of these fractions yielded a sticky, partially crystalline mass which could not be purified by crystallization. The crystalline component was separated on porous plate and after recrystallization from petroleum ether, melted at 65-66°. In a mixed melting point with authentic 2-acetoxy-1-(3,4-dimethoxyphenyl)-propanone-1 it showed no depression. This

compound represented about 50% of the total product; the remainder was unidentified but appeared to be isomeric with this compound.

(f) Formation of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 and 1-(3,4-dimethoxyphenyl)-propanedione-1,2 from 3-Chloro-1-(3,4-dimethoxyphenyl)-propanone-2.

3.3 g. of 3-chloro-1-(3,4-dimethoxyphenyl)-propanone-2 were refluxed for 4½ hours with 250 cc. of 5% aqueous potassium acetate. A small amount of charcoal was added and refluxing continued for 15 minutes. The solution was filtered and cooled, then extracted with chloroform until the aqueous layer gave no further reaction with 2,4-dinitrophenyl-hydrazine (5-6 extractions were required).

The chloroform extract was dried over sodium sulphate, the solvent removed under reduced pressure, and the residue distilled under high vacuum in an atmosphere of carbon dioxide. The distillate, a yellow oil which slowly set to a crystalline solid, was taken up in a small volume of ether (A) and cooled to -10°. 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 crystallized out and was filtered off. After recrystallizing from ether, it melted at 75-77°. Yield 1.5 g. (50%).

Further recrystallizations from small volumes of ether and benzene raised the melting point to a constant value at 76-77°.

Analyses - Calcd. for $C_{11}H_{14}O_4$: C, 62.9; H, 6.7; OCH_3, 29.6;
Found: C, 62.8; H, 6.9; OCH_3, 29.7.

The ether mother liquors (A) from which 1-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 had been isolated, were taken to dryness and a sample of the residue fractionated in a small but efficient column under high vacuum in an atmosphere of carbon dioxide. About 20% of the material was obtained as a yellow, crystalline solid, but the remaining 80% of the material could not be separated into its components. The solid fraction, after recrystallization from ether, melted at 68-69°. Its mixed melting point with authentic 1-(3,4-dimethoxyphenyl)-propanedione-1,2 showed no depression.

(g) Formation of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 from 1-Bromo-1-(3,4-dimethoxyphenyl)-propanone-2.

1-Bromo-1-(3,4-dimethoxyphenyl)-propanone-2 prepared in these laboratories by Mr. H.E. Fisher (from 1-(3,4-dimethoxyphenyl)-propanone-2 by direct bromination) was hydrolysed with 5% aqueous potassium acetate in exactly the same way as 3-chloro-1-(3,4-dimethoxyphenyl)-propanone-2 (see pg. 117). 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 was again obtained, this time in a yield of 55%.

(h) Preparation of the Semicarbazones of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 and 2-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-1.

0.10 g. of 1-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 were dissolved in 4 cc. of water with 0.10 g. of semicarbazide -

HCl and 0.15 g. potassium acetate. Precipitation started immediately but the mixture was allowed to stand overnight at room temperature, then cooled and filtered. The product was washed carefully with water, then dried. Yield 0.095 g. (65%), m.p. 155-156°.

Recrystallization from water failed to raise the melting point.

Analyses: Calc'd. for $C_{11}H_{17}O_4N_3$: C, 53.9; H, 6.4; OCH_3, 23.2.
Found: C, 53.8; H, 6.4; OCH_3, 23.0.

0.19 g. of 2-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-1, 0.13 g. of semicarbazide·HCl and 0.15 g. of potassium acetate were dissolved in 7-8 cc. of water and allowed to stand 2-3 days. The semicarbazone slowly precipitated. Yield 0.15 g. (55%), m.p. 153-155°. Several recrystallizations from water and dilute aqueous methanol raised the melting point to 154-155°.

Analysis Calc'd. for $C_{11}H_{17}O_4N_3$. OCH_3, 23.2
Found OCH_3, 23.0

A mixed melting point with the semicarbazones of 1-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 and 2-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-1 (155-156° and 154-155° respectively) gave a depression of 23°.

(i) Oxidation of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 and of 2-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-1 to 1-(3,4-dimethoxyphenyl)-propanedione-1,2.

1.45 g. of $CuSO_4 \cdot 5H_2O$ were dissolved by warming in a mixture of 2.4 cc. of pyridine and 1.2 cc. of water. To the hot solution was added 0.050 g. of 1-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 and heating was continued on the steam bath for 2 hours. The mixture was then poured slowly with stirring, into 14 cc. of 3N hydrochloric acid and a dirty brown crystalline precipitate was thrown down. The mixture was extracted with ether; the extract was dried, concentrated to a small volume and cooled. 1-(3,4-dimethoxyphenyl)-propanedione-1,2 crystallized out in beautiful, blunt yellow needles. Yield 0.3 g. (60%), m.p. 68-70°. Recrystallization from ether raised the melting point to 69-70° only.

0.4 g. of 2-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-1 were treated similarly and gave the same yellow crystalline product. Yield 0.15 g. (40%). Mixed melting point determinations between the two products showed no depression. Analyses - Calcd. for $C_{11}H_{12}O_4$: CH_3O, 29.8; Found: CH_3O, 29.7.

(j) Oxidation of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 with Periodic Acid.

To a solution of 0.135 g. of 1-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 in 100 cc. of water were added

0.15 g. of $HIO_4 \cdot 2H_2O$ and 10 cc. of 2N sulphuric acid. The mixture was allowed to stand 24 hours at room temperature and was then extracted with ether. The ether extract was washed with 5% Na_2CO_3 solution, then with water and finally dried over sodium sulphate. Addition of petroleum-ether (30-50°), and cooling, precipitated veratraldehyde. Yield 0.05 g. (50%), m.p. 43-44°.

A mixed melting point with authentic veratraldehyde showed no depression.

(k) Ethanolysis of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2.

0.62 g. of this hydroxy-ketone were refluxed for 48 hours with 65 cc. of ethanol-HCl (2.1%). The reaction was carried out under an atmosphere of carbon dioxide in "all-glass" apparatus.

Solid sodium bicarbonate was added to the reaction mixture until effervescence ceased and the solution was then filtered and evaporated to dryness under reduced pressure. The residue, which set to a sticky solid, was recrystallized from petroleum ether. The product was identified by mixed melting point determination, as 2-ethoxy-1-(3,4-dimethoxyphenyl)-propanone-2. Yield 0.32 g. (50%), m.p. 77-80°.

The yield of petroleum-ether insoluble, amorphous material was low (about 5%).

(l) Klason Lignin Determination on 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2.

0.23 g. of the hydroxy-ketone were stirred with 2 cc. of 72% sulphuric acid for two hours. The solution was then diluted with water to 75 cc. and refluxed for four hours.

The product was extracted with chloroform, the extract washed with water, dried over sodium sulphate, concentrated to a small volume and precipitated into 75 cc. of petroleum-ether (30-50°). 0.080 g. of light brown amorphous powder was obtained. The filtrate was evaporated to dryness, the residue taken up in 3 cc. of ether and precipitated again into 75 cc. petroleum-ether, yielding a further 0.080 g. of amorphous material. A third precipitation from ether into petroleum-ether gave an additional 0.025 g. of material. Total yield 0.165 g. (72%).

(m) Treatment of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 with Aqueous Sulphuric Acid (5%).

0.49 g. of the hydroxy-ketone were warmed at 70-80° for 3½ hours with 100 cc. of aqueous sulphuric acid (5%). The solution, which remained clear and colorless, was extracted with chloroform, the extract dried, and the solvent then removed under reduced pressure. The residue was crystallized from ether to give 0.35 g. (70%) of the unchanged starting material. No evidence of any rearrangement was obtained in spite of a loss of 30% of the original material.

(n) Treatment of 2-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-1 with Aqueous Potassium Acetate.

0.5 g. of this hydroxy-ketone were refluxed for 4 hours with 75 cc. of aqueous potassium acetate (5%). The product was extracted from the aqueous solution with chloroform and distilled to give 0.40 g. of yellow oil. On treatment with semicarbazide.HCl in aqueous potassium acetate solution it slowly precipitated the semicarbazone of 2-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 (identified by mixed melting points) in 48% yield. The purity of this semicarbazone as judged by the melting point of the crude product (153-155°), was high.

The remaining 52% of the product was unaccounted for. However when pure 2-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-1 was treated with semicarbazide under exactly similar conditions the yield was only 55%. Furthermore, when 1-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 is treated with semicarbazide, precipitation of the semicarbazone is rapid. It therefore seems probable that very little of the latter ketol was present in the product.

III. Attempted Preparation of Various Ethers Related to Wood Ethanolysis Products and Lignin Progenitors.

(a) Reaction of 3-Chloro-1-(3,4-dimethoxyphenyl)-propanone-2 with Sodium Methylate and with Potassium Hydroxide in Methanol.

2.5 g. of the chlor-ketone were dissolved in 15 cc.

of methanol and a solution of 0.32 g. (1.3 equiv.) of sodium in 16 cc. of methanol added dropwise. The alkaline solution was neutralized with a drop of hydrochloric acid and the excess acid neutralized with solid sodium bicarbonate. The solution was filtered and then concentrated under reduced pressure. The residue was crystallized from petroleum-ether (30-50°). Yield 1.75 g. (70%), m.p. 36-39°.

Recrystallization from petroleum-ether and then from 20% ethanol (aq.) raised the melting point to a constant value at 40-41°.

Analyses - Calcd. for $C_{12}H_{17}O_4$: C, 64.3; H, 7.1; CH_3O, 41.5;
Found: C, 64.2; H, 7.0; CH_3O, 41.7.

Rast molecular weight determinations gave an average value of 234. Calculated for the above formula - 224.

Treatment of this substance under a variety of conditions with semicarbazide gave no semicarbazone. Similarly, with 2,4-dinitro-phenylhydrazine in acid solution, the compound was recovered unchanged except when drastic conditions were used. Prolonged treatment in hot solution with dilute acids converted the product to an oil which was not identified.

These experiments were repeated by substituting potassium hydroxide in methanol for the sodium methylate and using phenolphthalein as indicator. The yield was somewhat higher (80%).

(b) Behaviour of 3-Chloro-1-(3,4-dimethoxyphenyl)-propanone-2 towards Sodium Ethylate.

2.3 g. of chlor-ketone were dissolved in 25 cc. of ethanol and a solution of 0.33 g. of sodium in 18 cc. of ethanol added slowly. The reaction product was treated as in the experiment with sodium methylate. The residual oil was fractionally distilled and boiled at 103-105°/0.04 mm. $[n]_D^{25°} = 1.5150$.

Analyses - Calc'd. for $C_{13}H_{19}O_4$: Alkoxyl (as methoxyl), 39.1;
Found: 39.2

After prolonged treatment with 2,4-dinitrophenylhydrazine in dilute HCl a small amount (10 mg.) of a crystalline product was isolated. It had a methoxyl content of 15.1% and a melting point of 114-117°, but was not further investigated.

(c) Reaction of 3-Chloro-1-(3,4-dimethoxyphenyl)-propanone-2 with Potassium Acetate in Ethanol.

1 g. of chlor-ketone and 2 g. of potassium acetate were refluxed with 50 cc. of ethanol for 12 hours. The ethanol was distilled off and the residue extracted with petroleum-ether (60-70°). The petroleum-ether soluble material was distilled under high vacuum and yielded a yellow oil showing no carbonyl activity.

Alkoxyl (as methoxyl) = 37.1% $[n]_D^{25°} = 1.5170$

This product was probably composed largely of the compound previously obtained from the chlor-ketone by action of sodium ethylate.

(d) (i) Oxime of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2.

0.63 g. of 1-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 (pg.117), 0.23 g. of hydroxylamine hydrochloride and 0.33 g. of potassium acetate were dissolved in 18 cc. of water and allowed to stand for 15 hours at room temperature. The product was extracted with chloroform and the extract dried over sodium sulphate and concentrated. On cooling the solution a beautifully crystalline product separated out. It was very unstable when removed from the solution and decomposed at 65-68°. It had a methoxyl content agreeing fairly well with that of a chloroform addition product of the oxime.

Analyses - Calcd. for $C_{11}H_{15}O_4N.CHCl_3$: CH_3O, 18.1; Found: CH_3O, 18.7.

The addition compound decomposes even on standing which explains the somewhat high methoxyl value.

The crystals on drying at 60° under reduced pressure for several hours lost the greater part of the chloroform of crystallization leaving 0.48 g. of a stiff glassy product which could not be freed completely from chloroform under these conditions.

(ii) Ethylation of the Oxime.

0.4 g. of chloroform-free oxime were dissolved in 18 cc. of 0.2N sodium hydroxide (2 equivs.). 0.48 cc. of diethyl sulphate were added at room temperature, with constant stirring, over a period of 30 minutes. Stirring was continued for 4 hours. The neutral solution was thoroughly extracted with chloroform, the extract dried and the solvent removed leaving 0.45 g. of a sticky solid.

This residue was taken up in petroleum ether and the solution cooled. A white solid crystallized out and was recrystallized from petroleum ether to a constant melting point of 67-68°.

Analyses - CH_3O found - 29.7.

Molecular weight - Calcd. on assumption of two methoxyl groups, 230. Found (Rast method in camphor), 210.

That the compound was not 1-hydroxy-1-(3,4-dimethoxyphenyl)-propanone-2 was shown by mixed melting point determination. It was not examined further.

(e) Methylation of the Semicarbazone of 2-Ethoxy-1-(3,4-dimethoxyphenyl)-propanone-1.

0.53 g. of the semicarbazone were dissolved in a mixture of 5 cc. of dioxane, 4 cc. of 1N sodium hydroxide and 5 cc. of water and 0.38 cc. of dimethyl sulphate were added slowly, at room temperature, with constant stirring. One-half hour after the initial addition, a further 4 cc.

of alkali and 0.38 cc. of dimethyl sulphate were added, followed after a further 1/2 hour by 9 cc. of alkali and 0.76 cc. of dimethyl sulphate. The solution was stirred for 1-1/2 hours before the final addition of 8 cc. of alkali and 0.74 cc. of dimethyl sulphate. Stirring was continued for 1 hour. The solution was then slightly acidified with HCl, filtered, the filtrate extracted with chloroform, and the extract dried over sodium sulphate. Removal of the solvent left a semi-solid mass. Recrystallization from petroleum-ether gave 0.23 g. of 2-ethoxy-1-(3,4 dimethoxyphenyl)-propanone-1 (m.p. 78.5-80°). A mixed melting point determination with an authentic sample showed no depression.

IV. Preliminary Experiments on the Synthesis of 3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propanone-2.

(a) Preparation of Homovanillin.

20 g. of freshly distilled eugenol were dissolved in 100 cc. of pure dry ethyl acetate*, the solution cooled to -10° to -15°, and a stream of ozonized air, containing 1.0-1.2% of ozone by volume, passed in at a rate of 500 cc. per minute until 110% of the theoretical amount of ozone had been added. About 9 hours were required.

The ethyl acetate was removed by distillation under reduced pressure at 35-40°. The ozonide, a reddish brown oil

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* Eastman Kodak Co. "anhydrous ethyl acetate" extracted with sodium carbonate, washed with water & dried several days over calcium chloride, then distilled.

was added dropwise, with alternate additions of small amounts of zinc dust to 50 cc. of glacial acetic acid and the mixture stirred vigorously throughout the addition. 25 cc. portions of ether were added occasionally to aid stirring . The addition of zinc dust was continued until it caused no further evolution of heat (about 40-50 g.). The mixture was stirred for a further 1/2 hour, then 150 cc. of ether were added gradually and the mixture filtered.

The filtrate was mixed with an equal volume of water, stirred for about an hour with excess calcium carbonate, filtered, and the filtrate stirred with a little sodium bicarbonate until all effervescence ceased. (The removal of all acid before distillation is important). The ether layer was separated and the aqueous layer thoroughly extracted with ether. The ether solutions were combined, washed with water, dried over sodium sulphate, the ether removed, and the residual reddish oil distilled as rapidly as possible under high vacuum. The distillate was pure homovanillin and crystallized on standing. Yield 8-10 g. (40-50%), m.p. 49-50°.

The product, after recrystallization from carbon disulphide or carbon tetrachloride and melted at 50-51°.

(Harries (110) reports the melting point to be 50-51°).

(b) Preparation of Homovanillin Oxime.

7.5 g. of homovanillin and 7.5 g. of potassium acetate were dissolved in a mixture of 20 cc. of methanol and 50 cc. of water. To this solution were added 4 g. of hydroxylamine sulphate in 50 cc. of water. The mixture was allowed to stand 24 hours at room temperature and the methanol distilled off under reduced pressure. The residue, containing some precipitated oxime, was extracted with ether. The ether solution, on drying and concentrating gave an almost quantitative yield of oxime. The product was recrystallized from a little ethyl acetate. Yield 7.8 g. (95%), m.p. 114-115°.

(Hahn and Schales (100) give the melting point of this oxime as 115°)

(c) Preparation of Homovanillic Acid.

Homovanillin oxime was converted to homovanillic acid exactly according to the procedure of Hahn and Schales (100). 10 g. of the oxime were refluxed with acetic anhydride for three hours and yielded 9.0 g. of pure acetyl homovanillonitrile (79%), m.p. 52-53°. 8.4 g. of the nitrile were refluxed with aqueous sodium hydroxide and gave 7.2 g. of homovanillic acid (96%), m.p. 141-143°.

(These melting points are in agreement with those of Hahn and Schales i.e. 52° and 143° for acetyl homovanillonitrile and homovanillic acid respectively).

(d) Preparation of Acetyl Homovanillic Acid.

7.5 g. of homovanillic acid were refluxed 2-1/2 hours with 40 cc. of acetic anhydride. The reaction mixture was poured into 500 cc. of water and the solution taken to dryness under reduced pressure at 100°. The residue was dissolved in 100 cc. of water, refluxed with charcoal and filtered. (At 60-70° the filtrate should be absolutely clear.) Cooling the solution precipitated 6.4 g. of acetyl homovanillic acid. The mother liquors, on concentration, gave a further 0.7 g. Yield 7.1 g. (78%), m.p. 138-139°.

(Acetyl homovanillic acid is reported by Tiemann and Nagai (103) to melt at 140°.)

(e) Preparation of Acetyl Homovanilloyl Chloride.

2.5 g. of acetyl homovanillic acid were gently warmed for 45 minutes with 5 cc. of pure thionyl chloride. The excess reagent was distilled off under reduced pressure, and the residue distilled under high vacuum. A reddish oil, which crystallized on standing, was obtained. Yield 2.27 g. (85%), m.p. 54-56°.

Recrystallization from dry petroleum ether gave the pure acid chloride. M.p. 56-57°.

Analyses - Calcd. for $C_{11}H_{11}O_4Cl$: CH_3O, 12.8; Cl, 14.7;

Found: CH_3O, 12.9; Cl, 14.4.

(f) Preparation of 3-Chloro-1-(4 hydroxy-3 methoxy-phenyl)-propanone-2.

0.5 g. of crystalline acid chloride was added to a well-cooled ethereal solution of diazomethane prepared from 3 g. of nitrosomethyl urea. A vigorous reaction ensued. The solution was allowed to stand for three hours and then was treated with ethereal-HCl until reaction ceased. The solution was washed twice with water, twice with 5% $NaHCO_3$, and finally once more with water. After drying over sodium sulphate, the ether solution was concentrated, and gave 0.4-0.5 g. of yellow oil which resisted all attempts at crystallization and which decomposed on attempted distillation. It was placed under vacuum at room temperature to remove as much as possible of the solvent.

Analyses - Calcd. for $C_{12}H_{13}O_4Cl$: CH_3O, 12.1; Cl, 13.9.

Found: CH_3O, 12.2; Cl, 13.4

(g) Hydrolysis of 3-Chloro-1-(4 hydroxy-3 methoxyphenyl)-propanone-2 with Lead Oxide.

2.2 g. of the crude chlor-ketone were refluxed for 3 hours with 5 g. of lead oxide and 500 cc. of water. The solution was cooled, filtered and extracted with chloroform until it no longer gave a carbonyl reaction with 2,4 dinitrophenylhydrazine (about 6 extractions were necessary).

The chloroform extract was dried over Na_2SO_4, the solvent removed and the residue distilled under vacuum

(0.1 mm. b.p. 147-152°) giving 0.5 g. of bright yellow oil.

Analyses - Calcd. for $C_{10}H_{12}O_4$: CH_3O, 15.8; Found: CH_3O, 15.9.

The product was carefully fractionated and found to be a mixture. From the higher boiling fractions a small amount of crystalline material was obtained (m.p. 92-97°). This, on recrystallization from ether-petroleum-ether, melted at 100-102°. A mixed melting point with 2-hydroxy-1-(4 hydroxy-3-methoxyphenyl)-propanone-1 showed no depression.

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