SYNTHESES OF CARBONYL DERIVATIVES OF POLYHYDROXY CYCLOHEXANES

by

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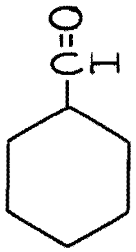
STRUCTURES

In the structural formulae throughout the text the saturated cyclohexane nucleus is represented by , and the unsaturated benzenoid nucleus by .

GENERAL INTRODUCTION

Cyclohexylaldehyde, I, is a reactive substance reported to be polymerized by a trace of alkali to a high-boiling oil of the same composition and undetermined molecular weight (1). Since the aldehyde contains only one α-hydrogen atom, it is likely that the high-boiling oil is a linear condensation product of the aldol type, II.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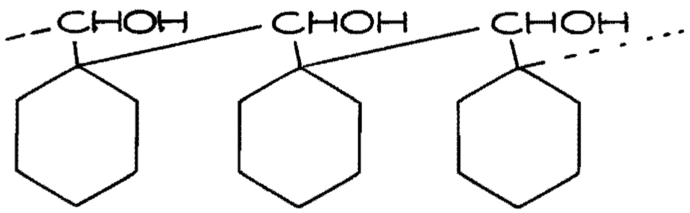
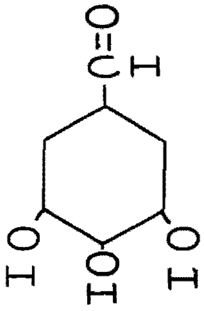

II

It is also likely that 3,4,5-trihydroxycyclohexyaldehyde, III, would produce the polymer IV under similar conditions.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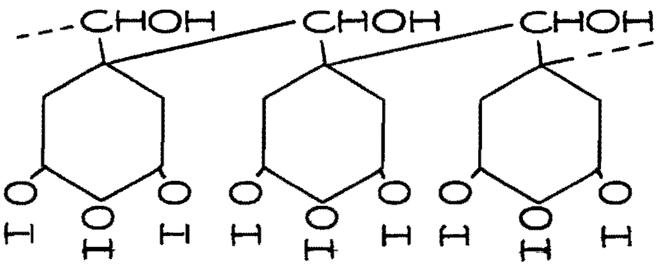

IV

A polyhydroxy linear polymer of type IV is of great theoretical interest because its properties could be compared with those of other linear polymers, especially cellulose and polyvinyl alcohol. Such comparisons would be highly informative in regard to the relationship of substitution and degree of polymerization to physical and chemical properties. If a convenient synthesis were available, the polymer IV might also find a use in the polymer field as, possibly, an adhesive or synthetic resin. A versatility in properties analogous to that possessed by cellulose might be anticipated since four hydroxyl groups per unit might be either partially or completely substituted by esterification, etherification, or by other reactions.

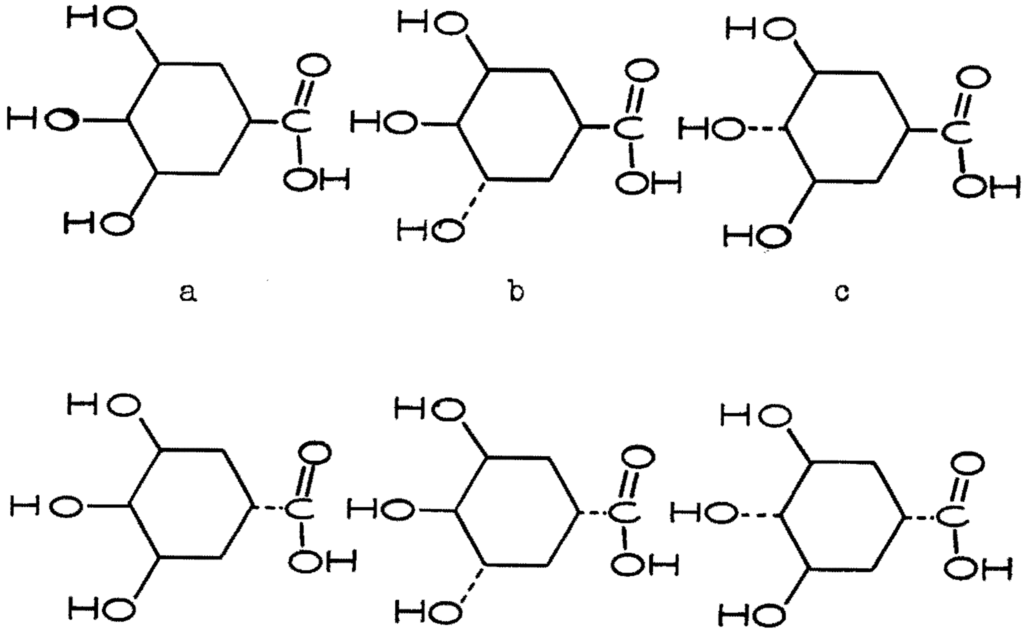
The main interest of the present work was to study synthetic methods likely to yield 3,4,5-trihydroxycyclohexylaldehyde, III, the unknown monomer for the desired polymer. The first approach consisted of efforts to synthesize acetals of phenolic aldehydes like gallic aldehyde (3,4,5-trihydroxybenzaldehyde) in the hope that the acetal group would survive the conditions necessary for the catalytic hydrogenation of the aromatic ring. The free aldehyde could then be obtained by mild acid hydrolysis of the resulting hydroxylated cyclohexylacetal.

Although several new acetals of hydroxybenzaldehydes were isolated, these compounds, like the few previously known, were extremely unstable to acid, even to the acidity of laboratory air. Investigation showed however that their stability to anhydrous alkali was greater than might have been expected and that the acetal could be in part recovered after high pressure hydrogenation under certain anhydrous conditions and with various catalysts. During hydrogenation unfortunately the stability failed just short of conditions generally necessary to effect nuclear reduction to a cyclohexyl compound, and the acetals yielded aromatic products derived from hydrogenolysis of the acetal group.

A less direct alternative method for the synthesis of III was next considered. The nuclear reduction of ethyl gallate to 3,4,5-trihydroxy-1-carbethoxycyclohexane was successfully carried out after proper conditions were discovered in pilot experiments with p-hydroxybenzoic ester and pyrogallol. Since proven methods are available to convert aliphatic acids in high yield to aldehydes, this aspect of the research ceased with the conversion of the trihydroxycyclohexyl ester to the free acid and lactone. It was considered more advantageous to complete the Thesis with a fundamental study of cis-trans isomerism in the little-known hexahydrogallic acid series.

Six cis-trans hexahydrogallic acids are possible and all might well be formed by the hydrogenation of gallic acid. The six isomers are represented by structures Va-f in which trans orientations are represented by dotted bonds. One of these configurations, Vb, had been assigned to dihydroshikimic acid (2), a derivative of shikimic acid isolated from the fruit of a Japanese plant (Shikimi or

Illicium religiosum). The hydrogenation mixture from ethyl gallate has been found to contain a large proportion of a trihydroxycyclohexane carboxylic ester which was not dihydroshikimic acid and which was not readily isolable in good yield by purely physical methods. Studies of the corresponding lactone, isopropylidene acetal, and similar derivatives not only revealed a more efficient method for isolating the substance, but showed that its configuration probably corresponded to Va or Ve.

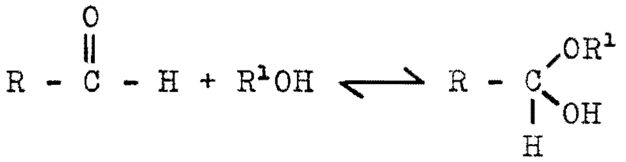


V

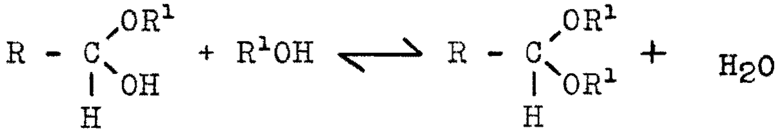
HISTORICAL INTRODUCTION

Synthesis of Acetals

Acetals, whose general formula is $RCH(OR^1)_2$ where R,R^1 are alkyl or aryl radicals, were first mentioned by Liebig (3) in 1833. The interaction of an aldehyde and an alcohol is an equilibrium reaction thought to proceed with formation first of an unstable hemiacetal, and then the acetal. The latter undergoes hydrolysis back to the aldehyde and alcohol in aqueous acid but is characteristically stable in alkaline media.

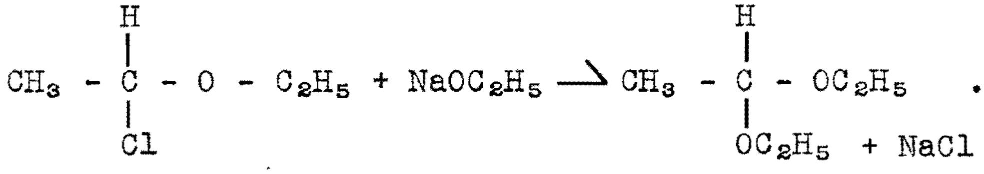


$$R - \overset{O}{\overset{\|}{C}} - H + R^1OH \rightleftharpoons R - \underset{H}{\underset{|}{C}}\begin{matrix}\diagup OR^1 \\ \diagdown OH\end{matrix} \qquad \ldots(1)$$

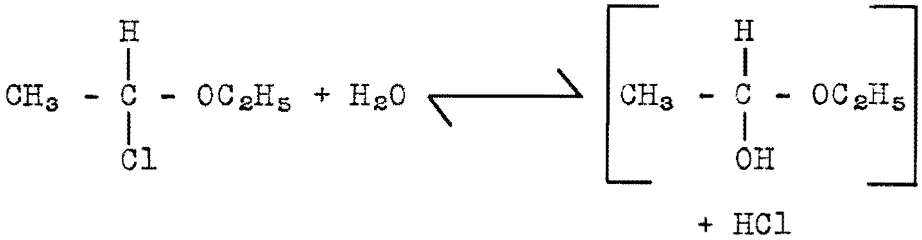


$$R - \underset{H}{\underset{|}{C}}\begin{matrix}\diagup OR^1 \\ \diagdown OH\end{matrix} + R^1OH \rightleftharpoons R - \underset{H}{\underset{|}{C}}\begin{matrix}\diagup OR^1 \\ \diagdown OR^1\end{matrix} + H_2O \qquad \ldots(2)$$

de Leeuw (4) determined the specific gravities of a series of aldehyde-alcohol mixtures by the dilatometer method and found maximum values when the components were present in equimolecular quantities. Inflection points were also found by him at this concentration in curves relating boiling points, molecular heat of reaction, viscosity and refractive index with the mole fraction of the components. The absorption spectra of solutions of aldehydes in alcohols (5) and in water (6) clearly indicated that constitutional changes occurred with the formation of a new linkage of the type postulated in the hemiacetal theory. Hemiacetal formation was also investigated by Adkins (7). A maximum deviation of the observed refractive index from the calculated value was found when the components were present in equimolecular quantities, a result similar to the earlier work (4) and again evidence of constitutional changes. Perhaps also worthy of note is the work of Jacobson (8) who, in his studies of chlorosubstitution products of ethyl ether, demonstrated the presence of a chloroether which could be coupled with sodium alcoholate to yield a true acetal and which also could be hydrolysed to what he believed to be a hemiacetal, equations (3) and (4). However, the product was incompletely characterized and was probably a mixture of acetaldehyde and alcohol because the hemiacetal of this aldehyde has never been isolated, being recognized as a transient intermediate only (7).

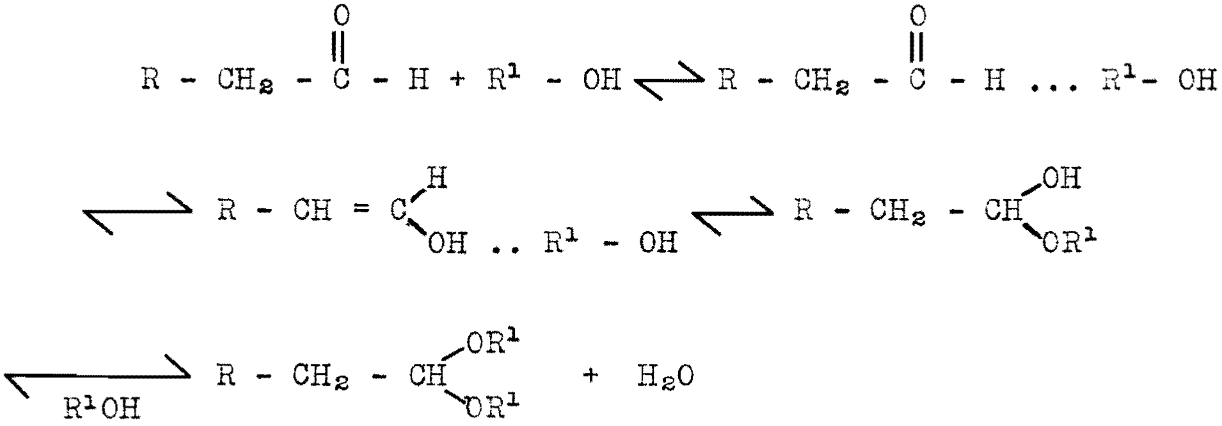


$$CH_3 - \underset{\displaystyle Cl}{\overset{\displaystyle H}{C}} - O - C_2H_5 + NaOC_2H_5 \rightarrow CH_3 - \underset{\displaystyle OC_2H_5}{\overset{\displaystyle H}{C}} - OC_2H_5 + NaCl \qquad ...(3)$$



$$CH_3 - \underset{\displaystyle Cl}{\overset{\displaystyle H}{C}} - OC_2H_5 + H_2O \rightleftharpoons \left[CH_3 - \underset{\displaystyle OH}{\overset{\displaystyle H}{C}} - OC_2H_5 \right] + HCl \qquad ...(4)$$

According to Müller (9) the acetal reaction proceeds through the formation of a molecular compound of the alcohol and the enolic form of the aldehyde according to the mechanism represented by equations (5), (6) and (7).



$$R - CH_2 - \overset{O}{\overset{\|}{C}} - H + R^1 - OH \rightleftharpoons R - CH_2 - \overset{O}{\overset{\|}{C}} - H \;...\; R^1 - OH \quad ...(5$$

$$\rightleftharpoons R - CH = C\begin{matrix} H \\ OH \end{matrix} \;..\; R^1 - OH \rightleftharpoons R - CH_2 - CH\begin{matrix} OH \\ OR^1 \end{matrix} \quad ...(6$$

$$\xrightleftharpoons[R^1OH]{} R - CH_2 - CH\begin{matrix} OR^1 \\ OR^1 \end{matrix} + H_2O \quad ...(7$$

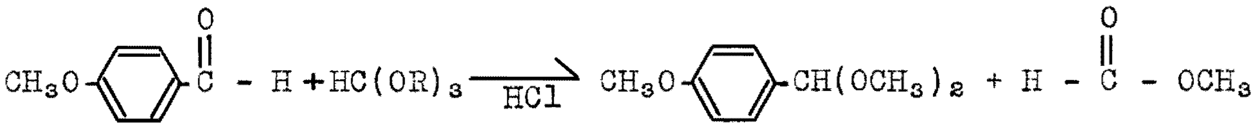
He based this conception on the observation that the reaction of phenyl acetaldehyde and benzyl alcohol was first endothermic, and then strongly exothermic. The first change was explained by the splitting of associated molecules and formation of a molecular compound, while the exothermic change was caused by the formation of primary valence bonds.

The classical method of Liebig (3) was investigated by Fischer and Giebe (10, 11) who used a one per cent solution of anhydrous hydrogen chloride catalyst in alcohol and the required amount of aldehyde. They secured diethyl acetal in 50 per cent, and p-anisaldehyde dimethyl acetal in 40 per cent yield, but failed to obtain the methyl acetals of vanillin, salicylaldehyde and p-hydroxybenzaldehyde. The p- and o-nitrobenzaldehydes gave high yields of acetals by this method. These investigators were the first to observe the irregularity of the phenolic aldehydes in the acetal reaction and contrasted the unfavourable effect of the hydroxyl substituent with the promotion of acetal formation by the nitro group. They did not venture to account for the difference because insufficient data were available at that time. The fact that unsaturated aldehydes gave lower yields of acetals than the saturated compounds was noted also. Many variations of the classical method have been applied, in most cases to the synthesis of aliphatic acetals. In general, they involve the use of a chloride or nitrate of a metal, with or without hydrochloric or other acid, in conjunction with the alcohol and aldehyde (12). A study of catalysis and equilibrium in acetal formation, made by Adkins with Nissen (13) and with Adams (7), differentiated between two functions exerted by calcium chloride and other metal salts in the condensations. The salts were shown to possess the dual role of true catalyst and dehydrating agent in most cases. For example, calcium chloride and hydrogen chloride caused the production of the same amount of acetals if the homogeneity of the reaction mixtures was maintained by the use of excess alcohol or of small amounts of the salt catalyst. This result agreed with the traditional view that in a homogeneous system the position of equilibrium in a balanced reaction is unaffected by the nature of the catalyst. When, however, sufficient calcium chloride was used to cause the separation of an aqueous salt layer, the percentage of acetal formed was in some cases almost double that obtained with hydrogen chloride. The solubility of higher alcohols and acetals in water is so much less that no salt was needed to separate the water from the sphere of reaction and in these cases the calcium chloride lost some of its value as compared with hydrogen chloride. A close correlation was shown to exist between the ability of a salt to form an alcoholate and its ability to catalyse acetal formation (7). All of the salts which catalysed acetal formation, in addition to forming alcoholates, were acid in solution (pH value less than 7) but the catalyst was not hydrogen ion, and there was no apparent relationship between acidity and efficiency as an acetal catalyst. For example, zinc chloride was more acidic than calcium chloride yet is not so good a catalyst. The presence of water in the reaction was conducive to the production of hydrogen ions by hydrolysis of the catalyst and ionization of the hydrogen chloride formed but the velocity constants of the acetal reaction fell off rapidly as water accumulated. It seemed probable to Adkins that the seat of catalytic activity was to be found around the anion end of the undissociated acid or salt rather than in dissociated hydrogen ions, whose presence was merely incidental. The yields of acetals obtained by means of these improvements on the classical method varied considerably with the structure of the reactants and the nature of the catalyst but cases were few in which the amount of acetal formed exceeded 50 per cent of theory. This limitation was connected with the balanced nature of the reaction.

Further extensive investigations of the per cent conversions and equilibrium constants in acetal formation from a variety of aldehydes and alcohols were made by Adkins and his School (14, 15, 16, 17, 18, 19). The reaction was considered to be essentially bimolecular because the rate-determining stage was the formation of the acetal from the hemiacetal, equation (2). The first stage, equation (1), the formation of the hemiacetal, was believed to occur immediately when the reactants were mixed in the absence of a catalyst (14). In his investigations Adkins used the term "affinity for acetal formation" when referring to the equilibrium constant, that is to say, to the yield. When referring to the velocity constant, the term "reactivity" was used. The reactions were classified in two ways, first the condensation of an alcohol with various aldehydes and second, the condensation of an aldehyde with various alcohols. The results of a large number of experiments were summarized in several general statements regarding the relationship of structure to "affinity" and to "reactivity". Branching and lengthening of chains at the 2-position of acetaldehyde, and also unsaturation, decreased the "affinity" or the yield (15). Branching of the alcohol chain, except on the carbinol carbon atom, had little effect on the "affinity". Primary had a greater "affinity" for acetal formation than secondary alcohols which, in turn, gave better yields than tertiary alcohols. This order was reversed as regards "reactivity". The effect of unsaturation was less in the alcohol than in the aldehyde but the rate was greater with unsaturated compounds. Unsaturated monoplanar cyclic aldehydes such as benzaldehyde and furfural had low affinity values (19).

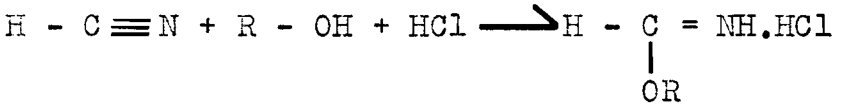
By far the greatest number of open chain acetal reactions studied involved aliphatic aldehydes and alcohols and much data are available in this field. Although benzaldehyde, anisaldehyde and m-nitrobenzaldehyde were included, little is known about the behaviour of other benzaldehyde analogues.

A number of more complicated procedures, based upon the condensation of an orthoester with an aldehyde, give higher yields of acetals than the older, better known method already described. The originator of the orthoester method was probably Claisen (20) who prepared acetals by condensing orthoformic esters with aldehydes dissolved in an alcohol containing an acidic catalyst such as hydrogen chloride, ammonium chloride or ferric chloride, the byproduct always being a formate, equation (8).

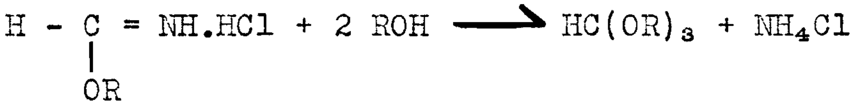


...(8)

A modification was devised by Claisen (21) which differed from the above reaction by the use of what he called "nascent orthoformic ester". Anhydrous hydrogen cyanide first forms a formimide hydrochloride ether when dissolved in an alcohol containing dry hydrogen chloride and, in the presence of excess alcohol, the desired orthoester and ammonium chloride result; equations (9) and (10).



$$H - C \equiv N + R - OH + HCl \longrightarrow H - \underset{\underset{\displaystyle OR}{|}}{C} = NH.HCl \qquad ...(9)$$



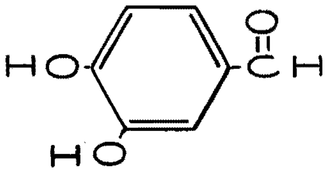
$$H - \underset{\underset{\displaystyle OR}{|}}{C} = NH.HCl + 2\ ROH \longrightarrow HC(OR)_3 + NH_4Cl \qquad ...(10)$$

When an aldehyde was added to the mixture an acetal was formed without the necessity of isolating the orthoester or adding any further catalyst. This method is complicated by the necessity of a special apparatus for the preparation of anhydrous hydrogen cyanide and by the instability of the "nascent" orthoester. Although the method is cheap and convenient when large quantities of acetals are desired, the use of the more expensive free orthoester, derived from chloroform and sodium alcoholate, was in general to be preferred (22).

$$HCCl_3 + 3\ NaOR \longrightarrow HC(OR)_3 + 3\ NaCl \qquad ...(11)$$

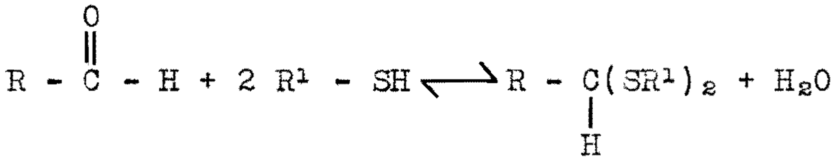
Both modifications gave about the same yields. Claisen emphasized that the orthoformic ester method was superior to the classical method (3) especially in the preparation of acetals of aromatic aldehydes. The yields of acetals from benzaldehyde, m-nitrobenzaldehyde, anisaldehyde, piperonal and many similar aldehydes were almost quantitative whereas many of them had been obtained in lower yield than acetals of aliphatic aldehydes by the older method (10, 11). However, no reference was made by Claisen to an acetal of an hydroxybenzaldehyde.

Pauly and Buttlar (23) noted that phenolic aldehydes exhibited abnormal behaviour not only in the formation of acetals but in several other reactions including the Cannizzaro reaction, the benzoin condensation and the Grignard reaction. They reviewed the existing experimental data and compared the behaviour of hydroxy-substituted benzaldehydes with other aromatic and aliphatic aldehydes. By employing Claisen's orthoformic ester method they succeeded in preparing methyl acetals of o-, m-, and p-hydroxybenzaldehyde for the first time. The p-hydroxy compound was a crystalline material with a broad melting point, 60-64°. It was found to be extremely unstable and underwent rapid hydrolysis to the aldehyde in contact with aqueous alkalies and acids and in moist air. The o- and m-hydroxy acetals were equally unstable, did not crystallize, and could not be distilled without decomposition. A number of substituted benzaldehydes containing phenolic ether groups all formed acetals in substantially quantitative yields. These acetals were stable compounds. Attempts to obtain acetals of protocatachualdehyde, VI, or other dihydroxy-benzaldehydes (2,4-; 2,5-; and 2,3-) were unsuccessful; part of the original aldehyde was recovered from the reaction mixture but the remainder became resinous.



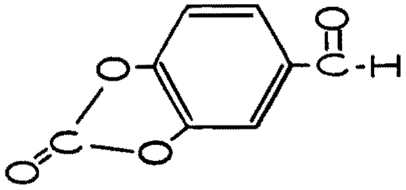
VI

The investigation was extended to the preparation of thioacetals from aldehydes and thioalcohols with an acid catalyst as described by Baumann (24), and therefore analogous in method to the older acetal synthesis; equation (12).



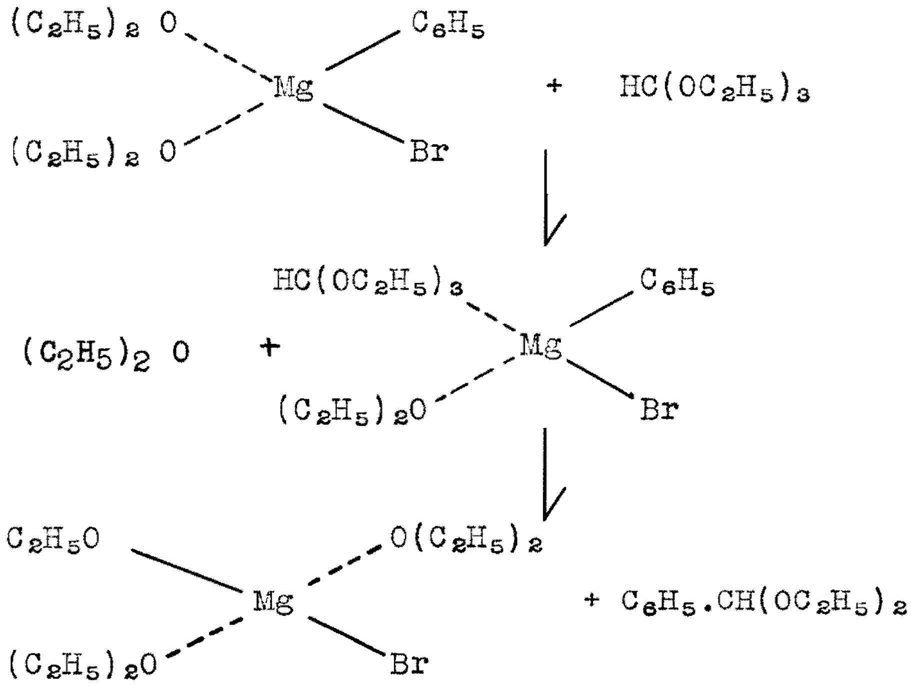
$$R - \overset{O}{\overset{\|}{C}} - H + 2\,R^1 - SH \rightleftharpoons R - \underset{H}{\underset{|}{C}}(SR^1)_2 + H_2O \qquad \ldots(12)$$

In this reaction all of the phenolic aldehydes, as well as the other type of aldehyde, readily formed thioacetals which were stable compounds. The stability of thioacetals was noted by Baumann (24) to be somewhat greater than the stability of ordinary acetals since the former hydrolysed much more slowly when heated under reflux with strong acids. The exceptional behaviour of the phenolic aldehydes was thus limited to their incapacity to form stable acetals by the ordinary methods. Pauly and Buttlar (23) stated that the instability was independent of the position of the phenolic oxygen atom in the nucleus and could not be accounted for by steric influences. In some way, the mere presence of the hydroxyl group was sufficient to cause reduction in the activity of the aldehyde function. These investigators presented at considerable length an argument, based on an obsolete valence theory, to account for the facts. However, they failed to explain why the cyclocarbonate of protocatachualdehyde, VII, resembled the free phenol in not yielding an acetal although similar aldehydes with phenolic ether groups behaved normally. It is difficult to understand their reasoning in view of this exception.



VII

The original orthoester synthesis of Claisen (22) has undergone a number of variations. Wood and Comley (25) described the preparation of aldehydes via their acetals by condensing a Grignard reagent with an orthoformic ester. The method had been suggested independently by Bodreux (26) and Tschitschibabin (27) but little information as to the conditions for a successful preparation was given by the latter pair. Wood and Comley prepared benzaldehyde diethyl acetal, cyclohexylaldehyde diethyl acetal, and a few other aliphatic acetals. The reaction was recognized to proceed through two stages because a precipitate immediately appeared when the orthoester was added to the Grignard reagent dissolved in ethyl ether. As the reaction proceeded, the solid material disappeared. The mechanism represented by equations (13) and (14) was suggested by Wood and Comley.



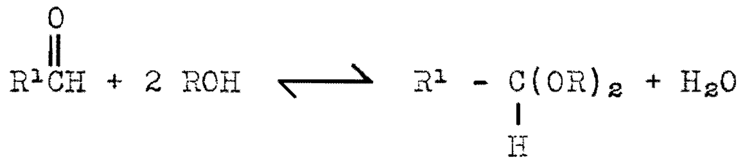
...(13)

...(14)

Unfortunately the reaction lent itself more to the preparation of aldehydes, obtained by hydrolysis of the products, than to isolation of the intermediate acetals.

Helferich and Hausen (28) used orthosilicates, the silicon analogues of the orthoformates, to prepare acetals. The more easily prepared orthosilicates rendered the method superior to Claisen's in some respects, and the claim was made that their use avoided the risk of adding the elements of the alcohol to double bonds in unsaturated aldehydes. An acid or acid salt such as ammonium sulfate was found to be a suitable catalyst. The method did not always give the desired result, although it worked smoothly in many cases, including benzaldehyde, but no phenolic aldehydes were studied. Voss (29) used esters of sulfurous acid for coupling alcohols with aldehydes to prepare acetals, his method being based on the reactions:

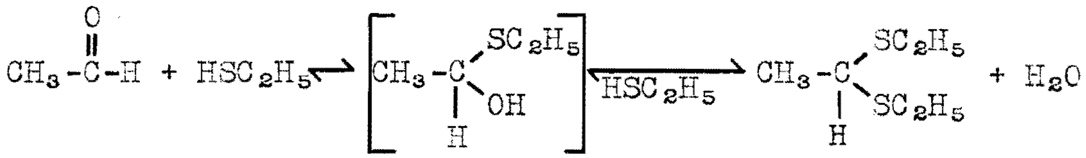
$$O = S(OR)_2 + H_2O \rightleftharpoons SO_2 + 2\,ROH \qquad \ldots(15)$$



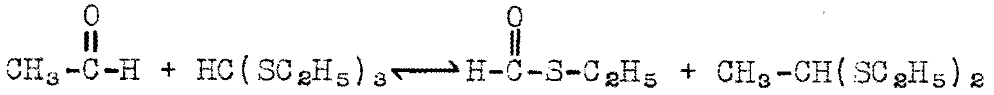
$$R^1\overset{\overset{O}{\|}}{C}H + 2\,ROH \rightleftharpoons R^1 - \underset{\underset{H}{|}}{C}(OR)_2 + H_2O \qquad \ldots(16)$$

The method appears to offer no advantages over the orthoformic ester method.

The more recent work of Post (30) on thioacetals provided information about the linkages formed in the production of acetals by both the classical method (3) and the orthoformic ester method (22). The following reactions were carried out after the method of the originator, Baumann (24).

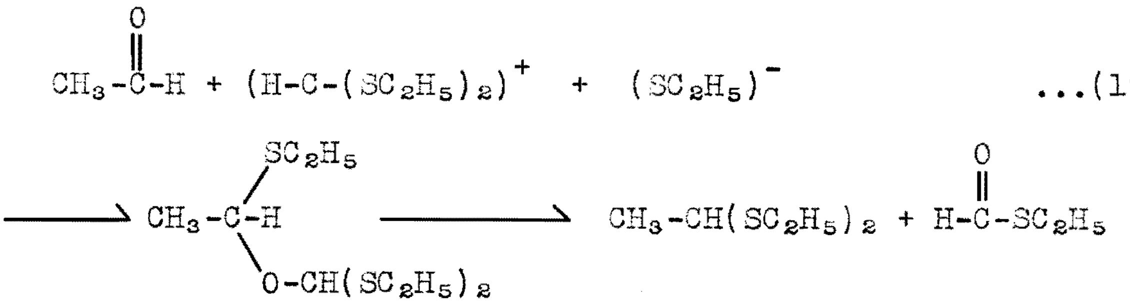


$$CH_3-\overset{\overset{O}{\|}}{C}-H + HSC_2H_5 \rightleftharpoons \left[CH_3-\underset{\underset{H}{|}}{C}\begin{matrix} SC_2H_5 \\ OH \end{matrix} \right] \underset{HSC_2H_5}{\rightleftharpoons} CH_3-\underset{\underset{H}{|}}{C}\begin{matrix} SC_2H_5 \\ SC_2H_5 \end{matrix} + H_2O \qquad \ldots(17)$$



$$CH_3-\overset{\overset{O}{\|}}{C}-H + HC(SC_2H_5)_3 \rightleftharpoons H-\overset{\overset{O}{\|}}{C}-S-C_2H_5 + CH_3-CH(SC_2H_5)_2 \qquad \ldots(18)$$

Post postulated the attachment of acidic mercaptan hydrogen to the carbonyl oxygen and of the mercaptan sulfur to the carbonyl carbon atom in (17). Making use of this mechanism, he formulated the course of the orthoester reaction, (18), as follows, (19).



$$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + (H\text{-}C\text{-}(SC_2H_5)_2)^+ + (SC_2H_5)^- \qquad \ldots(19)$$

$$\longrightarrow CH_3\text{-}\overset{SC_2H_5}{\underset{O\text{-}CH(SC_2H_5)_2}{C}}\text{-}H \longrightarrow CH_3\text{-}CH(SC_2H_5)_2 + H\text{-}\overset{O}{\overset{\|}{C}}\text{-}SC_2H_5$$

On this basis, the course of the thioacetal reaction was analogous to ordinary acetal formation. Attempts by Post to repeat Pauly and Buttlar's (23) preparation of the monohydroxybenzaldehyde acetals, using a small quantity of sulfuric acid catalyst instead of hydrochloric acid, were entirely unsuccessful. Lower yields of aliphatic acetals were also obtained with the sulfuric acid catalyst than had been observed by previous workers using hydrogen chloride, but no explanation of the discrepancy was ventured.

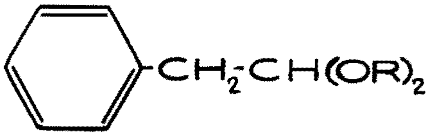
The foregoing survey of acetal formation has been restricted as much as possible to the relatively few references relevant to acetals of substituted benzaldehydes, more especially to those containing phenolic hydroxyl groups. In brief it can be stated that in the main, two methods have been used, first the classical aldehyde-alcohol reaction which gives low yields especially with aromatic aldehydes except nitrobenzaldehydes, and second, the aldehyde-orthoformic ester reaction which is much superior in all cases. The majority of the recorded data concerns aliphatic aldehydes and only one reference to the successful preparation of acetals of hydroxy benzaldehydes was observed, the work of Pauly and Buttlar (23).

Cyclic acetals have not been considered because no reference to the successful preparation of a phenolic cyclic acetal was found. This lack is doubtless because an application of the orthoformic ester method to cyclic acetal synthesis is unlikely, and no other method seems capable of forming the unstable phenolic acetals. Furthermore, cyclic acetals are very readily cleaved by hydrogen (31), a feature that renders them of little interest for the purpose of the present research.

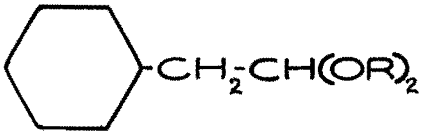
Hydrogenation of Aromatic Acetals and Acids

The problem of the reduction of an aromatic nucleus attached to an acetal group has been considered by a number of investigators. Much valuable information on the general subject of catalytic hydrogenation is available in a book by Adkins (32), another by Berkmann, Morrell and Egloff (33), and in a review by Campbell and Campbell (34).

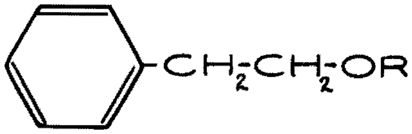
Sigmund and Marchart (35) were unable to reduce the methyl and ethyl acetals of phenylacetaldehyde, VIII, to the corresponding hexahydrophenylacetaldehyde acetals, IX, over nickel in a stream of hydrogen at 180°. Hydrogenolysis occurred and the corresponding methyl and ethyl phenyl ethers, X, were obtained.



VIII



IX



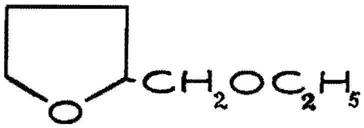
X

Sigmund (36) succeeded in reducing the dimethyl acetal to the dimethyl acetal of hexahydrophenylacetaldehyde in 81 per cent yield over a platinum black catalyst in a stream of hydrogen at room temperature, using carefully purified glacial acetic acid as a solvent. Other solvents were unsuitable for nuclear reduction over this catalyst.

The diethyl acetal of furfural, XI, was reduced to the diethyl acetal of tetrahydrofurfural, XII, by Adkins and co-workers (31) in 76 per cent yield over a nickel-kieselguhr catalyst at 175° and with 100-200 atmospheres pressure of hydrogen.

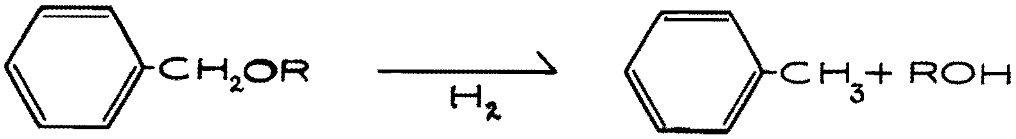
XI

XII



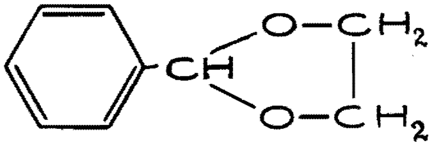
XIII

However, unless a small quantity of any of a number of aliphatic amines was present, the reaction was primarily one of hydrogenolysis and hydrogenation to tetrahydrofurfuryl ethyl ether, XIII. Benzyl ethers, XIV, were very readily cleaved over Raney nickel at temperatures of 100-150° (37), or over palladium catalysts at ordinary temperatures (38), toluene, XV, and an alcohol being formed invariably.



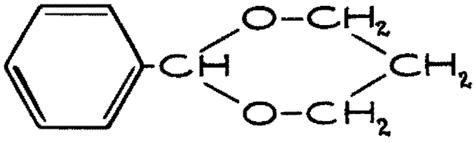
XIV XV

The aryl ethers reduced at a somewhat lower temperature than the alkyl ethers (32). The readiness of cleavage of benzyl ethers is an illustration of the well-known effect of a double bond in the 2-position in labilizing a carbon-to-oxygen bond (32). Nickel catalysts supported by kieselguhr favoured nuclear reduction somewhat while Raney nickel caused hydrogenolysis of the ethers to a greater extent (37). The conditions which were favourable to the hydrogenolysis of ethers also resulted in the hydrogenolysis of acetals (32). Attempts by Adkins (31) to reduce the aromatic nucleus of a cyclic acetal of benzaldehyde; benzylidene ethylene glycol, XVI, over nickel on kieselguhr at 125° resulted in hydrogenolysis to toluene, benzylethyl ether, ethyl ether, ethanol and the monobenzyl ether of ethylene glycol.

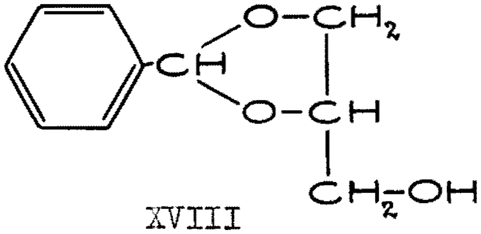


XVI

Analogous results were obtained by Adkins (31) in the hydrogenation of benzylidene trimethylene glycol, XVII, and of the 1,2-benzylidene acetal of glycerol, XVIII.



XVII

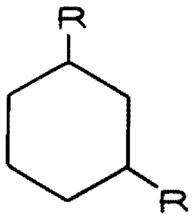


XVIII

No reference to a successful hydrogenation of the nucleus of an acetal of benzaldehyde or substituted benzaldehyde has been observed in the literature and it was concluded (32) that the labilizing effect of unsaturation in the 2-position of benzaldehyde acetals accounted for their instability to hydrogen. In phenyl acetaldehyde acetals however the unsaturation is in the 3-position and the greater stability of the carbon-oxygen bonds towards hydrogenolysis doubtless accounts for their survival during the successful reduction of the nucleus (36). The reduced compounds more closely resemble alkyl ethers, which are more stable to hydrogen (32), than the aryl-alkyl or aryl ethers. The reduction of the furanoid nucleus attached to an acetal group is of interest because of the many similarities in the behaviour of furanoid and benzenoid nuclei, although hydrogenation of the former occurs under somewhat milder conditions than the latter (32).

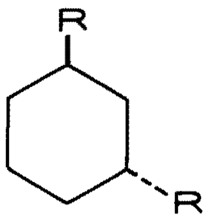
The foregoing information has shown clearly the difficulties encountered in attempts to hydrogenate a benzenoid nucleus directly attached to an acetal group without hydrogenolysis of the latter. Unfortunately, in the few cases in which the reaction was investigated, there were no other substituent groups and the probable effect of the latter must be estimated from hydrogenation studies in other series.

The hydrogenation of a benzenoid nucleus having two or more substituents will give rise to cis and trans isomers, e.g. XIX and XX. There have been several attempts to formulate a general theory to account for the predominance of either cis or trans configurations under given hydrogenation conditions, but at present only the broadest conclusions can be drawn. This matter was reviewed by Christian (39) and need not be further discussed here.



cis

XIX



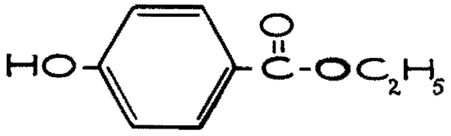
trans

XX

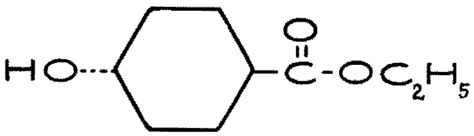
For present purposes the most relevant portion of the field concerns the hydrogenation of polyhydric phenolic substances, which was also discussed in detail by Christian (39) and in the book by Adkins (32). In brief, the present state of knowledge may be roughly summarized by stating that the nucleus of all of the mono- and dihydroxy phenols could be saturated with hydrogen over nickel catalysts at temperatures ranging from 125-150°. Pyrogallol underwent reduction very easily at 100° over Raney nickel (39). However, the cyclohexyl products were not in general stable under the reaction conditions and underwent cleavage by hydrogen with the loss of one or more hydroxyl groups. The susceptibility of glycols to hydrogenolysis was most pronounced with 1,3-glycols and somewhat less so with the 1,2- compounds (40). An extensive study of the hydrogenation of pyrogallol by Christian (39) showed that the maximum yield of pure 1,2,3-cyclohexanetriols (pyrogallitols) was of the order of 30 per cent, and of the diols, 33 per cent under optimum conditions. This work again illustrated the difficulty of obtaining good yields of polyhydric alcohols by catalytic hydrogenation particularly when the hydroxy groups were in a 1,3- or a 1,2- relationship. Undesired hydrogenolysis, however, could frequently be kept to a minimum by careful control of reaction conditions (32).

There is comparatively little information to be found in the literature concerning the catalytic hydrogenation of hydroxybenzoic acids and esters. Balas and Srol (41) reduced salicylic acid in ethanol with a platinum black catalyst; m- and p-hydroxybenzoic acids gave the cis-hexahydro derivatives, the latter of which was accompanied by a small quantity of the trans isomeride. Adkins (31) reduced salicylic ester over nickel, at 200° and with 175 atmospheres hydrogen pressure, to a mixture of cis and trans hexahydrosalicylic esters. Edson (42) investigated the hydrogenation of benzoic acid, o-, m- and p-hydroxybenzoic acids in aqueous solution over a platinum oxide catalyst. The hydroxy acids underwent substantial hydrogenolysis; p-, m-, o-hydroxybenzoic acids gave 75%, 60% and 10% yields of hexahydrobenzoic acid respectively. Low yields of the hexahydrohydroxy acids accompanied this product.

More recently, Martin and Robinson (43), using a new catalyst, 2% palladized strontium carbonate, in carefully purified anhydrous dioxane at 155-160° and 150 atmospheres pressure, quantitatively reduced the ethyl ester of p-hydroxybenzoic acid, XXI, to trans-4-hydroxy-1-carbethoxycyclohexane, XXII.



XXI



XXII

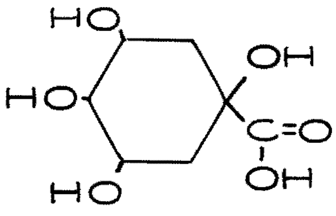
Previous to this work, palladium does not appear to have been employed as an hydrogenation catalyst at elevated temperatures. The new catalyst was stated to be superior to Raney nickel for the reduction of substituted aromatic compounds such as quinol dimethyl ether and more complex compounds related to the sterols. Martin and Robinson stressed the necessity for highly pure solvent because the catalyst was rapidly deactivated when heated in even slightly contaminated solvent under hydrogen without stirring. Ethyl acetate was suggested as an alternative solvent to dioxane for use in conjunction with this catalyst but no application of the ester was recorded. No reference to the catalytic hydrogenation of di- and trihydroxybenzoic acids or esters has been observed.

Chemical reductive methods appear to have been more effective than catalytic hydrogenation for the reduction of monohydroxybenzoic acids. m-Hydroxybenzoic acid was reduced to cis-3-hydroxycyclohexane-1-carboxylic acid by Einhorn and Coblitz (44) using sodium in ethanol, also by Perkin and Tattersall (45). Perkin and co-workers (46) also reduced the monohydroxytoluic acids by means of sodium-ethanol and sodium-isoamyl alcohol. They isolated a variety of cis and trans isomeric monohydroxy methyl cyclohexane carboxylic acids. No reference to a successful application of chemical reduction to di- and trihydroxybenzoic acids has been found.

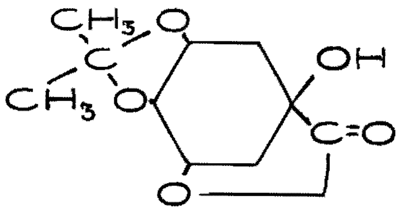
The Hydroxy Cyclohexane Carboxylic Acids

The monohydroxycyclohexane carboxylic acids have been prepared, as stated above, by either chemical or catalytic reductive methods from the corresponding hydroxybenzoic acids. A number of others have been isolated from cyclohexene carboxylic acids derived from cyclohexanone (47), but discussion of such syntheses is beyond the scope of this thesis. Very few are known which contain more than a single hydroxyl group.

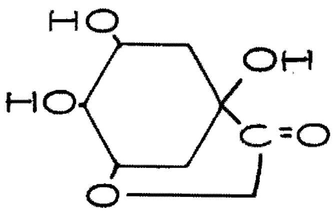
Quinic acid, a levorotatory tetrahydroxy cyclohexane carboxylic acid occurring in cinchona bark, was investigated by Fischer (48) who believed that the compound was a 1,3,4,5-tetrahydoxycyclohexane-1-carboxylic acid, XXIII. At that time both the cis-trans configuration of the hydroxyl groups and their positions in the ring were doubtful. Fischer's conclusions were based partly on the fact that quinic acid condensed with acetone in the presence of hydrogen chloride catalyst to yield an acetone quinide, XXIV, which lost acetone under mildly acidic conditions to give a quinide, XXV, also obtainable directly from the acid on heating.



XXIII

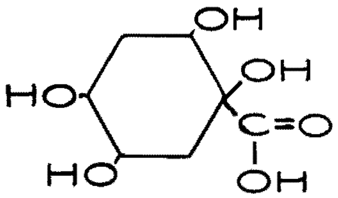


XXIV

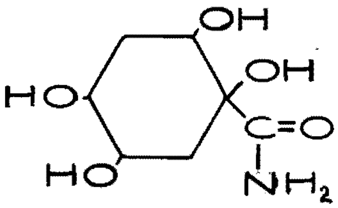


XXV

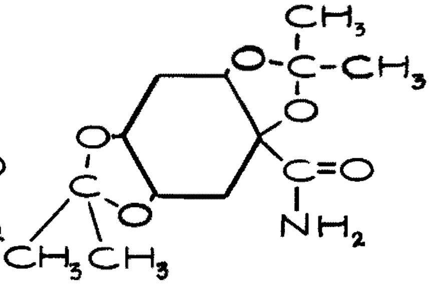
The lactone ring was believed to involve the 3- or γ-hydroxyl group in the acetone quinide in order to conform to the known preference of acetone for condensation with contiguous cis hydroxyl groups. Examples of the condensation were recently reviewed by Gogek (49) in connection with a proof of the cis-trans configurations of the pyrogallitols. During this work, Gogek noted that acetone condensed with trans-1,2-cyclohexanediol to form the isopropylidene derivative when special conditions, including the use of p-toluene sulfonic acid as a catalyst, were adopted. This preparation of a trans isopropylidene derivative, although unique, obviously weakens the confidence with which the formation of an isopropylidene acetal can be accepted as diagnostic of <u>cis</u>-1,2-glycols. Karrer, Widmer and Riso (50) in a subsequent paper disagreed with Fischer's tentative formula, XXIII, for quinic acid and favoured a 1,3,4,6-tetrahydroxycyclohexane-1-carboxylic acid, XXVI, on the basis of the formation of a diacetone amide, XXVIII, by the condensation of quinic amide, XXVII, with acetone.



XXVI

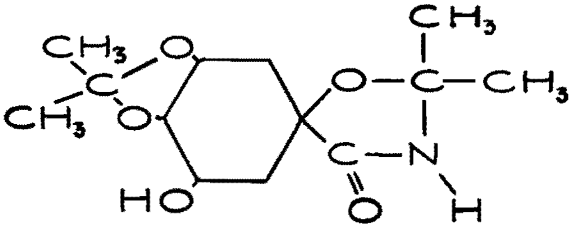


XXVII



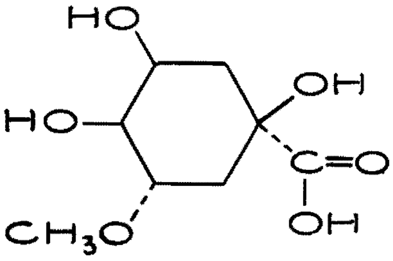
XXVIII

However, Fischer and Dangschat (51) disproved structure XXVIII for the diacetone quinic amide by demonstrating that the compound was not a normal amide and that the amide group was actually involved in an acetone ring. The correct structure for the diacetone amide, XXIX, was confirmed by them



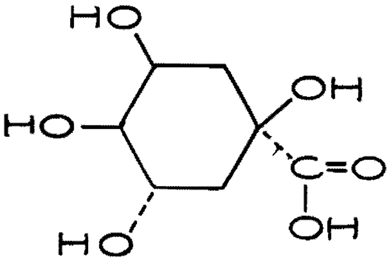
XXIX

by means of a number of other reactions. Having established the location of the four hydroxyl groups as 1, 3, 4 and 5, they proceeded to establish the configuration with respect to the carboxyl group (51, 52). The hydroxyl group in the 1-position must obviously be trans to the carboxyl group. The 3-hydroxyl was certainly cis to the carboxyl group in its ability to form a lactone. The 4- and 5-hydroxyl groups were cis because they condensed with acetone to form an isopropylidene acetal and this pair was inferred to be trans to the carboxyl group by the failure of 3-methyl quinic acid, XXX, to form a lactone.



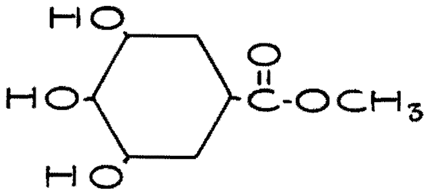
XXX

The occurrence of optical activity in the quinic acid series was further evidence of the asymmetry of the 3, 4, and 5 hydroxyl groups. From these arguments, and on the basis of much additional data, Fischer and Dangschat were able to assign the configuration XXXI to quinic acid.

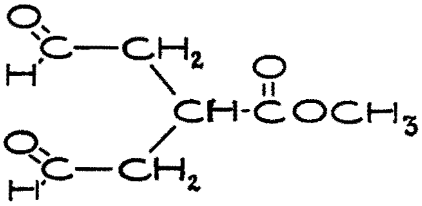


XXXI

Shikimic acid, a naturally-occurring 3,4,5-trihydroxy-Δ^1- cyclohexene-1-carboxylic acid, was also investigated by Fischer and Dangschat (53). Mild reduction over palladium yielded dihydroshikimic acid, a 3,4,5-trihydroxycyclohexane-1-carboxylic acid which is one of the isomeric hexahydrogallic acids, Va-f. The location of the three hydroxyl groups was established by a quantitative oxidation with periodic acid. The consumption of exactly two moles of periodic acid by methyl dihydroshikimate, XXXII, and isolation of the methyl ester of tricarballylic acid-1,5-dialdehyde, XXXIII, as its bis-p-nitrophenylhydrazone showed conclusively that the compound contained three contiguous hydroxyl groups in the 3,4,5-positions.

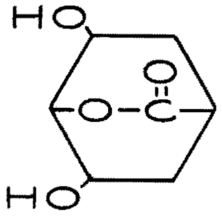


XXXII

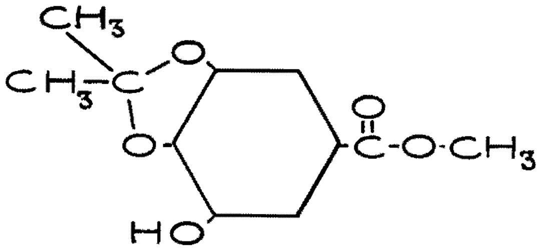


XXXIII

In subsequent papers (2, 54, 55, 56), Fischer and Dangschat established the configuration of dihydroshikimic acid and its relationship to quinic acid, XXXI. A lactone was obtained by heating dihydroshikimic acid at 200°. The lactone was unreactive to periodic acid and therefore contained no 1,2-glycol units. Accordingly, the 4-hydroxyl group must be cis to the carboxyl, and the lactone a δ-lactone, XXXIV. The methyl ester of dihydroshikimic acid, XXXII, condensed with acetone (2) to form isopropylidene dihydroshikimic acid methyl ester, XXXV.



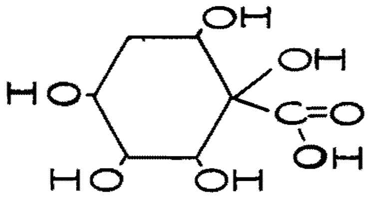
XXXIV



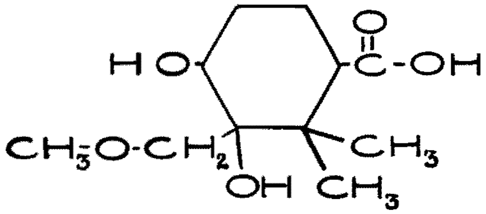
XXXV

The configuration of dihydroshikimic acid was therefore known to be represented by structure Vb (p.4). The occurrence of optical activity in this series also was further confirmation of the asymmetry of the hydroxyl groups. Dihydroshikimic acid, Vb, is levorotatory but its raceme and dextrorotatory isomer are not known.

Eykman (57) prepared a pentahydroxycyclohexane carboxylic acid of uncertain structure by an alkaline treatment of shikimic acid dibromide. The hydroxyl groups were believed to be located in the 1,2,3,4 and 6-positions, XXXVI. In an investigation of the structure of comphorquinone, Evans and Simonsen (58) obtained a 3-hydroxy-3-methoxymethyl-2, 2-dimethyl-cyclohexane-4-ol-1-carboxylic acid, XXXVII which formed a γ-lactone.



XXXVI



XXXVII

The information presented in this introduction formed the basis of the following investigation of the preparation and hydrogenation of phenolic acetals and esters. The work of Fischer on quinic acid and shikimic acids proved to be of great value as a guide to the probable structure of the trihydroxycyclohexane carboxylic acid that was encountered.

DISCUSSION OF RESULTS

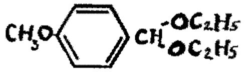
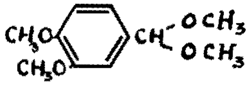
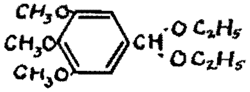
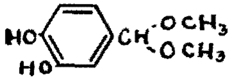
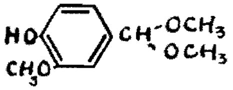
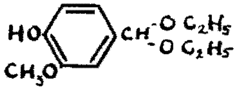
Synthesis of Phenolic Acetals

The Claisen method of acetal synthesis (22), with isolated orthoformic esters, was used and seven different acetals of substituted benzaldehydes were successfully prepared. Only two of them were previously known, although unsuccessful attempts to obtain two of the others are recorded.

The aldehydes containing phenolic ether groups all formed methyl or ethyl acetals (Table I) in substantially quantitative yields. Mechanical losses of up to 10 per cent occurred, especially when a second distillation was necessary to yield an analytically pure product. These non-phenolic compounds were all isolated by distillation and were viscous, colourless oils with a pleasant, light aromatic odour. Of the phenolic acetals, p-hydroxybenzaldehyde dimethyl acetal was prepared by Pauly and Buttlar (23) in 87 per cent yield. This high value could not be duplicated but this highly unstable compound was obtained in yields of 75 to 80 per cent. Protocatachualdehyde (3,4-dihydroxybenzaldehyde) yielded the new dimethyl acetal, m.p. 89.5-90°, when great care was taken to exclude moisture from the reactants and when a slight modification of the Claisen method was employed. The acid catalyst was neutralized with a slight excess of alkali **rather** than with the exact amount employed by Claisen (22) and by

TABLE I

ACETALS OF SUBSTITUTED BENZALDEHYDES

No.	Structure	Molecular Formula	m.p.	b.p. mm.	Yield per cent		C	H	Alkoxyl[a]
1		$C_{12}H_{18}O_3$	-	(b) 261-3°/760	92-95	Calcd. Found	68.6 68.4,68.5	8.6 8.4,8.4	44.3 44.0,44.1
2		$C_{11}H_{16}O_4$	-	100-105/0.03	90-92	Calcd. Found	62.1 62.1,62.3	7.6 7.6,7.7	58.8 57.9,58.2
3		$C_{14}H_{22}O_5$	(c) 26-29°	100-105/0.04	89-93	Calcd. Found	62.2 62.2,62.1	8.2 7.8,7.8	57.4 56.4,56.6
4	(d) 	$C_9H_{12}O_3$	(e) 60-64°	-	75	Calcd. Found	64.3 64.0,64.3	7.1 7.2,7.3	36.9 36.7,36.8
5		$C_9H_{12}O_4$	89.5-90°	-	70	Calcd. Found	58.7 58.8,59.0	6.5 6.4,6.6	33.7 33.5,33.5
6	(f) 	$C_{10}H_{14}O_4$	-	97-100/0.03	68-72	Calcd. Found	60.7 60.3,60.5	7.1 6.9,7.0	47.0 46.3,46.4
7	(f) 	$C_{12}H_{18}O_4$	-	102-105/0.01	56-62	Calcd. Found	63.7 63.4,63.5	8.0 8.0,8.0	41.2 40.6,40.7

(a)-(g) on page 36.

(a) All alkoxyl values are calculated as per cent methoxyl although acetals nos. 1, 3, and 7 were diethyl acetals.

(b) Reported to be 263°/760 m.m. (21)

(c) Trimethylgallic aldehyde diethyl acetal crystallized only after it had been distilled and had stood for some time at room temperature

(d) Attempts to prepare p-hydroxybenzaldehyde *diethyl* acetal were unsuccessful. The crude acetal did not crystallize and attempted distillation caused decomposition.

(e) Reported to be 60-64° (23).

(f) Substantial resinous material was always left in the still after distillation of the two vanillin acetals. The yields are quoted for a 5 g.-scale preparation. The preparation of these two acetals on a larger scale (20 g.) caused a further reduction in yield to about 50 per cent.

(g) The refractive indices, n_D^{25}, for the liquid acetals were: No. 1, 1.4893; No.2, 1.5200; No. 6, 1.5250; No. 7, 1.5072.

Pauly and Buttlar (23). Excess alkali was then removed as the insoluble carbonate after the alcohol solution had been treated with an excess of dry carbon dioxide gas. This minor innovation precluded the possibility of exposure of the newly-formed phenolic acetal to even a trace of hydrogen chloride. Pauly and Buttlar failed to isolate this compound, recovering only part of the original aldehyde together with a resin. It is probable that hydrolysis occurred because their preparation contained residual traces of the catalyst. Vanillin also yielded unstable methyl and ethyl acetals but yields were reduced by the necessity of isolating these compounds by distillation, a process which brought about their partial decomposition. Fischer and Giebe (10) failed to isolate this methyl acetal, and also acetals of p-hydroxybenzaldehyde and salicylaldehyde by the older synthetical method although the m-, p-, and o-nitrobenzaldehydes readily formed methyl acetals as noted earlier.

Pauly and Buttlar noted colour changes during the acetal reaction, the colour varying with the aldehyde used and also changing when the acid was neutralized. Similar effects were noted in the present syntheses and are recorded in Table II. These sharp unexplained colour changes, most pronounced with the phenolic aldehydes, are probable a clue to the mechanism of the reaction.

Several attempts were made, observing the utmost

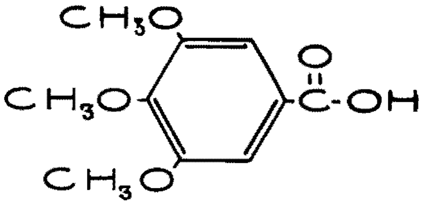
TABLE II

COLOUR CHANGES IN THE ORTHOFORMIC ESTER -ALDEHYDE REACTION

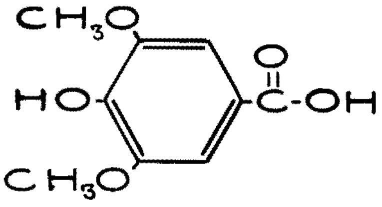
Acetal Preparation	Colour	
	in acid	in base
p-anisaldehyde diethyl acetal	pale red	orange
veratraldehyde dimethyl acetal	pale yellow	pale orange
trimethyl gallic aldehyde diethyl acetal	pale orange	pale yellow
p-hydroxybenzaldehyde dimethyl acetal	pale orange	blue
(a) p-hydroxybenzaldehyde diethyl acetal	purple	red
protocatachualdehyde dimethyl acetal	orange red	orange
vanillin dimethyl acetal	bright red	orange
vanillin diethyl acetal	bright red	deep blue

(a) See note (d), Table I.

precautions to exclude moisture and acidic gases, to prepare an acetal of gallic aldehyde (3,4,5-trihydroxybenzaldehyde) but all were unsuccessful. A viscous oil with an alkoxyl content approximating to the calculated value for gallic aldehyde acetal, was obtained, but the oil could not be crystallized or indeed maintained in its original, colourless state for very long. The liquid rapidly darkened and became resinous on standing in a sealed, dry container. Attempts to methylate the phenolic hydroxyl groups of what was believed to be the transient acetal failed to yield a definite product. However, methylation of the unstable protocatachualdehyde dimethyl acetal with diazomethane converted it, in part at least, to vanillin dimethyl acetal (16 per cent yield). It is interesting to note that the product retained the original p-hydroxyl group which apparently was not methylated by diazomethane. This result is somewhat analogous to the ease with which trimethylgallic acid, XXXVIII, is demethylated in the para position to syringic acid, XXXIX, in the presence of concentrated sulfuric acid (59).



XXXVIII



XXXIX

The present result is another example of the reduced tendency of a phenolic hydroxyl group, para to a carbonyl group, to form an ether.

In the light of the work which has been done on phenolic acetals by Fischer and Giebe (10), Pauly and Buttlar (23) and by the present author, it appears that hydroxysubstituted benzaldehydes are inhibited in the acetal reaction and that the acetals, if formed at all, are unstable to traces of acid. Increasing numbers of phenolic groups appear to increase the difficulty encountered in isolating these compounds. The collective results bear out the contention of Pauly and Buttlar that the position of such groups in the aromatic ring is not the major determining factor; their mere presence, irrespective of position, is sufficient to cause instability in the acetal.

A series of experiments (Tables III and IV) was carried out to investigate the reported instability (23) of the acetals in alkaline media, since acetals as a class are well-known to be very stable in such conditions. As expected, the acetals containing phenolic ether groups were stable in alcoholic alkaline solutions and could be recovered over 90 per cent whether or not the medium was entirely anhydrous. The phenolic acetals were partially recoverable from anhydrous alcoholic alkaline solutions only, the presence of water apparently causing complete hydrolysis even in the

TABLE III

RECOVERY OF ACETALS FROM ANHYDROUS ALCOHOLIC SODIUM HYDROXIDE SOLUTIONS(a)

Acetal	Temp. °C	Time, Hours	Recovery per cent	Analysis(b) and/or m.p.
p-anisaldehyde diethyl acetal	20	48	91	Calcd. CH_3O, 44.3 Found: 43.7
veratraldehyde dimethyl acetal	20	24	93	Calcd. CH_3O, 58.8 Found: 57.9
trimethyl gallic aldehyde dimethyl acetal	20	48	92	m.p. 27-29°
	100	48	89	m.p. 26-29°
p-hydroxy benzaldehyde dimethyl acetal	20	48	75	m.p. 75-77° (c) Calcd. C, 64.3; H, 7.14; CH_3O, 36.9 Found: C, 64.1, 64.3; H, 7.16, 7.25; CH_3O, 36.7
vanillin dimethyl acetal	20	48	19	Calcd. CH_3O, 47.0 Found: 46.4
	redistillation only (d)		67	46.5
vanillin diethyl acetal	20	48	17	Calcd. CH_3O, 41.2 Found: 40.7
	70	1.5	14	40.5
	redistillation only (d)		64	40.7
protocatachualdehyde dimethyl acetal	20	48	72	Calcd. CH_3O, 33.7; Found: 33.0 m.p. 86-89°
	100	4	17	Found: CH_3O, 33.1 m.p. 86-89°

(a)-(d) on page 42.

(a) The mole ratio of acetal: sodium hydroxide was 10:1 and the acetal concentration was 10 per cent by weight.

(b) See note (a) page 36.

(c) The reported melting point for p-hydroxybenzaldehyde dimethyl acetal is 60-64° (23). This value was also found for the synthesized acetal but, after recovery from alkaline solutions, the material melted at 75-77°. It was analysed again but the C, H, and CH_3O content were unaltered. Apparently the alkaline treatment purified the sample.

(d) Control experiments in which the acetal was redistilled only in order to estimate losses during heating and manipulation.

TABLE IV

RECOVERY OF ACETALS FROM ALCOHOLIC SODIUM ALCOHOLATE SOLUTIONS AT 100°(a) FOR FOUR HOURS

Acetal	Mole Ratio Acetal:Base	Recovery per cent	Anal. and/or m.p.
Trimethylgallic aldehyde diethyl acetal	10:1	91	26-29°
p-hydroxybenzaldehyde dimethyl acetal	10:1	26	75-77° CH_3O, Calcd. 37.0 Found 37.0
protocatachualdehyde dimethyl acetal	10:1	43	88-90° CH_3O, Calcd. 33.7 Found 33.1
" "	5:1	25	87-88° CH_3O, Found 33.0
" "	1:1	21	90-91° CH_3O, Found 33.3
" "	(b) no base	38	86-88° CH_3O, Found 32.9
" "	(c) 10:1 (and water)	0	

(a) The solutions contained 10 per cent acetal by weight.

(b) A control experiment carried out without alkali.

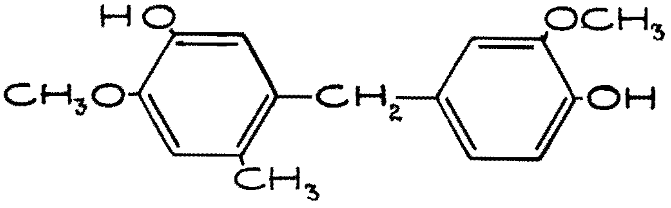
(c) A control experiment with water present, 4 moles per mole of acetal, and sodium hydroxide, one tenth of a mole per mole of acetal.

presence of alkali. It is believed that the recovery figures exaggerate the extent of decomposition because, being obtained by mechanical methods, substantial loss of the sensitive acetals must have occurred during recovery by distillation or recrystallization. The control experiments in Table III bore out this belief. A more accurate method of estimating aldehyde-acetal mixtures seemed desirable and was sought for in the literature. The formation of some aromatic acetals (7) has been followed by determining the aldehyde present in the reaction mixture by oxidation to the corresponding acid with alkaline hydrogen peroxide, the acid formed being subsequently determined by back-titration of the excess sodium hydroxide with sulfuric acid. However, the method is not quantitative with phenolic aldehydes because the oxidation contunues to a quinone. Measurement of the hydrogen absorption during reduction of the aldehyde to an alcohol by catalytic hydrogenation was another method considered, but benzaldehyde, vanillin and salicylaldehyde cannot be rapidly and quantitatively reduced even at 2-3 atmospheres pressure of hydrogen, over platinum or palladium catalysts (60,61). The method employed, although rough, was sufficient to establish the fact that the phenolic acetals possessed at least a degree of stability toward anhydrous alkali which offered some encouragement for the proposed hydrogenation of these compounds. Pauly and Buttlar stated that phenolic acetals were unstable to aqueous acids and alkalies. The statement is correct but misleading because no remarks were made concerning stability to anhydrous alkalies. These results also tend to explain the failure of a few attempts to isolate the dimethylacetal of p-hydroxybenzaldehyde by the classical method, using the aldehyde in a large excess of anhydrous methanol and one per cent hydrogen chloride catalyst. No acetal was obtained but the aldehyde was recovered unchanged, just as Fischer and Giebe (10) reported. It can be assumed that the aldehyde-alcohol equilibrium, in the case of phenolic aldehydes, lies far on the side of the aldehyde and prevents the isolation of even a small quantity of the unstable acetal. In the Claisen reaction, however, the equilibrium seems much more favourable to the acetal and isolation of the latter is facilitated by the absence of water in the products. The volatile nature of the formate by-product and of any excess orthoformic ester also improve the chance for isolating the acetal.

Any attempt to rationalize the reduced affinity of the aldehyde group in phenolic aldehydes for acetal formation must account for the fact that the position of the phenolic hydroxyl group is independent of the effect. The pronounced difference in stability between the acetals of phenolic as opposed to phenolic ether and nitro aldehydes must also be explained. Hydroxyl and alkoxyl groups ordinarily produce very similar mesomeric effects on groups which are ortho or para to them (62). For example, when in the ortho and para positions they depress the ionization of benzoic acid; when in the meta position they enhance ionization. According to a modern electronic theory (62) the nitro group in all positions increases the ionization of an aromatic carboxylic acid; through a reverse mesomeric effect when in the ortho and para positions, and through an inductive effect when meta. The tendency of electronic theory to align methyl phenolic ethers with phenols, rather than with nitro compounds seems not to be consistent with the relative stabilities of the aromatic acetals and suggests that an explanation of the latter anomalies is not to be found in such theories. Perhaps the great instability of the phenolic acetals is connected with the mobility of the phenolic hydrogen atom which may co-ordinate with the acetal. Similar co-ordination of the phenolic with the carbonyl group was assumed by Lieff and Hibbert (63) in vanillin to account for the abnormal behaviour of the carbonyl group in the Grignard reaction.

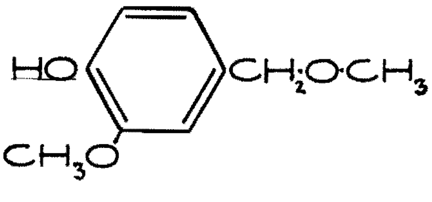
Hydrogenation of Phenolic Acetals

Vanillin dimethyl acetal was the most convenient member of the present group to prepare, because of the availability of the aldehyde, and the comparative ease of distillation of the acetal. Recrystallizations of large quantities of the solid phenolic acetals were tedious and wasteful. For these reasons the vanillin acetal was selected for study under hydrogenation conditions. Various solvents, catalysts and reaction conditions were used but in no case did nuclear reduction occur before disruption of the acetal group. In anhydrous methanolic sodium hydroxide over Raney nickel the acetal was converted mostly to a solid phenolic condensation product of resinous nature which was not investigated further. It was assumed to resemble the dimer, vanillyl creosol, XL, obtained by St Pfau (64) from the catalytic hydrogenation of vanillin over a palladium catalyst.

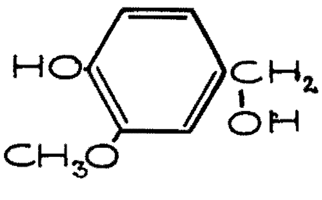


XL

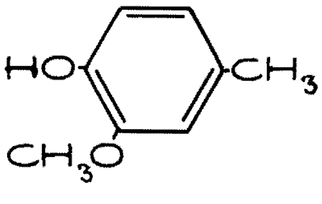
In anhydrous methanol over Raney nickel in the presence of n-heptylamine, vanillin dimethyl acetal underwent hydrogenolysis to 4-hydroxy-3-methoxybenzyl methyl ether, XLI, vanillyl alcohol, XLII, and creosol, XLIII, at 100-120° (See Tables XII and XIII).



XLI



XLII



XLIII

The course of the reaction had obviously followed the usual hydrogenolysis pattern observed by Adkins and co-workers (31, 32). The methyl ether, XLI, at first isolated as an oil by distillation, was contaminated with small quantitites of the other two products but was obtained in a pure condition as its crystalline 3,5-dinitrobenzoyl derivative. Neither compound has been reported previously. It was interesting to note that the methyl ether strongly resembled phenol, rather than vanillin in its odour and taste.

Vanillin dimethyl acetal exhibited some stability to hydrogenolysis at higher temperatures in anhydrous dioxane over Raney nickel in the presence of n-heptylamine. Comparatively little hydrogen absorption occurred at 135° during thirty minutes and some impure acetal was recovered from the products. The low recovery figure (22 per cent) could not have represented adequately the amount of acetal still present, because the latter had poor stability to distillation in the presence of contaminants, especially when one of them was traces of water derived by hydrogenolysis. When the temperature was raised to 195-200° for forty-five minutes, hydrogenolysis occurred and the three products isolated (XLI, XLII, XLIII), were the same as those obtained when methanol was the solvent. Little absorption occurred over a nickel-kieselguhr catalyst in anhydrous methanol up to 195° over a period of seventy three minutes. This catalyst was used successfully by Adkins (31) to prepare tetrahydrofurfural diethyl acetal from the furfural derivative. Again impure acetal was recovered. Over 2 per cent palladized strontium carbonate catalyst in anhydrous dioxane, hydrogenolysis occurred at 155° and the same products as those isolated from the Raney nickel experiment were obtained (Table XV). These results are summarized in Table V. A control hydrogenation of vanillin in dioxane over Raney nickel at 135° gave vanillyl alcohol in almost quantitative yield. Thus the acetal group provided a degree of protection because vanillin and vanillin acetal were isolated from the reaction products of hydrogenation (c), Table V, with conditions identical to those of the control experiment. The hydrogen absorption figures indicated in every case that substantial hydrogenolysis had occurred because little, if any, of the hydrogen was used to saturate the ring. It should be pointed out that the absorption figure is not very accurate because the measurement had to be taken over a broad temperature range.

These hydrogenation studies of vanillin dimethyl acetal showed that the acetal group was unlikely to afford an adequate means of protection for the aldehyde carbonyl group during reduction of the nucleus. It is of interest to note that the hydrogenolysis followed the same course as with ordinary unsaturated acetals. The acetal linkage

TABLE V

HYDROGENATIONS OF VANILLIN DIMETHYL ACETAL

	Catalyst	Solvent	Other Material	Temp. °C.	Time min.	H_2 Absn Moles per mole	Main Products
(a)	Raney nickel	methanol	sodium hydroxide	130°	60	4.4	resin
(b) A	" "	"	n-heptylamine	115-120°	30	2.8	methyl ether, XLI, vanillyl alcohol and creosol
(b) B	" "	"	"	100°	90	2.1	
(c)	" "	dioxane	"	135°	30	0.9	crude acetal
(d)	" "	"	"	195-200°	45	2.8	methyl ether, XLI, vanillyl alcohol and creosol
(e)	Nickel-kieselguhr	methanol	"	195°	73	1.1	crude acetal
(f)	palladized strontium carbonate	dioxane		155°	15	2.8	methyl ether, XLI, vanillyl alcohol and creosol.

was evidently labilized in characteristic fashion (65) by the double bond in the 2-position of the aromatic ring. It is also probable that the formation of the secondary products, vanillyl alcohol and creosol, occurred via two routes; the first being hydrogenolysis of the acetal to the methyl ether, XLI, then to vanillyl alcohol, XLII, and to creosol, XLIII, and water. A second series of reactions, starting with the reduction of vanillin, which would certainly be formed by acetal hydrolysis in the presence of the water from the first scheme, would also yield vanillyl alcohol and creosol, but would fail to yield vanillyl methyl ether (Figure 1).

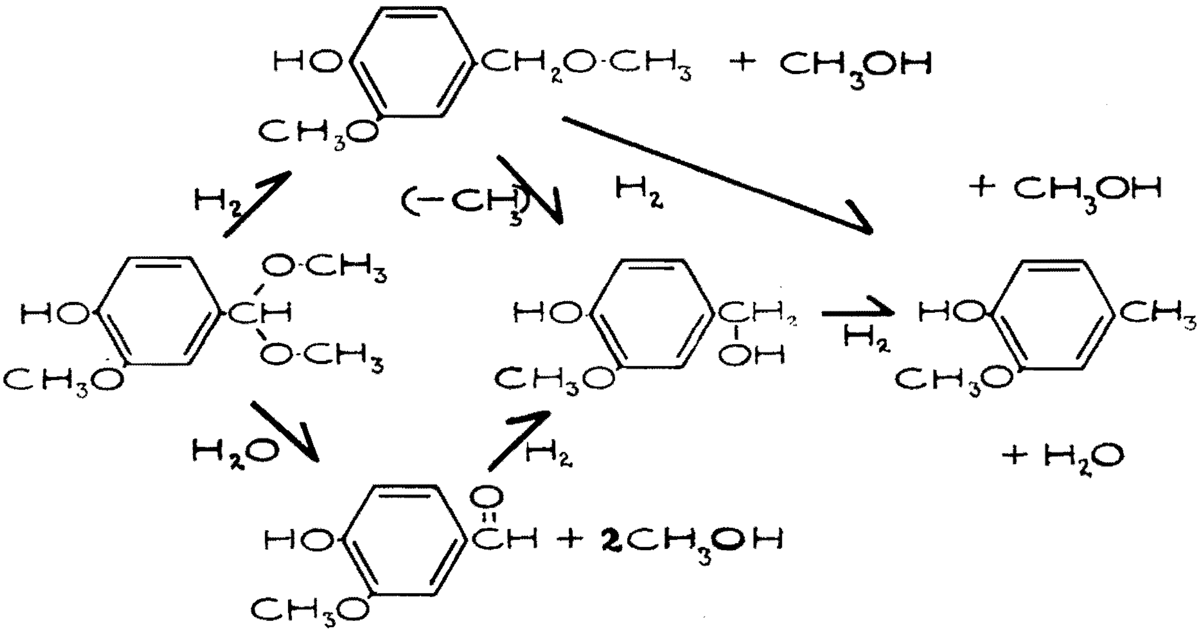


Fig. 1 Hydrogenolysis of Vanillin Dimethyl Acetal

The other phenolic acetals were not examined extensively under hydrogenation conditions, in view of the results obtained with the methyl acetal of vanillin. A few preliminary attempts, carried out under conditions similar to the above, yielded mixtures of hydrogenation products of an analogous nature rather than cyclohexylacetals. These preliminary attempts, however, are not now regarded as conclusive, because Gleason's recent work in this laboratory (66) clearly demonstrated that the substitution of a methoxyl for a phenolic group in an aromatic nucleus increased the temperature requisite for the hydrogenation of the latter by at least 40°. This work, together with the results of the present research, suggest that the acetal of a <u>non-methylated</u> phenolic aldehyde might be reduced at a temperature low enough to avoid hydrogenolysis of the acetal unit. Raney nickel with anhydrous dioxane, or nickel-kieselguhr with anhydrous methanol, would seem to be suitable conditions.

In view of the results of the experiments with phenolic acetals the approach to the problem of synthesizing polyhydroxycyclohexane carbonyl compounds was altered, as mentioned earlier (page 3), to a consideration of the catalytic hydrogenation of hydroxybenzoic acids or their esters.

Hydrogenation of Ethyl Gallate and Related Compounds

Martin and Robinson (43) gave no detailed method for the preparation of their palladium strontium carbonate catalyst which was used exclusively in the following work. A suitable method of preparation, described in the experimental section, resembled those used for other supported palladium catalysts such as palladium on barium sulfate (67). In the present case, however, the basic properties of the carrier made it unnecessary to employ the customary sodium hydroxide solution to precipitate palladium. An interesting feature of the work was that palladium catalysts do not appear to have been employed previously for hydrogenations at elevated temperatures (43).

The activity of the new catalyst was checked by hydrogenations of ethyl p-hydroxybenzoate, XXI, at 180-185° to trans-4-hydroxy-1-carbethoxycyclohexane, XXII, in almost quantitative yields. These hydrogenations also served to standardize the apparatus, for good agreement between the yield of reduced product and the hydrogen absorption was found in many cases (Fig. 2 and Table XVI). As Martin and Robinson (43) observed, the catalyst was occasionally less active and the absorption rate was reduced unless somewhat higher than the customary temperature was used.

Pyrogallol was hydrogenated for the first time over this catalyst. The hydrogen absorption was quantitative

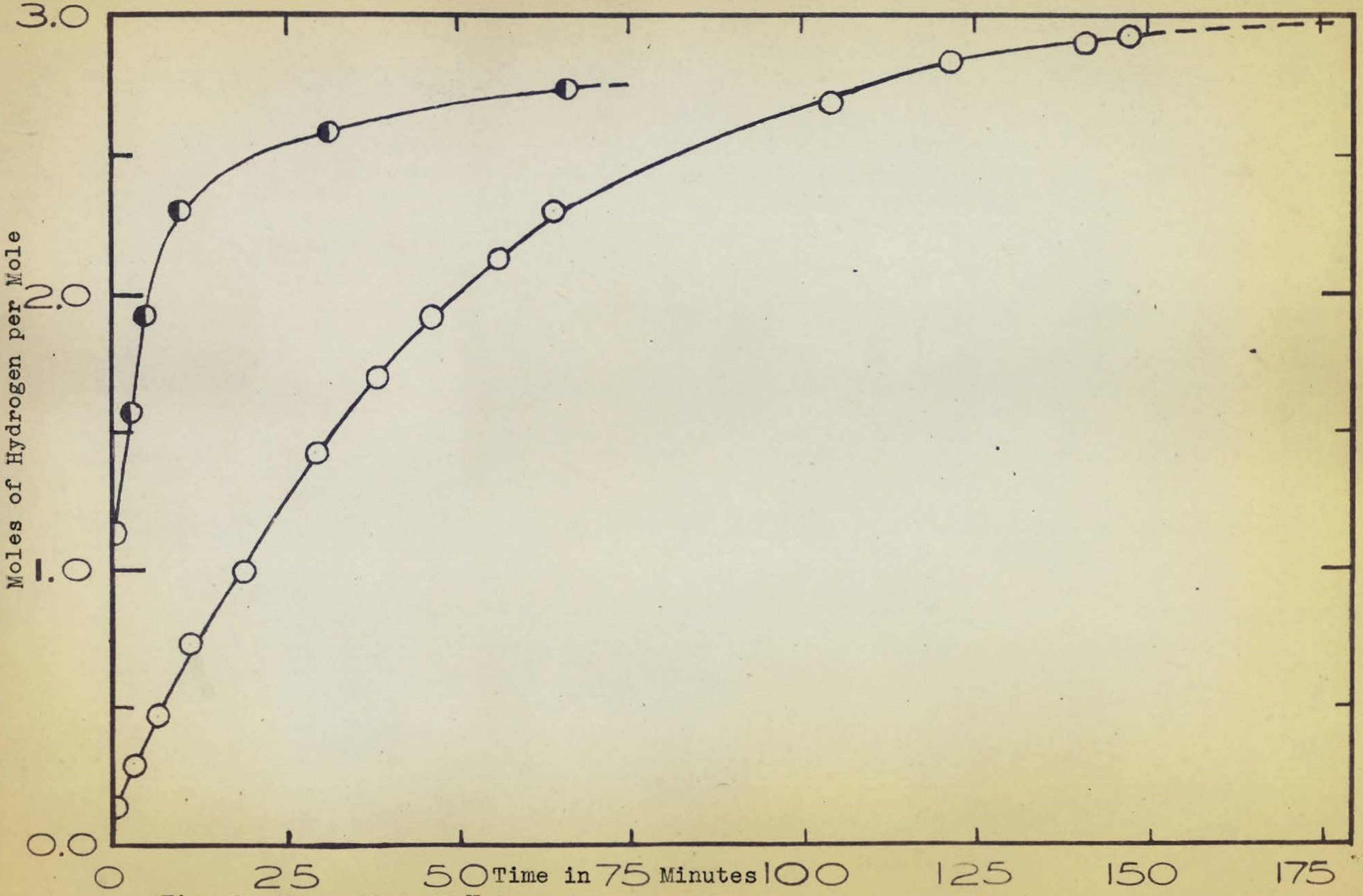


Fig. 2 Absorption of Hydrogen by ethyl p-hydroxybenzoate (◐), and pyrogallol (○).
See Tables XVI and XVII

(Fig. 2 and Table XVII), no cyclohexanediol fraction was found on fractional distillation of the products and a 50 per cent yield of γ-pyrogallitol (cis-cis-cis-1,2,3-cyclohexanetriol) was isolated in a pure condition. The remainder of the reduced material was not examined extensively because a careful separation of the other isomeric pyrogallitols (α and β) is complicated and time-consuming (39, 49). The combined yield of 75 per cent of the pyrogallitols, including 50 per cent of the pure γ-isomer, is believed to be the highest yield so far obtained in this reaction. Over Raney nickel, the combined yield of the three isomeric primary products was reported to be of the order of 30 per cent (39), the γ-isomer comprising five-sixths of this quantity. It is noteworthy that the γ-isomer was the predominating product over both the nickel and palladium catalysts. Also of great importance was the apparent lack of any hydrogenolysis over the latter catalyst, to judge from the theoretical hydrogen absorption and the absence of any low-boiling diols in the product.

The method of esterifying gallic acid with ethanol containing sulfuric acid was similar to those reported (68) and the yields were of the same order (70 per cent). A rapid recrystallization of the crude product by an azeotropic distillation of an ethanol-benzene solution was employed and this method of purification is an improvement that does not appear in the literature. Various melting points for ethyl gallate have been reported (69, 70, 71, 72) probably because very slight traces of impurities, such as water, produce a marked depression from the true value of 160° (73). The material was considered sufficiently pure for hydrogenation purposes if it melted at 158° or higher. Any remaining impurities could not have been responsible for the variable rates of hydrogenation observed, for the same behaviour was characteristic of samples of ethyl gallate purified until they melted sharply at 160°.

In the presence of the new hydrogenation catalyst and in anhydrous dioxane, ethyl gallate was found to undergo hydrogenation at 155-165°, 100-200 atm. pressure. Three of the five hydrogen absorption curves in Figure 3 show a fair agreement, but the other two illustrate reactions which were considerably slower despite the fact that the temperature was raised 5 to 10° above the 155-165° range which gave good results in the three cases. This effect, in all probability connected with the inherent sensitivity of this catalyst to deactivation, could not always be avoided, despite the precautions which were taken to maintain a high standard of purity of reagents, solvent and ethyl gallate. The thermal instability of this catalyst would make a study of the relevant reaction kinetics a difficult problem.

In the three cases in which rapid reduction occurred, nos. 2, 5 and 6, the conversion averaged nearly 80 per cent. This figure was obtained by the difference between the initial

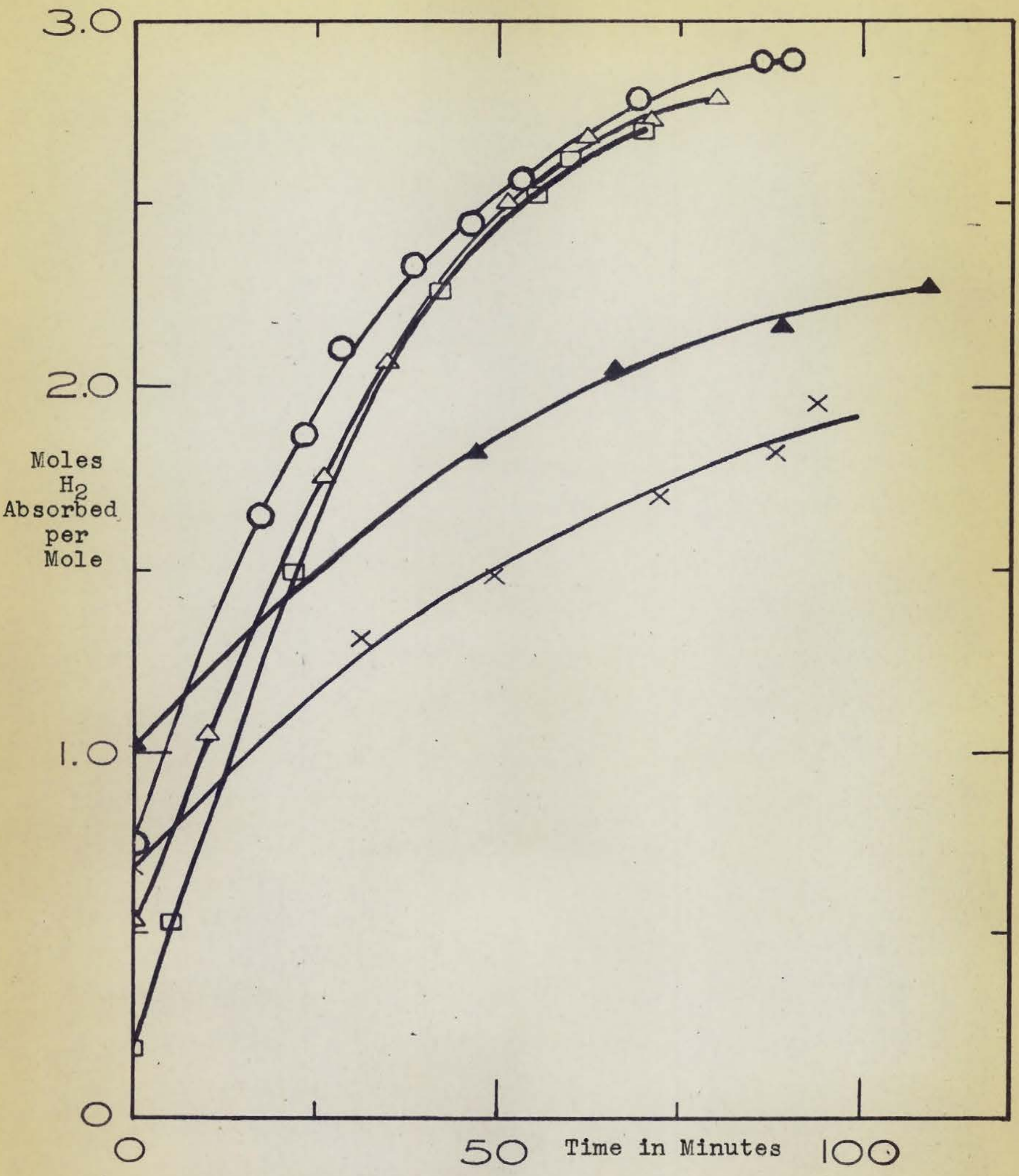
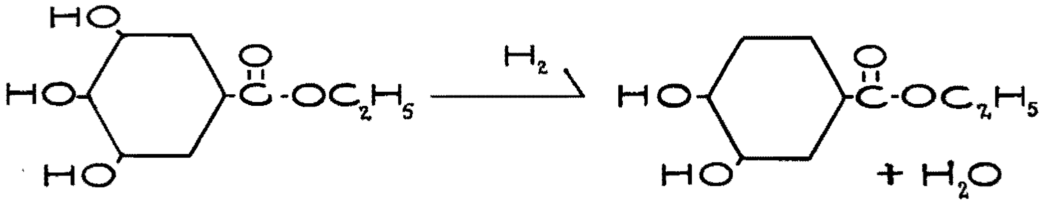


Fig. 3 - Absorption of Hydrogen by Ethyl Gallate. See Table XIX. Hydrogenation No.2 (○), No.3 (▲), No.4 (×), No.5 (□), and No.6 (△).

weight of ethyl gallate and the weight of purified, recovered ethyl gallate. The poor conversions in the two retarded reactions, nos. 3 and 4, ranged from 55 to 60 per cent. In all cases the hydrogen absorption was 10 to 15 per cent higher than the theoretical value calculated from the per cent conversion. The error in the hydrogen absorption figures could not have been large because the absorptions in the control hydrogenations of ethyl p-hydroxybenzoate and pyrogallol closely checked the other experimental data. It was concluded therefore that some hydrogenolysis of the primary product, ethyl hexahydrogallate, must have occurred to account for the discrepancy, as would be expected from the well-known susceptibility of glycols to cleavage by hydrogen (32). By analogy with the hydrogenolysis of the pyrogallitols (39, 74), ethyl hexahydrogallate, XLIV, might be expected to yield a diol ester, XLV. The failure to detect such diols in the crude reaction product from ethyl gallate (see below) was evidence that in the present case hydrogenolysis played only a minor role.



XLIV

XLV

The data listed in Tables VII, XVIII, XIX, and in Figure 3 were all obtained from hydrogenations carried out in a 400 ml. Parr stainless steel bomb using no glass liner. Neither was a liner used for four larger scale hydrogenations (150 g. ethyl gallate) in a non-stainless steel 2500 ml. bomb made by the American Instrument Co. In this bomb the conversion rarely exceeded 50 per cent before the rate became negligible. In addition, the product was contaminated with deep blue-coloured insoluble material. The latter was believed to be the ferric complexes which are reported by Zwenger and Ernst (70) to be formed by ethyl gallate in the presence of ferric salts. In no case did the product from the small stainless steel bomb have any appreciable colour. It is probable that either the iron surface or the greater period of time necessary to raise the temperature of the larger bomb to the absorption range, or both these factors together, contributed to the deactivation of the catalyst before the reaction could proceed very far.

The crude mixture of unchanged ethyl gallate and reaction products was usually a colourless semi-crystalline material. It dissolved readily in water from which the ethyl gallate was recovered by several ether extractions according to the method developed by Gogek (49) for the recovery of unreduced pyrogallol in similar hydrogenations. The residual material was a microcrystalline mass varying in colour from

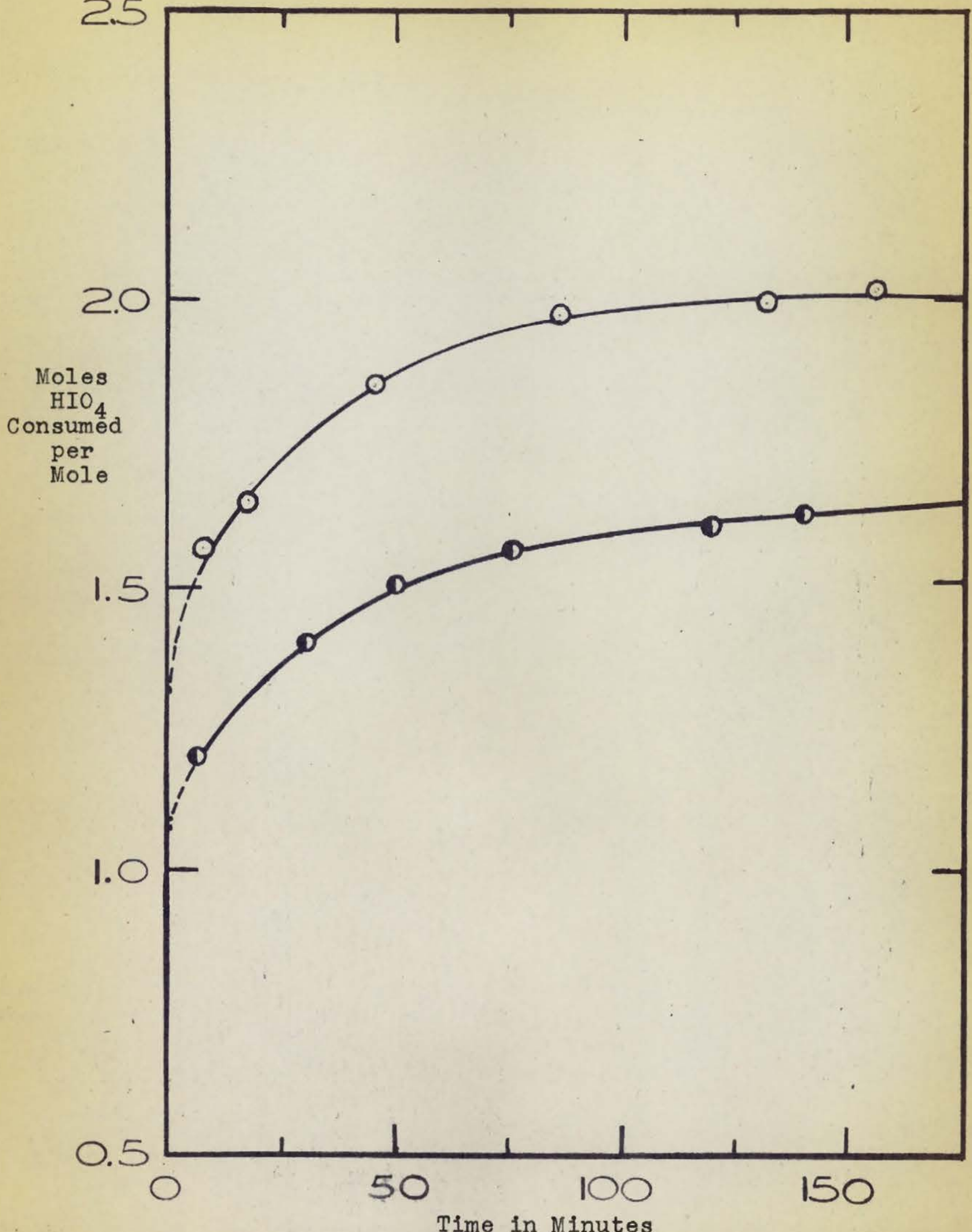
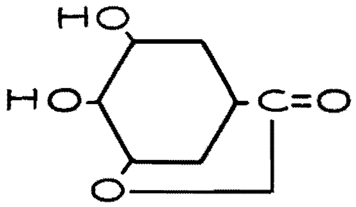


Fig. 4 - Periodate oxidations at pH 4 of ethyl hexahydrogallate (○), and crude reduced ethyl gallate (◐) in 0.00750M periodic acid solution at room temperature. See Tables XX and XXI.

nearly white to a pale brown, extremely soluble in water, and with no phenolic reactions. As described later, this residue yielded a small amount of a crystalline hexahydrogallic γ-lactone, XLVI, in addition to much of the corresponding crystalline ester.



XLVI

The crude extracted material was analysed on one occasion (hydrogenation no. 1, Tables VI and VII) both for ethoxyl and unsubstituted 1,2-glycol units, the latter determination being made by the periodate method as described by Price and Knell (75). A simple equation, based on the assumption that the mixture consisted entirely of ester, XLIV, and lactone, XLVI, showed that the latter were present in a molar ratio of 0.77 to 0.23 (average molecular weight 193) when the alkoxyl analysis of 17.9 per cent was used as a basis of calculation, but the ratio became 0.64 to 0.36 when the glycol determination was employed. This discrepancy suggested that a third substance, and presumably an ethyl dihydroxyhexahydrobenzoate, XLV, was also present. Since the trihydroxyester, XLIV, the trihydroxy acid lactone, XLVI, and the presumed dihydroxy ester, XLV, have molecular weights of 204, 158 and 188 respectively, it is possible to set up the following three simultaneous equations to express the observed alkoxyl percentage and glycol content (as moles HIO_4 consumed per gram sample) in terms of the mole fractions x, y, and z, of the three constituents of the mixture.

$$x + y + z = 1 \qquad \ldots(i)$$

$$\frac{4500\,(x + z)}{204x + 158y + 188z} = \text{per cent } OC_2H_5 = 17.9\% \qquad \ldots(ii)$$

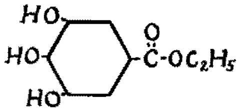
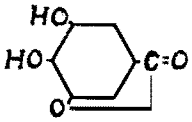
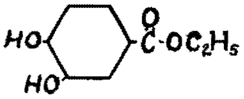
$$\frac{2x + y + z}{204x + 158y + 188z} = \begin{array}{l}\text{moles glycol} \\ \text{per gram}\end{array} = 0.00875 \qquad \ldots(iii)$$

These equations are based upon the absence of an alkoxyl group in the lactone, the presence of one glycol group both in the lactone and the dihydroxy ester and of two glycol units in the trihydroxy ester. Solution of the equations (Table VI) suggests that 0.68 moles (x) of ethyl hexahydrogallate, 0.24 moles (y) of hexahydrogallic acid lactone and 0.08 moles (z) of the dihydroxy ester were present in the original mixture.

Although the calculation tacitly assumes the accuracy of the analytical data and the absence of a fourth component or other contaminant in the mixture, the result strongly suggests that little or no hydrogenolysis of the carboxylic ester groups had occurred. The hydrogenolysis of hydroxyl groups, leading to compounds analogous to XLV, was also of little importance and, indeed, no substances of type XLV were found. It was nevertheless possible that more were present originally but were removed, together with unchanged ethyl gallate, when the aqueous solution of the crude hydrogenated product was extracted with ether. The occurrence of products of the type XLV in the ether extract would account for the slightly excessive (10 to 15 per cent) hydrogen absorption observed in most cases (Table XVIII).

TABLE VI

ANALYSES OF CRUDE ETHYL HEXAHYDROGALLATE

	Compound	Calcd. % OC_2H_5	Calcd. Moles HIO_4	Mol. Wt.
XLIV		22.0	2.0	204
XLVI		0.0	1.0	158
XLV		23.9	1.0	188
Found:		17.9	0.00875[a] (duplicate analyses)	

Calcd. Molar ratio of XLIV: XLVI: XLV = 0.68:0.24:0.08

[a] Moles glycol per gram sample, see Fig. 4 and Table XXI.

By means of a tedious fractional crystallization of the crude extracted reduction product from anhydrous acetone, one of the six theoretically possible ethyl hexahydrogallate isomers was isolated (m.p. 146-147°). The yield of this pure isomer ranged from 16 to 20 per cent calculated on the ethyl gallate reduced, but high mechanical losses were incurred in the recrystallizations. The ethyl hexahydrogallate came out of solution as a voluminous mass of very thin plates which caused plugging in the filter. In the preliminary stages of preparation these crystals were difficult to handle without considerable losses. These factors indicated the necessity of finding a more efficient, chemical method of isolating this compound after some knowledge of its chemical behaviour had been collected.

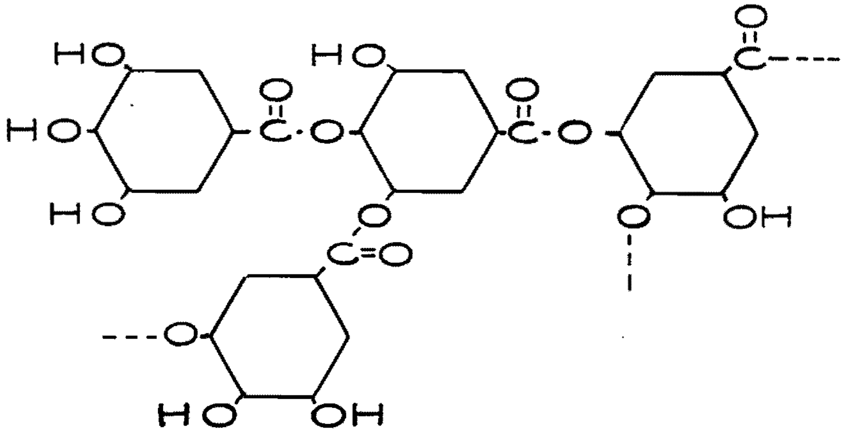
The mother liquors from the recrystallizations, after standing for several days, yielded well-formed, rod-like crystals of a different compound which, on further purification by recrystallization from ethanol or acetone, melted at 186-189° and analysed for the γ-lactone, XLVI, of a hexahydrogallic acid. The yield of pure lactone, 2 to 7 per cent, was naturally much lower than the 24 per cent already estimated to be present in the crude mixture from hydrogenation 1 (see Tables VI and VII). The combined yield of pure, crystalline ester and lactone constituted together between 20 and 25 per cent (in one case, no. 4, Table VII, 40 per cent) of the weight of the ethyl gallate reduced. Further work on the residues, using various solvents, failed to yield any other chemical individual despite the fact that 55 per cent or more of the material remained. The mother liquors yielded only

TABLE VII

SUMMARY OF PRODUCTS FROM ETHYL GALLATE HYDROGENATIONS

		Crude Mixture from Bomb		Ether-Extracted Water-Soluble Fraction			Ether Extract Ethyl Gallate			Combined % Yield Calcd. as Ester on Reduced Ethyl Gallate
				Recryst. from Acetone		Residue Acetonated	Recovered	Reduced (by diff)		
No.	Ethyl Gallate g.	Ether Extract g.	Water Soluble Residue g.	Ester	Lactone	Acetone-Lactone	g.	g.	%	
1	28.2	8.3	18.5	4.53	0.55		7.0	21.1	75	24
2	35.0	9.6	25.2	4.60	1.20		7.5	27.5	79	22
3	35.0	20.5	14.6	4.30	0.36	2.90	13.9	21.1	60	36
4	35.0	19.3	15.7	7.70	-	1.06	16.0	19.0	54	45
5	45.0	10.9	31.8	7.80	-	7.00	8.7	36.3	81	40
6	45.0	11.5	32.5	7.50	-	6.90	9.4	35.6	79	40

sticky amorphous precipitates which could not be further purified by physical methods alone. Distillation was attempted in one instance but these products, probably by virtue of the reactive ester or lactone groups, were susceptible to decomposition, and perhaps transesterification on heating. They yielded glassy solids, presumably of the following type, XLVII.



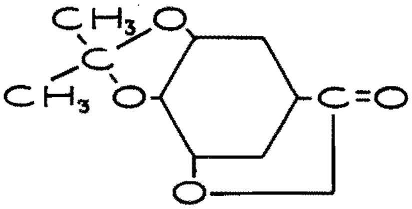
XLVII

Chemical Reactions of the Ethyl Hexahydrogallate

Before a chemical method of isolating the products of the hydrogenation could be worked out, it was necessary to study the reactions of the isomer isolated by crystallization from acetone. A selective reaction was needed to permit a more efficient method of separating this compound, which appeared to predominate in the mixture. In addition, information about the configuration of the substituent groups in this isomer was considered desirable.

The condensation of acetone with glycols was the most logical reaction to investigate first, in view of the close structural relationship of the hexahydrogallates to the pyrogallitols, whose condensation with acetone was recently studied by Gogek (49).

Suitable conditions for converting the new ester to its free acid were worked out first. A difficult saponification with excess barium hydroxide solution under reflux, over a period of ten hours or more, gave the acid in about 66 per cent yield. Although the reaction was not studied extensively, lactone formation was believed to have caused some loss of the main product. The hexahydrogallic acid crystallized as white microcrystals, m.p. 199-200°, which were very soluble in water, slightly soluble in acetone, but insoluble in ether. The acid was converted in part to a lactone when kept near its melting point for several hours.

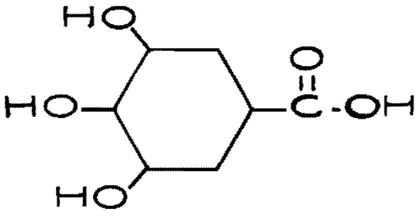


XLVIII

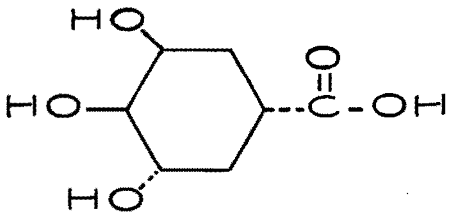
Both the ester and the free acid yielded the same isopropylidene lactone, probably structure XLVIII, when they were condensed with acetone using dry hydrogen chloride catalyst. This product was easily purified by recrystallization from ethanol and formed large thin transparent crystals. Although the lactone could not be distilled, it was found to undergo sublimation above its melting point (170°) and was recoverable in almost quantitative amounts when heated at this temperature under reduced pressure. It was a stable, not appreciably hygroscopic substance. Hydrolysis under mildly acidic conditions removed the isopropylidene residue and yielded the same lactone, m.p. 186-189°, as that directly isolated from the hydrogenation of ethyl gallate. The consumption of exactly one mole of periodic acid by one mole of this lactone, XLVI, established the fact that the two hydroxyl groups it contained were adjacent to each other and that, in consequence, the lactone ring engaged a meta hydroxyl group and was five-membered. This lactone was also obtained directly although in low yield, by heating the ester in anhydrous dioxane.

Considering first the lactone ring in XLVI, it is certain that the 3-hydroxyl group is cis with respect to the carboxyl because no case of lactone formation in the cyclohexane series has ever been observed involving a carboxyl and an hydroxyl group in the <u>trans</u> configuration. Also, an examination of Fischer-Hirschfelder-Taylor models of the various possibilities indicated that hydroxyl groups in the γ and δ positions are favourably located for lactone formation providing they are cis to the carboxyl group (Figs. 6 and 7).

As regards the isopropylidene lactone, XLVIII, acetone is known to condense readily with contiguous hydroxyl groups when dry hydrogen chloride is the catalyst, provided the groups are cis. As already mentioned, the sole known exception to this rule was Gogek's discovery (49) that isopropylidene-trans-1,2-cyclohexanediol formed, although in only 3 per cent yield, from the trans diol and acetone in presence of dry hydrogen chloride. No case of a condensation with a cis or trans-1,3-cyclohexanediol has been reported although isopropylidene acetals of a few 1,3-glycols in the open chain series are known (76). The very reasonable inferences were that acetone engaged adjacent cis hydroxyl groups in XLVIII, and that XLVIII, like XLVI, was a γ-lactone. Since lactones in the hydroxycyclohexane carboxylic acid series are known to form only when the hydroxyl and carboxyl groups are on the same side of the ring, it appears probable that the free acid corresponding to the lactone under discussion was either Va or Ve.



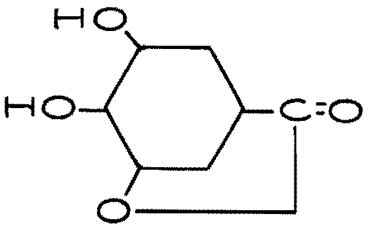
Va



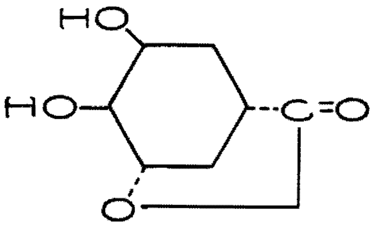
Ve

The former acid may be regarded as a derivative of cis-cis-cis pyrogallitol and the latter as derived from the cis-cis-trans isomer.

Attempts were made to differentiate between these structures by noting the rate at which the ester was oxidized by periodic acid, but, unlike Christian's experience in the pyrogallitol series (39), no satisfactory bimolecular rate constant could be obtained. Although the overall rate of oxidation was nearly the same as that observed for cis-cis-trans pyrogallitol by Christian, and was much too fast to belong to a cis-trans-cis (α-pyrogallitol) structure, in the circumstances little weight could be attached to the observations and they are omitted from the Experimental Procedures. Preliminary experiments with the lactone (XLIX or L) gave similar unsatisfactory results.



XLIX



L

Another attempt to distinguish between structures Va and Ve was based upon the fact that the former was that of a symmetrical, optically inactive molecule whereas the latter was that of a raceme, theoretically capable of resolution into optically active D and L forms. The free trihydroxycyclohexyl carboxylic acid was accordingly converted to the highly crystalline brucine salt and the latter was fractionally crystallized from several solvents. All fractions, however, possessed specific rotations lying between the limits ±0.9° and no resolution was brought about. Less extensive experiments with the crystalline cinchonine salt also failed to resolve it, and the free acid failed to form a salt with strychnine in the conditions tried. Much of the base, indeed, crystallized out of the solution independently. These results, although constituting negative evidence, point strongly to the symmetrical configuration Va as the more likely.

The tentative conclusion that the hexahydrogallic acid isolated in the present research possesses the all-cis configuration Va is not inconsistent with the fact that the all-cis γ-pyrogallitol was the preponderating isomer formed when pyrogallol was hydrogenated over Raney nickel (39, 49, 74). The same isomer also preponderated when the hydrogenation was carried out over palladium-strontium carbonate during the present research. It is supposed that the formation of such products, with all the substituents in the cis configuration, probably arises through the addition of hydrogen to one side of the aromatic ring. On the other hand, the hexahydrogallic acid actually isolated displayed great similarity in its chemical behaviour (Figure 5) to quinic acid, and quinic acid, XXXI, is formulated as an α-hydroxy derivative of the configurational structure Ve (51). Both substances readily formed 1,3-lactones which were readily oxidized by periodic acid, and the two adjacent hydroxyl groups they therefore possessed condensed readily with acetone. With anhydrous

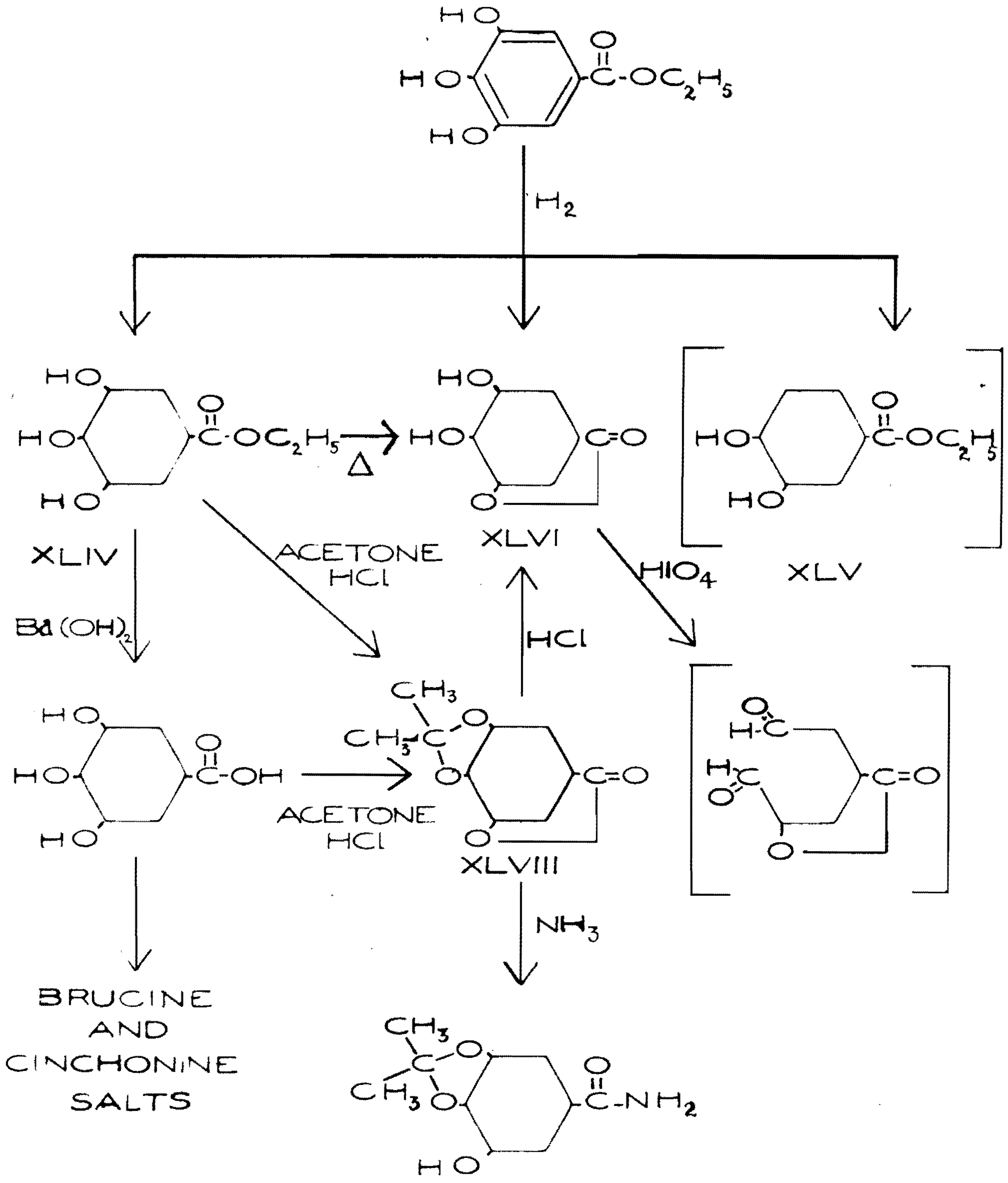
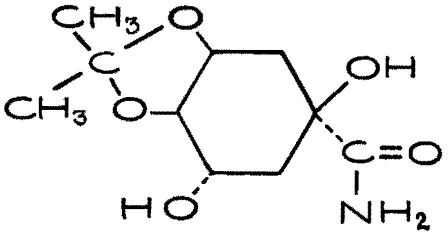
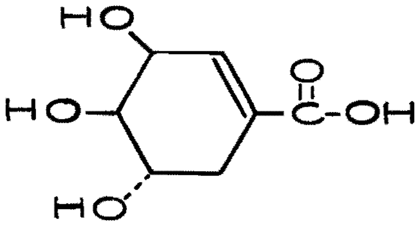


Fig. 5 - Summary of Ethyl Hexahydrogallate Reactions

ammonia, the isopropylidene quinic lactone, XXIV, readily formed a crystalline isopropylidene hydroxy amide, LI, and the corresponding lactone, XLVIII, from the hexahydrogallic acid, a new substance of melting point 170.5-171°, was found to behave similarly. These resumblances tend to suggest that the latter substance was a derivative of the structure Ve.



LI



LII

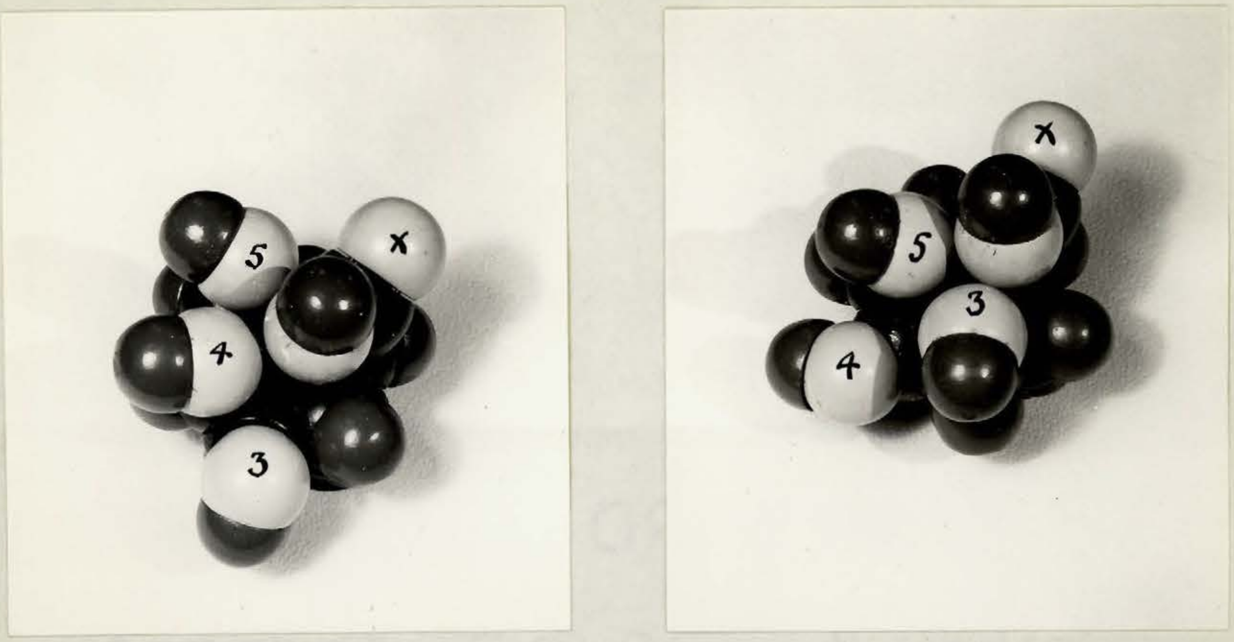
Fischer and Dangschat (56) showed that the conversion of the naturally-occurring levorotatory quinic acid, XXXI, to shikimic acid, LII, and thence to dihydroshikimic acid, Vb, involved an inversion of the configuration of the carboxylic acid group. The cis-cis-trans configuration of the hydroxyl groups in this substance, as well as in quinic acid, were proved by the fact that both were strongly levorotatory. Dihydroshikimic acid, however, readily formed a lactone, XXXIV, that was stable to periodic acid and possessed no adjacent hydroxyl groups. This lactone was obviously of the 1,4 variety. The methyl ester of dihydroshikimic acid, XXXII, readily formed an isopropylidene derivative, XXXV, without the elimination of the ester group

(2). Such differences prove the non-identity of dihydroshikimic acid, Vb, and the isomer under discussion. It is worth mentioning that the different melting points of the two substances, 183-4° and 199-200° respectively, did not prove this non-identity, since the former was an optically active form and the latter might have been the corresponding raceme.

Inspection of the formula Vb for dihydroshikimic acid shows that one of the two meta-hydroxyl groups, as well as the para hydroxyl, is cis to the carboxylic acid group. Nevertheless, the only known lactone is of the δ-variety, XXXIV, although the formation of a γ-lactone seems equally probable. The anomaly suggests that the cyclohexane ring in dihydroshikimic acid has a non-planar, but strainless Sachse-Mohr shape (77, 78) that favours the formation of a δ-lactone and inhibits ring closure in the γ-position. Linstead (47), noting the greatly increased stability of γ-cyclohexanolides when substituted with alkyl groups in the γ-position, concluded that the ease of lactone formation depended on the nature of the substituents in neighbouring positions as well as on the location of the hydroxyl group which reacts. The polar effects of adjacent hydroxyl groups can be surmised to influence lactone formation either by altering the Sachse-Mohr configuration of the ring or by altering bond strengths.

Mechanical models of the probable alternative structures Va and Ve for the new trihydroxy cyclohexane carboxylic acid were constructed from a Fischer-Hirschfelder-Taylor set, in which relative atomic sizes and bond lengths are preserved. Figure 6 reproduces photographs of both structures, each being represented in one "chair" and one "boat" form, and Figure 7 illustrates the same four forms diagramatically. It is to be noted especially that when all three hydroxyl groups are cis to the carboxyl group (structure Va), the "boat" form (C) suggests either a γ - or δ -lactone is almost equally probable. The "chair" form (Z) greatly favours the γ-lactone because the hydroxyl in the fourth position is removed from the carboxyl group. The "chair" form of structure Va is therefore consistent with the observed formation of a γ-lactone from the cyclohexane carboxylic acid under discussion. On the other hand, both the "boat" and "chair" forms of the alternative structure exclude the easy formation of any but a γ -lactone. This study of molecular models therefore failed to decide between the competing structures Va and Ve.

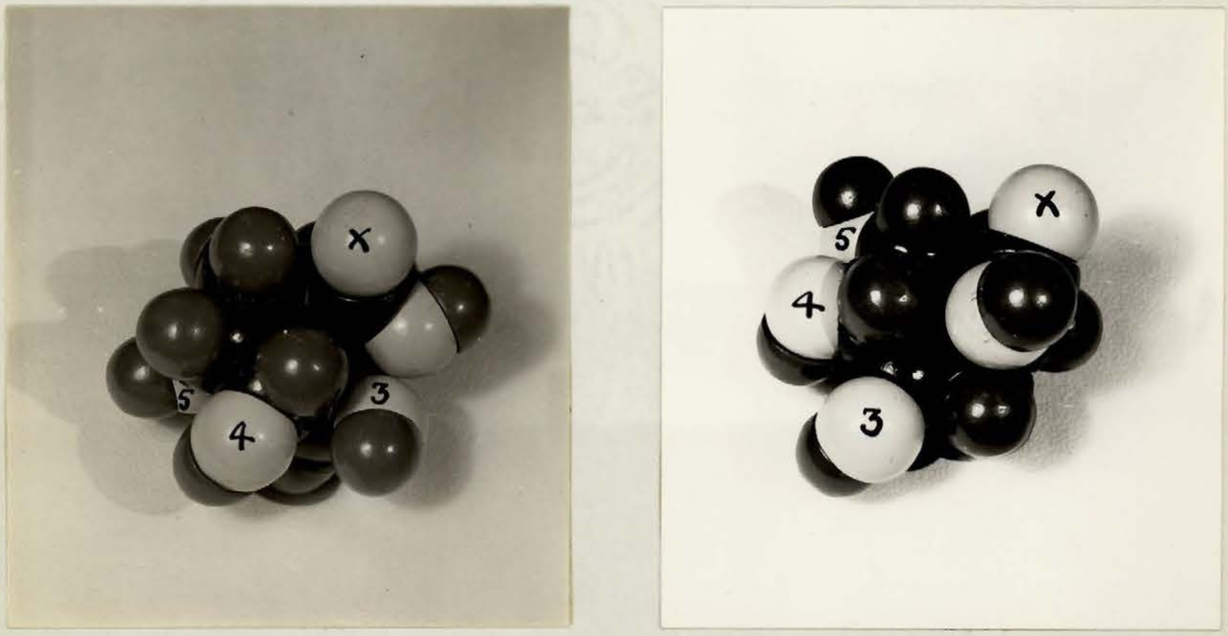
The work done in this thesis appears to provide a basis for a future decision to be made between Va and Ve along lines used by Fischer (51) in his proof of the configuration of quinic acid. Selective alkaline hydrolysis of the lactone ring in the isopropylidene lactone, XLVIII, should yield an isopropylidene carboxylic acid, LIII. Methylation of this acid with silver oxide and methyl iodide, to form LIV, followed by acid hydrolysis of the isopropylidene and ester groups,



C

Z

Va



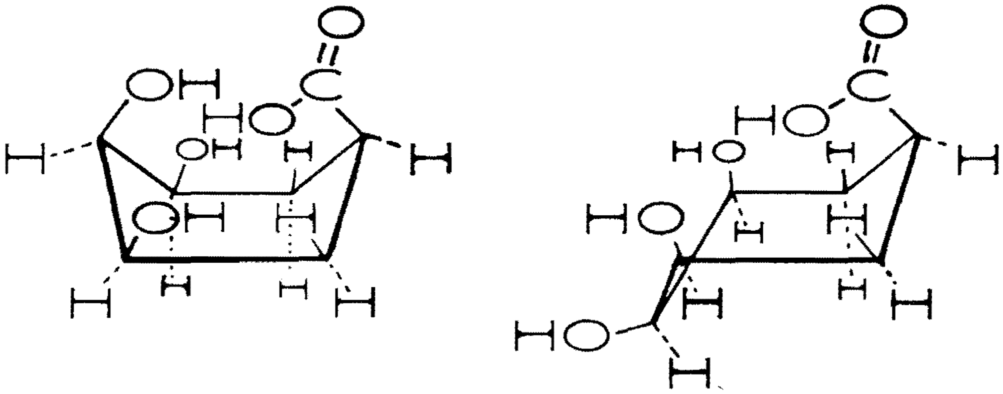
C

Z

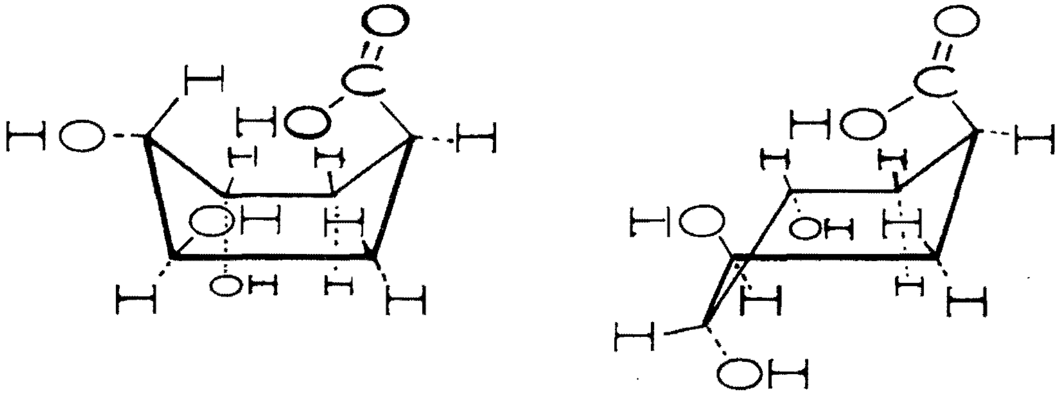
Ve

Fig. 6 Photographs of Fisher-Hirschfelder-Taylor Models of Structures Va and Ve

C, black; H, gray; O, white. Hydroxyl oxygen atoms bear number of ring carbon to which attached. C=O = x



Va

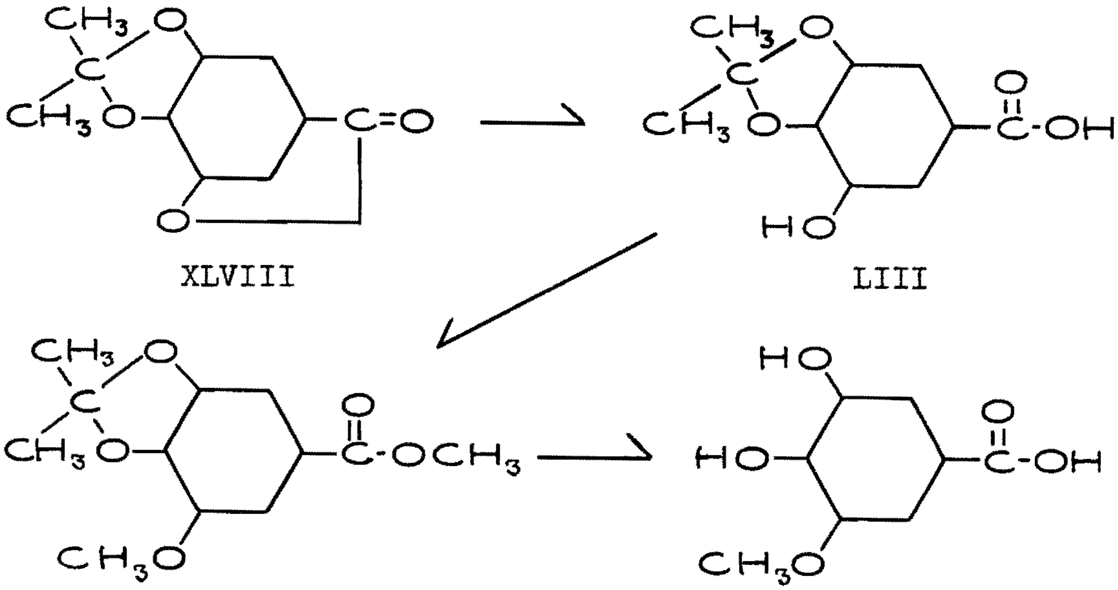


Ve

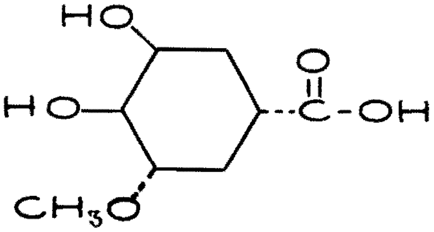
Fig. 7 - Diagrams of one "boat" form and one "chair" form of Structures Va and Ve.

See Fig. 6

would then yield the monomethyl ether, LV, of the hexahydrogallic acid. If the latter had the structure Ve, the alternative structure for the monomethyl ether would be, LVI, the position originally occupied by the lactone ring being taken up by the methoxyl group in both cases.


XLVIII LIII

LIV LV

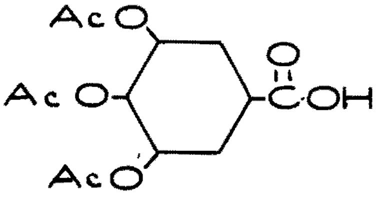

LVI

Since in LV, the remaining meta hydroxyl group is cis to the carboxylic acid group, a γ-lactone should readily form, even if the molecule retained a "chair" form that made a δ-lactone unlikely. Structure LVI, in which both of the remaining hydroxyl groups are trans to the carboxyl, would not be expected to produce a monomeric lactone of any kind. If the monomethyl ether, LV or LVI, were available, it would be desirable to study its oxidation by periodic acid or lead tetraacetate, since the presence of only two adjacent hydroxyl groups, instead of the original three, might simplify the course of the oxidation and provide rate plots readily interpreted in terms of cis or trans configuration.

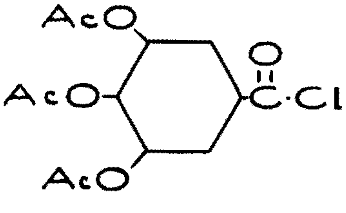
Improved Separation of the Hydrogenated Ethyl Gallate Mixture

As already mentioned, an aqueous solution of the crude product was extracted with ether to remove unchanged ethyl gallate, and, perhaps, some ethyl dihydroxycyclohexyl carboxylic esters, XLV. Some of the ethyl hexahydrogallate, and a little of the corresponding lactone, were separated from the residue by tedious recrystallizations from acetone. The preceeding research, by showing that the ethyl ester yielded the lactone when heated, suggests that the latter arose from the former during the hydrogenation or isolation. Both these substances readily yielded the same highly crystalline isopropylidene lactone when condensed with acetone. The residues from the acetone mother liquors in the original preparation were accordingly condensed with fresh, dry acetone exactly as described for the pure ester or acid. Substantial amounts of the same isopropylidene lactone were obtained and the overall yields of crystalline products were increased from about 20 to about 40 per cent in most cases. In one case (Table VII, no. 5), the residues from the acetonation were heated under reduced pressure to the melting point (170°) of the isopropylidene lactone and an additional 7 per cent of the latter was isolated by sublimation to give an overall yield of 47 per cent. The nature of the remaining syrup was not determined, but, if other of the six isomeric hexahydrogallates were present, each isomer was probably present in small quantities only and probably did not condense with acetone.

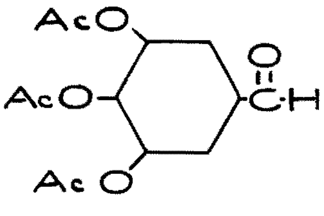
The above observations showed that the isopropylidene lactone could readily be prepared in fair yield from ethyl gallate by a two-stage synthesis involving hydrogenation and subsequent acetonation. Little difficulty is anticipated in the synthesis from this lactone of the corresponding cyclohexylaldehyde, III, whose production forms the ultimate object of the research. Acetylation of the isopropylidene lactone with an acidic catalyst should eliminate the isopropylidene residue and produce the triacetate, LVII. Palladized barium sulfate and hydrogen at atmospheric pressure should reduce a boiling xylene solution of the corresponding acid chloride, LVIII, (The Rosenmund reaction (79)) to the triacetate of the required aldehyde, LIX, in an overall yield of 70 to 80 per cent.



LVII



LVIII



LIX

Polymerization of the substituted cyclohexylaldehyde, the final step in the proposed scheme, could probably be achieved either before or after removal of the acetyl groups to yield the desired polyhydroxycyclohexyl aldol condensation product, IV. It is however possible that the aldehyde, like cyclohexylaldehyde (1), might be extremely susceptible to polymerization and be difficult to isolate as the monomer under some conditions.

EXPERIMENTAL PROCEDURES

Materials and Purification

Solvents

A considerable number of reagents and starting materials were used in the experimental work. The majority of the methods of purification and synthesis were well-known and merit a brief description only.

Stock methanol and ethanol were heated under reflux in the usual manner (80, 81) over sufficient magnesium alcoholate to render them anhydrous. They were distilled shortly before use.

The dioxane employed in the hydrogenations was purified by the method of Fieser (80). In brief, stock dioxane was heated under reflux with hydrochloric acid to hydrolyse any acetal present, and a continuous stream of nitrogen was bubbled through the solution to carry away the acetaldehyde formed. The acid and water were removed by means of potassium hydroxide pellets and final drying was effected by heating under reflux for twelve hours over sodium, and finally by distillation. To ensure a peroxide-free product, this distillation was carried out within an hour or two of the charging of the hydrogenation bomb.

Stock acetone was dried for several days over anhydrous calcium chloride. The solvent was decanted, heated under reflux with a few crystals of potassium permanganate and distilled after any acids had been neutralized with excess potassium carbonate.

Aldehydes

p-Anisaldehyde was prepared exactly as described by Tiemann and Herzfeld (82) by methylation of p-hydroxybenzaldehyde (Eastman Kodak Co.) in methanolic potassium hydroxide solution with methyl iodide. The methylation of vanillin (Howard Smith Co.) with dimethyl sulfate as described by Buck (83) yielded veratraldehyde.

Gallaldehyde was prepared from gallic acid (General Chemical Co.) essentially by the synthesis described in detail by Rosenmund and Zetsche (84). The acid was acetylated to triacetylgallic acid which was converted to the acid chloride with thionyl chloride by the usual method (85) instead of with phosphorus pentachloride. The latter reagent, in the older method used by Rosenmund, suffered from the disadvantage that its by-products were more difficult to eliminate than those from thionyl chloride. Triacetylgallic acid, 25 g. (0.096 mole), m.p. 169-170°, purified thionyl chloride, 15 ml. (24 g., 0.20 mole) and anhydrous benzene, 75 ml., were heated under reflux until solution was complete (one and one half hours) and then for an additional half hour. The unused thionyl chloride was thoroughly removed by co-distillation with benzene and the white crystalline residue, m.p. 105-108°, was obtained in theoretical amount. It was found unnecessary to remove the product from the flask before proceeding with the reduction of the acid chloride to the aldehyde. This reduction was accomplished by bubbling hydrogen at atmospheric pressure through a solution in 200 ml. of dry, boiling xylene in which 5 per cent palladized barium sulfate (67) was suspended. The acetylated aldehyde was subsequently hydrolysed to free gallaldehyde by an ethanolic solution of potassium acetate in an inert atmosphere.

Trimethylgallaldehyde was also obtained from gallic acid. The latter was methylated with dimethylsulfate (86) then converted to the trimethyl acid chloride with thionyl chloride in benzene by the method already described for the preparation of triacetylgalloyl chloride. The aldehyde was finally obtained by a Rosenmund reduction of the acid chloride by Nierenstein's (87) application of Rosenmund's (84) original method over 5 per cent palladized barium sulfate (67) in boiling xylene.

p-Hydroxybenzaldehyde (Eastman Kodak Co.) was recrystallized from water and thoroughly dried, m.p. 116-117°. Protocatachualdehyde (3,4-dihydroxybenzaldehyde, Kahlbaum Co.) was recrystallized from water and thoroughly dried, m.p. 153-4°. Vanillin (Howard Smith Co.) was recrystallized from water, aqueous ethanol and thoroughly dried, m.p. 80-81°.

Orthoformic esters

Ethyl orthoformate was obtained by the method of Wood and Comley (25) by condensing chloroform with sodium ethylate. The product was identical with their product in its physical properties.

Methyl orthoformate was prepared in essentially the same way from chloroform and sodium methylate and the product, b.p. 99.5-99.7 (corr), n_D^{25} 1.3773, was obtained in 40-45 per cent of the theoretical amount. Deutsch (88) reported a boiling point of 101-102°, but no yield data. Sah and Tsu Sheng Ma (89) observed a boiling point of 103-105°, a refractive index of n_D^{25} 1.3773, and a yield of 30 per cent of theory.

Diazomethane

Arndt's (90) method was used, a 4 per cent aqueous potassium hydroxide solution being treated with the necessary amount of N-nitrosomethylurea (91) at 0° with stirring in contact with ethyl ether. The etherial solution of diazomethane was separated and dried for four hours over pure potassium hydroxide pellets before use in the methylation experiments. A gas mask was worn at all times during the handling of this extremely poisonous compound and all the customary precautions were observed (92).

Hydrogenation Catalysts

Raney nickel catalyst was prepared by the method of Mozingo (93) from a nickel-aluminium alloy (Gilman Paint and Varnish Co., Chattanooga, Tenn.)

A nickel-kieselguhr catalyst was derived exactly as described by Adkins (31) from nickel nitrate and kieselguhr, upon which the nickel was precipitated by means of ammonium carbonate. Just prior to use the catalyst was reduced by heating at 450° for one hour in a stream of hydrogen.

The preparation of a palladium-strontium carbonate catalyst was an adaptation of the usual method of preparation for palladium on barium sulfate (67). Twenty five grams of strontium carbonate (Merck, C.P.) was dissolved in 500 ml. of water containing 40 ml. of concentrated hydrochloric acid. The solution was heated to approximately 60° and the strontium was reprecipitated as the carbonate by adding an excess of a hot saturated solution of sodium carbonate (20 g. of anhydrous sodium carbonate in approximately 50 ml. of water). The precipitate was washed repeatedly with distilled water and the washings were removed by siphon after the solid had settled. Washing was continued until the washings were free of chloride ion.

One gram of palladium chloride (Johnson Matthey Co.) was dissolved in 500 ml. of water containing 5 ml. of concentrated hydrochloric acid, with stirring and heating to 60°. The pH of the solution was adjusted to approximately 4 by careful addition of sufficient concentrated sodium carbonate solution to neutralize the acid. If too much of the salt was added, a sharp deepening of colour occurred and this mishap could be corrected by addition of the appropriate amount of hydrochloric acid. The hot solution was filtered to remove traces of insoluble matter and was added to the freshly precipitated and washed strontium carbonate, suspended in 500 ml. of water at approximately 60°. Seventy five millilitres of 40 per cent formalin was poured in and the mixture was heated to the boiling point with continuous stirring. The colour changed from a pale brown through gray to black as the reduced precipitated material was adsorbed on the carrier. When there was no further deepening of the colour, the mixture was boiled for an additional five minutes, then allowed to cool and settle. After a few minutes, the colourless supernatant liquor was removed through a siphon, and the catalyst was washed repeatedly with distilled water, the washings being conveiently removed in the same way. Ten to twelve litres of wash water was found sufficient to remove chloride ion. The washed catalyst was collected on a Büchner funnel and dried thoroughly over potassium hydroxide pellets in a vacuum desiccator for three or four days. Prior to use, the dry gray-coloured cake was crushed in a mortar to a dust. The yield of catalyst was 23-24 g.

Miscellaneous Compounds

Salicylic acid (Merck and Co.) was fused with potassium carbonate at 240° for one and one half hours to yield phenol and p-hydroxybenzoic acid exactly as described by Buehler and Cate (94).

p-Hydroxybenzoic acid was esterified with ethanol by the method of Hewitt and Winmill (95). The ester was recrystallized from a mixture of ether and petroleum ether and melted at 115-116°.

n-Heptylamine was prepared by a synthesis from heptaldehyde (Kahlbaum Co.). The aldehyde was converted to the oxime (96) and the latter reduced to the amine by sodium in ethanol (97).

Melting points are uncorrected unless otherwise specified.

Preparation of Acetals of Substituted Benzaldehydes

By the method of Claisen (22)

A series of acetals of a number of substituted benzaldehydes was prepared, in every case by means of a slight modification of the method of Claisen using an orthoformic ester and dry hydrogen chloride catalyst. Because this method was used exclusively in the preparation of all of the compounds listed in Table I, the majority of them being reported for the first time, the method will be described once only in detail.

The aldehyde was dissolved in a minimum of the appropriate anhydrous alcohol and 1.1 molar equivalents of the corresponding orthoformic ester was added. Enough of the same anhydrous alcohol, previously made 0.05 N with hydrogen chloride, was added to introduce 0.01 mole of the gas per mole of aldehyde, and the acidic solution was refluxed for five minutes in a system protected from external moisture with a drying tube containing soda-lime. At the end of this time, the solution was cooled and 1.05 molar equivalents of sodium hydroxide, contained in an 0.05 N anhydrous alcoholic solution was added to neutralize the acid catalyst and to ensure a slightly alkaline solution. The latter was transferred quickly to a Claisen flask and concentrated under reduced pressure at not more than 50° in a continuous stream of dry carbon dioxide gas introduced through a capillary during at least three hours to ensure complete neutralization of the excess base. The residue, after complete removal of the solvent and cooling, crystallized in two cases only (nos. 4 and 6 Table I) otherwise it was a viscous oil. All residues corresponded closely in weight with the theroetical weight of the acetal. The liquid acetals were immediately distilled under reduced pressure through a 3-inch Vigreux type column. The main fraction was nearly always analytically pure acetal but occasionally a second distillation of the product was necessary. The crystalline acetals were taken up in approximately 20 per cent more ether than the minimum necessary to dissolve them, and the tightly stoppered container was placed in the refrigerator at 0° or less overnight. After this period the solution was filtered quickly to remove the inorganic salts which had precipitated, and the filtrate was mixed with sufficient low-boiling petroleum ether to cause incipient cloudiness at room temperature. Gradual cooling and occasional rubbing with a glass rod caused crystallization to start. The first crop was generally analytically pure. Second and third crops were obtained by further addition of petroleum ether to the mother liquors, but these latter crops generally required one additional recrystallization from the same solvents to raise their purity to that of the first crop. The yields quoted in Table I include first crops and secondary recrystallized crops. At all times, all possible precautions were taken to exclude moisture and acidic gases from these sensitive compounds.

In most cases a sharp colour change was observed after addition of the catalyst to the reactants and the colour deepened during the reflux period. A further colour change was also observed when the catalyst was neutralized and the solution made slightly alkaline. These phenomena were most pronounced during the preparation of phenolic acetals. The different effects are recorded in Table II.

All of the acetals were analysed within twenty four hours of their preparation. This precaution was found to be absolutely necessary in the case of the phenolic acetals because of their rapid hydrolysis, even in well-stoppered containers at low temperatures. Indeed, it was found difficult to obtain two acceptable values in consecutive analyses of the same sample, the second figure always exhibiting a wider divergence from the theoretical value than the first owing to hydrolysis during the brief interim. Alkoxyl values were generally somewhat below theory, especially when the latter was 40 per cent or more. However, when extra precautions were taken, such as quick closure of the apparatus after intoduction of the sample and a gentle application of heat at the start, higher values, near the theoretical, were obtained.

Attempted Preparation of an Acetal of Gallaldehyde

By the method of Claisen (22)

Gallaldehyde, 3.1 g. (0.020 mole), was dissolved in a minimum of anhydrous methanol and the solution was mixed with 1.1 molar equivalents of methyl orthoformate before 0.01 molar equivalents of dry hydrogen chloride in 0.05 N methanolic solution was added. The remainder of the method described for the preparation of the acetals listed in Table I was followed exactly.

The residue, after removal of the solvent, was always a brown resinous material which rapidly solidified to a dark gray mass, although it was contained in a tightly closed system. In several attempts to isolate the acetal the brown resin was extracted with pure ether immediately after evaporation of the solvent. The colourless oil which remained after filtration of the extract and evaporation of the ether under reduced pressure at not more than 25° weighed approximately 60 per cent of the original weight of gallaldehyde. This residue showed no tendency to crystallize, indeed it became discoloured in a few minutes and, after a half hour it was a gray-coloured amorphous solid only slightly soluble in ether but very soluble in water. Several attempts to obtain consistent alkoxyl analyses for the unstable oil gave various results.

Anal. Calcd. for $(HO)_3C_6H_2CH(OCH_3)_2$: CH_3O, 31.00.
Found: 32.3, 29.5, 26.2

Attempts to distil the oil were unsuccessful. The material darkened and resinified rapidly on heating.

Two attempts were made to methylate the ether-soluble oil obtained from the reaction of gallaldehyde and methyl orthoformate and to isolate a methylated acetal from the reaction.

The ether solution, 40 ml., containing the oily product from the reaction between gallaldehyde, 0.88 g. (0.0057 mole), and methyl orthoformate, 0.67 g. (0.0063 mole), was cooled to 0°. To it was added a solution of 0.88 g. (0.021 mole) of diazomethane in a tightly stoppered flask in 31 ml. of dry ether. The yellow solution was kept at 0° for ten minutes in one case, and for two hours in the second case. At the end of the period the diazomethane and ether were removed by distillation under reduced pressure at not more than 25° but the orange-coloured, viscous, oily residue (0.53 g.) showed no tendency to crystallize. Attempted distillation caused decomposition of the oil to a dark tarry mass.

Methylation of Protocatachualdehyde dimethyl acetal

Protocatachualdehyde dimethyl acetal, m.p. 89-90°, 1.47 g. (0.0080 mole), was dissolved in 20 ml. of pure ether. The solution was cooled to 0° and to it was added a solution of 0.81 g. (0.019 mole) of diazomethane in 29 ml. of ether. The yellow solution was kept in a tightly stoppered flask at 0 to 5° for two hours. No colour change was observed during this period. At the end of this time the ether and diazomethane were removed by distillation under reduced pressure at not more than 25° and the orange-coloured oily residue (1.44 g.) was distilled. A small fraction (0.20 g.) of a viscous, colourless oil was obtained, b.p. 98-101°/0.05 mm., n_D^{25} 1.5249. The remainder of the material in the still had undergone decomposition to a dark resinous mass. The refractive index of vanillin dimethyl acetal (n_D^{25} 1.5250) was almost identical with the value obtained for this compound.

Anal. Calcd. for vanillin dimethyl acetal: CH_3O, 46.97.
Found: CH_3O, 46.3

The oil was left to stand in an open tube for three days after which time it had become completely crystalline and possessed the characteristic odour of vanillin. The white material was recrystallized from water and yielded needle-like crystals, m.p. 80-81°. A mixed melting point with vanillin was not depressed. The 0.20 g. of vanillin dimethyl acetal represented a yield of 16 per cent of the theoretical amount.

Recovery of Acetals from Anhydrous Alkaline Solutions

The acetals listed in Table I were dissolved in anhydrous alcoholic sodium hydroxide and also in a few cases in sodium alcoholate solutions and were kept in sealed glass tubes maintained at a constant temperature for various periods of time. After this treatment, dry carbon dioxide gas was bubbled rapidly through the cooled solutions until no further precipitation of sodium carbonate occurred. The salt was removed by rapid filtration in a closed, moisture-free system and the solvent was evaporated from the filtrate at not more than 50° under reduced pressure. The acetals were recovered as quantitatively as possible, either by crystallization from ether-petroleum ether in the case of the solid acetals, or by distillation in the case of the liquid acetals. The alkoxyl content of the recovered material was used to confirm its identity with the original and also to determine purity. In some cases the melting point only was determined. The data obtained are recorded in Tables III and IV.

Hydrogenations of Vanillin Dimethyl Acetal (see Table V)

(a) In 0.1 N anhydrous methanolic sodium hydroxide over Raney nickel

Freshly prepared vanillin dimethyl acetal, 13.5 g. (0.0682 mole,, was dissolved in 68.2 ml. of an 0.1 N solution of sodium hydroxide in anhydrous methanol (0.0682 mole of sodium hydroxide) contained in a glass liner for a 500 ml. Parr Hydrogenation bomb. Raney nickel, 3.0 g. (weighed wet) was added and the liner was immediately capped and placed in the bomb. The latter was closed, flushed three times with hydrogen at 500-600 p.s.i. then charged with hydrogen to a pressure of 2300 p.s.i. The shaker was started and the bomb was heated at a rate of approximately 4° per minute. Absorption of hydrogen started at approximately 125° and the temperature was subsequently held at 130° (±1°) until the absorption was complete (one hour). The total absorption was approximately 0.30 mole or 4.4 moles per mole of acetal. Heating and shaking were discontinued and the bomb was quenched in cold water. The pressure was released when the bomb had cooled to room temperature and the contents were removed and filtered through sintered glass. A quantity of pale brown resinous material remained mixed with the catalyst on the filter. The resin was separated from the latter by washing with cold water on a filter paper and, after drying, weighed 0.50 g. Dry carbon dioxide was bubbled rapidly through the pale yellow methanol filtrate for four hours after which time the liquid was concentrated under reduced pressure. The flocculent pale brown residue, 11.4 g., was extracted with three 35 ml. portions of ether and this extract was concentrated to 4.40 g. of a colourless oil. The latter was distilled under reduced pressure to yield two rather indefinite fractions exhibiting phenolic reactions.

TABLE VIII

DISTILLATION OF ETHER-SOLUBLE PRODUCT FROM HYDROGENATION (a)

Fraction	b.p. °C	n_D^{25}	CH_3O per cent	Appearance	Weight g.
1	135-175°/0.1 mm.	1.5111	25.1	fluid white oil	0.70
2	175-300°/0.1 mm.	1.5865	-	yellow tacky resin	1.00
Still residue	-	-,	-	charred	2.20

The bulky resinous ether-extracted material was slightly soluble in hot water but much more soluble in cold aqueous 0.05 N sodium hydroxide, from which it was reprecipitated by acidification with 0.05 N hydrochloric acid. The reprecipitated material, after washing with cold water, weighed 4.50 g. and was considerably lighter in colour than the crude material. It softened at 35-45° and resolidified on cooling to a brittle pale brown glass.

Anal. Calcd. for vanillyl creosol ($C_{16}H_{18}O_4$) (64): CH_3O, 22.6

Found: CH_3O, 21.7, 21.5

To summarize, 13.5 g. of vanillin acetal on hydrogenation yielded 5.0 g. of a brown resin and 4.4 g. of ether solubles. The former gave a total of 1.70 g. of volatile products and left 2.20 g. as a charred residue when vacuum distilled. These phenolic condensation and hydrogenolysis products were not investigated further.

(b) In anhydrous methanol over Raney nickel in the presence of n-heptylamine

Vanillin dimethyl acetal was hydrogenated in anhydrous methanol as already described. However, a small quantity of n-heptylamine was used as an alkaline reagent in the present case instead of sodium hydroxide. Two hydrogenations (A and B) were carried out at different temperatures with an initial pressure of 2000 p.s.i. of hydrogen. The conditions and quantities are recorded in Table IX.

TABLE IX

HYDROGENATIONS OF VANILLIN DIMETHYL ACETAL IN METHANOL OVER RANEY NICKEL

Hydrogenation	Acetal g. moles	Methanol ml.	Raney nickel g(wet)	n-heptylamine g.	Approx. initial absn. temp.	Temp °C	Time (min)	Total absn. moles per mole
A	15.8 0.080	119	3.0	0.31	100°	115-120°	30	2.8
B	18.9 0.095	120	3.8	1.20	60°	100°	90	2.1

In both cases the methanol solution, after removal of the catalyst, was water white and concentration at a maximum temp. of 60°/20 mm. yielded a pale yellow oil. The crude products were fractionated by distillation through a 3-inch

Vigreux-type column under reduced pressure and similar fractions were obtained in each case. The results are recorded in Tables X and XI.

TABLE X

FRACTIONAL DISTILLATION OF CRUDE OIL FROM HYDROGENATION (b) A.

Fraction No.	1	2	3	4
b.p. °C	55-60°/0.15 mm.	60-61°/0.15 mm.	65-85°/0.14 mm.	83-85°/0.13 mm.
Bath Temp.	83°	84-93°	97-115°	115-135°
n_D^{25}	(n_D^{40} 1.5260)	1.5346	1.5360	1.5380
CH_3O, per cent	20.6	23.0	34.2	35.0
weight, g.	1.5	3.6	1.2	3.7
appearance	-white needles in colourless oil-		-colourless oils-	
soly. hot water	Yes	Yes	No	No

Initial weight of crude oil	11.9
Total weight of distillates	10.0
Still residue	0.9
Losses	1.0 g.

All of the fractions from the distillations were phenolic in character. In order to identify the main products, fractions A-2, B-2, A-4 and B-3 were individually treated in the following manner.

TABLE XI

FRACTIONAL DISTILLATION OF CRUDE OIL FROM HYDROGENATION (b) B

Fraction No.	1	2	3	4
b.p. °C	50-52°/0.05 mm.	51-77°/0.02 mm.	76-77°/0.01 mm.	78°/0.01 mm.
Bath Temp.	81-90°	92-120°	120-160°	160-180°
n_D^{25}	-	1.5350	1.5369	1.5280
CH_3O, per cent	20.3	23.5	34.2	-
weight, g.	2.6	4.0	4.1	0.3
appearance	-white needles in colourless oil-		-colourless oils-	
soly. hot water	Yes	Yes	No	No

Initial weight of crude oil	13.8
Total weight of distillates	11.0
Still residue	0.8
losses	2.0 g.

Identification of Fractions A-2 and B-2:- The pasty mass was transferred to a small funnel containing a glass nail and filter paper and the crystalline portion was relieved of as much of the adhering oil as possible by applying suction for three hours. The crystals were then removed from the filter and pressed between filter papers. Two recrystallizations from benzene yielded white needles, m.p. 114-115°. A mixed melting point with an authentic sample of vanillyl alcohol, m.p. 115° (98) was not depressed. The product, like vanillyl alcohol, gave a brilliant red colouration on heating with concentrated sulfuric acid (99).

The oily filtrate, assumed to be impure creosol, XLIII, (mol. wt. 138) was dissolved in approximately ten times its volume of dry pyridine and treated with 1.1 molar equivalents of 3,5-dinitrobenzoyl chloride to convert it to the dinitrobenzoate by the method of Phillips and Keenan (100). The reactants were heated under reflux for one hour, cooled, and poured into cold 5 per cent sulfuric acid solution from which the crude ester precipitated. The solid material was taken up in ether, washed with water, 2 per cent sodium hydroxide solution, and finally again with water. The ether solution was evaporated and the crystalline residue was recrystallized twice from ethanol. White crystals were obtained, m.p. 168-169°. A mixed melting point with an authentic sample of creosol 3,5-dinitrobenzoate was not depressed. The reported melting point is 170.6° (100). The yields of vanillyl alcohol and creosol 3,5-dinitrobenzoate obtained from fractions A-2 and B-2 are listed in Table XII.

TABLE XII

YIELDS OF VANILLYL ALCOHOL AND CREOSOL 3,5-DINITROBENZOATE FROM FRACTIONS A-2 AND B-2

Fraction	Weight g.	Weights of crude crystals and filtrate g.	Pure Vanillyl Alcohol g.	Pure Creosol dinitrobenzoate g.
A-2	3.6	Crystals 1.8	0.3	
		Filtrate 1.6		1.5
B-2	4.0	Crystals 1.3	0.2	
		Filtrate 2.6		2.0

Identification of Fractions A-4 and B-3:- Fractions A-4 and B-3 (Tables X and XI) had very similar characteristics and represented the bulk of the highest boiling products in each case. For these reasons they were assumed to be similar and were treated in the following manner. Fraction A-4, 2.0 g., was washed with 2.0 ml. of water, redistilled and analysed. The main fraction consisted of 1.2 g., b.p. 81-82°/0.06 mm., n_D^{25} 1.5387.

Anal.

Calcd. for creosol, $C_8H_{10}O_3$: C, 69.6; H, 7.25; CH_3O, 22.5.

vanillyl alcohol, $C_8H_{10}O_4$: C, 62.3; H, 6.50; CH_3O, 20.1.

4-hydroxy-3-methoxybenzylmethyl ether $C_9H_{12}O_3$: C, 64.2; H, 7.14; CH_3O, 36.9.

Found: C, 63.5, 63.6; H, 7.23, 7.13; CH_3O, 35.2, 35.4.

Fraction A-4 redistilled, and fraction B-3 were accordingly assumed to consist mainly of 4-hydroxy-3-methoxybenzylmethyl ether (mol. wt. 168), XLI, and were separately converted to the 3,5-dinitrobenzoyl derivative with 1.1 molar equivalents of 3,5-dinitrobenzoyl chloride in pyridine by the method already described. The crystalline product in each case, after three recrystallizations from 95 per cent ethanol, consisted of white needles, m.p. 115.5-116.5°. A mixed melting point was not depressed.

Anal.

Calcd. for $C_{16}H_{14}N_2O_8$ (mol. wt. 362):
C, 53.04; H, 3.87; N, 7.73; CH_3O, 17.1.

Found: C, 53.0, 53.1; H, 3.92, 4.00; N (micro-Kjeldahl), 7.65, 7.70; CH_3O, 16.9, 17.0.

The yields of benzylmethyl ether dinitrobenzoate are recorded in Table XIII.

The yields of methyl ether in column 5, Table XIII, were calculated on the basis of pure dinitrobenzoate actually isolated. These figures could not accurately represent the amount of methyl ether originally present in the products because of the inefficiency of the distillations, benzoylations and recrystallizations. The same statement holds with regard to the yields of vanilly alcohol and creosol. The methods used were considered satisfactory in that they served to identify the three major products of the reaction.

TABLE XIII

YIELDS OF METHYL ETHER DINITROBENZOATE FROM FRACTIONS A-4 AND B-3

Fraction	Weight used for derivative g.	Dinitrobenzoate m.p. 115.5-116.5° g.	Yield of ester Calcd. on weight of crude ether, per cent	Yield of methyl ether from acetal, per cent.
A-4 (washed and redistilled)	1.00	1.20	55	9
B-3	4.10	4.02	46	13

(c) <u>In anhydrous dioxane over Raney nickel in the presence of n-heptylamine</u>

Vanillin dimethyl acetal, 15.3 g. (0.077 mole), was hydrogenated in 100 ml. of dioxane containing 0.30 g. of n-heptylamine and 3.0 g. Raney nickel at an initial pressure of 2000 p.s.i. The bomb temperature was raised rapidly (7-8° per min.) until absorption of hydrogen began at approximately 125°. The temperature was subsequently maintained at 135°(±2°) for thirty minutes during which time the absorption rate was very low and the total absorption was approximately 0.07 mole or 0.9 mole per mole of acetal. The bomb was quenched and the products removed, filtered and concentrated under reduced pressure as before. The viscous oily residue, 15.1 g., darkened gradually on standing in a sealed flask. Its odour resembled that of vanillin dimethyl acetal. The crude oil was distilled under reduced pressure and yielded one fraction, a pale brown oil, 3.4 g., n_D^{25} 1.5275, b.p. 124-127°/0.03 mm. (bath 165-190°) strongly resembling the original acetal, n_D^{25} 1.5250. Substantial decomposition occurred during the distillation and the still residue consisted of charred solid material.

A sample of distillate yielded red crystals on treatment with 2,4-dinitrophenyl hydrazine and hydrochloric acid. The solid, after recrystallization from acetic acid, melted at 267-268°. A mixed melting point with vanillin 2,4-dinitrophenyl hydrazone, prepared by the same method (101), was not depressed.

(d) <u>In anhydrous dioxane over Raney nickel in the presence of n-heptylamine</u>

Vanillin dimethyl acetal, 22.3 g. (0.11 mole), was hydrogenated in 100 ml. of dioxane containing 0.45 g. of n-heptylamine (2 per cent of the acetal weight) and 4.5 g. of Raney nickel at an initial pressure of 2000 p.s.i. at 20°.

The temperature was raised rapidly (9-10° per min.) until absorption started at approximately 130°. The rate of heating was decreased and the temperature was raised more slowly (2° per min.) but at no point was there any sharp increase in the rate of absorption. The bomb was finally held at 195-200° for forty five minutes. The absorption rate was very low at the end of this period and the total absorption was approximately 0.31 moles or 2.8 moles per mole of acetal. The bomb was quenched and the contents removed, filtered and distilled after removal of the solvent as before. The products obtained in the distillation are listed in Table XIV. All of the products were phenolic and strongly resembling vanillyl alcohol fractions A-2, B-2 of run (b). Fractions 1 and 2 were tested with a few drops of concentrated sulfuric acid and heated. Both gave the brilliant red colouration characteristic of vanillyl alcohol. They were not examined further, being assumed to consist of vanillyl alcohol, creosol and some dioxane. A portion, 2.0 g. of fraction 3 was treated with dinitrobenzoyl chloride as before and yielded the same dinitrobenzoate, 2.30 g., m.p. 115.5-116.5°, obtained previously (run (b) p.102). A mixed melting point was not depressed. A yield of benzylmethyl ether, XLI, was therefore 7.5 per cent based on the amount of dinitrobenzoate isolated.

TABLE XIV

DISTILLATION OF CRUDE PRODUCT FROM HYDROGENATION (d)

Fraction No.	1	2	3
b.p. °C	90-125°/19 mm.	125-145°/19 mm.	145-150°/19 mm.
Bath Temp.	125-140°	140-165°	165-180°
n_D^{25}	1.5178	1.5208	1.5293
CH_3O, per cent	22.8	-	34.4
weight, g.	8.7	2.8	2.6
appearance		-colourless oils-	
soly. hot water	Yes	Yes	No

Initial weight of crude oil	17.7
Total weight of distillates	14.1
Still residue	1.2
Losses	2.4 g.

(e) <u>In anhydrous methanol over a nickel kieselguhr catalyst in the presence of n-heptylamine</u>

Vanillin dimethyl acetal, 18.6 g. (0.094 mole), was hydrogenated in 120 ml. of anhydrous methanol containing 0.20 g. of n-heptylamine (approximately 1 per cent of the acetal weight) and 2.0 g. of nickel kieselguhr catalyst at an initial pressure of 1400 p.s.i. The temperature of the bomb was rasied rapidly to 195° over fifty three minutes but practically no absorption of hydrogen occurred. After holding the temperature at 195° for an additional twenty minutes, during which time only slight absorption occurred, the bomb was cooled rapidly and the contents removed, filtered and concentrated as before. The overall absorption was 0.10 mole or 1.1 mole per mole of acetal. The viscous white oil, 16.9 g., resembled the acetal. It rapidly became yellow in a sealed flask after removal of the solvent. Distillation yielded one fraction only, of impure acetal, 4.5 g., b.p. 125-129°/0.03 mm. (bath 170-200°), n_D^{25} 1.5265, and a large quantity of dark, resinous still residue.

Anal.

Calcd. for vanillin dimethyl acetal ($C_{10}H_{14}O_4$): CH_3O, 47.0

Found: 43.1

A sample of distillate, treated with 2,4-dinitrophenyl hydrazine with hydrochloric acid as before, run (c), yielded red crystals which, after recrystallization from acetic acid, melted at 267-268°. A mixed melting point with an authentic sample of vanillin 2,4-dinitrophenylhydrazone was not depressed.

(f) In anhydrous dioxane over 2 per cent palladized strontium carbonate

Vanillin dimethyl acetal, 15.5 g. (0.078 mole), was hydrogenated in 100 ml. of dioxane over 7.0 g. of 2 per cent palladized strontium carbonate catalyst at an initial pressure of 2000 p.s.i. The temperature of the bomb was raised rapidly (8° per min.) and absorption of hydrogen started at approximately 140° but was very slow. The temperature was raised to 155° at a lower rate (0.5-1° per min.) and held at this temperature for fifteen minutes after which time no more absorption occurred. The total absorption was approximately 0.22 mole. or 2.8 moles per mole of acetal. The bomb was cooled and the contents removed, filtered, concentrated and distilled as before. The products were similar to those obtained over Raney nickel (see runs (b), (d)).

TABLE XV

DISTILLATION OF CRUDE PRODUCT FROM HYDROGENATION (f)

Fraction	1	2	3
B.p. °C	53-55°/0.06 mm.	58-76°/0.03 mm.	93-95°/0.05 mm.
Bath Temp.	85-95°	95-125°	125-145°
n_D^{25}	1.5180	1.4990	1.5296
CH_3O, per cent	23.0	-	34.9
weight, g.	6.1	2.6	3.0
appearance		-colourless oils-	

Weight of crude oil	13.1
Total weight of distilates	11.7
Still Residue	0.4
Losses	1.0 g.

Fractions 1 and 2 were phenolic and gave a brilliant red colouration with sulfuric acid as before. A portion, 2.0 g., of fraction 3 yielded 2.05 g. of the 3,5-dinitrobenzoate derivative, m.p. 115.5-116.5°. A mixed melting point with an authentic sample of 4-hydroxy-3-methoxybenzylmethylether 3,5-dinitrobenzoate was not depressed. The yield of methylether from the acetal was 11 per cent based on the amount of dinitrobenzoate isolated.

Hydrogenation of Vanillin

A control hydrogenation of vanillin was made duplicating as closely as possible the conditions of hydrogenation (c) of vanillin dimethyl acetal.

Vanillin, 11.7 g. (0.077 mole) was hydrogenated in 100 ml. of dioxane containing 0.30 g. of n-heptylamine and 3.0 g. of Raney nickel at an initial pressure of 2000 p.s.i. The bomb temperature was raised rapidly (7-8° per min.) to 135° and held at that temperature for thirty minutes. Absorption had started at approximately 100° but the rate increased rapidly with rising temperature. Although it appeared complete after six minutes at 135°, this temperature was maintained for the same length of time as in (c). The total absorption was 0.10 mole or 1.3 moles per mole of vanillin.

The mixture was removed from the bomb, filtered and concentrated as before. The white crystalline residue (12.0 g.)

was recrystallized from benzene and large, white needles, 10.8 g., m.p. 113-115°, were obtained. One additional recrystallization raised the melting point to 114.5-115° A mixed melting point with an authentic sample of vanillyl alcohol, m.p. 115° (98) was not depressed. The yield was therefore 91 per cent of the theoretical amount.

Trial Hydrogenations with Palladized Strontium Carbonate Catalyst

Hydrogenation of ethyl p-hydroxybenzoate, XXI, to trans-4-hydroxy-1-carbethoxycyclohexane, XXII

Ethyl p-hydroxybenzoate, 17.9 g. (0.108 mole), m.p. 115-116°, was hydrogenated in 35.8 ml. of purified dioxane with 6.0 g. of 2 per cent palladized strontium carbonate catalyst according to the method of Martin and Robinson (43). The reaction was carried out in a Parr 400 ml. stainless steel bomb without a liner.

Hydrogen absorption started at approximately 140° but was not rapid at this temperature. At 180-185° the reaction rate increased and the absorption was substantially complete (2.78 moles per mole of starting material) after one hour. The data for the hydrogen absorption at 180-185° for a typical experiment are listed in Table XVI (see also Fig. 2). Zero time was taken as the moment the bomb reached 180°.

The bomb was quenched in cold water and the contents removed. The catalyst was removed by filtration through a sintered glass filter and was washed with 10 ml. of ether. The combined filtrate and washings were concentrated under reduced pressure and the colourless, oily residue (18.5 g.) was distilled. The distillate consisted of one fraction, 15.5 g. of a water white non-phenolic mobile liquid, b.p. 175-180°/33 mm., n_D^{25} 1.4610-1.4632, having a pleasant fruit-like odour. The still residue, 1.90 g., was phenolic in nature but was not examined further. It was assumed to be crude, unreduced ethyl p-hydroxybenzoate.

TABLE XVI (See Fig. 2)

ABSORPTION OF HYDROGEN BY ETHYL p-HYDROXYBENZOATE(a)

Time (minutes)	Hydrogen Absorption (moles per mole of reactant)
0	1.11
3	1.58
5	1.94
10	2.31
31	2.59
66	2.78 (93% of 3.0)

(a) At 180-185°, over palladized strontium carbonate and with about 2000 p.s.i. initial hydrogen pressure.

The yield of crude trans-4-hydroxy-1-carbethoxycyclohexane, XXII, was 84 per cent of the theoretical amount. It was not analysed but its refractive index (n_D^{25} 1.4626) corresponded closely with the reported value (43), 1.463.

The crude ester (15.5 g.) was hydrolysed by heating under reflux for three hours with 1.1 molar equivalents of 10 per cent aqueous potassium hydroxide. At the end of this time the solution was cooled and the alkali was neutralized with a slight excess of 3 N hydrochloric acid. The acidic aqueous solution was saturated with ammonium sulfate and extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, yielded a crystalline residue (m.p. 115-118°) which was dissolved in a minimum of hot ethanol. This solution slowly deposited crystals of trans-4-hydroxycyclohexane-1-carboxylic acid after standing overnight. The total yield, consisting of several crops of recrystallized material, amounted to 11.0 g., or 85 per cent of the theoretical amount, m.p. 120-121°. The melting point reported for the trans compound is 120-121° and 152° for the cis isomer (102).

Hydrogenation of Pyrogallol

The 400 ml. Parr bomb contained 33.3 g. (0.264 moles) of pyrogallol (Fisher, C.P.), 210 ml. of anhydrous dioxane freshly distilled over sodium and 12.0 g. of 2 per cent palladized strontium carbonate catalyst. After admitting hydrogen to a pressure of 2400 p.s.i, the temperature was raised as rapidly as possible to 130° at which point some absorption of hydrogen had already taken place. The temperature was carefully maintained at 130-135° until the absorption reached the theoretical level of 0.79 moles.

TABLE XVII (See Fig. 2)

ABSORPTION OF HYDROGEN BY PYROGALLOL[a]

Time (minutes)	Moles of Hydrogen per mole of pyrogallol
0	0.11
3	0.30
6	0.49
11	0.72
16	0.91
19	0.99
29	1.40
38	1.70
46	1.92
56	2.12
64	2.31
104	2.69
121	2.85
141	2.91
147	2.95

[a] At 130-135°, over palladized strontium carbonate and with 2400 p.s.i. initial pressure of hydrogen.

It was found that the rate decresed to an almost imperceptible value at this stage and the heating and shaking were discontinued.

The hydrogenation mixture contained a large quantity of white crystalline material mixed with the catalyst. This solid mixture was recovered by filtration, shaken with 125 ml. of water and filtered to remove the catalyst, and the filtrate was extracted with four 50 ml. portions of stock ether prior to concentration under reduced pressure. A white micro-crystalline solid, 17.8 g., resulted which, after two recrystallizations, once from ethanol and once from acetone, gave 15.2 g. of cis-cis-cis or γ-pyrogallitol, m.p. 146-147°. The ether extract, after evaporation to dryness, yielded 1.0 g. of a crystalline material. One recrystallization from ethanol yielded an additional 0.4 g. of γ-pyrogallitol, m.p. 146-148°.

The original dioxane filtrate was concentrated under reduced pressure to a pale yellow, oily residue which was diluted with 15 ml. of anhydrous ethanol. After standing for twenty four hours in the cold, the solution deposited 2.4 g. of crystals. One additional recrystallization from ethanol yielded another 2.0 g. of γ-pyrogallitol, m.p. 146-147°.

The ethanolic mother liquors from the latter two recrystallizations were concentrated and the oily residue, which gave a positive phenolic reaction with ferric chloride, was distilled under reduced pressure. The single fraction obtained, 12.4 g. of a pale yellow oil, b.p. 125-130°/0.02 mm.

(bath 160-180°) was also partly phenolic. After the latter constituent had been extracted from an aqueous solution, 50 ml., by ether, the remainder was recovered as a semi-crystalline mass, weight 9.4 g. Repeated recrystallization of this non-phenolic fraction from acetone and ethanol failed to yield a product with a sharp melting point (successive melting points were: 125-128°, 126-129°, 126-129°). The reported (74) melting points for the pyrogallitols are: α, 108°; β, 124°; γ, 148°.

The total yield of γ-pyrogallitol was 17.6 g., m.p. above 146°. This was a yield of 50 per cent of the theoretical amount calculated on the original weight of pyrogallol hydrogenated (33.3 g.). The residual 9.4 g., almost certainly a mixture of cis-trans-cis, or α-pyrogallitol, and cis-cis-trans, or β-pyrogallitol, raised the total recovery to 75 per cent of theory. Christian (39) studied the tedious separation of similar mixtures in detail.

PREPARATION AND STRUCTURE OF HEXAHYDROGALLIC ACID

Preparation of ethyl gallate

A solution of 225.6 g. of gallic acid monohydrate (General Chemical Co.), (1.20 moles), in 1200 ml. (950 g., 20.7 moles) of stock anhydrous ethanol containing 45 ml. (0.81 mole) of concentrated sulfuric acid was heated under reflux for three and one half hours. The dark brown liquid was transferred to a two-litre Claisen flask and the solvent was removed as completely as possible on the steam bath under reduced pressure; the residue, a pale brown cake, being redissolved in 2 litres of stock ether. Acidic material was neutralized by the cautious addition, with stirring, of an equivalent quantity (140 g.) of sodium bicarbonate in a saturated aqueous solution. The washed ether layer was separated and dried for several hours over anhydrous magnesium sulfate. Filtration and removal of the solvent then yielded a hard white cake of the crude product which was taken up in approximately 400 ml. of stock anhydrous ethanol. It was found convenient to carry out the next step with approximately 80 ml. batches of the ethanolic solution. The 80 ml. was first diluted to 1500 ml. by addition of benzene. The solution was heated to the boiling point on the steam bath, treated with decolourizing charcoal, cooled by about 10°, and filtered. The filtrate was transferred to a two-litre distilling flask and subjected to an azeotropic distillation to remove a large portion of the ethanol, and thereby to cause the product to come out of solution as a flocculent white mass which formed a dense white slurry in the distilling flask. This precipitation occurred quite suddenly after the collection of 500-600 ml. of distillate. At this point heating was stopped and the mixture was allowed to cool slowly to 10°, the product was collected on a Büchner funnel and the total yield after drying was 155-160 g., or 65-68 per cent of the theoretical amount. Ethyl gallate was a white powder, m.p. (after sintering at

150°) 158-160°. This product was found to be satisfactory for hydrogenation purposes.

Additional small amounts of less pure ester were recovered from the mother liquors but it was necessary to reprecipitate them two or three times before they were as pure as the first crop. The total yield was raised to 70 per cent by including these crops. However, in most cases the mother liquors were saved for solvent recovery and the tedious purification of the secondary crops was not carried out. Benzene alone could be used for the recrystallization of ethyl gallate but its low solvent capacity made it impractical for the large quantities of ester desired.

Hydrogenation of Ethyl Gallate

Ethyl gallate was hydrogenated in anhydrous dioxane with 2 per cent palladized strontium carbonate catalyst, the relative quantities used in six different hydrogenations being recorded in Table XVIII. The reactions in all cases were carried out in a 400 ml. stainless steel Parr Hydrogenation bomb. The initial hydrogen pressure at 20° was 2000-2300 p.s.i.

As soon as the bomb had been closed and charged with hydrogen, the shaking apparatus was set in motion, and the temperature was raised as rapidly as possible up to the absorption range (155° approximately). In some cases the absorption was less rapid and the temperature was raised an additional 10-15° to increase the rate. When the temperature

TABLE XVIII

SUMMARY OF ETHYL GALLATE HYDROGENATION CONDITIONS

No.	Ethyl Gallate g.	Catalyst g.	Dioxane ml.	Time from 20° to temp. range min.	Temp. range °C and Time, min.	Total absorp. moles H_2 per mole (b)	Per cent absorp (b)	Per cent Gallic ester reduced(c (by recovery)
1(a)	28.2	10.0	93	43	145-160° 25	2.36	78	75
2	35.0	12.0	210	45	155-160° 90	2.89	96	79
3	35.0	12.0	210	39	165° 109	2.27	76	60
4	35.0	15.0	210	88	165-170° 94	1.88	63	54
5	45.0	13.0	210	35	155-160° 65	2.70	90	81
6	45.0	13.0	210	38	155-160° 80	2.78	93	79

(a) The hydrogen absorption data were not plotted in this instance because the temperature range was too broad.

(b) See Table XIX, Fig. 3

(c) See Table VII

TABLE XIX (See Fig.3)

ETHYL GALLATE HYDROGEN ABSORPTION DATA

Hydrogenation No.	Time (minutes)	Moles H_2 per mole ethyl gallate
2 (155-160°)	0	0.75
	17	1.65
	23	1.87
	28	2.10
	38	2.33
	46	2.44
	53	2.56
	69	2.78
	86	2.89
	90	2.89 (96% of 3.00)
3 (165°)	0	1.02
	47	1.82
	66	2.05
	89	2.16
	109	2.27 (76% of 3.00)
4 (165-170°)	0	0.68
	31	1.31
	49	1.48
	72	1.70
	88	1.82
	94	1.88 (63% of 3.00)
5 (155-160°)	0	0.18
	5	0.53
	22	1.50
	42	2.26
	55	2.52
	60	2.62
	70	2.70 (90% of 3.00)
6 (155-160°)	0	0.53
	10	1.05
	26	1.75
	35	2.07
	51	2.50
	62	2.68
	71	2.72
	80	2.78 (93% of 3.00)

at which absorption occurred reasonably quickly (0.05 moles per min.) had been reached, the heater controls were manipulated to maintain temperature control within as narrow a range (±2.5°) as possible. After sixty to ninety minutes the absorption rate was low and shaking was discontinued even if the hydrogen absorption figure was below the theoretical value, as occasionally happened since the catalyst used is liable to sudden inactivation (43). This precaution was necessary in order to reduce contamination of the primary, by secondary products. After quenching the bomb in cold water, the dioxane solution was removed and filtered through sintered glass to remove the catalyst. The filtrate was a water white solution. The catalyst was washed in the filter with 15-20 ml. of acetone to remove a small quantity of product which had crystallized from the dioxane solution.

The filtrate and washings were combined and the solvents were removed as completely as possible under reduced pressure on a steam bath. The residue, a viscous colourless oil, became partly crystalline on standing, and corresponded closely in weight with that of the ethyl gallate used. The product was dissolved with slight warming in sufficient water to make the solution 25 per cent by weight (e.g. 35 g. in 105 ml. water) and the solution was extracted with ether until the extracts gave a negative phenolic test with a ferric chloride solution. The ether solution was dried over magnesium sulfate for several hours, then concentrated to give a white crystalline residue, consisting substantially of unreduced ethyl gallate. This material was recrystallized from ethanol-benzene as already described and the weights of pure recovered ethyl gallate are noted in column 8, Table VII. Per cent conversions (column 10) were based on the difference between the weight of ethyl gallate initially used and the weight recovered.

The ether-extracted aqueous solution was concentrated under reduced pressure on the steam bath to a white or grayish-white crystalline material, which was thoroughly dried under reduced pressure for several hours (weight, column 4, Table VII). This fraction, which consisted of the reduced ethyl gallate products, was taken up under reflux in approximately 10 per cent more dry acetone than the minimum necessary to dissolve it all. After a rapid filtration, and gradual cooling to 15°, a voluminous crop of thin crystals was obtained. In most cases this first crop melted at 145-147°. One recrystallization from dry acetone yielded larger flake-like white crystals, m.p. 146-147°.

Anal.

Calcd. for ethyl hexahydrogallate,
$C_9H_{16}O_5$ (mol. wt. 204): C, 52.94; H, 7.84; C_2H_5O, 22.0

Found: C, 52.9, 52.9; H, 7.84, 7.83; C_2H_5O, 21.8, 21.7

Samples, 18.56 mg. and 20.40 mg., consumed 24.28 ml. and 26.80 ml. of 0.00750 M periodate after two and a half hours. Calcd. for 2.0 moles of periodate per mole of ester, 24.27 ml.

and 26.67 ml.

A pure sample of the ester, 18.56 mg. (0.0000909 mole), was quantitatively oxidized at room temperature in 0.00750 M periodic acid solution buffered at pH 4.0. The course of the oxidation was followed using the method of Price and Knell (75), the data being listed in Table XX (See Fig. 4).

TABLE XX (See Fig. 4)

PERIODIC ACID CONSUMPTION OF ETHYL HEXAHYDROGALLATE[a]

Time (minutes)	IO_4 consumption (moles per mole of ester)
0	0
6	1.56
15	1.63
41	1.84
85	1.96
130	1.98
154	2.02

(a) At pH 4.0, room temperature, initially 0.00750 M in periodic acid and 0.000909 M ester.

In two such hydrogenations (1 and 2, Table VII) the product was isolated by fractional crystallization only. Many fractionations from acetone yielded only small additional crops of this isomer (m.p. 146-147°). After standing for several days some of the acetone mother liquors deposited crystals of a different compound, in some cases alone, and in others, together with the first product. This second compound (later found to be lactone, XLVI, derivable from the ester) occurred as hard, rod-like crystals which could be separated mechanically from the flake-like ester crystals. After two or three recrystallizations from ethanol this second product melted at 186-189°. Further purification did not alter the melting point. The yields varied and were low (Table VII). As noted later in the Experimental Section (p.131) this compound did not depress the melting point of a lactone obtained from the ester. The lactone isolated by crystallization only was oxidized with periodic acid at pH 4.0.

Anal.

Samples, 43.14 mg. and 40.20 mg., consumed 36.76 ml. and 34.57 ml. respectively of 0.00750 M periodate (buffered at pH 4). Calcd. for 1 mole of periodate per mole of γ-lactone (mol. wt. 158) 36.40 ml. and 34.71 ml.

Alkoxyl, Calcd. 0.0 Found: 0.0

In the remaining four hydrogenations the reduction products were isolated by combined physical and chemical methods and the total yield was substantially improved to about 40 per cent. In one case (No. 4) for no apparent reason the yield of ester isolated by crystallization alone was nearly double the usual value and the combined yields in this instance were 45 per cent.

The crude material in the last four hydrogenations was subjected to one recrystallization only. The first crop was recrystallized if necessary to raise the melting point to 145°. In one case some lactone was isolated as well (No. 3) but in the remaining ones no attempt was made to isolate this slowly crystallizing compound because the manipulation tended to cause reduction in overall yield by mechanical losses (No. 3). The combined mother liquors were concentrated and the residue dried thoroughly for the purpose of subjecting it to chemical treatment described in a later section.

In one case only, that of run No. 1, the crude dry, water soluble, ether-extracted product (18.5 g.) was analysed for alkoxyl and oxidized quantitatively with periodic acid at pH 4.0, room temperature, by the method of Price and Knell (75). The solution was initially 0.0075 M in periodic acid and contained 30.29 mg. of crude dry product per 100 ml. of solution. The oxidation data are tabulated in Table XXI.

Anal.

Alkoxyl (calcd. as per cent ethoxyl) Calcd. for ethyl hexahydrogallate: 22.0

Found: 17.9, 17.9

TABLE XXI (See Fig. 4)

PERIODIC ACID CONSUMPTION OF CRUDE REDUCED ETHYL GALLATE(a)

Time (minutes)	IO_4 consumption (Moles per 193 g. of product)
6	1.20
30	1.40
50	1.50
76	1.56
120	1.60
141	1.63
1110	1.69 (0.00875 moles per gram)

(a) In a 0.0075 M periodate solution buffered at pH 4.0 and containing initially 30.29 mg. of crude dry product per 100 ml. of solution at room temperature.

Saponification of Ethyl Hexahydrogallate, XLIV, to Hexahydrogallic Acid

Ethyl hexahydrogallate, 4.40 g., (0.0216 mole) m.p. 146-147°, was dissolved in 85 ml. of water to which barium hydroxide octahydrate, 6.80 g. (0.0216 mole, 100 per cent excess), was added. The mixture was shaken with warming to dissolve the base and was subsequently heated under gentle reflux in a nitrogen atmosphere for eighteen hours.

At the end of this period, dilute sulfuric acid exactly equivalent to the base (0.0216 mole) was added to the hot solution. The resulting mixture, which contained suspended barium sulfate, was digested at 80 to 90° for one hour, then filtered by gravity through a dense paper. The precipitate was washed with 10 ml. of water, the combined filtrate and washings were transferred to a Claisen flask and the water was removed under reduced pressure. The solid white product, after further drying for several hours under reduced pressure at 50 to 60°, was then dissolved in 38 ml. of boiling glacial acetic acid, filtered and cooled slowly to 15°. The first crop consisted of 2.30 g. of white microcrystals of hexahydrogallic acid, m.p. 198-200°. The mother liquor yielded a second crop after it had been concentrated and this crop, after one additional recrystallization amounted to 0.20 g., m.p. 197-199°. The total yield was 66 per cent of the theoretical amount.

A small sample of the first crop was recrystallized for analysis and melted at 199-200°.

Anal.

Calcd. for $C_7H_{12}O_5$ (mol. wt. 176): C, 47.72; H, 6.82.

Found: C, 47.4, 47.6; H, 6.75, 6.95.

Neutralization equivalent, Calcd. 176.0, Found: 175.2, 176.8.

Moles of periodic acid consumed per mole of product:

Calcd. 2.00; Found: 1.97, 1.98.

Condensation of Ethyl Hexahydrogallate, XLIV, with Acetone to Yield an Isopropylidene Lactone, XLVIII

Fischer's method (48) was used. Ethyl hexahydrogallate, 1.60 g., m.p. 146-147° (0.0078 mole) was dissolved in 40 ml. of pure, anhydrous acetone containing 3 per cent of dry hydrogen chloride by weight. The solution was kept in a glass-stoppered flask at room temperature for twenty four hours. The acid in the pale yellow liquid was then neutralized by shaking for thirty minutes with a slight excess (4.50 g.) of basic white lead ($2PbCO_3.Pb(OH)_2$). The solid material was removed by filtration and the filtrate was concentrated under reduced pressure to a white crystalline residue which was recrystallized from anhydrous ethanol. The first crop, thin platelike crystals, consisted of an isopropylidene lactone, XLVIII, 1.0 g., m.p. 170.5-171°. The mother liquor was worked up and yielded 0.30 g. of impure starting material, m.p. 145-147°. The yield, calculated on 1.60 g. ester, was therefore 65 per cent.

Anal.

Calcd. for $C_{10}H_{14}O_4$: C, 60.60; H, 7.07; Acetone, 29.3.
Found: C, 60.8, 60.5; H, 6.93, 7.25; Acetone, 29.0, 29.5.

This compound was found to undergo sublimation when heated to its melting point under reduced pressure (0.05 mm.). It was recoverable in almost quantitative amounts.

Condensation of Hexahydrogallic Acid with Acetone to Give an Isopropylidene Lactone, XLVIII

The experimental conditions used in this reaction were similar to the conditions applied to the condensation of ethyl hexahydrogallate with acetone.

Hexahydrogallic acid, 0.95 g., m.p. 199-200° (0.054 mole) was dissolved with continuous shaking and warming to 50° in 100 ml. of purified anhydrous acetone containing 5.3 per cent of dry hydrogen chloride by weight. The acid, unlike its more soluble ethyl ester, dissolved gradually over a period of about one hour. The colourless solution was left to stand in a glass-stoppered flask at room temperature for twenty four hours, after which time it had become pale yellow. The hydrochloric acid was neutralized by shaking for thirty minutes with a slight excess of basic white lead (21.4 g. in all). The solid material was removed by filtration, washed with a few millilitres of dry acetone and the solvent was removed from the combined filtrate and washings under reduced pressure. The white crystalline residue was recrystallized from a minimum of anhydrous ethanol and yielded the same isopropylidene lactone, XLVIII, obtained from the ethyl ester. The first crop was 0.60 g., m.p. 170.5-171°. Concentration of the mother liquor yielded a second crop, 0.15 g., m.p. 170-171°. The combined yield was 70 per cent of the theoretical amount. A mixed melting point with a sample of the isopropylidene lactone, obtained from the condensation of the ethyl ester with acetone, was not depressed.

Hydrolysis of the Isopropylidene Lactone of Hexahydrogallic Acid, XLVIII, to Lactone, XLVI

Following Fischer's method (48), isopropylidene hexahydrogallic lactone, 1.70 g., m.p. 170.5-171°, (0.0086 mole), was dissolved in 25 ml. of 0.1 N aqueous hydrochloric acid at 50° with shaking. After ten minutes the solid material had gone completely into solution and the mixture was maintained at 50° for an additional sixty minutes. The hydrochloric acid was then neutralized by agitation for fifteen minutes with approximately a 20 per cent excess of the theoretical amount of silver carbonate (0.42 g. in all). After filtration, the residue was washed with 5 ml. of warm water and the combined filtrate and washings were concentrated under reduced pressure on the steam bath. The voluminous white solid residue, when dried over night under reduced pressure, darkened to a light brown colour.

The crude product was extracted with five 10 ml. portions of boiling anhydrous ethanol and the combined extracts were filtered to remove the undissolved material. After concentration under reduced pressure to 10-12 ml. and gradual cooling, 0.80 g. of a lactone was obtained as small, well-formed crystals m.p. (after sintering at 178°) 186-189°. Further concentration yielded a second crop, 0.10 g. m.p. (sintered at 178°) 184-189°. Two additional recrystallizations of the first crop did not alter the melting point. The second crop yielded 0.08 g., m.p. (sintered at 178°) 185-189°, after one recrystallization from ethanol. The yield of material melting above 185° was 65 per cent of the theoretical amount. A mixed melting point with a sample from the mother liquors obtained from the hydrogenation of ethyl gallate (p.123) was not depressed.

Anal.

Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.33; Alkoxyl, 0.0

Found: C, 53.1, 53.3; H, 6.40, 6.36; Alkoxyl, 0.0

The lactone was oxidized at room temperature with periodic acid buffered at pH 4 by means of sodium acetate and sulfuric acid. The solution initially was 0.00273 M in the lactone, and 0.00700 M in periodic acid. The lactone consumed 0.996 mole of periodic acid per mole in thirty minutes, 1.01 moles per mole in seventy five minutes, and the value 1.01 was unchanged after four and a half hours. Calcd. for a γ-lactone: 1.00 mole; for a δ-lactone, 0.0 mole.

Partial Lactonization of Ethyl Hexahydrogallate

Ethyl hexahydrogallate, 2.0 g. (0.0098 mole), m.p. 146-147°, was dissolved in 150 ml. of pure dioxane and heated to 160-170° in the Parr bomb under hydrogen with no catalyst. After eight hours the bomb was cooled and the colourless solution was concentrated under reduced pressure. The white microcrystalline residue, 1.9 g., was dried thoroughly for several hours under reduced pressure at 60°. The melting point was broad, 120-157° approximately.

Anal.

Calcd. for ethyl hexahydrogallate, alkoxyl (as C_2H_5O): 22.0

Found: 13.1, 13.2

The crude material was recrystallized from acetone and yielded 0.80 g. of impure ester which, after one additional recrystallization from the same solvent, melted at 145-147°. The mother liquor from the first recrystallization of the ester was left to stand at 10°. After one week a small crop of crystals, 0.25 g., was obtained which, after recrystallization from ethanol, melted at 186-189°. A mixed melting point with an authentic sample of the γ-lactone, XLVI, previously obtained was not depressed.

Ammonolysis of the Isopropylidene Lactone, XLVIII, to an Isopropylidene Amide

Again following Fischer (51), anhydrous ethanol, 50 ml., was cooled to -10° in a 125 ml. suction flask and saturated with dry ammonia gas, the solution being protected from external moisture by means of calcium chloride drying tubes. The saturated solution was transferred to a 125 ml. glass-stoppered Erlenmeyer flask and was mixed with 1.90 (0.0096 mole) of isopropylidene lactone, m.p. 170.5-171°, obtained from the condensation of ethyl hexahydrogallate. with acetone. The glass stopper was wired firmly in position, the mixture was subjected to mechanical shaking at room temperature and, after about six hours, the solid had completely dissolved, forming a colourless solution. The solution was then allowed to stand for four days at room temperature. After evaporation at not more than 50° and under reduced pressure, the crude white crystalline residue (2.00 g.) was recrystallized from 30 ml. of boiling anhydrous ethanol. The first crop consisted of flat crystals, 1.10 g., m.p. 203-205° with evolution of ammonia. Concentration of the mother liquor and recrystallization of the second crop thus obtained yielded an additional 0.50 g., m.p. 204-205° (with decomp). The yield of isopropylidene trihydroxy cyclohexylcarboxamide calculated on these two quantities was 78 per cent of the theoretical amount. Further recrystallization of these fractions did not raise the melting points. When rapid heating was obtained by inserting the sample into the melting point bath at 190°, the melting point was raised to 205-207°.

Anal.

Calcd. for $C_{10}H_{17}NO_4$: C, 55.81; H, 7.91; N, 6.51.
Found: C, 55.7, 55.7; H, 7.7, 7.8.; N (micro Kjeldahl, 6.45, 6.46.

Condensation of Crude Hydrogenation Products with Acetone

The crude hydrogenation products of ethyl gallate which remained in the acetone and ethanol mother liquors after removal of the crystalline ethyl hexahydrogallate and some lactone (Table VII) yielded gray-coloured solid residues. Each residue was dried thoroughly under reduced pressure for several hours and was then dissolved in acetone containing about 3 per cent of dry hydrogen chloride. The condensations in every case yielded one crystalline product only, namely the isopropylidene dihydroxycyclohexanolide, XLVIII, (m.p. 170.5-171°) obtained in identical fashion from the pure ester and the pure acid as already described. The first crop was of high purity (m.p. 170-171°) and small second crops (5-10 per cent of the weight of the first crops) melted above 167°. One additional recrystallization of the second crops from ethanol gave a product m.p. 170-171°. The weights listed in Table VII consist of the combined yields of material melting at 170-171°.

The amounts obtained varied considerably in the different hydrogenations, but the combined per cent yield of ester, lactone and isopropylidene lactone (calculated as ester) was fairly constant at 40 per cent of theory.

The ethanolic mother liquors from the recrystallization of the acetonated residue from hydrogenation number 5 were concentrated to a brown-coloured viscous oil (12.5 g.) which was distilled under reduced pressure. One fraction only was obtained, 3.2 g., as a white crystalline solid which sublimed into the receiver at a bath temperature of 170-180°/ 0.04 mm. Recrystallization from ethanol yielded 2.1 g., of the isopropylidene lactone, XLVIII, m.p. 169-170°. The residue in the distilling flask was a dark gummy material, very soluble in water.

The isolation of the above lactone fraction, in addition to the previous isolation of the same lactone, XLVI, and of hexahydrogallic ester, XLIV, from the hydrogenation of ethyl gallate (run 5) raised the total recovery of crystalline material from 40 per cent (Table VII) to 47 per cent of theory.

Attempted Resolution of Hexahydrogallic Acid into Optical Isomers

(a) With brucine

Hexahydrogallic acid, 0.400 g. (0.0023 mole) was dissolved in 38 ml. of ethanol and brucine, 0.896 g. (0.0023 mole), was added. The alkaloid dissolved gradually when the mixture was gently warmed. The solution was filtered and allowed to cool to room temperature. Crystallization occurred after it was induced by scratching and the first crop consisted of 0.48 g. of white crystals. The mother liquor was concentrated by the removal of 14 ml. of solvent by distillation. During gradual cooling to room temperature, a second crop, 0.16 g., was obtained. A third crop, 0.20 g., separated in identical fashion after the removal of an additional 7 ml. of ethanol from the mother liquor. Concentration of the final mother liquor gave a residue, 0.43 g., which was recrystallized from ethanol and yielded a fourth crop, 0.35 g., of white crystals. The four crops were dried separately for several hours at 60° under reduced pressure and their rotations were determined in water using a one decimeter tube.

TABLE XXII

SPECIFIC ROTATIONS OF BRUCINE HEXAHYDROGALLATE FRACTIONS

Fraction No.	$[\alpha]_D^{20}$ in water	C
1	-22.1	2.0
2	-21.3	1.6
3	-20.2	2.0
4	-21.2	1.8

The experiment was repeated using identical quantities of the acid, brucine and solvent. Four crops of the salt of approximately equal weights were obtained in the same fashion. Each crop was treated in the following manner. The crystals (approximately 0.2 g.) were dissolved in 6 ml. of water and 0.3 ml. of concentrated ammonium hydroxide (0.004 mole approximately) was added. The precipitated alkaloid was removed by extraction of the aqueous solution with two 2 ml. portions of chloroform, and the extracted aqueous solution was diluted to exactly 10 ml. with water. The aqueous solutions, containing the ammonium salt of the acid, were individually examined in the polarimeter using a one decimeter tube. No rotation, beyond the limits of experimental error of the method (±2.5°), was observed in any of the four cases. Each sample was acidified with concentrated hydrochloric acid and re-examined. As before, no rotation was observed.

(b) With cinchonine

Hexahydrogallic acid, 0.400 g. (0.0023 mole), was added to 30 ml. of ethanol. Most of the acid dissolved when the solvent was boiled. To the boiling mixture 0.668 g. (0.0023 mole) of cinchonine was added and all of the solid material dissolved after boiling for a few more minutes. The solution was filtered and allowed to cool slowly. Scratching with a glass rod and cooling to 10° failed to induce crystallization. The solution was concentrated by distilling 12 ml. of solvent, and 15 ml. of dry acetone was added. Gradual cooling to 10° caused the appearance of 0.50 g. of long feather-like crystals. Two additional crops, 0.23 g. and 0.18 g. were obtained by further additions of acetone. The three crops were dried at 60° under reduced pressure for several hours and their rotations were determined in water using the same tube as before.

TABLE XXIII

SPECIFIC ROTATIONS OF CINCHONINE HEXAHYDROGALLATE FRACTIONS

Fraction No.	$[\alpha]_D^{20}$ in water	C
1	+124.8	2.0
2	+124.3	2.0
3	+124.5	1.8

No resolution had been effected.

(c) With strychnine

Hexahydrogallic acid, 0.400 g. (0.0023 mole), and strychnine, 0.760 g. (0.0023 mole) were dissolved in 60 ml. of boiling ethanol. The solution was filtered and allowed to cool slowly to room temperature. Crystallization occurred very slowly and, after standing overnight, a crop, 0.30 g. of large symmetrical crystals was obtained. After drying, the material melted at 273-276° with rapid heating. A mixed melting point with a sample of pure strychnine was not depressed. The crystals were dissolved in chloroform and examined in the polarimeter in a one decimeter tube.

Found: $[\alpha]_D^{20}$ in chloroform	-138.4 (C=2.0)
Reported for strychnine (103):	-137.7 (C=2.5) -140.7 (C=1.5)

The mother liquor deposited similar crystals after standing for several days but the experiment was not pursued, since the formation of strychnine hexahydrogallate was obviously incomplete.

SUMMARY

1. A study of the preparation and properties of acetals of hydroxybenzaldehydes revealed that the compounds were partially recoverable from anhydrous alkaline solutions nevertheless they were insufficiently stable under hydrogenation conditions to be suitable starting materials for the synthesis of hydroxylated cyclohexylaldehydes. Attempts to prepare an acetal of 3,4,5-trihydroxybenzaldehyde were unsuccessful. Vanillin dimethyl acetal, b.p. 97-100°/0.03 mm., vanillin diethyl acetal, b.p. 102-105°/0.01 mm., and protocatachualdehyde dimethyl acetal, m.p. 89.5-90°, were isolated and characterized for the first time, and they were found to behave like the few previously known phenolic acetals in being unstable to traces of moisture. Acetals of benzaldehydes containing methyl ether substituents were prepared for purposes of comparison of which veratraldehyde dimethyl acetal, b.p. 100-105°/0.04 mm., and trimethylgallaldehyde diethyl acetal, m.p. 26-29°, were prepared and characterized for the first time. The non-phenolic acetals were found to be stable to anhydrous or aqueous alkaline conditions as anticipated.

2. A recently developed catalyst, palladized strontium carbonate, was investigated to determine its suitability for the hydrogenation of polyphenolic aromatic nuclei.

Pyrogallol yielded 50 per cent of cis-cis-cis cyclohexane-1,2,3-triol and 25 per cent of mixed isomeric triols. Comparatively little hydrogenolysis of these susceptible compounds was shown to have occurred over the new catalyst which was therefore much superior to Raney nickel and other catalysts in the reduction of polyphenolic compounds.

3. Palladized strontium carbonate was subsequently used in the hydrogenation of ethyl gallate and this compound was successfully reduced for the first time to give the desired ethyl hexahydrogallates. The hydrogenation mixture was shown to contain a γ-lactone, m.p. 186-189°, derived from the major product, an ethyl hexahydrogallate isomer, m.p. 146-147°, either during the course of the reduction or during isolation of the products. A condensation with acetone permitted the isolation of the ester and related lactone as an isopropylidene lactone, m.p. 170.5-171°, which amounted to 47 per cent of the reduced material.

4. A number of reactions of the new ethyl hexahydrogallate isomer were investigated in an effort to establish the cis-trans disposition of the substituents. In addition to the γ-lactone and isopropylidene lactone, the free acid, m.p. 199-200°, and an isopropylidene carboxamide, m.p. 205-207°, were obtained from the ester.

The reactions indicated that the new acid was not dihydroshikimic acid, the only previously known isomeric hexahydrogallic acid, and that the configuration of the new compound was limited to cis-cis-cis- or cis-trans-trans-3,4,5-trihydroxycyclohexane-cis-1-carboxylic acid. The product has been made a readily accessible compound and is considered to be a suitable material for conversion to the corresponding 3,4,5-trihydroxycyclohexylaldehyde by well-known methods.

CLAIMS TO ORIGINAL RESEARCH

1. Published literature implies that acetals of phenolic aldehydes possess the unexpected property of being excessively unstable toward alkaline as well as acid hydrolysis. By using a modification of Claisen's condensation of an aldehyde with an orthoformic ester, it was found possible to prepare vanillin dimethyl acetal, b.p. 97-100°/0.03 mm., vanillin diethyl acetal, b.p. 102-105°/0.01 mm., and protocatachualdehyde dimethyl acetal, m.p. 89.5-90°, for the first time. These acetals swiftly hydrolysed when exposed to the acidity of the laboratory air, but could be recovered in variable yield from hot alkali, providing the latter was anhydrous.

2. The dimethyl acetal of vanillin survived fairly drastic conditions of high pressure hydrogenation at temperatures up to 195° provided an anhydrous non-acidic medium was employed. The still more drastic conditions required to hydrogenate the aromatic ring, however, could not be attained owing to prior hydrogenolysis of the acetal group. Hydrogenolysis yielded a new liquid compound with strong phenolic properties, 4-hydroxy-3-methoxybenzyl methyl ether, b.p. 81-82°/0.06 mm., which was characterized as the 3,5-dinitrobenzoate, m.p. 115.5-116.5°.

3. Only one reference to the use of a palladized strontium carbonate catalyst at an elevated temperature (160°) was found. Trial showed that this catalyst under such conditions was much superior to those formerly used for the hydrogenation of pyrogallol to the isomeric cis-trans cyclohexane-1,2,3-triols and is the first found to hydrogenate ethyl gallate to the isomeric ethyl hexahydrogallates successfully.

4. One of the six possible ethyl hexahydrogallates was isolated in pure crystalline condition as a new compound, m.p. 146-147°, as the free acid, m.p. 199-200°, as the γ-lactone, m.p. 186-189°, as an isopropylidene lactone, m.p. 170.5-171°, and as the isopropylidene carboxamide, m.p. 205-207°. Studies of the structural relationships existing between these compounds made it probable that the configuration of the acid was cis-cis-cis- or cis-trans-trans-3,4,5-trihydroxycyclohexane-cis-1-carboxylic acid. An improved method of separation showed one or other of these configurations to be the major product of the hydrogenation.

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