Reduction of Trimethyl Gallic Acid by Sodium and Isoamyl Alcohol

Spivack

THE REDUCTION OF TRIMETHYL GALLIC ACID

BY SODIUM AND ISOAMYL ALCOHOL

A Thesis

by

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

GENERAL INTRODUCTION

The research reported in this thesis on the chemical reduction of trimethyl gallic acid, (XLVI), is part of a larger project concerned with the nuclear hydrogenation of polyhydric phenols which is being carried out in the laboratories of the Division of Industrial and Cellulose Chemistry. Others (147, 148, 149) have worked on the catalytic hydrogenation of pyrogallol and gallic acid (XLV) and have successfully isolated some of the stereoisomers of the cyclohexane analogs of these aromatic compounds. the object of the present work is to study the chemical reduction of gallic acid (XLV) and trimethyl gallic acid (XLVI) by means of sodium and isoamyl alcohol.

Complex polyhydric phenols are more or less readily available from the lignin portion of hard or soft wood or from bark. In Canada, where large quantities of lignin and bark are available as waste products from the forest industries, the production of useful chemicals from these materials might become of considerable economic importance. The study of the chemistry of the simpler polyhydric phenols might, therefore, open up important ways in which lignin and bark could be utilized.

The presence of an abundant supply of hydro-electric power in this country makes possible an economical production of alkali metals, which can be used as chemical reducing agents

either alone or in amalgams. Furthermore, electrolytic reduction with high overvoltage cathodes (copper, lead, mercury, zinc, tin and cadmium) resembles reductions by chemical agents (1). The chemical reduction of the above polyhydric phenols, therefore, would indicate under what conditions electrolytic reduction of more complex naturally occurring phenols might be successful.

The nuclear reduction of these polyhydric phenols present problems which have held the attention of chemists for some time. Some of these problems are the mechanism of nuclear reduction, the structure of the reduced products, and the conditions under which hydrogenolysis of carbon-oxygen bonds could be minimized. It was one of the aims of this research, to determine under what conditions the reduction of the benzene ring of trimethyl gallic acid, (XLVI), could be accomplished while keeping hydrogenolysis of the bond between the ring carbon and the ether (or hydroxyl) oxygen at a minimum.

HISTORICAL INTRODUCTION

Chemical Reduction of the Benzenoid Nucleus

Chemical reducing agents include all the hydrogen liberating combinations such as sodium in alcohol, sodium in liquid ammonia, zinc and tin in neutral, acid or basic media, zinc, sodium, and aluminum amalgams, as well as soluble lower valency metal salts such as vanadous, chromous and titanous chlorides. As a matter of fact, however, most chemical reductions of the benzenoid nucleus have been carried out with the alkali metals (1).

The following generalizations may be made concerning the effectiveness of chemical reducing agents:

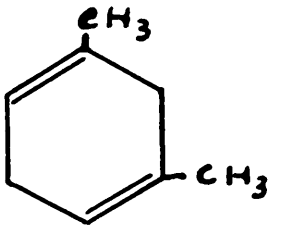
(1) Simple olefins are not reducible.

(2) The presence of an aryl, carboxyl or ethylene group conjugated with, or in some cases cumulated with, the unsaturation is essential for reduction to occur, although their presence does not make reduction certain.

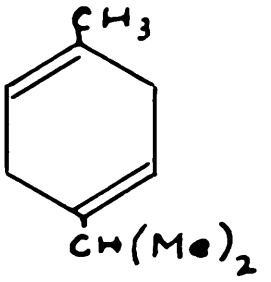
(3) The acetylenes are reduced by some reagents, especially by sodium in liquid ammonia. The products are generally olefins since olefins are not further reduced by this means.

In general, benzene and toluene are not attacked by alkali metals. No metal salt is obtained when the hydrocarbons are treated with sodium or lithium in inert solvents, and no reduction takes place with sodium and alcohol (1). Wooster

and Godfrey (2) have, however, found that when a solution of toluene and sodium in liquid ammonia is treated with water, far less than the theoretical amount of hydrogen is evolved and a highly unsaturated compound is obtained. A recent patent (3) in extension of this work, describes the preparation of 1, 4 dihydrobenzene and 1,4 dihydrotoluene by reducing the hydrocarbons with sodium in liquid ammonia in the presence of a hydrolytic agent such as methyl alcohol. In similar fashion Birch (4) successfully reduced m- and p-xylene and p-cymene to the corresponding 2,5 dihydro derivatives (I and II).



I



II

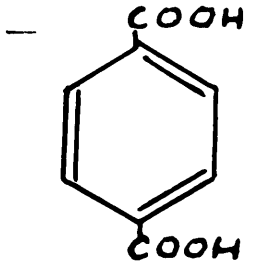
Calcium ammonia, Ca $(NH_3)_6$, made by passing ammonia vapours over metallic calcium, is a powerful reducing agent for aromatic compounds. It will reduce benzene and its homologs at room temperatures to cyclohexene derivatives, in yields as high as 90 percent. With alkylbenzenes, the double bond of the cyclohexene is linked to the same carbon atom as the alkyl group (5,6). The ammonia complexes of lithium strontium and barium can also be used (7) but they are much less effective.

Hydriodic acid and red phosphorous may be used to reduce most aromatic hydrocarbons; frequently a mixture of products

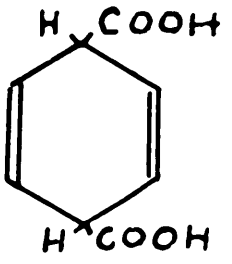
is obtained, and the reduction can be made complete if a sufficiently high temperature is used. Other methods of reduction are generally preferable (1).

The aromatic hydrocarbons are not as a rule reduced by zinc and acid, but Breteau (8) has reported the reduction of phenanthrene with zinc activated by palladium chloride, in hydrochloric acid solution. The tetrahydro derivative was obtained, regardless of the amount of reducing agent used, and no dihydro or hexahydro-phenanthrene could be isolated. This reduction may possibly be a case of catalytic hydrogenation, in which the palladium functioned as catalyst and the hydrogen was generated by interaction of the zinc and hydrochloric acid.

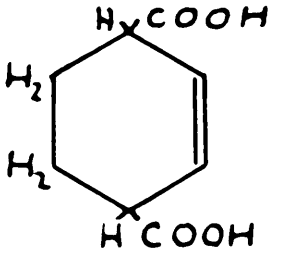
Substitution of one or more of the hydrogen atoms of the benzene ring by hydroxyl or carboxyl groups renders the products more susceptible to reduction by chemical agents (1). Willstatter and his students (9) studied the reduction of terephthalic acid (III) by pure sodium amalgam. The course of this reduction is markedly affected by the hydrogen-ion concentration of the medium; at a pH of 10 to 12 nuclear reduction occurs and a mixture of the 1,4-dihydro (IV) and 1,2,3,4-tetrahydro acids (V) is obtained.



III

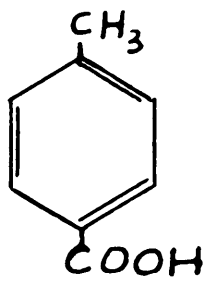


IV



V

When, on the other hand, the pH is maintained at 9 to 9.5 by the use of buffers, nuclear reduction ceases to be the main reaction and instead, one of the carboxyl groups is attacked, with the formation of p - toluic acid.

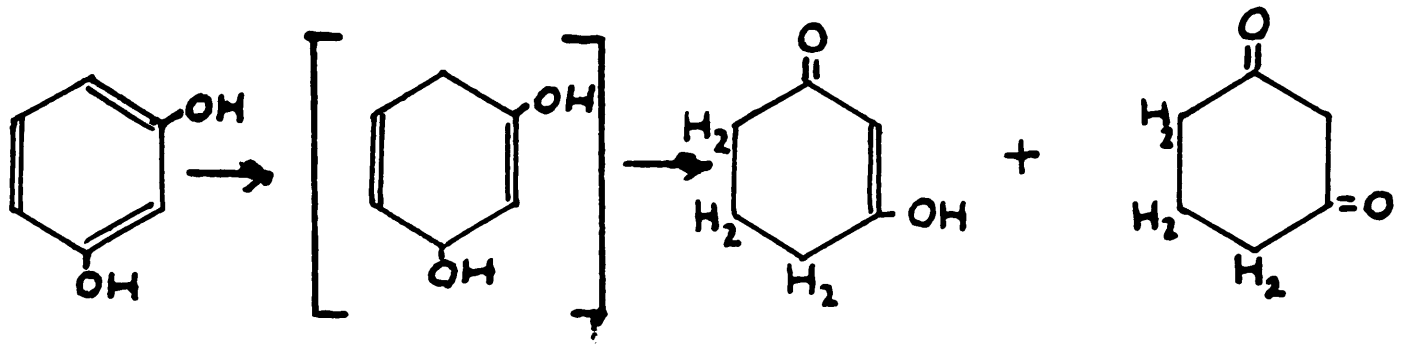


VI

Similar results have been obtained with benzoic acid (10). Reduction by sodium amalgam in alkaline solution yields a tetrahydro acid, whereas reduction in acid medium forms benzyl alcohol.

The chemical reduction of phenols preceded the discovery of catalytic hydrogenation and initially met with only indifferent success because a large variety of unpredictable products resulted. In many cases, dehydroxylation without nuclear reduction occurs, while in others, dehydroxylation and nuclear reduction take place simultaneously.

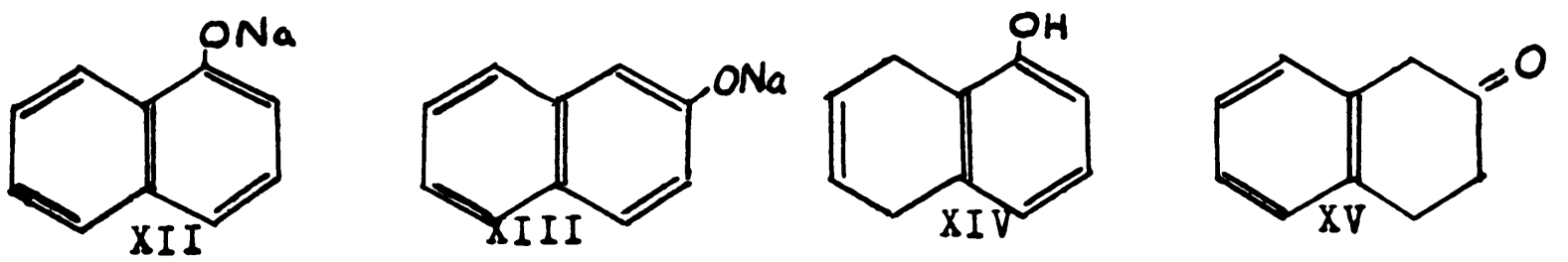
In some cases, the reduction of the aromatic ring is accomplished without cleavage of the hydroxyl group. Thus Merling (11) reduced 1,3 dihydroxy benzene (VII) in small yields to a mixture of cyclohexane - 1,3 dione (VIII) and the tautomeric enol Δ_1 cyclohexene 1-ol-3one by means of sodium amalgam (IX).



VII IX VIII

Wislicenus (12) claims he succeeded in completely saturating 1,3,5 trihydroxy benzene, obtaining the corresponding cyclohexantriol in minor yields using sodium amalgam as the reducing agent.

Sodium metal and liquid ammonia have been employed to reduce sodium α and β naphthoxides (XII and XIII) (4). The interesting observation was made that in the absence of a proton source such as t-amyl alcohol, very little reduction occurred but that in the presence of this reagent good yields of the 5,8 dihydro α naphthol (XIV) were obtained from sodium α naphthoxide and fair yields of β tetralone (XV) from sodium β naphthoxide. Sodium phenoxide, however, was not reduced by these means.

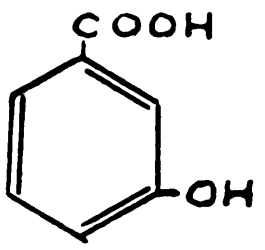


XII XIII XIV XV

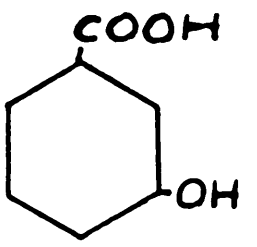
The reduction of aromatic carboxylic acids, containing a phenolic hydroxyl substituent, to the corresponding saturated compounds was carried out successfully by Einhorn (13), Einhorn and Willstatter (14) and Perkins and co-workers (15, 16) by

means of sodium metal and ethanol.

Einhorn (13) and Perkins and co-workers (16) reduced m-hydroxy benzoic acid (X) to the corresponding cis and trans cyclohexanol (3) carboxylic acids (XI).



X



XI
cis and trans

On the other hand, Einhorn and Willstatter (14) discovered that salicylic acid (XVI) undergoes ring fission as well as nuclear reduction with the same treatment yielding pimelic acid (1,7 heptane dicarboxylic acid) (XVII). The compounds studied by Perkins and co-workers (15) were the hydroxy toluic acids. Optimum yields and ease of reduction were reported with the 4-hydroxy 1-methyl benzoic acids (XVIII), the reduction products being the corresponding cis and trans 1-methyl cyclohexanol-4 carboxylic acids (XIX).

The Reductive Cleavage of Phenol Ethers

The well known oxidative changes which phenols, especially polyhydric phenols, undergo in alkaline as well as in acidic media, make the protection of the phenolic hydroxyl group of prime importance in many reactions. This object may be accomplished by the established techniques of acylation and etherification. Such protection is especially necessary in

the chemical reduction of polyhydric phenols, in some of which irreversible changes may take place under alkaline conditions before chemical reduction has had the opportunity to proceed to any extent. Furthermore, etherification does not greatly alter the electronegative character of the molecule, according to Lucas' table of electronegativities (141). A study of the phenol ether reveals the behaviour of the compound under conditions in which a labile phenolic hydrogen is not involved. The behaviour of phenol ethers under reducing conditions is, therefore, an integral part of the study of the chemical reduction of phenols.

Alkali metal, either alone or with an alcohol, is an efficient means of cleaving phenol ether linkages although no apparent reduction of the aromatic ring takes place. Durand (17) first noticed the effect of sodium wire on diethyl ether and the formation of sodium ethoxide and hydrogen. Diisoamyl ether behaves similarly, but with great rapidity at the boiling point, the metal being molten. Anisole, phenetole, veratrole, ethyl benzyl ether, all reacted rapidly at elevated temperatures, but a great deal of carbonization resulted with diphenyl ether. Potassium-sodium alloy reacted more vigorously than sodium alone and proved especially useful where it was desirable to maintain lower temperatures.

In general, ether cleavage takes place as follows:-

$$ROR^1 + Na \longrightarrow RONa + R^1$$

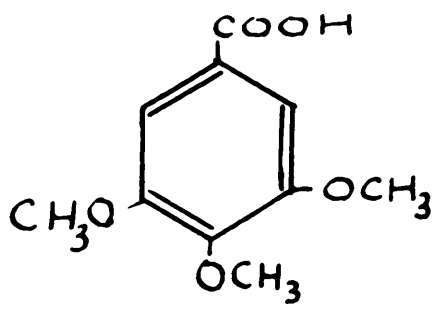
The free radical R^1 may couple and will do so if aromatic, but if aliphatic (other than methyl) it may also undergo disproportionation.

Schorigin (18) treated a series of mixed ethers with sodium metal, and reasoned that the more firmly a radical is bound with the oxygen, the greater would be the yield of the corresponding phenolate or alcoholate. In this way, he arrived at the following sequence in which the radicals are arranged in increasing bond strength with oxygen:

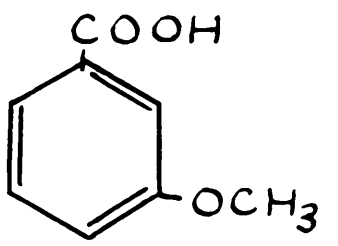
benzyl, ethyl, isoamyl, β-naphthyl, α-naphthyl, phenyl

This order is the same as that representing the relative firmness of attachment of the radicals to nitrogen, sulphur and carbon as determined by other workers.

Luttringhaus and Saaf (19) considered the cleavage of the central methoxy group in pyrogallol trimethyl ether, with sodium and ethanol, as unusual, since in normal ether cleavage the oxygen-phenyl link remains intact. Semmler (20) similarly obtained m-methoxybenzoic acid (XXI) in the sodium and ethanol reduction of trimethyl gallic acid (XX):



XX



XXI

This type of fission, however, soon loses its novelty when reference is made to the action of other dissolving metal reducing agents, as will be seen later.

Standing alone in splendid isolation is the claim by Einhorn (21) that he succeeded in saturating the benzenoid nucleus of 3,5 dimethoxy benzoic acid with sodium and amyl alconol without causing ether cleavage.

The action of alkali metals in liquid ammonia has produced very interesting results. Freudenberg, Lautsch and Piazolo (22) found that potassium metal in liquid ammonia acts on methoxy benzene derivatives merely as a demethylating agent, and Birch (23) confirmed this observation when he substituted sodium as the alkali metal. Wooster (2), however, reduced a number of compounds containing an isolated benzene ring when he added a small amount of methanol to a solution of sodium and liquid ammonia. He concluded that dihydro derivatives were formed, although this was proven definitely only for benzene itself. Birch (4, 23, 24) also succeeded in reducing anisole, a series of alkyl monomethoxybenzenes, simple and substituted dimethoxy-benzenes, as well as pyrogallol trimethyl ether. In general, the products obtained as primary intermediates were the dihydro derivatives of these phenol ethers. Examples of some of the reactions studied by Birch are shown in Figure 1.

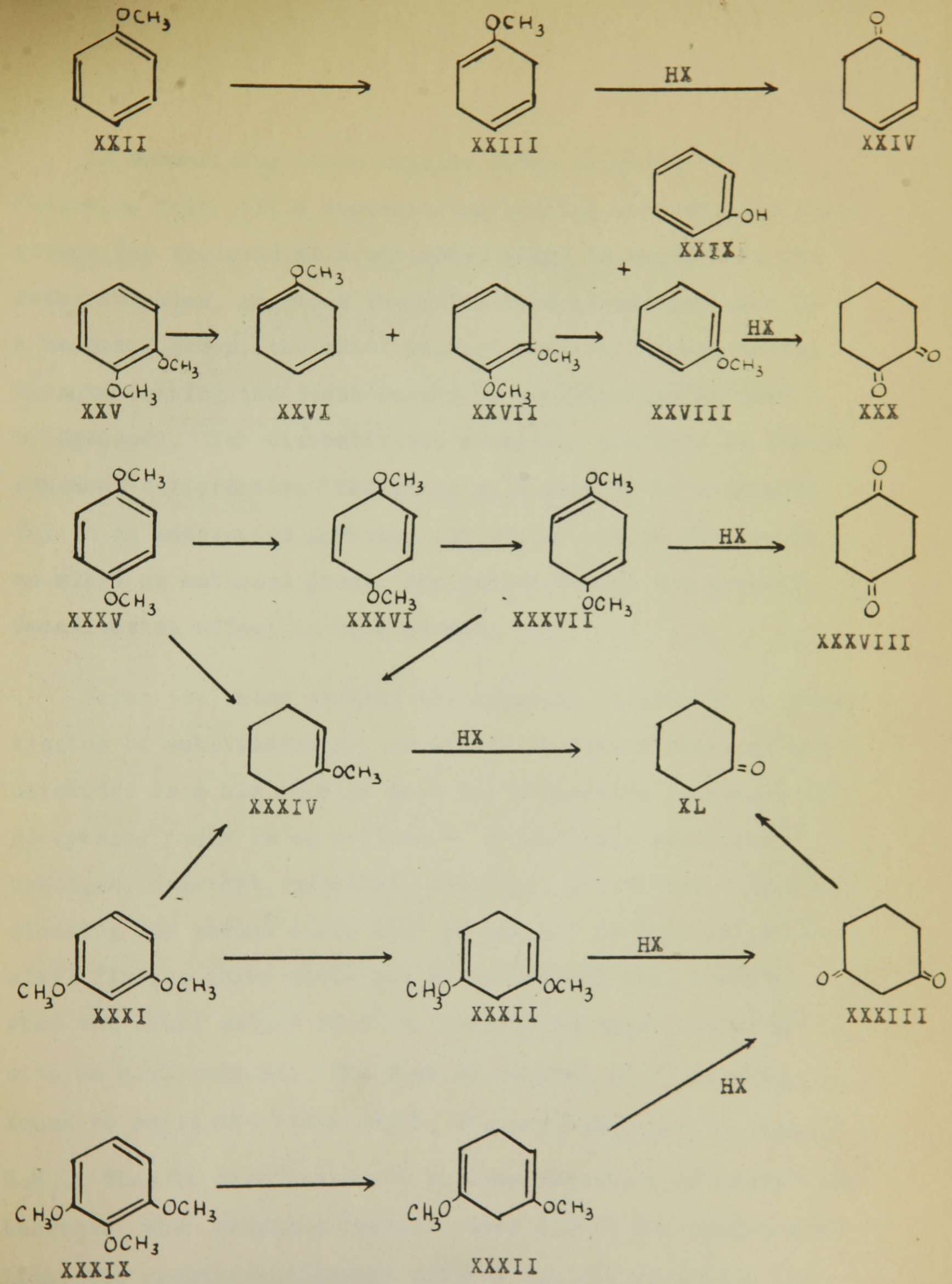


Figure 1 - The Reduction of Phenol Ethers with Sodium in Liquid Ammonia (4,23,24).

In summarizing these results Birch proposed (4) the following rule: "If a benzene ring bearing methoxyl and alkyl groups (or the ends of a saturated ring) is written in the Dewar formulae, in which the bridgehead is not occupied by a methoxyl group, the chief product will correspond to the formula bearing the least number of substituents at the bridgehead". For disubstituted anisoles, the rule is stated somewhat differently: "Reduction will tend to be initiated (a) in an unoccupied position (b) o-, m- rather than p- to an alkyl or methoxyl group, the latter having the greater deactivating effect in both cases".

Birch (24) also studied the apparent resistance to ether fission of substituted o-, m- and p- dimethoxy benzenes and concluded from his results that the activating influence in decreasing order is as follows:- o-methoxyl, m-methoxyl, hydrogen, o-methyl, m-methyl, p-methyl, p-methoxyl. In considering any phenol ether ROR^1 in which R is aryl and R^1 is alkyl fission takes place and R^1 is removed most readily when the alkyl nature of R^1 is reduced by substituting R^1 with an aryl radical. The ease of removal of R^1 is then found to be in the order CH_2Ph, $CH_2COOH > CH_3 > n\text{-}C_3H_7$, $iso\text{-}C_3H_7$. Thus in distinction to nuclear reduction of polyalkoxy benzenes, when extended reaction does cleave the oxygen-aryl link, the reductive cleavage without nuclear reduction invariably causes fission of the oxygen-alkyl link.

A similar fission of the methylene dioxy group in piperonal was observed by Papa and Schwenk (25) to yield mainly m-cresol. Raney's aluminium-nickel alloy was used in conjunction with alkali.

Theories of the Chemical Reduction of Phenols and Phenol Ethers

General Theories of Chemical Reduction

Any general mechanism proposed to explain the chemical reduction of unsaturated carbon-carbon linkages must satisfy several conditions. It must account for the bimolecular products sometimes encountered, for the mixture of 1,4 - and 1,2 dihydro products obtained from conjugated dienes, for the trans reduction of acetylenes, and for the influence of activating groups. Several theories fulfilling most of these requirements have been proposed; they differ chiefly in attributing the reduction to the addition of "nascent" hydrogen atoms (or sodium atoms) or to the addition of electrons and positive ions (1).

The oldest theory is that of Baeyer (26) who considered that the dissolving metal reacted with the solvent to liberate hydrogen atoms, and that these "nascent" hydrogen atoms then reacted with the organic compound before they could combine with each other to form molecular hydrogen. The solvent according to this theory would have a direct role in the reaction.

Until recent years the theory of "nascent" hydrogen was widely accepted and is still used by many authors. Willstatter and his co-workers (27) have, however, rejected this "nascent" hydrogen mechanism as the result of a careful study of the course of reductions by sodium amalgam. They showed that it was possible to obtain yields of reduced product as high as ninety percent (based on sodium), and considered that this would be impossible if hydrogen atoms were the actual reducing agent. They also showed that the ability of sodium amalgam to react with water with the liberation of hydrogen, and its activity in reducing double bonds are not parallel properties. It is possible to prepare a sodium amalgam which does not react appreciably with water, and yet shows a high degree of efficiency in reducing a compound such as terephthalic acid. These facts led Willstatter to propose that sodium amalgam reductions occur by the addition of metallic sodium to the double bond, followed by hydrolysis by the solvent. In this case the solvent takes no direct part in the fundamental reaction.

$$C_6H_5CH{=}CHC_6H_5 + 2Na \longrightarrow C_6H_5\underset{\displaystyle Na}{\underset{|}{CH}} - \underset{\displaystyle Na}{\underset{|}{CH}}C_6H_5 \xrightarrow{H_2O} C_6H_5CH_2CH_2C_6H_5$$

If it is postulated further that the two sodium atoms add not simultaneously but consecutively, it is possible by this

mechanism to account for the dimolecular pinacol-like products that are frequently obtained, especially in the reduction of unsaturated ketones by alkali metals; and for the mixture of 1,2 and 1,4 dihydro products formed in the reduction of diene acids by sodium amalgam.

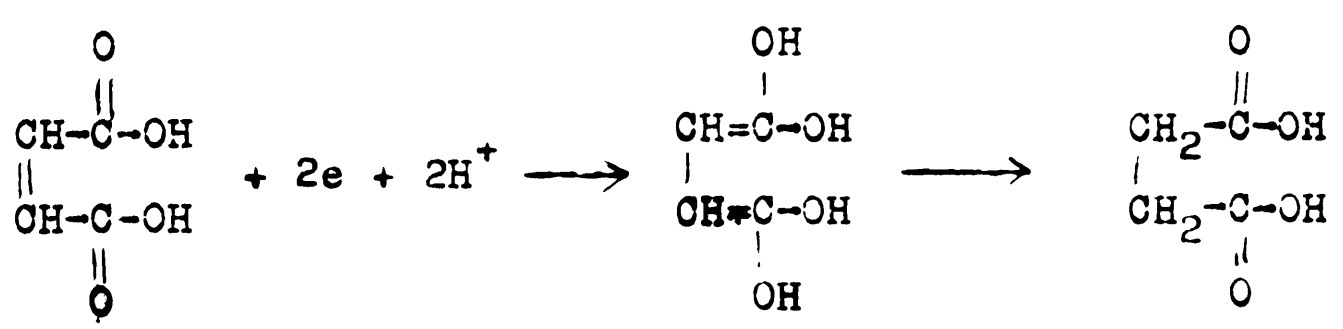
Willstatter's theory has received considerable support from the studies that have been made in the last two decades on the addition of alkali metals to olefins in inert media. In general, it is true that those olefins such as cyclohexene, which cannot add sodium or other alkali metals, cannot be reduced by dissolving metal combinations. Olefins that readily add sodium, such as styrene, stilbene, tetraphenyl-ethylene, etc., are reducible by dissolving metals. Wooster and Smith (28) have also shown that alkali organic compounds are intermediates in the reduction of many substances, such as naphthalene, by sodium in liquid ammonia.

However, it does not follow from these experimental facts that the theories of "nascent" hydrogen reduction and of reduction by the addition of the metal atom are necessarily mutually exclusive. It may be that each mechanism might be valid to explain the reduction of specific classes of compounds. Geib and Harteck (29) have shown that in the gaseous state hydrogen atoms are capable of reducing benzene. Birch (4) points out that metallic iron catalyses the reaction $2H\cdot \longrightarrow H:H$ and that the reduction of 6-methoxy tetralin

and sodium β naphthoxide by sodium in liquid ammonia was inhibited by the presence of a little finely divided metal. This inhibition may be due merely to the preferential combination of sodium with ammonia - a reaction also catalyzed by iron, but since this reaction also produces "nascent" hydrogen the state of the latter must be important. It is inferred that the metallic iron increases the rate of combination of hydrogen atoms to molecular hydrogen so much that the rate of reduction by hydrogen atoms is overtaken and suppressed. Several other objections have been raised against Willstatter's theory. Huckel (30) considered that it is reasonable to assume the mechanism of reduction by dissolving metals to be the same for all the metals used - sodium, aluminum zinc, calcium, etc., - and that it seems unlikely that a polyvalent atom such as calcium could add to the 1,4 positions of naphthalene, for example. Yet naphthalene is reduced to the 1,4 dihydro derivative by both sodium and calcium in liquid ammonia. Huckel has further emphasized the fact that organic-alkali compounds like disodium naphthalene and calcium naphthalene do not have a covalent bond between the metal and the carbon atom, but are in reality salts. Hence in the formation of these substances from the metal and the hydrocarbon, only electrons need to be transferred from the former to the latter. Wilson (31) and Isaacs and Wilson (32) have shown that the electrolytic reduction of conjugated acids such as sorbic

acid by high overvoltage electrodes (mercury, lead) seems to take the same course as reduction by sodium and sodium amalgam, and may well proceed by the same mechanism. In which case, of course, the reduction cannot involve addition of metal atoms to the double bond.

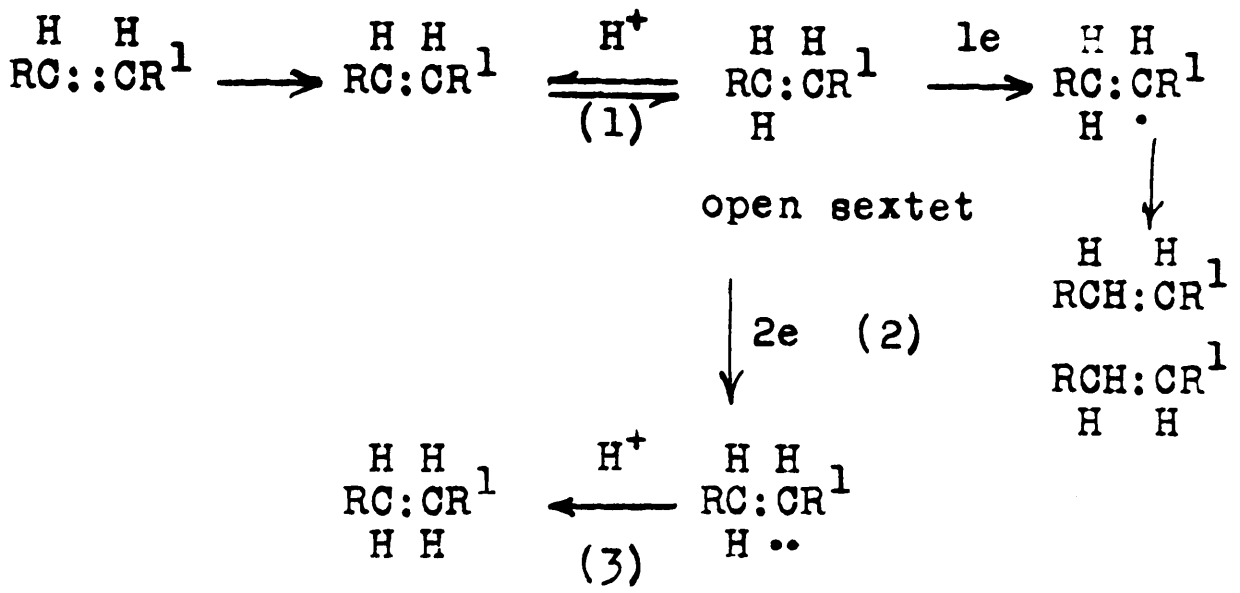
Several investigators have proposed an ionic mechanism to account for reduction by chemical reducing agents. Conant and his students (33, 34) suggested that the reduction of maleic acid by soluble reducing salts consists of the stepwise addition of two electrons and two hydrogen ions to the oxygen atoms at the ends of the conjugated chain followed by irreversible ketonization.



Similar theories have been put forward by Michaelis and Schubert (35) who considered that reduction consisted in the consecutive addition of two electrons, followed by two protons; and by Prins (36) who suggested that a proton-electron complex first added to the unsaturated linkage, and that this step was followed either by dimerization or by addition of a second proton-electron complex.

The ionic theory put forward by Burton and Ingold (37) can be elaborated to cover practically all types of reduction

by chemical reducing agents. In brief, this theory assumes that the double bond polarizes in the reaction medium. For polarization to occur, at least one carbon atom of the double bond must be attached to a strongly electron-attracting group (aryl, carboxyl), so that this atom can provide a seat for a negative charge. The polarized molecule then adds a proton from the solution, forming a positive fragment which can stabilize itself by acquiring two electrons from the metal surface, or from the reducing salt, followed by another proton. If the fragment acquires but one electron instead of two, a free radical will be formed which can stabilize itself by dimerization. It will be seen that this theory can be adapted to explain the mixture of 1,4 and 1,2 dihydro products sometimes obtained from conjugated compounds, for the intermediate positive fragment can undergo an allylic rearrangement to a tautomeric form. If it is assumed that a sodium ion can be added in place of a proton when the reaction is carried out by sodium in liquid ammonia, then this mechanism will also explain the formation of disodium naphthalene as an intermediate in the reduction of naphthalene under these conditions.



Consideration of stage (1) shows that this conception of the process offers an immediate explanation of the well-known fact that the only olefinic acids which are reducible by metals in aqueous media are the α,β unsaturated acids. The possession of this structure is but one of the ways in which an olefinic substance can satisfy the more general theoretical requirement that for facile reduction at least one ethenoid carbon atom must be attached to an electron-sink. The electron-sink may be either an electron-attractor, (Carbonyl, carboxyl, phenyl, etc.) the permanent state of polarization of which confers on the adjoining carbon atom an affinity for a negative charge, or a polarisibility of the carbon atom. It is necessary to envisage the operation of both the inductive and tautomeric effect. At the conclusion of stage (2) negative hydrogen, in effect H+2e, has been added to the double bond. There is now a close analogy with the halogen additions to olefin linkages; for just as in

these additions unstable positive halogen first unites, leaving the ordinary halide ion to combine later, so unstable negative hydrogen is first added on, leaving the ordinary positive hydrogen to add subsequently.

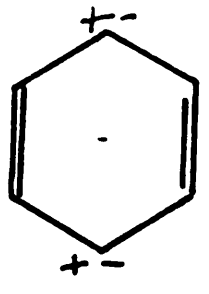
The merits of this theory are twofold. First, it provides an explanation for reduction of unsaturated linkages in a manner consistent with their behaviour to other addends, susceptible in many cases to closer study; and second, it provides a working theory indicating what the requirements for successful reduction of multiple carbon to carbon bonds are.

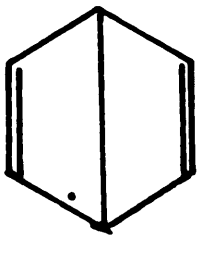
The Mechanisms of the Chemical Reduction of Phenol and Phenol Ethers

Sodium in liquid ammonia behaves as a solution of metal cations and solvated electrons in equilibrium with metal atoms (38) and might therefore be expected to provide a suitable environment for chemical reduction. Nevertheless, reduction in liquid ammonia of isolated benzene rings requires a ready source of protons, e.g. water or alcohol. This observation has been interpreted as in favour of adopting the "nascent" hydrogen theory of chemical reduction of isolated benzene rings. Naphthelene, on the other hand, reduces by the addition of two electrons to form a bivalent anion capable of adding two protons. Birch (4) states that the greater resonance in an isolated benzene ring renders the production of such an anion difficult. Actually

the energy of resonance stabilization is greater for naphthalene (75Kcal per mole) than for benzene (39Kcal per mole), although it is true that the resonant energy associated with a possible resonating unsaturated bond must be less in naphthalene (15 positions) than it is in benzene (6 positions). On this basis it may be said that any one of the napthalene bonds would be more likely to polarize and undergo reduction by addition than those in benzene. The greater resistance to polarization in the benzene ring might thus require a simple proton as addend. Following the same trend, the sodium α and β naphthoxides may be reduced in the presence of an alcohol by sodium and liquid ammonia, but sodium phenoxide cannot be reduced by chemical reducing agents. Sodium α-naphthoate, however, was readily reduced in the absence of alcohol probably because the carboxyl ion is capable of taking up electrons by an electromeric mechanism despite its negative charge (4).

The reduction of the benzene ring in both benzene and the phenol ethers takes place with the introduction of hydrogen atoms α,δ to each other. According to Birch (4) the polarization of the benzene nucleus takes place as follows either when expressed in terms of an ionic mechanism or in terms of the Dewar formula:-





On the assumption of anionoid addition (or electron addition) it was found possible to correlate the orientation influence of alkoxyl and alkyl groups with those observed for other anionoid reagents. Sartoretto and Sowa (39) by a comparison of the effect of substituents on the direction of cleavage of diphenyl ethers by sodium in liquid ammonia, showed that deactivation was produced in increasing measure as follows: $O\text{-}CH_3 < p\text{-}CH_3 < p\text{-}OCH_3$ and activation by $O\text{-}OCH_3$. It is evident from these results, and from the known inductive effect of alkyl groups, that these will tend to prevent addition of an anionoid reagent in the substituted position or para to it, so that the bridge of the Dewar formula corresponding to the principal reduction product will end on the carbon atom bearing the least number of alkyl groups. In the methoxy alkyl benzene series the unshared electrons of the ether oxygen tend to repress anionoid addition to the carbon atom joined to the methoxyl and in the position para to it. Thus the ortho-methoxy isomer alone is activating, and the Dewar formula having a methoxyl on the bridgehead must be left out of any consideration of the probable principal products in the reduction. These considerations are summarized in the rule proposed by Birch which has already been stated.

In the absence of alcohol, or other proton source, sodium and liquid ammonia causes fission of the monomethoxy and dimethoxy benzenes to yield monophenolic compounds. In

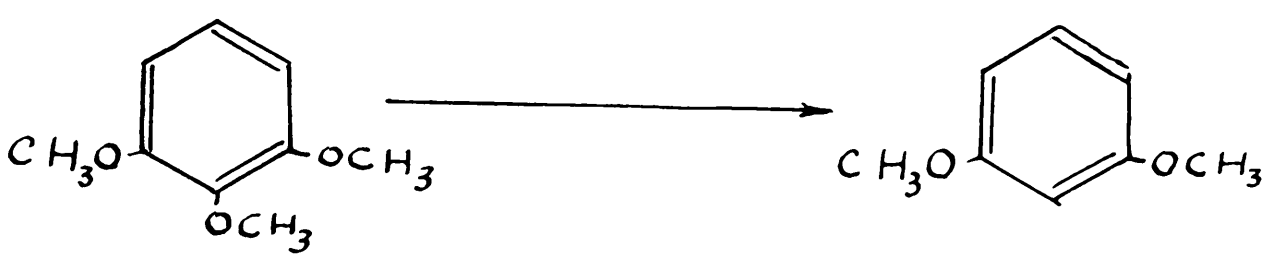
mixed aryl alkyl ethers it is evident that the ability of the aryl group to act as an electron-sink will lead to increased charge stability of the aryl group and thus to the cleavage of the oxygen-alkyl bond. The order of activating influence of these phenol ethers is o-methoxyl> m-methoxyl> hydrogen> o-methyl> m-methyl> p-methyl> p-methoxyl. These results are in harmony with those obtained from the cleavage of diphenyl ethers (39, 40). In the cleavage of ROR^1 (R,R^1 = aryl) for example the one which is favoured by the oxygen in fission appears to be determined by the relative substitutions of the aryl ions (R,R^1 respectively) - rather than the phenoxide ions, and the substituents have the order of activating influence noted above. This must, therefore, express the relative effects of the groups on the stability of a negative charge on a ring carbon atom or an oxygen atom attached to it. The significance of this conclusion, especially the stabilizing effect of the o-methoxyl, has already been discussed in connection with ring reduction. One added consideration governs the fission of substituted benzene rings also bearing 3,4 methylene dioxy groups. If the substituent on the one position has an inductive effect (e.g. CH_3) the meta positions will become electron deficient and thus react with an anionoid reagent; if the 1-substituent, however, is electron accepting through a mesomeric effect (e.g. COOH,CHO) the para position will become electron poor and be susceptible

to cleavage. In fact 3,4 methylenedioxy toluene does give p-cresol as product and piperonal does yield m-cresol (24).

The fact that in the presence of alcohol, phenol ethers form α,δ dihydro compounds as intermediates seems to favour Birch's concept of the primary addition of two electrons followed by proton absorption.at the extremities of the Dewar bridge. On the other hand, Ingold's theory would attribute the α,δ addition of hydrogen to the type of polarisibility exhibited, in the case under discussion - 1,4 , because as is already known, the anionic charge, the location of which controls the final proton, is stabilized terminally. The fact that in the absence of a proton source cleavage of the phenol ether can be explained most satisfactorily by the primary addition of one electron does not exclude the possibility of initial proton addition in the saturation of multiple carbon to carbon bonds. In both variations of the ionic mechanism, the net effect, expressed as a two stage reaction, is the primary addition of a negative hydrogen analogous to other additions to multiple carbon to carbon bonds.

The sodium and ethanol cleavage of pyrogallol trimethyl ether (41, 42) splits off the central methoxy group to give resorcinol dimethyl ether. Semmler (20) obtained m-methoxy benzoic acid as his principal product from the sodium and absolute ethanol reduction of trimethyl gallic acid. Luttringhaus and Saaf (19) point out that in both these cases of reductive

cleavage it is the aryl-oxygen bond that is severed rather than the oxygen-methyl bond as is the case with alkali metals alone or alkali hydroxides in some solvent. They suggest that the reaction proceeds through the primary addition of sodium to the aromatic ring followed by subsequent cleavage of sodium methylate and rearomatization accord.ng to the following example of pyrogallol trimethyl ether:



According to the authors, the accumulation of methoxy groups accompanied as it is by an increased mesomeric effect, makes possible the metal addition to the aromatic ring. It is probable that this reaction is more easily explicable by the theory developed by Birch (4) which does not rely on the improbable addition of sodium to an isolated benzene ring. The presence of the two other methoxy groups will through a mesomeric effect activate the cleavage of the central methoxy group. The fission will stop here because the influence of meta is less activating than that of ortho methoxy groups.

Keto-Enol Tautomerism

The reduction of phenol ethers with dissolving metals presents the possibility of obtaining, as primary intermediates, the dihydro and tetrahydro phenyl ethers. Upon hydrolysis with

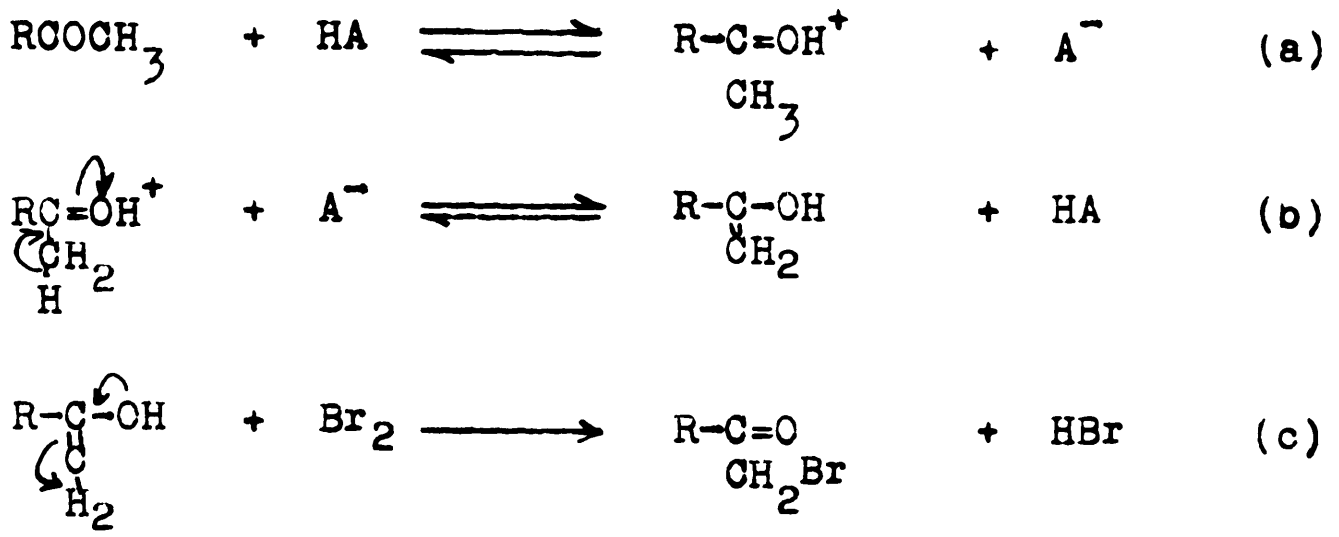
mineral acid the latter would yield unsaturated and saturated ketonic derivatives. It, therefore, becomes necessary to consider the general conditions under which keto-enol tautomerism would exist and the properties of the tautomers. Such a study might also show how products derivable from enols are produced.

Extensive studies of the halogenation of ketones by Lapworth (43), Dawson and co-workers (44 to 47) Hughes and Watson (48) and others, have established that the characteristic replacement by halogens of the α hydrogen atom in carbonyl compounds involves a preliminary change of the compound to its enolic form as follows:-

$$R_1R_2CH\overset{R}{C} = O \rightleftharpoons R\overset{OH}{C} = CR_1R_2$$

The mechanism of enolization, as well as other related prototropic changes, has been discussed in terms of the electronic theory of valency by Lowry (49), Ingold Shoppee and Thorpe (50), Baker (51), Watson (52), and more recently by Arndt and Martius (53), Hammett (54), and Remick (55).

Remick (55) and Hammett (54) in summarizing the concepts of the English School offer the following mechanism as being in accord with all known facts concerning the acid catalyzed reaction:-



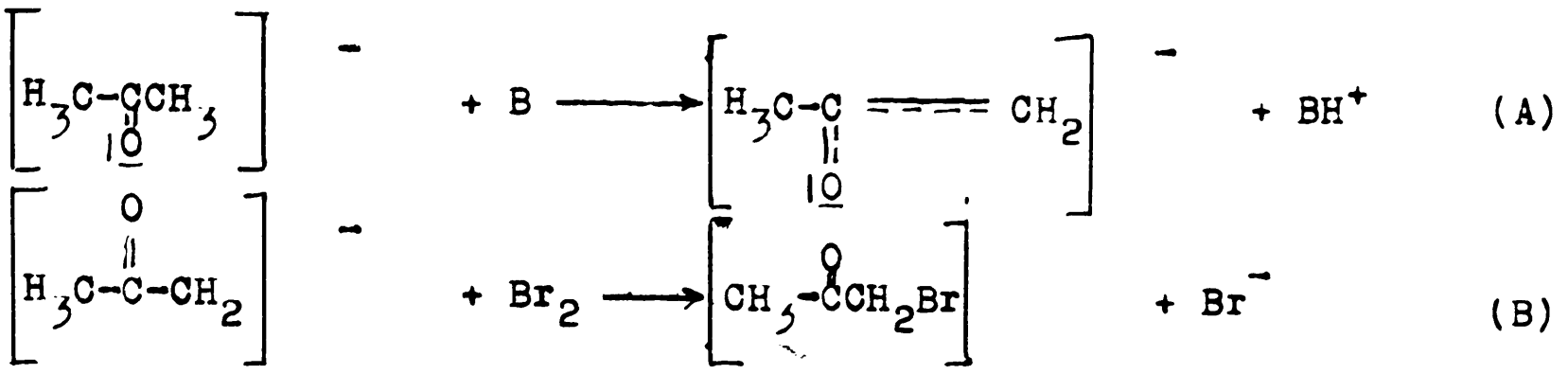
(a)

(b)

(c)

The first step (a) should be instantaneous because it involves the reaction of a primary acid with a primary base. The second step (b) will be slow because the formation of a C = C bond furnishes insufficient driving force to break both the C - H and C = O bonds. The third step (c) willpresumably be more rapid since the rupture of the double bond is facilitated by the tautomeric effect of the hydroxyl group and by the fact that the "ionic bond energy" of $\overline{O}\rightarrow Br$ (the bond being formed) is 294 whereas that of $Br^{-}Br^{+}$ (the bond being broken) is only 236 Kcal. The proton is probably eliminated subsequently to form HBr, another exothermic step. Thus the second step is rate-controlling. The tautomeric displacements indicated are aided by the free positive pole on the catalyzing proton. The coordination of A^{-} with the hydrogen atom of the methyl group gives the necessary added increment of driving force to make the step successful.

Hammett (54) holds that the base catalyzed reaction proceeds as follows:-



(A)

(B)

Strictly speaking, the halogenation of a ketone is not catalyzed by bases and is not, therefore, subject to general basic catalysis, because the strict definition of a catalyst is a substance that accelerates a reaction without entering into the final products. Reaction (A) followed by (B) converts the catalyzing base to its conjugate acid.

An extensive investigation of the keto-enol tautomerism of the β diketones and β-ketonic esters (e.g. acetylacetone, ethyl acetoacetate) by K.H. Meyer, Knorr and others showed that these substances exhibit this type of isomerism with great clearness. In the case of acetone, an enolide has never been demonstrated although Freer (56 to 61) has attributed an enolic structure to certain metallic derivatives and the presence of enolide in alkaline solutions has been inferred from the nature of its oxidation products (62 to 64). The β-diketones and β-ketonic esters on the other hand, are normally equilibrium mixtures of the ketonic and enolic forms and the relative amounts of each have been determined by both physical and chemical measurements. Moreover, in a number of instances, the individual taut-

omerides have been isolated in the pure state (65 to 67).

$CH_3C(O)CH_2COOEt$

(a)

e.g. two forms

$CH_3C(OH)=CHCOOEt$

(b)

XLI

Bromine reacts instantaneously with the enolides but not with the ketonic isomers.

It has been demonstrated, particularly by Dufraisse and Moureu (68, 69) that α-diketones also are tautomeric substances, and these workers have isolated the individual isomerides of phenyl benzyl, phenyl anisyl and benzyl methyl diketones. The existence of the same phenomenon in substituted α-ketonic acids was indicated by the work of Schiff (70), Bougault and Hemmerle (71), Gault and Weick (72). Gault and Weick isolated three forms of ethyl phenyl pyruvate (the ketonic and two isomeric monoenolic forms). Further evidence of the enolization of α-ketonic acids has been obtained (48) by an investigation of the kinetics of bromination of pyruvic acid.

Although keto-enol tautomerism is clearly possible also in γ diketones and γ-ketonic acids, its existence was not demonstrated until 1929 (48) through a study of the bromin-

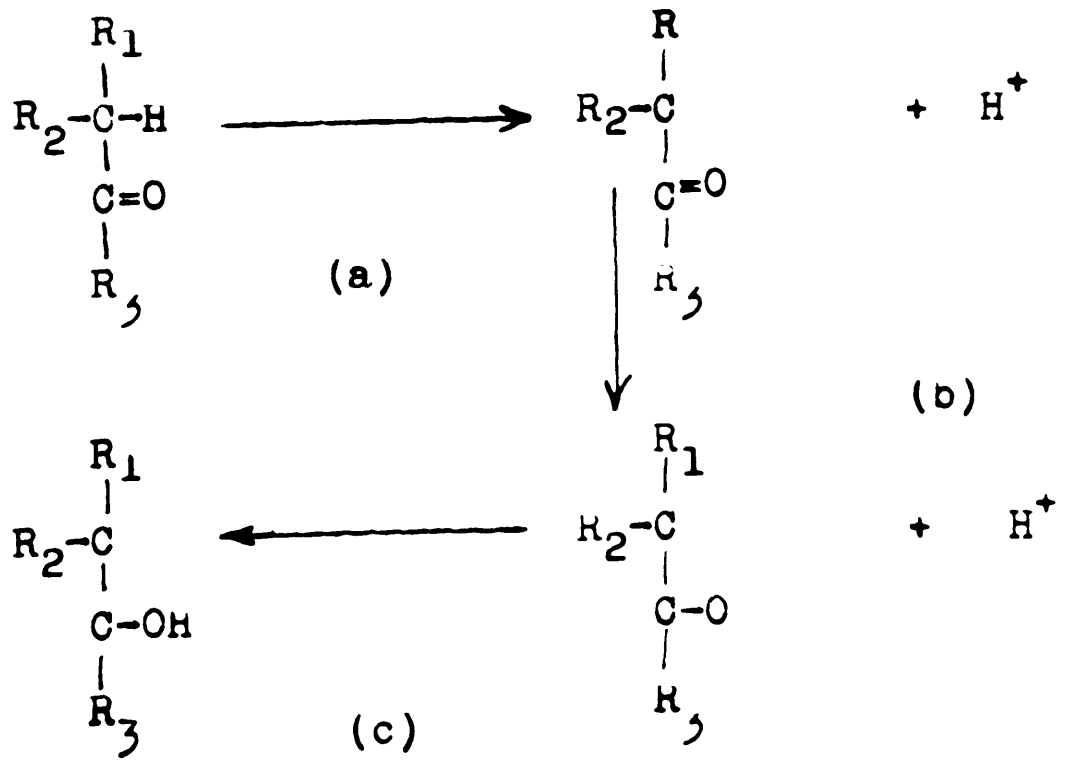
ation of levulinic acid in aqueous solution.

$$\overset{\delta}{CH_3}\overset{}{CO}\overset{\beta}{CH_2}\overset{\alpha}{CH_2}COOH$$

XLII

Bromine substitution occurred in positions β and δ but not α.

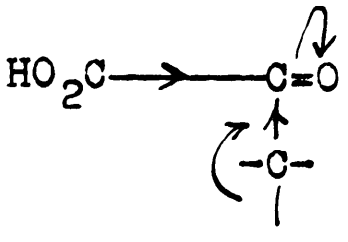
Arndt and Martius (53) have attempted to present a thermodynamic treatment of the process of voluntary enolization as one aspect of mesomerism. The change of a ketone to its enol form involves (a) the transfer of a proton from a place where it is firmly held to one where it is attached more loosely, and (b) associated with this proton transfer is the shift of a double bond from the ketonic carbonyl to form the olefinic C=C bond. Process (a) has a negative free energy which Arndt termed the "prototropic expenditure of work", whereas associated with the bond shift is a positive free energy change and is essentially a resonance energy which Arndt designates as an enotropic effect.



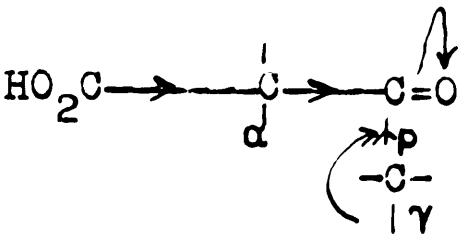
This division of the free energy of enolization into two components makes it understandable why the acidity of an enolizable compound may not be proportional to its degree of enolization. It is true that enolization always does increase the acidity because the proton is held in the enol more loosely than in the keto form, but even in the enol form the proton may be more or less firmly attached, thus influencing the degree to which process (c) may take place. In fact then, the acidity will be proportional to the degree of enolization only in the limiting case where process (c) occurs to an inappreciable extent, if at all. Arndt in numerous examples introduced various substituents as R_1, R_2, R_3 and attempted to classify these substituents as either increasing the acidity of the keto-enol tautomers or as increasing the actual enolization, i.e. the bond shift or the enotropic effect. Schwarzenbach and Felder (73) while accepting the main principles of Arndt's contribution, noted that the classification of substituents into the two types already mentioned, could not be substantiated in practice. When R_2=Br or CH_3SO_2 as in the substituted acetylacetones, the enol content is reduced but the acidity is increased as compared to acetylacetone itself. Thus the effect of substituents cannot be regarded as influencing <u>independently</u> either the enotropic or prototropic process. On the contrary, in the above example it was shown that just as the acidifying

(negative) substituent weakens the carbon-proton bond, it also decreases the existence of C=C bond of the enol form. The actual results show that a negative substituent decreases both the prototropic expenditure of work and the enotropic effect to about the same extent. Schwarzenbach and Felder (73) further point out that bond energy calculations show that the heat of enolization, due to the formation of a conjugated system, is about -10 to -15 Kcal per mole. If the enolizing system is itself conjugated with another unsaturated linkage, the increased resonance stabilization would tend to cancel the previous small endothermic effect and the heat of enolization would be nearly zero or perhaps slightly positive. Under these conditions, voluntary enolization would take place. β diketones have a heat of enolization which varies among different compounds from -3 to +3 Kcal per mole, the degree of enolization varying from one to 99 percent.

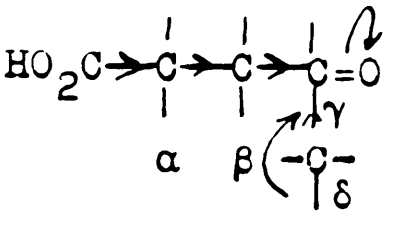
Considering now the special case of the ketonic acids and taking pyruvic (XLIII), acetoacetic (XLIV), and levulinic acids (XLII) as typical examples of the α, β and γ types, it requires but a simple extension of the previously discussed electronic mechanism to account for their relative degrees of enolization:-



XLIII



XLIV



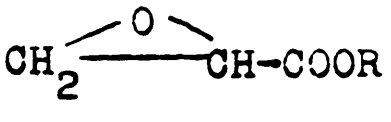
XLII

In acetoacetic and levulinic acids, the effect is promoted by an α and γ-hydrogen and by a β and δ hydrogen atom respectively. Superimposed, however, is the inductive effect of the carboxyl group assisting the displacement of electrons in the direction shown (52). This inductive effect causes pyruvic acid to enolize more rapidly than acetone and tends powerfully toward ionization of the α hydrogen of acetoacetic acid and the β hydrogen of levulinic acid. This behaviour is in harmony with the facts that (a) in ethyl acetoacetate only the one enolide(XLIb) is known and (b) the β hydrogen atom of levulinic acid enolizes more readily than the δ hydrogen atom.

The tendency to enolization is undoubtedly stronger in acetoacetic acid than in levulinic acid, probably because the α-carbon atom has a screening effect on the influence of the carboxyl group (52).

It has been repeatedly accepted that pyruvic acid partially enolizes in solution and the same must, therefore, hold true for the ester. The results of optical measurements (74)

chemical reactions (75) and finally biochemical studies seem to bear out this supposition. Optical studies have the advantage of being able to determine the properties of molecules free from external chemical influences. On the other hand, the relation between these optical effects and constitutive properties must be drawn by analogy and are not fully known. It has been pointed out in this connection that Fromageot's formula for pyruvic acid is also possible.



The chemical argument is based on the fact that oxidation of pyruvic acid with sodium chlorate and osmium yields oxalic acid. Splitting of the methyl group is attributed to the olefinic bond present in the enol form. The biochemical argument rests on the observation that in certain biochemical processes the hydrogen of an enolic hydroxyl group is replaced by a substituent, for example, to form the phosphoric acid ester. These derivatives, however, are not necessarily proof of the existence of an enol form, because many non-enolizable ketones are known which undergo methylation with diazomethane (53) to form the enol ether. The similar formation of enol acetates from non-enolizable ketones is also well-known (77) and their successful preparation is not a definite proof of the existence of the enol form. In the

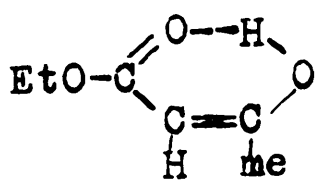
case of methyl pyruvate Arndt was unsuccessful in preparing the corresponding enol methyl ether, thus proving that in this case the enol form had no voluntary existence. Phenyl pyruvic acid and o,o^1 biphenylene pyruvic ester enolize, however, to a considerable degree (77).

Arndt and co-workers (77) offer two possible explanations for the absence of the enol form of methyl pyruvate: (a) The acidifying influence of the C(O)COOR is definitely stronger than the simple COOR and the methyl group of pyruvic ester is, therefore, more strongly acidified than those of the simple acetic acid esters. Since the enol hydroxyl group is attached to the same C-atom as the methyl of the ketone form, it is subject to an equal acidifying influence and the expenditure of work in proton transfer will be very large owing to proton oscillation. In acetoacetic ester, the influence of the COOR is stronger on the CH_2 group of the keto form than on the OH of the enol form and the prototropic expenditure of work is less, the proton statistically finding a seat on the enol oxygen. If the enol form of pyruvic ester should exist, it would be strongly acid, just as the dissociation constant for oxalic acid is larger than that for simple carboxylic acids, because the field effect of the strong positive carboxyl-C atoms repels protons. (b) The electromeric effect of the C(O)COOR is greater as judged by its enolizing tendency, which lies between aldehydes

and ketones. An enol bearing the C(O)COOR group has an "improved" conjugated system compared to that of the keto form. The resulting increase in electromeric effect of this "improvement", however, only brings about a weak enolization. If this enol form is conjugated with the phenyl (or the fluorene) group enolization is greatly increased.

The work of Meyer (78 to 80), Sidgewick (81) and, more recently, Conant and Thompson (82) on the effect of solvent on the enolization of β-diketones and β-keto esters has been interpreted to amend the previous explanations based on electron displacement only. Their results show that the order of solvent influence on the keto-enol equilibrium cannot be correlated with either the dielectric constants or relative basicities of the solvents.

Sidgewick is of the opinion that the enolic forms are chelated, acetoacetic ester, for example, having the formula



The resonance associated with the hydrogen bond stabilizes the enol relative to the keto form. A solvent could do this either by acting as a donor to the hydroxylic hydrogen atom of the enol or by acting as an acceptor toward the atomic oxygen of the enol. Thus either the basic or acidic properties of a solvent might be called into play and would in either case

favour the ketonic form (83).

Another influence is probably also at work. The ketonic form is almost surely more polar than the enolic form, since ketones have significantly larger dipole moments than alcohols and the differences would be augmented by chelation. This being so, the more polar solvents would associate preferentially with the keto form (dipole association) and this association would be tantamount to preferential solvation of the keto form in the absence of other associating influences.

Grignard and Blanchon studied the enolization of ketones under the influence of various Grignard reagents (84, 85). Among the ketones studied were a number of quite typical cyclic ketones such as cyclopentanone, cyclohexanone, p-methyl cyclohexanone, menthone, thujone, and carvone. They were able to come to a number of conclusions as a result of this work:-

(1) Primary organomagnesium halides induce 6 to 8% enolization; secondary organomagnesium halides 13.5 to 16%, and tertiary organometallic compounds, about 20%.

(2) The presence of negative groups favours enolization.

(3) An ethylenic linkage conjugated with the enolic double bond seems to favour formation of the enol.

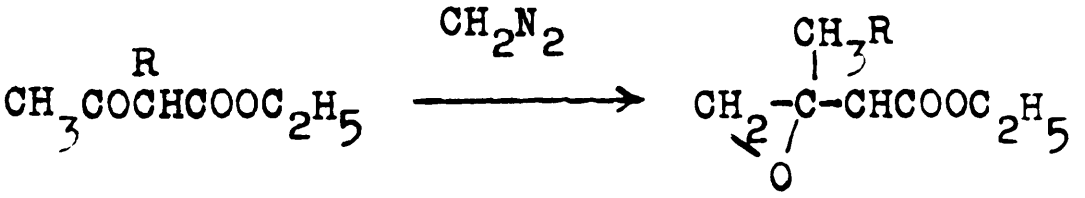
In each case, the enol was isolated as the enol-acetate by reaction with acetyl chloride; the ester was subsequently hydrolyzed with aqueous oxalic acid and the predominantly enol product was isolated. On storage for a considerable time, the

enol reverted to the ketone. In the case of cyclohexenol, reversion to the ketone took ten hours; in that of the thujone-enol, fifteen hours.

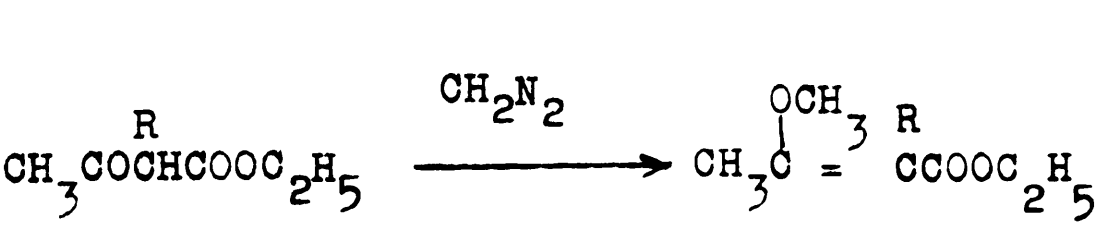
Kohler and Thompson (76) very strongly disputed the claims of Grignard and Blanchon to have enolized cyclohexanone with isopropyl magnesium bromide, since they were unable to duplicate the experiment. Kohler and Thompson concluded that Grignard reagents containing secondary and tertiary hydrocarbon residues frequently act as condensing and reducing agents, but that there was no evidence to show that Grignard reagents converted monoketones into enolates unless hindrance to normal addition was prohibitive. Arndt and Martius (86) confirmed this work and stressed the inability of simple ketones, in contrast to enols, to add bromine in the absence of a catalyst. It was suggested, also, that the formation of enol acetates is not characteristic of the enol form only, but results from some non-enolizable ketones as well.

The alkylation of enolic oxygen atoms was carried out by Arndt and co-workers (87 to 90) using diazomethane. For example, α cyanoacetophenone yielded predominantly trans β-methoxycinnamonitrile. Similar results were obtained with ethyl acetoacetate (88) and with methyl acetoacetic ester (89). In both the latter cases, the presence of some hydroxylic solvent was found to accelerate the O-alkylation reaction enormously. Indeed, in the absence of appreciable amounts

of methyl alcohol, for example, the yield of enol methyl ether might be negligible even after several days. In both cases the ethylene oxide product was also formed. The chief difference between the reaction of C-methyl ethyl aceto-acetate ($R=CH_3$) and ethyl acetoacetate ($R=H$) with diazomethane was that the former yielded the ethylene oxide predominantly (reaction A) while ethyl acetoacetate gave the enol ether as the principal product (reaction B).



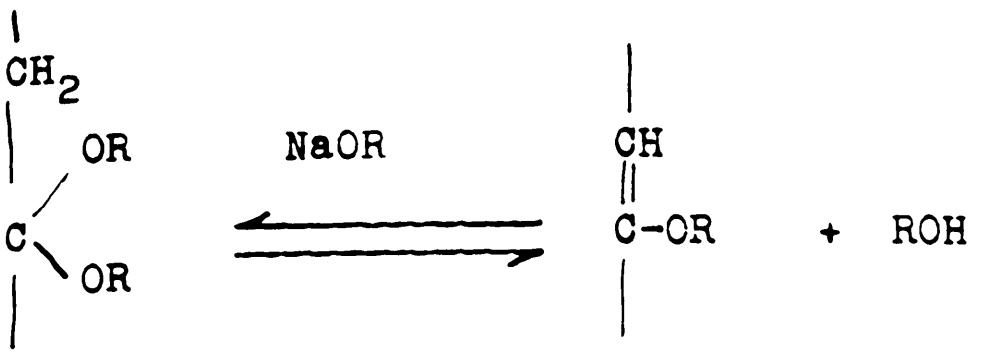
(A)



(B)

Apparently both of these reactions proceed competitively. When $R=CH_3$, the acidity of the enolic hydroxyl group is reduced and its velocity of methylation with diazomethane therefore fails to keep pace with the rate of formation of B (90).

Arndt and co-workers (89) also showed that sodium alcoholate is a catalyst that establishes an equilibrium between the ketone acetal on the one hand and the alkylated enol plus alcohol on the other:-



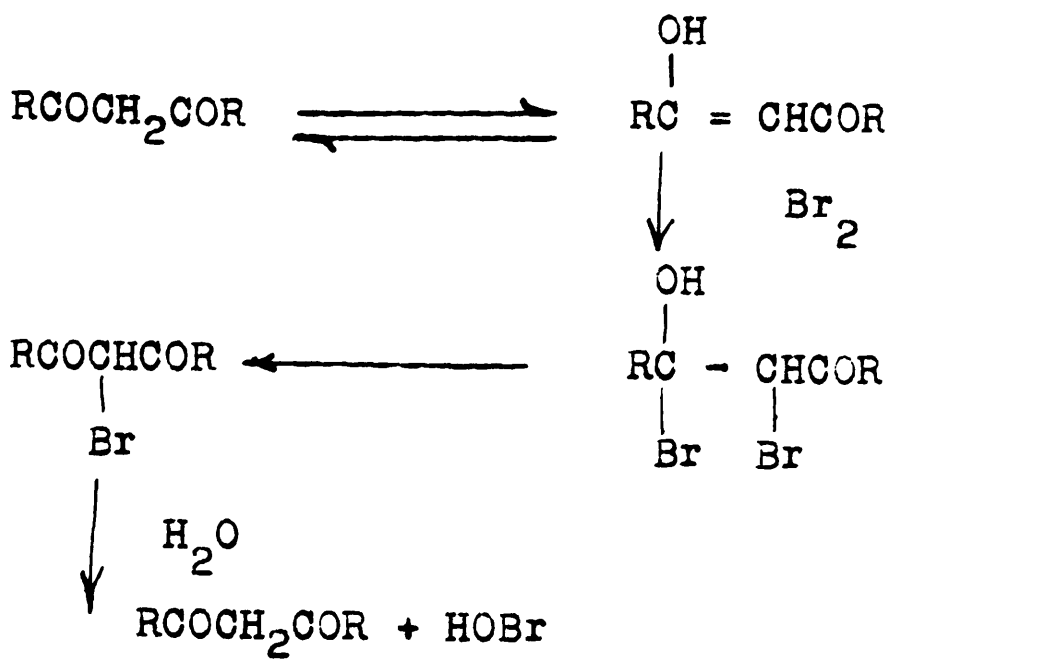
With non-conjugated enol ethers this equilibrium lies wholly on the acetal side, whereas with conjugated enol ethers the equilibrium is shifted more or less extensively toward the enol ether. This effect was demonstrated with the ethyl enol ether of ethyl acetoacetate. In the case of β methoxy cinnamonitrile some of the trans enol ether was changed to the cis form (87).

Skrabal and Skrabal (91) studied the kinetics of acid hydrolysis of enol ethers like ethyl vinyl ether, divinyl ether, and α,α dimethyl furan. In all such cases, the hydrolysis rates were much faster than for ordinary ethers and approached the order of magnitude characteristic of the hydrolysis of ortho esters and acetals.

Fjøder investigated (92) the bromination of certain enol ethers and discovered that bromination was by substitution on the α position just as for ketones.

The Determination of Enol

One of the oldest quantitative methods, and by most accounts still one of the best, is based upon the titration of the bromine which adds to an enolic double bond. This method was first proposed by Meyer (93) and has recently been revised by Cooper and Barnes (94). The chemical reactions involved are as follows:-



$$HOBr + HBr + 2KI \longrightarrow I_2 + 2KBr + H_2O$$

$$I_2 + 2Na_2S_2O_3 \longrightarrow 2NaI + Na_2S_4O_6$$

Whitmore and co-workers (95 to 97) investigated the enolizing influence of Grignard reagents upon various ketones. They came to the conclusion that the enolization of a ketone by a Grignard reagent is not an inherent property of the ketone, the amount of enolization depending upon the Grignard reagent used (95) as well as upon the substitution on the carbon atom (97)alpha to the carbonyl of the ketone. Thus the enolization of a given ketone with various Grignard reagents may vary from 0 to nearly 100% (95). Substitution on the β carbon atom of the ketone had no noticeable effect (97). Substitution in the active methylene group of a β diketone decreased the extent of both enolization and addition. It is thus evident that the Grignard reaction, if adapted as a method for measuring the degree of enolization, gives relative results

useful only for comparison in a whole series of compounds treated with the same Grignard reagent and under the same conditions. Results obtained by these means have no absolute meaning and cannot be compared with other methods which measure the inherent degree of enolization.

Seidel and co-workers (98) proposed an acidimetric enol titration. Bohme and Fischer (99), comparing Seidel's method with that of Meyer's (93), found the acidimetric one inferior both as to precision and accuracy as well as open to criticism on theoretical grounds.

A number of workers (100 to 105) investigated spectrometric means of measuring keto-enol tautomerism. v. Auwers (100) and Michalek and Post (101) obtained substantial agreement for several β-keto esters between molecular refraction measurements and results obtained by the bromine titration method. Hayashi (102) and Milone (103) suggested that Raman spectra might be used for the quantitative estimation as well as for the qualitative detection of keto-enol equilibria. Infra-red measurements by Hilbert, Wulf, Hendricks and Liddel (104), as further elucidated by Buswell, Rodebush and Roy (105), demonstrate how absorption spectra in this region may be used to detect keto-enol tautomerism.

Since the investigations of Baly and Desch (106) and Hantzsch (107), the absorption of light in the ultraviolet region has been successfully applied to the detection of the

enolide as well as to its quantitative estimation. The ultraviolet absorption spectra of cyclic diketones in particular have been carefully studied. In contrast to compounds having isolated keto groups which absorb very weakly in the ultraviolet (logϵ 1 to 2, $\lambda_{max.}$ 270 to 300 mμ), cyclic β diketones are characterized by intense absorption (logϵ 4 approximately $\lambda_{max.}$ 250 to 300 mμ). Substituents, dilution and acidity of the media have been studied as factors causing the absorption region to be shifted (108). The absorption spectra of the cyclic β diketones are distinguishable from the α, β unsaturated ketones in that the latter have a minor absorption band characteristic of the isolated carbonyl group, as well as an intense absorption maximum attributed to the conjugated system (109). Compared to cyclic β diketones, cyclic α diketones show an absorption band shifted somewhat towards the visible region (110), while cyclic 1,4 diketones, as expected, show the characteristic absorption band of the isolated keto group (111). Ultraviolet absorption, therefore, can serve as a useful tool for distinguishing between these different types of carbonyl compounds.

EXPERIMENTAL

Analytical methods

The Bromine Number Determination

A standard "bromide-bromate" method (112) was adapted to 50 to 75 mg. samples of less reactive unsaturated acids:- Five c.c. of 10% sulphuric acid saturated with potassium bromide, and 10 c.c. of C.P. chloroform were introduced into a 100 c.c. volumetric flask fitted with a glass stopper. The volumetric flask was used because the long, narrow neck reduced evaporation and spillage losses. The weighed sample was introduced, the flask and contents being vigorously swirled. An accurately known volume of potassium bromide-bromate solution (0.1N, 10 c.c.) was added from a burette, the sides of the flask being washed down with distilled water. The ground glass stopper was then held firmly in place with friction or adhesive tape and the flask and contents were mechanically shaken for thirty minutes or whatever time was found necessary. Potassium iodide (1 g.) was added and the contents titrated with 0.05N sodium thiosulphate, using starch solution as an indicator. The "bromine number" was given by the following equation:-

$$\text{Bromine Number} = \frac{0.0799 \times N_{KBr\text{-}KBrO_3} \times \text{net ml. } KBr\text{-}KBrO_3 \times 100}{\text{wt. of sample in grams}}$$

Manual shaking of the reaction mixture was found to be sufficient for samples containing double bonds of normal reactivity (113).

Neutralization Equivalent

The micro method recommended by Niederl and Niederl (114) was used and was defined as the number expressing in grams the quantity of the acid required for the neutralization of one liter of normal alkali.

Saponification Equivalent

The saponification equivalent was determined on the micro scale by the method recommended by Schneider (115) and was defined as being the quantity in grams of a compound required to consume one liter of normal alkali.

Carbonyl Groups and "Active" Hydrogen

A comprehensive discussion on the applicability of the method is given by Lieff (116). The determinations were carried out on the "Grignard Machine" according to the directions of Kohler, Stone and Fusion (117).

Molecular Refraction M_D

The refractive index n_D was noted in an Abbé type refractometer made by Zeiss. The density (d) was determined by means of a small pycnometer of 0.14 c.c. capacity. From n_D and d, the molecular refraction M_D could be calculated from the equation of Lorentz and Lorenz:

$$M_D = M \cdot \frac{n^2-1}{n^2+2} \cdot \frac{1}{d}$$

where M is the molecular weight of the compound. The calculated value was obtained by the use of the atomic refractions

determined by Auwers and Eisenlohr (118).

Percentage "Enol" Form

The method developed by Meyer (93) and modified by Cooper and Barnes (94) for 0.2 to 0.4 g. samples was adapted to a semi-micro scale, the following reagents being required:

(1) Absolute methanol, freshly distilled from calcium oxide.

(2) An approximately 0.1 N solution of bromine in absolute methanol, prepared by dissolving bromine (2 g.) in absolute methanol (250 c.c.). This solution was always made up freshly and used immediately.

(3) An 0.05 N solution of standardized aqueous sodium thiosulfate.

(4) A 10% aqueous solution of potassium iodide.

(5) Soluble starch solution freshly made up.

(6) Diisobutylene of a practical grade, (Eastman-Kodak).

About 10 c.c. of absolute methanol was pipetted into an Erlenmeyer flask of 125 c.c. capacity and fitted with a ground-in stopper. The accurately weighed sample (20 to 50 mg.) was dissolved in the alcohol and without delay the solution was cooled in a brine bath to about -5°. The methyl alcoholic bromine was added from a burette until the excess, as indicated by the development of a yellow colour, was about 1 c.c. After swirling the flask in order to effect thorough mixing, 1 to

2 c.c. of diisobutylene was added to absorb the excess bromine. The time consumed in adding the bromine and absorbing the excess should not exceed fifteen seconds.

Five c.c. of the aqueous potassium iodide was then added, the mixture was warmed with shaking to 30° and was allowed to stand for five minutes, during which period the colour of iodine appeared. After being titrated with the standard thiosulfate solution to a faint yellow colour, distilled water (50 c.c.) and soluble starch (1 c.c.) were added and the titration was continued to the end-point. Allowance had to be made for a slight blank which never exceeded 0.1 c.c. Some of the results are in Table XVIII.

$$\% \text{ Enol} = \frac{\text{c.c. of N thiosulfate} \times \text{mol. wt.} \times 100}{2 \times 1000 \times \text{sample weight in grams}}$$

Alkoxyl Determination

The alkoxyl content was determined on the semi-micro scale by the method devised by Zeisel and modified by Clark (119) and Viebock and co-workers (120).

Elementary Analysis

Carbon and hydrogen determinations were carried out on semi-micro samples with a technique based on the Niederl and Niederl (121) micro-method. The instructions of Stepanow (122) as described by Kamm (123) were followed in the determination of bromine.

Calibration of the Adams Hydrogenation Machine (124)

The Adams' machine was calibrated by the low pressure hydrogenation of 11.0 g. (0.095 moles) of pure maleic acid, prepared by the hydrolysis of maleic anhydride with water. A platinum oxide catalyst (0.1 g.) was used at room temperature (29°) and hydrogenation carried out at four to five atmospheres of hydrogen pressure. The course of the hydrogenation was followed as shown in Table I.

TABLE I

Hydrogenation of Maleic Acid

Time mins.	Pressure (gauge) pounds / inch^2	Pressure Atmospheres (a)	Corrected Pressure Atmospheres (b)
0	53.4	4.63	4.63
7	50.0	4.40	4.40
14	46.3	4.15	4.15
20	46.0	4.13	4.13
33	45.6	4.10	4.10
63	45.3	4.08	4.08
90	45.1	4.07	4.08
120	45.0	4.06	4.08
150	44.9	4.05	4.08

Note:- (a) Conversion of gauge pressure to atmospheres, e.g.

$\frac{45.0 + 14.7}{14.7} = 4.06$ (b) A small leak (0.24 lbs. / hr.) which could not be traced, made it necessary to correct the pressure (atm.). Thus corrected pressure (atm.) =

$\frac{45.0 + 14.7 + 0.48}{14.7} = \frac{60.2}{14.7} = 4.08$ atm.

A graphical representation (Figure 2) shows that hydrogen absorption was complete in about thirty minutes.

The moles of hydrogen n present in any container of volume V liters at a modest pressure of p atmospheres, and at an absolute temperature T is given by

$$n = \frac{V}{RT} \cdot p \qquad (1)$$

Where R is the gas constant with a value of 0.0821 in liter-atmospheres.

Inserting initial and final conditions, equation (1) becomes

$$n_1 = \frac{4.63\ V}{0.0821(302)} \qquad (2)$$

$$\text{and } n_2 = \frac{4.08\ V}{0.0821(301)} \qquad (3)$$

$$\text{but } n_1 - n_2 = 0.095 \qquad (4)$$

Solving these three simultaneous equations, the volume of the Adams container, V, is 4.35 liters and from (1)

$$n = \frac{4.35}{0.0821(T)}\ p \qquad (5)$$

Equation (5) relates the pressure (p) and the number of moles (n) of hydrogen present in the Adams apparatus at any given temperature (T°K). Thus the hydrogen absorbed in a given hydrogenation, Δn, could be readily calculated.

MATERIALS

All melting points recorded are uncorrected.

Trimethyl Gallic Acid(XLVI)

Trimethyl gallic acid was prepared by a modification of the procedure of Graebe and Martz (125):-

Technical gallic acid monohydrate (XLV) (168 g. 0.90 mole) was dispersed in 750 c.c. of water contained in a one liter three-necked flask equipped with a stirrer and two dropping funnels, each of 300 c.c. capacity. The mixture was heated to about 50° on a steam bath. Sodium hydroxide solution, 200 g. dissolved in 400 c.c. of water, and dimethyl sulphate, 660 g., were added dropwise and simultaneously over a period of 90 minutes with constant stirring. The solution was heated and stirred for an additional 90 minutes. Sodium hydroxide, 60 g., dissolved in 100 c.c. of water was added to the brown suspension and heating and stirring was continued until solution became complete. The reaction mixture was cooled to 30° and made acid with concentrated hydrochloric acid. A voluminous white precipitate separated, which when recrystallized twice from ethanol and dried melted at 169°. Yield 140 - 150 g. (70%). The melting point recorded for trimethyl gallic acid (XLVI) is 167° (126).

Anal. calcd. for trimethyl gallic acid (XLVI) $C_{10}H_{12}O_5$: OCH_3 - 43.8%. Found - 43.5, 44.1 %.

Mauthner's method (126) for preparing the substance (XLVI) was also used. This convenient procedure employed smaller quantities of reactants but gave consistently superior yields of 89 to 92%.

m-Hydroxybenzoic Acid (XLVII)

The following preparation of m-hydroxybenzoic acid differs in minor particulars from that of Offermann (127):-

Benzoic acid, technical grade, 250 g., was dissolved by warming with fuming sulphuric acid, 25% SO_3, 500 g., contained in a 2-liter round bottom bull-necked flask. At 200° discoloration to a deep red color occurred, the solution being kept at 200 ± 10° for 90 minutes. After this period, a sample of the reaction solution was completely soluble in water and sulfonation was considered to be complete. The bulk of the mixture was then cooled in a brine bath and was poured into an ice-water mixture (1 liter). The clear aqueous solution was poured into 2 liters of concentrated aqueous sodium chloride (37.5%) and crystallization began immediately. After standing at 10° for one hour, the mixture was filtered, the residue washed with saturated sodium chloride (400 c.c.) and dried at 100° for twelve hours. The yield of sodium m-sulfobenzoic acid varied between 400 and 424 g. (88 to 92%) for the first crop. A small second crop, obtained by allowing the mother liquor to cool for a longer period, raised the yield almost to the theoretical value.

Sodium m-sulfobenzoic acid (150 g.) was stirred into a mush with 100 c.c. of aqueous caustic soda containing 40 g. of the base, and the mixture was heated on the steam bath with 30 g. of sodium hydroxide pellets. The cooled, solidified mass was ground in a mortar and added to a mixture of sodium hydroxide, 75 g., and potassium hydroxide, 75 g., kept just above the point of fusion. The mixture was stirred at 210-220°

for two hours, after which time the cooled melt was dissolved in 400 c.c. of water, and the solution made acid with concentrated hydrochloric acid. A copious precipitate of m-hydroxybenzoic acid (XLVII) was obtained. The aqueous mixture was cooled to 10 to 15° prior to filtration and recrystallization of the crude material (93 g.) from water gave 75 g. (81%) of a white product melting at 196 - 197°. Huntress and Mulliken (128) report the melting point of m-hydroxybenzoic acid (XLVII) to be 200°.

Diazomethane

The method of Arndt was used (129). Nitrosomethylurea, 12 g., was gradually added to ether, 100 c.c., and 30 c.c. of 40 percent potassium hydroxide solution contained in a 500 c.c. Erlenmeyer flask. The ethereal solution containing the diazomethane was decanted and dried over potassium hydroxide pellets for four hours prior to use.

p-Bromphenacyl Bromide

p-Bromphenacyl bromide was prepared by Langley's method (130) by the bromination of p-bromacetophenone.

Isoamyl Alcohol

The Eastman Kodak technical grade was fractionated through a small column and the fraction boiling at 130 - 132° was retained. A grade supplied by Hoskin Scientific Specialties was purified in a similar manner.

Sodium Metal

The sample used was Merck's reagent grade.

Preparation of Cis Cyclohexanol-3 Carboxylic Acid (XI)

m-Hydroxybenzoic acid (XLVII), 29 g., or 0.21 moles was dissolved in 200 c.c. of stock ethanol; sodium hydroxide pellets (17.5 g., reagent grade) and water (25 c.c.) were added to make a total volume of 235 c.c. The solution was poured into a small Parr bomb and 4 g. of Raney nickel were added.

TABLE II

Catalytic Hydrogenation of m-Hydroxy Benzoic Acid (XLVII)

Time Mins.	Temp. °K.	Pressure p.s.i.	N Moles H_2 (a)	Remarks
0	294	2000	1.49	
10	392	3100	1.74	f=0.22 (a)
15	403	3000	1.63	
25	401	2650	1.45	
45	393	2350	1.32	
70	423	2100	1.09	
110	417	1925	1.01	heat off
330	308	1200	0.85	

(a) N calculated from the formula $N = f \frac{p}{T°K}$ and f is read from the calibration chart for the Parr bomb in which f is plotted against the volume of charge.

Total hydrogen absorbed = 1.49 - 0.85 = 0.64 moles.

theory = 0.63 moles.

The Raney nickel was removed by filtration from the solution and glowed very vigorously when dry. The filtrate was reduced to

half volume by evaporating under reduced pressure on the steam bath and was acidified with concentrated hydrochloric acid. Precipitated salt was removed and the filtrate again reduced to half volume before more sodium chloride was removed by filtration. The reaction mixture was then brought to dryness at reduced pressure. In this condition no crystallization occurred and the material remained as a syrup even when seeded with an authentic sample of cis-cyclohexanol-3 carboxylic acid or when dissolved in such normally good crystallizing solvents as ethyl acetate or diethyl ether. The syrup, dissolved in 100 c.c. of ten percent sodium hydroxide, was then extracted once with ether. The alkaline solution was acidified with concentrated hydrochloric acid saturated with ammonium sulfate and was extracted about five times with ether. The ethereal solution was dried over anhydrous magnesium sulfate, the ether removed at reduced pressure, whereupon the whole mass solidified. This solid mass was then taken up in 50 c.c. of hot ethyl acetate and allowed to cool spontaneously to room temperature and finally was kept at 10°. Practically pure <u>cis</u> cyclohexanol-3 carboxylic acid (XI) separated as white crystals, m.p. 130 to 132°. The yield was 14.5 g. or about 50% of theory. XI is reported to melt at 131 - 132° (16).

<u>Anal.</u> <u>Calcd.</u> for $C_7H_{12}O_3$: C, 58.3; H, 8.3; neutralization equivalent, 144.0 <u>Found</u>: C, 58.4, 58.5; H, 8.6, 8.4; neutralization equivalent, 143.6, 143.8.

The mother liquor from the cis-acid was taken down to dryness and the residue eventually solidified, although attempts at recrystallization from any of the common solvents failed. Weight 7 g. or about 25% of theory. Boiling this solid under reflux with 15 c.c. of constant-boiling hydrobromic acid yielded exclusively trans 3-bromo cyclohexane carboxylic acid with the correct m.p. 167° (16), showing that the parent substance was mainly trans 3-hydroxy cyclohexane carboxylic acid. This bromine substitution, of course, may have caused some inversion of any cis-acid present.

p-Bromphenacyl Ester of cis 3-Hydroxy Cyclohexane Carboxylic Acid (XI)

Cis 3-hydroxy cyclohexane carboxylic acid (m.p. 131 to 132°, 0.1 g.) was added to water (0.5 c.c.) and was neutralized carefully with ten percent sodium hydroxide solution. One c.c. of stock ethanol was added together with 0.25 g. of p-bromophenacyl bromide. The mixture was heated on the steam bath at reflux temperature for one and one half hours, before being allowed to cool spontaneously to room temperature, precipitating white flocculent crystals. The mass was triturated with 2 c.c. of 50 percent aqueous alcohol and after recovery, was recrystallized from 3 to 4 c.c. of stock ethanol. Yield 0.15 g. m.p. 136°.

A second crop of 0.05 g. was obtained from the filtrate

(total yield 88%). Both the first and second crops were recrystallized from ethanol and melted sharply at 136°. The product was dried in the Abderhalden at 65 - 70° for thirty minutes prior to analysis.

Anal. Calcd. for $C_{15}H_{17}O_4Br$: C, 52.8; H, 5.1 Found: C, 53.0, 52.9; H, 5.3, 5.1%.

Oxidation of cis-Cyclohexanol-3 Carboxylic Acid (XI) to 3-Keto Cyclohexane Carboxylic Acid (XLVIII)

The procedure used was based on that developed by Perkin and Tatersall (16). A solution of 11 g. of cis-cyclohexanol-3 carboxylic acid m.p. 130 - 132° in 50 c.c. of water was warmed to 45° in a three-necked flask of 250 c.c. capacity. Then a solution of 15.5 g. of potassium dichromate and 11 g. of concentrated sulfuric acid in 66 c.c. of water was added in small quantities. Fresh oxidant was only added after the previous quantity had been reduced as shown by the green colour of chromous ion. The reaction mixture was cooled, saturated with ammonium sulfate and extracted about ten times with ether. The ethereal extract was dried over anhydrous magnesium sulfate and on evaporation a viscous oil remained, weighing 7 g. Continuous extraction of the residual aqueous solution with ether for three hours in a liquid-liquid extractor fitted with a sintered glass disperser brought the yield of viscous oil up to 10 g. Further extraction overnight increased the total yield to the theoretical amount, 11 g.

The oil was then distilled through a 3 inch Widmer flask of 20 c.c. capacity. A very viscous liquid (6.5 - 7 g.) boiling at 120 - 125° n_D^{20} 1.4822 was obtained, the latter part being somewhat colored. By allowing the product to stand overnight in the cold room, the whole mass solidified. The product could be readily crystallized from 10 c.c. of benzene and yielded 5.5 g. of white crystals melting at 76°. Perkin and Tattersall (16) report the melting point of 3-keto cyclohexane carboxylic acid (XLVIII) to be 76°.

The p-Bromphenacyl Ester of Cyclohexanone-3 Carboxylic Acid (XLVIII)

One-half gram of (XLVIII) was dispersed in water (2 c.c.) and carefully neutralized with 10 percent caustic soda to a pH of 7 to 8. After the standard condensation with 1.2 g. of p-bromphenacylbromide 1.3 g. of a white crystalline product melting at 115 - 120° resulted. The product was recrystallized from 15 c.c. of boiling stock ethanol and melted (after drying in the Abderhalden) at 121.5 - 122°. The yield was 1.1 g. or 92%.

Methyl 3-Keto Cyclohexane Carboxylate (XLIX)

A solution of cyclohexanone-3 carboxylic acid, 1 g., in 10 c.c. of neutral dry ether was mixed with an ethereal solution of diazomethane, obtained from 5 g. of nitrosomethylurea. After standing for thirty minutes at 10 - 15°, the excess diazomethane

and all of the diethyl ether were removed by co-distillation and the residue was distilled through a Widmer flask of 5 c.c. capacity. A colorless liquid, 0.76 g., (74%) n_D^{20} 1.4640 b.p. 78-79 / 1 mm. was obtained.

Anal. Calcd. for methyl 3-keto cyclohexane carboxylate, $C_8H_{12}O_3$: C - 61.54, H - 7.7, OCH_3 - 19.9 Found C - 61.5, 61.4; H - 7.7, 7.6; OCH_3 - 19.9, 19.9%.

An ethereal solution of this substance was extracted with saturated aqueous sodium bisulphite at room temperature. The extract was acidified, the sulfur dioxide removed by aeration, and the starting material recovered by an ether extraction. The recovery was 75% by weight.

The Attempted Enolization of 3-Keto Cyclohexane Carboxylic Acid (XLVIII)

An 0.2503 g. sample of the acid was dissolved in 50 c.c. of one percent sodium carbonate contained in a glass stoppered volumetric flask of 100 c.c. capacity and the solution kept at 25 $\pm$ 0.2° for about two weeks. During this time, 5 c.c. aliquots were removed at intervals and were rapidly mixed with 5 c.c. of 10 percent sulphuric acid saturated with potassium bromide and then 5.0 c.c. of bromide-bromate standard solution (0.1 N approx.). After the addition of 10 percent aqueous potassium iodide, titration with standard sodium thiosulphate solution was undertaken. There was negligible bromine absorption even with solutions which were allowed to stand about two weeks in sodium carbonate, showing that very little enolization had occurred.

Methyl cis 3-Methoxy Cyclohexane Carboxylate (L)

Cis 3-hydroxy cyclohexane carboxylic acid, 1.8 g., was dissolved in methyl iodide (15 g.) and dry silver oxide (6 g.) was added over a period of three and a half hours. The reaction mixture was stirred and maintained at reflux temperature during this time, and then was filtered and the ether was evaporated from the filtrate. Since the methoxyl content of the residue was only 27 percent instead of the expected 36 percent, the methylation was repeated with 10 g. of methyl iodide and 4 g. of silver oxide, heating under reflux and stirring being for twelve hours. The product, 2.1 g., was fractionally distilled through a semi-micro Cooke-Bower column (131) with the results shown in Table III.

TABLE III

Rectification[(a)] of Methyl Cis 3-Methoxy Cyclohexane Carboxylate (L)

Fraction Number		Column Temp. °C	Bath Temp. °C	n_D^{20}
1		67	72	1.4510
2		68	73	1.4510
3		68	73	1.4510
4	(b)	67	75	1.4510
5		72	75	1.4510
6		72	76	1.4510
7		73	77	1.4510

(a) Pressure 2.4 mm.

(b) Fraction (4) had density d_4^{20} 1.0351

Total yield 1.8 g. (91 - 92%)

Anal. Calcd. for methyl 3-methoxy cyclohexane carboxylate

C- 62.8; H - 9.3; OCH_3 - 36.0; M_D - 44.9 Found C - 62.8, 63.1; H - 9.6, 9.5; OCH_3 - 35.7, 35.4; M_D - 44.7

Attempted Reductions of Gallic Acid (XLV)

The reduction of gallic acid (XLV) was attempted using absolute ethanol with either sodium or potassium metal, also with isoamyl alcohol in conjunction with sodium metal. A molar ratio of alkali metal to gallic acid (XLV) of twenty-five to one was employed in all cases.

In a typical experiment, gallic acid (XLV) monohydrate, 22 g. or 0.118 moles, was dissolved in 125 c.c. of ethanol containing 15 c.c. of benzene, and the benzene and water were removed by azeotropic distillation. If the reaction medium was to be isoamyl alcohol the ethanol was removed by distillation and the residue dissolved in one liter of the alcohol. After the solution had been warmed to 40° to 50° in a 3-liter three-necked flask, a total of 2.95 moles of the clean metal was added as rapidly as possible in pieces the size of a bean. Vigorous reaction ensued, with rapid reflux, especially with the potassium, and the color of the mixture changed from light yellow to green and finally to dark green. Hydrolysis of the alkoxide was effected with 150 c.c. of water and after cooling by the introduction of dry ice, the mixture was made acid to pH 1 with dilute hydrochloric acid, the precipitated salt being removed by filtration. The evaporation of the filtrate under reduced pressure was carried on intermittently to allow

for the filtration of precipitated salt. The residue, a badly discolored dark brown material in all cases, yielded some unchanged gallic acid by recrystallization from ethyl acetate. The identity of the substance was proved by acetylation with acetic anhydride and pyridine to triacetyl gallic acid m.p. 166° not depressed by admixture with an authentic sample of triacetyl gallic acid. No reduced product was ever characterized.

Reductions of Trimethyl Gallic Acid (XLVI) By Means of Sodium and Isoamyl Alcohol

Trimethyl gallic acid (XLVI) (25 g. 0.118 moles) was dissolved in 1 liter of isoamyl alcohol contained in a three liter three-necked flask fitted with an efficient mercury-seal stirrer and two efficient reflux condensers in series one above the other. The third neck of the flask was reserved for the introduction of sodium. The temperature of the solution was raised to 100° before the proper amount of clean sodium was added in small pieces, the size of beans, as rapidly as possible with constant stirring. Boiling under reflux became vigorous and the reaction mixture turned slightly turbid. After a short while complete solution occurred but stirring was continued for an additional thirty minutes. The amount of sodium used in this reaction was varied from a minimum of 15 g. (0.65 moles) to 100 g. (4.35 moles), while

the amount of (XLVI) was kept constant at 0.118 moles. The reaction mixture, containing a large amount of the sodium alkoxide of isoamyl alcohol, was hydrolyzed by the addition of (300 c.c.) of water. The yellow water layer was separated, and the isoamyl alcohol layer was back-extracted with water until neutral. The alkaline water layer, together with the washings, was then acidified to pH 1 with concentrated hydrochloric acid with cooling in a water bath, whereupon an oil layer separated. As a rule, this acidified mixture was then continuously extracted with ether in a liquid-liquid extractor of 1 liter capacity fitted with a porous plate type disperser. The ether was removed from the extract at atmospheric pressure and the residue was weighed. Runs in which different amounts of sodium were used required important variations of procedure from this point onward and are best considered individually.

Experiments made in several runs showed that the residual isoamyl alcohol contained negligible amounts of the products and it was accordingly not investigated any further, but set aside for recovery of the alcohol.

Reduction of Trimethyl Gallic Acid (XLVI) with 5.5 Atoms of Sodium

(a) The methylated gallic acid (XLVI), 25 g. or 0.118 moles, was reduced as already described with 15 g. (0.65 moles) of sodium. Acidification of the aqueous alkaline solution containing the products caused 10 g. of a white precipitate to

separate. After drying for twelve hours in a vacuum dessicator over calcium chloride, this material was dissolved in 100 c.c. of ether and the insoluble part (3.5 g.) was removed by filtration. Upon recrystallization from water and after drying in a drying pistol for twelve hours this part yielded needles melting at 164 - 169°. A further recrystallization from water-methanol (75 c.c. water, 12 c.c. methanol) yielded after drying a material melting 168 - 169° and showing no depression in melting point when mixed with an authentic sample of trimethyl gallic acid. The 6 g. portion dissolved in the ether was recovered and recrystallized from water, whereupon white needles melting at 95 - 120° were obtained. Recrystallization from methanol-water raised the melting range to 135 - 147°. Recrystallization from ether yielded a fraction (1) melting at 158 - 170°. Evaporation to half-volume yielded another fraction m.p. 158 - 170° (2). The residue recovered and dissolved in hot methanol, upon cooling, deposited white needles melting at 145 - 168° (3). A fourth fraction was obtained by evaporation of the mother liquor after recrystallization from methanol-water m.p. 145 - 165°. A fifth fraction from methanol melted at 136 - 167° and a sixth was obtained by concentrating all the residues and crystallizing from methanol-water m.p. 145 - 167°. These fractions, all of which gave a negative test for phenol or enol with methanolic ferric chloride, were analyzed to determine whether non-aromatic material such as the saturated 3, 4, 5 trimethoxy cyclohexane carboxylic acids, was present

to any appreciable extent (Table IV).

TABLE IV

Analyses of Crude Trimethyl Gallic Acid

Fraction No.	Melting Range °C	OCH_3 %	Neutralization Equivalent	% C	% H
1	158 - 170	42.2, 42.4	216	57.4	6.1
2	158 - 170	----	219	----	---
3	145 - 168	42.8, 42.7	216	----	---
4	145 - 165	42.2, 42.6	213	----	---
5	136 - 167	42.7	217	----	---
6	145 - 167	42.9	217	55.7	6.6
Theory for trimethyl gallic acid (XLVI)			(126)		
	167	43.8	212	56.7	5.7

It was concluded that all these fractions were crude trimethyl gallic acid which could not be readily purified by fractional crystallization. The yield of this acid thus totalled about 7 - 8 g. or about 29% of theory. The clear aqueous solution from which these fractions had separated on acidification was then continuously extracted with ether for fifteen hours. During this time a white solid was precipitated in the still pot of the extractor. After washing with ether, this white material (5.3 g.) gave a pink color with methanolic ferric chloride, thereby indicating enolic or phenolic groups. A test for carbonyl with 2,4 dinitrophenyl hydrazine also became slowly positive. This substance was insoluble in benzene, petroleum ether and ether, but was soluble in ethyl acetate, chloroform, acetone, methanol, ethanol and water. From most of these solvents, (except water) it crystallized imperfectly, if at all. Efficient

crystallization occurred spontaneously from three parts of water. After drying in an Abderhalden pistol, the pale yellow crystals melted at 166 - 167° to a deep orange melt. Further recrystallization from water did not raise the melting point.

Anal. Calcd. for cyclohexanedione-3,5 carboxylic acid, $C_7H_8O_4$: C - 53.8; H - 5.12%; neutralization equivalent - 78

Found C - 53.7, 53.8; H - 5.23, 5.18%; neutralization equivalent (direct) - 77, 78; enol - 121, 122%.

When the neutralization equivalent of this compound was determined by boiling in 100% excess alkali for 15 minutes the values found were 74, 76.

(b) In another run, reduction of the trimethyl gallic acid was carried out as described but the manner of isolating products was different.

The isoamyl alcohol reaction mixture was neutralized to pH 2 with dilute hydrochloric acid, the precipitated salt being removed by filtration by suction. The isoamyl alcohol and incidental water were removed at reduced pressures in an atmosphere of carbon dioxide. Ethanol and benzene were successively added to the residue and were removed by distillation at reduced pressures in order to eliminate the remaining traces of water and isoamyl alcohol. When the thick oily residue was taken up in ether, 1 g. of an insoluble material remained. Complete removal of the ether at reduced pressures and addition of more ether yielded an additional gram of the white crystalline material.

The residual heavy oil, 26 - 27 g., was evidently partly esterified by isoamyl alcohol as shown by its excessive weight. This oil was dissolved in 100 c.c. of 10 percent sodium hydroxide, the mixture was heated on the steam bath for three hours under an atmosphere of nitrogen and was then cooled and acidified with hydrochloric acid. After being kept at about 5° for twelve hours, the precipitated material was recovered, combined with the two previous 1 g. precipitates and recrystallized from methanol. Four grams of pure trimethyl gallic acid, or 16 percent, was obtained. When the clear aqueous acid filtrate, 150 c.c., was continuously extracted with ether, a copious precipitate (7.8 g.) was obtained in the still pot after eighteen hours. This material was recrystallized from 25 c.c. of water and showed no depression in melting point when mixed with enolic material $C_7H_8O_4$ obtained from the previous run (a).

The prolonged heating involved in distilling isoamyl alcohol from the reaction mixture yielded more highly colored products than those from run (a) and apparently caused some esterification of the carboxylic acids produced.

The ether soluble residual oil from the ether extraction (3.5 g.) in either of runs (a) or (b) was esterified with diazomethane and after distillation at reduced pressures yielded 2 - 2.5 g. of a colorless liquid boiling at 66 - 68° / 0.3 mm. ;

n_D^{20} 1.4640. This oil has physical constants very similar to methyl 3-keto cyclohexane carboxylate (XLIX) (page 58), as well as to products obtained from other reductions of (XLVI) as will be seen later.

Periodate Oxidation of Compound $C_7H_8O_4$

A 23.25 mg. sample (0.149 millimoles) of compound $C_7H_8O_4$ was oxidized at room temperature (24°) and at pH 4.0 with 50 c.c. periodic acid (0.00605 M). The course of the reaction was followed by titrating 5 c.c. aliquots at intervals by the arsenite-iodine method described by Fleury and Lange (132) Table V.

TABLE V

Periodate Oxidation of Compound $C_7H_8O_4$

Time mins.	Moles of IO_4^- consumed (a)
0	0
7	0.93
14	1.05
27	1.05
42	1.13
121	1.50
146	1.58
206	1.71
345	1.84
591	1.97
711	2.00

(a) Per $C_7H_8O_4$ unit.

A graphical representation (Figure 6) shows quite clearly that one mole of periodic acid was consumed very rapidly and one mole was consumed much more slowly.

To make possible a comparison of this result with that obtained by the periodate oxidation of a known cyclic β diketone, 5,5 dimethylcyclohexanedione 1,3 (LI) was subjected to a similar treatment after recrystallization from 20 percent ethanol (m.p. 148-149°):

A 9.91 mg. sample of (LI) was oxidized at room temperature (32°) and at pH 4.0 with 50 c.c. of periodic acid (0.00482 M). The course of the reaction is shown in Table VI.

TABLE VI

The Periodate Oxidation of 5,5 Dimethylcyclohexanedione 1,3 (LI)

Time mins.	Moles of IO_4^- consumed (a)
0	0
6	0.89
11	1.00
24	1.34
54	1.71
84	2.00
114	2.00
174	2.00
234	2.00

(a) Per $C_8H_{12}O_2$ unit.

These results, expressed graphically (Figure 6), also show that one mole of periodic acid was consumed rapidly and that one mole was consumed more slowly.

The Catalytic Hydrogenation of Compound $C_7H_8O_4$

The compound $C_7H_8O_4$ (5 g., 0.032 moles) was dissolved in 90 percent aqueous ethanol and 0.1 g. of freshly prepared platinum oxide was added. Hydrogenation was carried out at 27° with a

hydrogen pressure of four to five atmospheres in the Adams' machine. The calibration of this apparatus has already been described (page 49). It was found impossible, however, to locate a small hydrogen leak that diminished the pressure at the nearly constant rate of 0.24 pounds per hour. The observed readings when converted to atmospheres were corrected for this leak as shown in Table VII.

TABLE VII

The Catalytic Hydrogenation of Compound

$C_7H_8O_4$

Time hrs.	Pressure (gauge) p. s. i.	Atmospheres Corrected	Moles Hydrogen present N
0	52.9	4.60	0.814
0.33	52.1	4.55	0.805
0.59	51.5	4.51	0.800
1.00	50.6	4.45	0.790
1.50	50.0	4.43	0.785
2.00	49.5	4.40	0.780
2.54	49.1	4.38	0.775
3.22	48.5	4.35 (a)	0.768 (a)
3.92	48.0	4.33	0.759
4.93	47.5	4.31	0.756
5.93	46.9	4.28	0.750
8.21	46.0	4.27	0.747
9.21	45.7	4.26	0.745
9.91	45.4	4.26	0.745

$N = 0.814 - 0.745 = 0.069$ moles hydrogen

Theory $= 0.064$ moles

(a) Sample calculation: $\frac{48.5 + 14.7 + 0.8}{14.7} = \frac{64.0}{14.7} = 4.35$ atmospheres

$N = \frac{4.35}{0.0821\ (T)} \cdot p = \frac{4.35\ (4.35}{0.0821\ (300)} = 0.763$ moles hydrogen

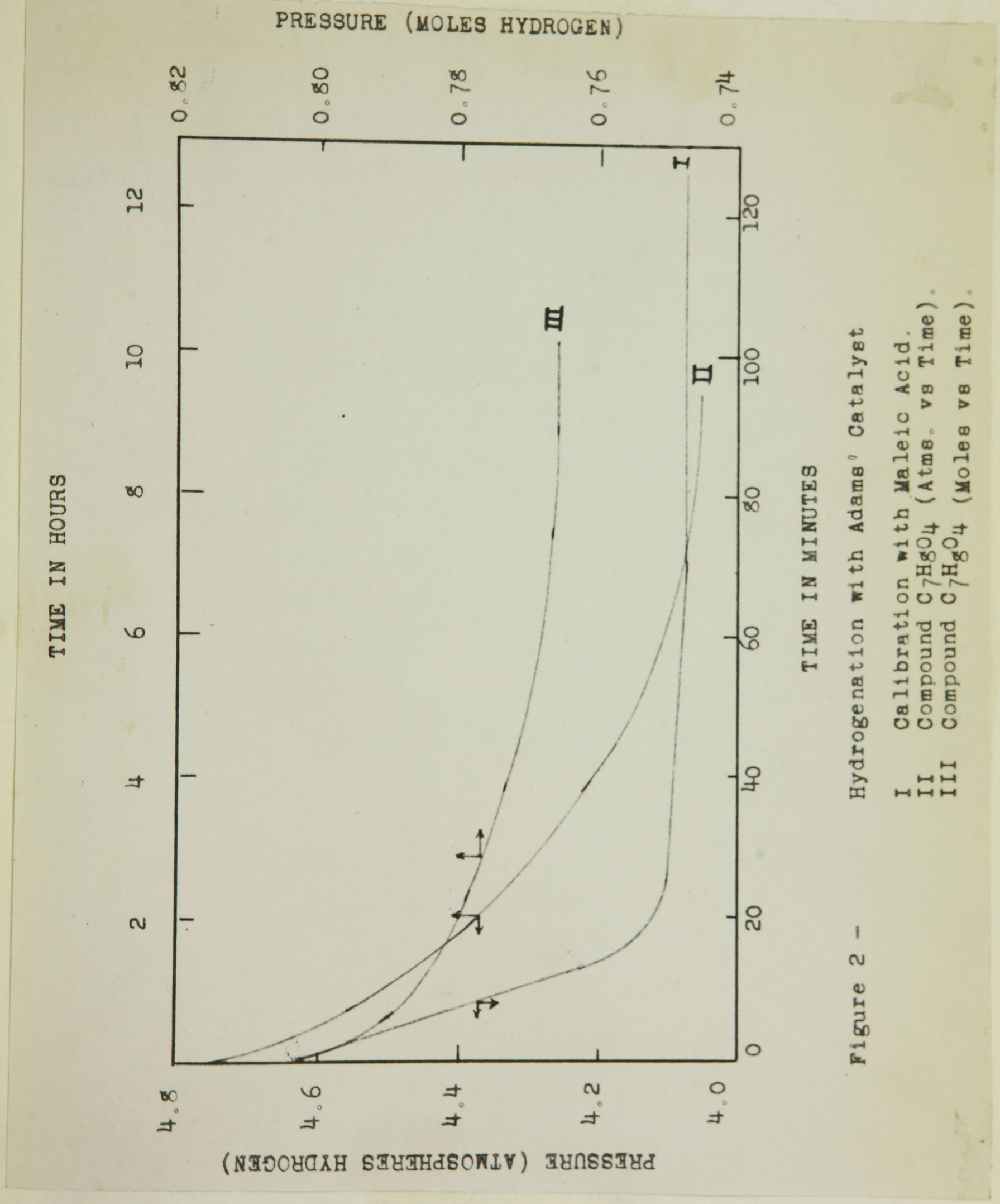


Figure 2 – Hydrogenation with Adams' Catalyst

I Calibration on with Maleic Acid.
II Compound $C_7H_8O_4$ (Atms. vs Time).
III Compound $C_7H_8O_4$ (Moles vs Time).

Since 0.032 moles of substance were hydrogenated, four atoms of hydrogen were absorbed per mole of compound $C_7H_8O_4$ (Figure 2). The ethanol was removed at reduced pressure and 4.9 g. (98% recovery) of a viscous pale yellow oil was obtained. After twenty-four hours, the mass became crystalline and was triturated with 10 c.c. of ether-acetone (1:1). A white crystalline material melting 98 - 101° was recovered by filtration which gave the following values on analysis.

Anal. Calcd. for $C_7H_{12}O_4$: C - 52.5; H - 7.5%; neutralization equivalent - 160 Found C - 52.2, 52.2; H - 7.7, 7.6 %; neutralization equivalent - 153, 153.

The neutralization equivalent for the residual oil, which remained in solution after trituration, was determined and by direct titration was found to be 148, unchanged by boiling with 100 percent excess alkali. These results showed that there was no lactonization and that the oil was about 92 percent pure.

Periodate oxidations of the crystalline and syrupy portions showed only a very small consumption of oxidant even after twelve to fourteen hours. Thus the material did not have an α glycol structure.

After standing for several days the residual syrup from the crystalline portion became solid, but could not be triturated with acetone, ether, ethyl acetate or a combination of these, the entire mass becoming waxy instead of crystalline. This be-

haviour suggested that the residual oil was less soluble than the crystalline portion in these solvents. The oily solid was then pressed between filter papers for two weeks. The solid crust (1.2 g.) thus obtained was crystallized from ethyl acetate, successive crystallizations giving two fractions melting 116 to 124° (neutralization equivalent 158, 158) and 116 to 118° (neutralization equivalent 158, 159) respectively. The theoretical value of the neutralization equivalent for the cyclohexanediol carboxylic acids is 160. Thus 1.45 g. (30%) was white crystalline material analysing for the cyclohexanediol 3,5 - carboxylic acids but melting softly over a wide range.

Reduction of Trimethyl Gallic Acid (XLV) with 11.1 Atoms of Sodium

(a) The reduction of 25 g. of (XLV) (or 0.118 moles) 30 g. of sodium (1.30 atoms) in 1 liter of isoamyl alcohol was carried out as previously described. After acidification of the aqueous liquor containing the products, continuous extraction with ether recovered about 17.2 g. of a viscous, red-brown syrup which was taken up in ether, dried over anhydrous magnesium sulfate and esterified with an ethereal solution of diazomethane. The end of the esterification was reached when the evolution of nitrogen ceased. The excess diazomethane was co-distilled with some of the ether into a receiver containing dilute hydrochloric acid to destroy the diazomethane. The still residue, having been made up to 100 c.c. with more diethyl ether, was extracted with

four 25 c.c. portions of saturated sodium bisulphite solution. Evidence of the formation of a bisulphite addition compound was found in that heat was evolved during the first extraction and a white solid was precipitated. This solid was dissolved by the addition of more distilled water to the separatory funnel. The bisulphite solution was then acidified with dilute sulfuric acid, aerated at reduced pressure and room temperature to remove the sulfur dioxide, and then continuously extracted for thirty-six hours with ether. After drying and removal of ether the oil (4.5 g) was distilled to yield 3.5 g. of a colorless liquid b.p. 76 - 78° / 1 mm. n_D^{20} 1.4640, OCH_3 - 19.9%. The substances not extracted by bisulphite from ether were recovered, after drying over anhydrous magnesium sulphate, and weighed 6 g. When distilled through a Widmer flask of 10 c.c. capacity, one fraction was obtained weighing 1.4 g. b.p. 72 - 74° / 1 mm. This fraction was not further investigated because of the large losses involved in this distillation.

(b) It was obvious from the above run that important quantities of product (6 - 10 g.) including both bisulphite extractable and non-extractable portions, were lost. Another run was therefore carried out using the "distillation method" of isolating products. Upon completion of the sodium reduction the isoamyl alcohol solution was acidified with concentrated hydrochloric acid to pH 2, the precipitated salt being separated by filtration. The removal of isoamyl alcohol was accomplished

by distillation at reduced pressures in an atmosphere of carbon dioxide. A syrupy residue weighing 30 g. was saponified with 100 c.c. of aqueous 10 percent sodium hydroxide for ninety minutes under an atmosphere of nitrogen. The alkaline solution was extracted with ether to remove any isoamyl alcohol formed and was then acidified with dilute hydrochloric acid. The solution remained clear, no precipitate being formed as in the experiment using 15 g. of sodium. Continuous extraction of this aqueous solution with ether yielded 20 to 22 g. of a reddish-brown syrup which gave a rapid positive test for carbonyl with 2,4 dinitrophenylhydrazine as well as a positive test (deep red in color) with methanolic ferric chloride. After standing for twenty-four hours at room temperature, a dry ether solution deposited crystals. After two weeks at 0°, 0.45 g. of a white crystalline material was obtained which on recrystallization from water melted at 166 - 167° and showed no depression with the enolic compound, $C_7H_8O_4$, obtained from the reduction with 15 g. of sodium. An attempt to prepare a 2,4 dinitrophenylhydrazone of the residual oil by the method recommended by Shriner and Fuson (132) gave no isolatable product, although the characteristic color of 2,4 dinitrophenylhydrazones was exhibited.

A portion (1 g.) of this oil was acetylated by the Schotten-Baumann reaction as modified by Chattaway (133). Ten grams of ice was mixed with the solution in 10 c.c. of 10 percent caustic soda, and then 1.5 g. of acetic anhydride was rapidly added with

stirring. The solution became pale yellow and somewhat turbid. On acidification and extraction with ether a yellow oil was obtained which gave a negative test with methanolic ferric chloride. The oil could not be crystallized either by itself or from any of the common laboratory solvents.

Reduction of Trimethyl Gallic Acid (XLV) with 14.8 Atoms of Sodium

The reduction employing 25 g. of (XLV) and 40 g. of sodium was carried out as previously described and the products were isolated by the extraction method, yielding 16 g. of a brown oil. After drying in ether solution over anhydrous magnesium sulphate, the carboxylic acids were esterified by diazomethane prepared from 22 g. of nitrosomethylurea. The excess diazomethane was removed by co-distillation with some of the ether. The residue was made up to 100 c.c. with stock ether and hand extracted with four 25 c.c. portions of saturated sodium bisulphite solution. Evidences of the formation of the bisulphite addition compound were shown by the liberation of heat and formation of a solid product which was dissolved in the separatory funnel by the addition of more distilled water. The bisulphite extract was acidified with dilute sulphuric acid, aerated under reduced pressure to remove the sulphur dioxide and continuously extracted for twenty-four hours with ether. After drying of the ether solution and removal of the ether, a residue (8 g.) was obtained. This residue was treated with a little

ethereal diazomethane to assure complete esterification. Distillation of this residue through a Widmer flask of 15 c. c. capacity yielded 4.5 g. of a colorless liquid, methyl 3-keto cyclohexanecarboxylate, b.p. 78° / 1 mm. n_D^{20} 1.4640. The residual ethereal solution, containing the bisulphite non-extractable material, was dried and the oil it contained distilled from a Widmer flask of 10 c.c. capacity at 0.8 mm. pressure. In addition to a residue (0.6 g.) the distillation yielded 0.3 g., b.p. 63 to 68°, n_D^{20} 1.4633; 0.9 g., b.p. 77 to 78°, n_D^{20} 1.4982; and 0.7 g., b.p. 105 to 120°, n_D^{20} 1.5130.

The Reduction of Trimethyl Gallic Acid (XLV) with 18.4 Atoms of Sodium

The reduction of 25 g. (0.118 moles) of (XLV) was carried out on several occasions using 50 g. (2.17 atoms) of sodium in one liter of isoamyl alcohol. The products were isolated from the acidified aqueous solution by the ether extraction method, which in some cases was interrupted after various times to follow the course of the extraction.

TABLE VIII

Fractions Removed by Successive Ether Extractions

Symbol	Extraction Time (hrs.)	Weight (g.)	n_D^{27}	Instantaneous Br. No.	OCH$_3$ %
A	1.5	12.5	1.4993	11	5.1
B	3.5	2.5	1.4995	16.5	0.7
C	23.5	1.0	1.5035	---	---

Part of fraction A, 7.5 g., was extracted with 50 c.c. of hot water. The clear water solution was decanted, and on evaporation

to dryness at reduced pressure an oil (fraction A-1) was left behind with the following properties; n_D, 1.5050; instantaneous bromine number 17.5 and OCH_3 0.6%. It was thus apparent that fraction (B) was very similar to (A-1). The latter, 4.5 g., was distilled through a 3-inch Widmer column to yield 2.5 g. of a colorless liquid boiling at 120 - 123° / 0.07 mm. and a still residue of 2 g. Refractive indices of the distillate at various temperatures were as follows:- 25.2°, 1.4970; 27.5°, 1.4960 and 28.5°, 1.4944.

Anal. Calcd. for a cyclohexanone carboxylic acid $C_7H_9O_3$: C - 59.0; H - 7.05. Acid equivalent - 142. Found C - 59.0, 58.95; H - 7.26, 7.27%. Acid equivalent - 138.0, 137.3.

The crude yield of this product was $(\frac{4.5}{7.5} \times 12.5) + 2.5 = 10$ g. or about 60% of theory.

p-Bromphenacyl Ester of Compound $C_7H_9O_3$

One gram of the A-1 distillate was dissolved in 5 c.c. of water and the pH of the solution was adjusted to 7 to 8 with dilute sodium hydroxide solution. Stock ethanol (10 c.c.) together with 2 g. of p-bromphenacylbromide (m.p. 109°) was added and the mixture was heated under reflux on the steam bath for one to one and one-half hours. After adding 5 c.c. of water the mixture was allowed to cool. The pale yellow precipitate was recovered and two recrystallizations from petroleum ether (b.p. 80-90°) left 1.4 g. (60%) of a white crystalline substance melting 118 - 119° and when recrystallized from ethanol

melted at 121° and showed no depression of melting point in an admixture with an authentic sample of p-bromphenacyl ester of 3-keto cyclohexane carboxylic acid.

Anal. Calcd. for the p-bromphenacyl ester 3-keto cyclohexane carboxylic acid (XLVIII) $C_{15}H_{15}O_4Br$: C - 53.1; H - 4.4; Found C - 53.1, 53.1; H - 4.5, 4.7%.

A-1 distillate was thus at least 60% 3-keto cyclohexane carooxylic acid.

Preparation of the Semi-carbazone of A-1

The positive carbonyl test given with 2,4 dinitrophenyl hydrazine suggested the preparation of the semi-carbazone.

(a) A-1 (1 g.) was added and finally semi-carbazide hydrochloride (1 g.). The mixture was heated on the steam bath for thirty minutes whereupon the reactants went into solution rapidly. The reaction mixture was allowed to cool to room temperature and finally left in the cold room at aoout 0° overnight. On warming to room temperature with occasional scratching, crystallization of a white substance melting at 180 - 183° ensued. Recrystallization from stock ethanol produced a white crystalline substance melting at 182.5 - 183° with yellowing and some decomposition. Yield 0.35 g. (25%).

(b) The following method substituting ethanol for water as the solvent was also used:-

A-1 (0.7 g.) was dissolved in 95 percent ethanol (10 c.c.). Sodium acetate (0.5 g.) was added and finally semi-carbazide hydrochloride (1 g.). The mixture was heated on the steam bath for

thirty minutes whereupon the reactants went into solution completely. The reaction mixture was allowed to cool to room temperature and finally left in an ice-water mixture for six hours. A crystalline product was obtained which on recrystallization from water and alcohol melted sharply at 182.5 - 183° with decomposition. Yield 0.18 g. (18.5%).

The reported melting point of the semi-carbazone of 3-keto cyclohexanecarboxylic acid (XLVIII) is 182 - 183° (134).

Methylation of Product A-1

(a) With Dimethyl Sulphate.

Fraction A-1, 7.5 g., was dissolved in 50 c.c. of water containing 5.2 g. of sodium hydroxide. Dimethyl sulphate (16.4 g.) was added to the deep yellow solution dropwise over a period of twenty to thirty minutes with constant stirring, the solution becoming pink in color. The final pH of the reaction mixture was about 7 but no solid had separated and apparently the methylation was unsuccessful. To the same reaction mixture was added dropwise an additional 20 c.c. of sodium hydroxide solution containing 5.2 g. of the base, and simultaneously an additional 16.4 g. of dimethyl sulphate. The solution was kept slightly alkaline throughout the addition and at the end was acidified with hydrochloric acid. The solution was evaporated to dryness and alcohol was used to extract the product from the inorganic salts. Evaporation of the alcohol under reduced pressure left a non-distillable gum soluble in water and alcohol.

(b) With Diazomethane.

Five grams of the crude fraction A-1 was treated in ethereal solution with 4 g. of diazomethane prepared from 12 g. of nitrosomethylurea. After being kept at 10 - 15° for two to three days, the ether and diazomethane were removed by co-distillation. The residue on distillation from a 20 c.c. Claisen flask at about 1 mm. pressure yielded fraction I 1.5 g., b.p. 66 - 72°, n_D^{25} 1.4695; fraction II 2.5 g., b.p. 75 - 82°, n_D^{25} 1.4642, and fraction III 1.0 g., b.p. 82 - 95°, n_D^{25} 1.4785.

Each fraction was then rectified through a Cooke-Bower semi-micro column with the results shown in Table IX.

TABLE IX

Fractionation of Diazomethane Methylated Fraction A-1.

Fraction		Bath Temp. °C.	Column Temp. °C.	Pressure mm.	n^{25}	OCH_3 %
I	1.	68 - 70	40	0.8	1.5006	21.8, 21.9
	2.	78 - 80	55 - 60	0.6	1.4800	
	3.	95 -100	85 - 89	1.3	1.4650	
	4.	100 -105	88 - 90	1.2	1.4648	
II	5.	84 - 87	75	0.6	1.4643	
	6.	94 - 97	84 - 86	0.6	1.4650	
	7.	90 - 95	86	1.7	1.4649	
	8.	97 -100	88	1.9	1.4650	20.1, 19.9
	9.	103	88 - 89	1.9	1.4652	
	10.	106	89	1.9	1.4650	20.1, 20.5
III	11.	105	85	2.0	1.4650	
	12.	105 -108	88 - 90	0.9	1.4650	
	13.	120	105 -110	0.8	1.4760	

About 90 percent of the product had a refractive index close to n_D^{25} 1.4650 and a methoxyl content near 20 percent.

Calcd. for methyl 3-keto cyclohexanecarboxylate, OCH_3 - 19.9%.

(c) With Silver Oxide and Methyl Iodide (135).

A crude 9 g. sample of fraction A-1 was dissolved in 50 c. c. of diethyl ether and 10 c.c. (23 g.) of methyl iodide contained in a 125 c.c. Erlenmeyer flask with a ground-in reflux condenser. After 22 g. of silver oxide had been added slowly and with cooling, the mixture was heated under reflux for thirty minutes, then filtered and evaporated. The residue on distillation from a 20 c.c. Widmer flask with a four inch columngave fraction I, 1.5 g., b.p. up to 67° / 1.2 mm., n_D^{22} 1.4655, OCH_3 24.4, 24.0%; fraction II, 6.0 g., b.p. 70 - 76° / 1.2 mm., n_D^{22} 1.4701 and fraction III, 0.5 g., b.p. 85 - 87° / 1.0 mm., n_D^{22} 1.4790. The still residue was 1 g. Fraction II was rectified through a Cooke-Bower column with the results shown in Table X.

TABLE X

Fractionation of Fraction II.

	Bath Temp. °C.	Column Temp. °C.	Pressure mm.	n^{25}	Yield g.	OCH_3 %
1.	130	97	2.3	1.4672	1.67	
2.	115	97	2.3	1.4700	0.87	
3.	125	105	2.3	1.4695	0.54	
4.	132	108	2.3	1.4720	0.55	19.5, 19.6
5.	131	111	2.2	1.4722	0.17	19.8, 19.6
6.	133	112	2.2	1.4721	0.40	19.8, 19.6
7.	135	116	2.1	1.4742	0.21	19.9, 19.5
8.	140 - 150	127	2.1	1.4760	0.13	19.9, 19.8
9.	150 - 155	140	2.1	1.4800	0.34	19.9, 19.9

It was obvious that fractions (1), (2), (3) were distilled too rapidly and they were accordingly redistilled in the semi-micro Cooke-Bower column (Table XI).

TABLE XI

Rectification of Fractions 1, 2 and 3 - Table X

	Bath Temp. °C.	Column Temp. °C.	Pressure mm.	n^{25}	OCH_3 %
10.	90	73	1.8	1.4651	20.6, 20.3
11.	85	72	1.7	1.4660	19.8, 19.9
12.	92	77	1.7	1.4675	19.8, 19.9
13.	110	78	1.7	1.4675	20.0, 19.9
14.	109	84	1.5	1.4690	20.0, 19.9
15.	109	85	1.7	1.4690	20.1, 20.2
16.	110	89	1.7	1.4710	19.7, 19.8

The cut I n_D^{22} 1.4655 was also fractionally distilled through the semi-micro Cooke-Bower column (Table XII).

TABLE XII

Rectification of Fraction I

	Bath Temp. °C.	Column Temp. °C.	Pressure mm.	n^{25}	OCH_3 %
1.	107	70	12	1.4705	30.7, 29.6
2.	112	78	13	1.4620	30.1, 29.0
3.	113	94	13	1.4640	23.4, 23.0
4.	113	94	13	1.4670	20.3, 20.4
5.	125	108	1.7	1.4723	

In another methylation with silver oxide and methyl iodide, a product was obtained with n_D^{25} 1.4780, OCH_3 23.3, 23.4%. Re-methylation with Purdie's reagents failed to increase the methoxyl content. Found n_D^{25} 1.4870; OCH_3-22.0, 22.1%.

With the exception of the initial portion of fraction I with OCH_3 about 30% (Table XII) the products from the silver oxide-methyl iodide methylation had methoxyl contents close to that (19.9%) calculated for the methyl ester, (XLIX), and not to the

enol ether of the ketone,(XLVII), (OCH_3 - 36.5%).

(d) With Silver Oxide and Methyl Iodide in a Sealed Tube.

Eleven grams of the crude fraction A-1 was dissolved in 6 c.c. of methyl iodide (13 g.) and dry ether (35 c.c.). Silver oxide (11 g.) was added slowly over a period of one hour. After the methylation standard procedures recovered 11 g. of crude A-1 methyl ester. A portion, 5.2 g., of this ester was added to 9.5 g. of methyl iodide and 8.5 g. of silver oxide contained in a pyrex tube of about 0.75 inches internal diameter and about eight inches long. The tube was sealed carefully and then immersed for three hours in an oil bath maintained at 80 ± 2°. Dry ether was used to extract the product from the brown, insoluble silver salts and, after filtration and evaporation, the residue was distilled through a three inch Widmer flask of 10 c.c. capacity. Fraction I, 2.5 g. had b.p. 70 - 75° / 1 mm., n_D^{23} 1.4630, OCH_3 24.0, 23.6% and fraction II, 1.0 g. had b.p. 75 - 85° / 1 mm., n_D^{23} 1.4740. The still residue was about 1g.

Fraction I was rectified in a semi-micro Cooke-Bower column and the following fractions obtained (Table XIII).

TABLE XIII

Fractionation of Fraction I of Product from Sealed Tube.

	Bath Temp. °C.	Column Temp. °C.	Pressure mm.	n^{25}	OCH_3 %
1.	90	69	11.5	1.4581	
2.	95	82	12.5	1.4590	31.9, 32.0
3.	96	85	12.5	1.4610	28.9, 28.3
4.	98	87	12.5	1.4660	21.2, 21.0

TABLE XIII (CONTINUED)

	Bath Temp. °C.	Column Temp. °C.	Pressure mm.	n^{25}	OCH_3 %
5.	100	98	12.5	1.4688	21.5, 20.8
6.	97	86	12.5	1.4690	
7.	98	84	12.5	1.4692	21.4, 21.4
8.	103	90	11.0	1.4719	20.1, 20.0

Fractions 5, 6, 7 together accounted for more than 75% of the distillate.

The above procedure of heating in a sealed tube was repeated at 109° for ten hours and the product had n_D^{22} 1.4531, OCH_3 23.8, 23.5%. After methylation at 130 - 135°, for eight hours the product had a methoxyl content of 25.2, 24.8% with a refractive index of 1.4910. It was, therefore, concluded that no appreciable increases in methoxyl content were achieved by carrying out a Purdie methylation at elevated temperatures. The analyses recorded in Table XIV show that some of the fractions had the composition C - 61.54; H - 7.7; OCH_3 - 19.9% required for the methyl ester of 3-keto cyclohexanecarboxylic acid. Nevertheless, the variable refractive indices suggested that a sharp separation into chemical individuals had not been effected.

TABLE XIV

Analyses of Some Fractions of Methyl 3-Keto Cyclohexanecarboxylate (XLIX)

Fraction No.	Table No.	n_D^{25}	Pressure mm.	% C.	% H	OCH_3 %
6	IX	1.4650	1.9	60.42 60.33	8.2 8.1	20.1, 19.9
10	XI	1.4675	1.7	61.51 61.47	7.96 7.67	20.0, 19.9
16	XI	1.4710	1.7	61.40 61.70	7.5 8.0	19.7, 19.8
14	XI	1.4690	11.0	61.35 61.30	7.5 7.5	
$C_8H_{12}O_3$ (XLIX) requires				61.54	7.7	19.9

Separation of the Reduced Products with Saturated Sodium Bisulphite Solution.

The oil obtained by the continuous ether extraction method from the acidified aqueous solution was esterified with diazomethane, prepared from 22 g. of nitrosomethylurea. The product, 19.5 g., dissolved in 100 c.c. of ether, was then extracted with four 25 c.c. portions of saturated sodium bisulphite solution; the first portion causing the precipitation of an addition compound. This precipitate was redissolved by the addition of 25 c.c. of distilled water. The combined bisulphite solution was acidified with dilute sulphuric acid and continuously extracted with ether in a liquid-liquid extractor of 250 c.c. capacity for twenty-four hours. After drying and removal of ether from the extract, the residue, about 8.5 g., was treated with diazomethane

to assure complete esterification. A colorless liquid b.p. 73 - 76° /0.7 to 1 mm. n_D^{20} 1.4640, OCH_3 - 19.9, 19.9% was obtained in 6.2 g. (or 34%) yield. This substance was later shown to be methyl 3-keto cyclohexanecarboxylate. The original ether solution containing material not extracted with bisulphite, was dried over anhydrous magnesium sulphate. After removal of ether the residue (7.5 g.) was distilled (Table XV).

TABLE XV

Initial Distillation of Non-Carbonyl Products

	Vapour Temp. °C.	Pressure mm.	n_D	Yield g.
1.	36 - 40	10	(a)	0.3
2.	76 - 79	10	1.4900	1.1
3.	40 - 46	0.5	1.4970	1.1
4.	68 - 71	0.8	1.4868	2.5
5.	68 - 71	0.04-0.05	1.4988	0.6
6.	75 - 80	0.05	(b)	0.4

(a) Strongodour of isoamyl alcohol, n_D^{18} 1.4084.

(b) Waxy crystalline material.

Fractions (2), (3), (4) were rectified at 26 mm. pressure through a Cooke-Bower column with the results shown in Table XVI.

TABLE XVI

Rectification of Fractions (2), (3), (4) from Table XV

	Column Temp. °C.	Bath Temp. °C.	n_D^{24}	Yield g.
1.	117	136	1.4830	0.14
2.	122	136	1.5042	0.47
3.	125	136	1.5048	0.55
4.	126	140	1.4995	0.40
5.	135	155	1.4840	0.40
6.	137	157	1.4760	0.48
7.	137	157	1.4770	0.48
8.	137	157	1.4770	0.40
9.	137	158	1.4778	0.46
10.	141	160	1.4840	0.35

Total yield of product n_D^{24} 1.5045 ± 0.0003 1.02 g. (6%) and of product n_D^{24} 1.4769 ± 0.0009 1.82 g. (9%). The portion with n_D^{24} 1.4770 was analyzed. Its density, d_4^{20}, was 1.0959. Anal. Calcd. for methyl 3-methoxy. cyclohexene carooxylate, $C_9H_{14}O_3$: C - 63.5; H - 8.25; OCH_3 - 36.4%; saponification equivalent - 170; M_D - 44.4 Found C - 63.6, 63.5; H - 8.3, 8.4; OCH_3 - 35.8, 35.9%; saponification equivalent - 170, 171; M_D - 43.9.

In another run, where the original ether extracted oil (17 g.) had been divided into water-soluble and water-insoluble portions and each portion extracted with sodium bisulphite solution, the yields were methyl 3-keto cyclohexanecarboxylate (XLIX) 5 g., (27%) n_D^{20} 1.4770, 2.5 g., (13%) n_D^{20} 1.5042, 2.5 g., (15%).

Saponification of Liquid Ester Fraction with n_D^{20} 1.5042

This fraction, n_D^{20} 1.5042, 0.5 g., was saponified by adding it to 10 c.c. of 3 percent aqueous sodium hydroxide solution and heating the reaction mixture on the steam oath for two hours. The mixture became clear and on acidification yielded a white precipitate which was dried and recrystallized twice from petroleum ether (30 - 60°). The white needles (0.35 g.), melting at 121° showed no depression in melting point when mixed with an authentic sample of benzoic acid (LII).

Since methyl benzoate has a refractive index of n_D^{20} 1.5164

(128) it follows that the original fraction contained another substance of lower refractive index, not readily separable by fractional distillation. The yield of benzoic acid showed that at least 75 percent of the fraction consisted of methyl benzoate.

Saponification of Methyl 3-Keto Cyclohexanecarboxylate (XLIX) from the Reduction of Trimethyl Gallic Acid (XLVI).

Methyl 3-keto cyclohexanecarooxylate (XLIX) (n_D^{20} 1.4640, OCH_3 - 19.9%) 9.5 g. obtained as one of the products in the sodium reductions of trimethyl gallic acid, was dissolved in 75 c.c. of methanol containing 5 g. of potassium hydroxide and the solution was allowed to stand for twenty-four hours at room temperature, during which time the color became deep red. The reaction mixture was then heated for fifteen minutes at reflux temperature and an equal amount of water was added. The methanol was removed by distillation at reduced pressure, the aqueous solution was acidified with dilute hydrochloric acid and was continuously extracted with ether. After drying over anhydrous magnesium sulfate and removal of ether, the extract yielded 8 to 8.5 g. of an oil which was distilled in a Claisen flask of 25 c.c. capacity. A colorless liquid was obtained boiling at 136° / 1.5 mm. and 131° / 0.8 mm. Yield 3.2 g. This supercooled liquid when dissolved in 6 c.c. of benzene and seeded gave white crystals m.p. 76° and not depressed by admixture with an authentic sample of (XLVIII) (yield 37%).

Reduction of Trimethyl Gallic Acid (XLVI) with 36.9 Atoms of Sodium.

The acid (XLVI), 25 g., (0.118 moles) dissolved in 1 liter of isoamyl alcohol was heated to 50°, instead of the usual 100°, before commencing the rapid addition of 100 g. (4.35 atoms) of sodium. This change in temperature was advisable to avoid any risk of the reaction passing out of control during the addition of the large amount of sodium. After all the sodium had been consumed, and the mixture had been stirred for a further hour, much of the sodium alkoxide solidified. Enough dilute hydrochloric acid was added to disperse this solid and the usual separation of the isoamyl alcohol from the still alkaline aqueous phase was carried out. The isoamyl alcohol was rejected after being washed with water and the combined aqueous alkaline liquors were extracted with ether to remove residual amounts of the alcohol. Acidification of the aqueous liquors, 1.5 liters, to pH 1 prepared them for a continuous extraction with ether for eighteen hours. After recovery, the dried extract, which weighed 18 g., was esterified in ethereal solution with the diazomethane prepared from 20 g. of nitrosomethylurea. An ethereal solution of this crude ester was then estracted in the usual way with sodium bisulphite to remove caroonyl compounds. Distillation of the 10 g. of residual oil from a Widmer flask gave the following fractions: I, 2.7 g. b.p. 89 to 92° / 24 to 25 mm., n_D^{22} 1.4510; II, 3.5 g. b.p. 45 to 47° / 0.5 to 0.8 mm., n_D^{22} 1.4780; III, 1.6 g. b.p. 48 to 52° / 0.5 mm., n_D^{22} 1.4645 and

IV, 0.5 g., b.p. 62 to 64° / 0.5 mm., n_D^{22} 1.4675. Since the separation was not good, the first three fractions were combined and redistilled from the Cooke-Bower column at 23 - 25 mm. pressure.

TABLE XVII

Rectification of Fractions I, II and III

Fraction No.	Bath Temp. °C.	Column Temp.°	$n_D^{20.5}$	Yield g.
1	83	67	1.4073	0.17
2	96	90	1.4071	0.06
3	102	87	1.4308	0.34
4	102	90	1.4438	0.19
5	100	85	1.4433	0.40
6	102	88	1.4900	0.49
7	104	88	1.4930	0.71
8	105	90	1.4938	0.71
9	105	92	1.4935	0.32
10	106	96	1.4940	0.46
11	110	96	1.4937	0.43
12	111	99	1.4930	0.22
13	113	100	1.4895	0.30
14	119	103	1.4653	0.38
15	119	103	1.4505	0.28
16	120	105	1.4507	0.32
17	131	116	1.4510	0.34
18	134	119	1.4527	0.30

A total of 6.75 g. was obtained as distillate from an initial charge of 7.8 g. This difference can be attributed to column holdup and to some material remaining behind as still residue. Fraction number 8 was selected as representative of fraction numbers 7 to 12 inclusive and number 16 of fraction numbers 15 to 18 inclusive.

The aqueous bisulphite extract was made acid with dilute sulphuric acid, aerated under reduced pressure to remove sulphur dioxide and continusously extracted with ether. The dry residual

oil (3.5 g.) was then distilled and yielded 1.9 g. (10%) of methyl 3-keto cyclohexanecarboxylate (XLIX) n_D^{20} 1.4640 c.p. 66 - 67° / 0.3 mm.

Saponification of Fractions with $n_D^{20.5}$ 1.4930

Since a consideration of physical constants suggested that these fractions (OCH_3 - 21.7, 21.8%; d_4^{20} 1.0615) consisted of methyl benzoate and a methyl cyclohexenecarboxylate, the whole of fraction number 7, 0.65 g., was saponified with 0.26 g. of sodium hydroxide in 5 c.c. of water. After heating on the steam bath under an air-condenser for two hours, the solution became clear and upon acidification and spontaneous cooling, yielded a white crystalline precipitate, which was dried over phosphoric anhydride for fifteen hours at room temperature. The material was then twice washed with petroleum ether (30 - 60°) and was recrystallized from water. The white plates so obtained melted at 38 - 39° and gave neutralization equivalent values of 125.5, 126 (Theory 126). Linstead (136) quoted 38° for the m.p. of Δ_1 cyclohexenecarboxylic acid (LIII).

p-Bromphenacyl Ester of Δ_1 Cyclohexenecarboxylic Acid (LIII)

Δ_1 Cyclohexenecarboxylic acid (LIII) (0.3 g.) was condensed in the usual way with 0.7 g. of p-bromphenacylbromide. A copious precipitate melting at 60 - 85° was recrystallized by dissolving in hot petroleum ether (b.p. 100 - 110°), decanting from a small amount of gum and allowing the solution to cool spontaneously.

After one more recrystallization from petroleum ether (b.p. 100 - 110°) 0.45 g. of long white needles melting at 97° was obtained. A mixed m.p. with a similar sample obtained in a previous run was not depressed. This earlier sample had the following analysis:

Anal. Calcd. for $C_{15}H_{15}O_3Br$: C - 55.8; H - 4.7; Br - 24.7; "Active" Hydrogen - 0.0; RMgX consumed - 2.0 Found C - 55.9, 55.5; H - 4.6, 4.7; Br - 24.9, 24.9%; RMgX consumed - 2.0.

Examination of Fraction Number 16 (Table XVII)

Fraction number 16 ($n_D^{20.5}$ 1.4507, d_4^{20} 1.0351) was considered representative of numbers 15 to 18 inclusive and gave the following results on analysis:

Anal. Calcd. for methyl 3-methoxy cyclohexanecarboxylate, $C_9H_{16}O_3$: C - 62.8; H - 9.3; OCH_3 - 36.0%; M_D - 44.9 Found C - 63.1, 62.8; H - 9.6, 9.5; OCH_3 - 35.8, 35.6%; M_D - 44.7.

Fraction number 16, was thus identical in physical properties and chemical composition with methyl cis 3-methoxy cyclohexanecarboxylate (L).

DISCUSSION AND RESULTS

The "Bromide-Bromate" method for detecting olefinic unsaturation was adopted because of the stability of the potassium bromide-bromate standard solution and its ability to distinguish between reactive and unreactive olefinic linkages. Linstead (137) showed that while isolated olefinic linkages add bromine instantaneously, α, β unsaturated acids do so slowly. The method of Lewis and Bradstreet (112) was adapted for use on the semi-micro scale. In a test run, duplicate samples of cinnamic acid were only partially brominated in five to ten minutes of manual shaking (bromine number calcd. 103; found 68, 79) while mechanical shaking for fifteen minutes gave complete absorption of bromine (found 106, 113).

Nearly all the methods used to determine the enol content of keto-enol equilibria were ultimately tested by comparison with results obtained from the indirect bromine titration developed by Meyer (93). Cooper and Barnes (94) introduced an improvement in the method by substituting diisobutylene for β naphthol as the reagent absorbing the excess added bromine. The present method (Experimental page 47) adapts the modified procedure of Cooper and Barnes for use with semi-micro quantities. Table XVIII shows that the results were satisfactory when checked against those obtained by better established macro methods.

TABLE XVIII

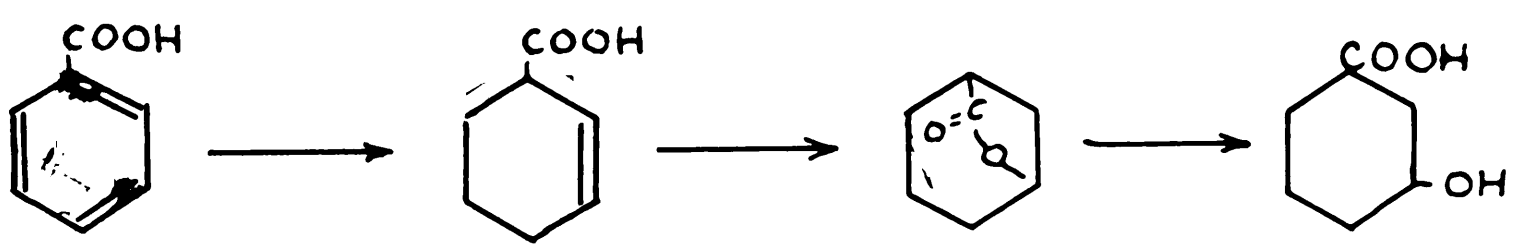
Comparison of New Semi-Micro with Macro Estimations for "Enol"

Compound	m.p. °	% Enol Semi-Micro Method	% Enol By Macro Methods
Acetophenone (a)		0.0, 0.0	
Ethyl acetoacetate (a)		6.75, 6.50	7.4 (e)
Dibenzoyl methane (b)	77 - 78	95.2, 96.4	95.34, 96.15 (c) 95.46, 96.34 (d)
p-Br phenacyl cyclohexanone-3 carboxylate	120 - 121	0.0, 0.0	
Cyclohexanedione 3,5 carboxylic acid (LIV)	166 - 167	120, 121	

Notes: (a) freshly distilled (b) prepared according to Organic Syntheses (138). (c) extreme values by Cooper and Barnes (94) (d) performed by the author according to the method of Cooper and Barnes (94). (e) value cited by Meyer (93).

Certain compounds needed for comparison with those obtained as products of the reduction of trimethyl gallic acid (XLVI), or as intermediates for the preparation of such compounds, were synthesized according to well-accepted methods. The exception was cis cyclohexanol-3 carboxylic acid (XI) which was prepared by a new method involving the catalytic reduction of m-hydroxy benzoic acid (XLVII). The purpose of this new preparation was to develop a convenient method of obtaining a sufficient quantity of the pure cis-isomer of (XI) for subsequent oxidation to 3-keto cyclohexanecarboxylic acid (XLVIII). Previous methods of preparing (XI) given by Perkin and Tattersall (16) and by Linstead and Boorman (136) are based on the sodium amalgam re-

duction of m-hydroxy benzoic acid and benzoic acid respectively. Both methods have the disadvantages of being time consuming and requiring very large amounts of reducing agent to give reasonable yields. The method of Linstead and Boorman has the additional disadvantage of requiring the lactonization of the intermediate tetrahydrobenzoic acid (LV) with the attendant sharp decrease in yields of (XI).



(LII) (LV) (LVI) (XI) cis

The hydrogenation of m-hydroxy benzoic acid, carried out at an initial hydrogen pressure of 2000 pounds per square inch and a temperature of 130 to 140° in the presence of Raney nickel, was complete in about one to one and one-half hours and yielded fifty percent of the required cis form.

cis-Cyclohexanol-3 carboxylic acid (XI) was then oxidized by dichromate to the ketone (XLVIII) in fifty percent yield according to the method of Perkin and Tattersall (16). Owing to the sensitivity of the ketone (XLVIII) to acid and alkali, it was necessary to use a neutral reagent, diazomethane, for its esterification. Two consecutive Purdie (135) methylations (silver oxide and methyl iodide) were necessary for the preparation of methyl cis-3 methoxy cyclohexanecarboxylate (L) from

(XI). Apparently the compounds (L) and the methyl ester of (XLIX) have never been previously reported or properly characterized. In addition, the p-bromphenacyl esters of (XLVIII), (XI) and (LIII) were prepared by the method recommended by Shriner and Fuson (140). The melting points of these products, together with the yields obtained are shown in Table XIX.

TABLE XIX

p-Bromphenacyl Esters of Some Cyclic Carboxylic Acids

p-Bromphenacyl Ester of	m.p.° (a)	Yield %
cyclohexenecarboxylic acid (LIII)	97	45
3-keto cyclohexanecarboxylic acid (LXVIII)	121.5-122	92
cis-3-hydroxy cyclohexanecarboxylic acid	136	88

(a) uncorrected.

The Reduction of Gallic Acid and its Trimethyl Ether by Sodium in Alcohols.

The survey of chemical reduction of the benzenoid nucleus presented in the Historical Introduction, makes possible some generalizations concerning cases where the alkali metals do prove effective. Sodium in liquid ammonia together with a hydrolytic agent produces dihydro compounds in the main. Sodium amalgam in water at a specific pH, and calcium hexammine, $Ca(NH_3)_6$, yield tetrahydro benzene derivatives. Sodium and alcohol, in certain cases, generally produce the fully saturated cyclohexane analog of the benzene derivative. In particular, the success attained with sodium and alcohol in the complete hydrogenation of the m-hydroxy benzoic acids (13 - 16) suggested that

a similar reduction would yield positive results with gallic acid. The reduction of gallic acid (XLV) using ethanol in conjunction with either potassium or sodium, and isoamyl alcohol with sodium did not lead to products from which non-phenolic materials could be isolated. Considerable difficulty was experienced in working up the black reaction mixture and the phenolic degradation products of gallic acid masked any possible positive results. It was inferred that under the strongly alkaline conditions of these experiments, the rate at which gallic acid (XLV) undergoes irreversible condensations far surpasses the rate at which reduction can take place.

The decision to methylate gallic acid completely to trimethyl gallic acid (XLVI) and to submit the latter to chemical reduction was taken for a number of reasons. In the first place, the methylation of the phenolic hydroxyl groups would avoid the very deep-seated and complex condensations to which unsubstituted gallic acid is prone. Since the electronegative character of the methoxy are not greatly different from those of the phenolic hydroxyl groups, according to Lucas (141), the results might perhaps serve as a guide to future successful reductions of gallic acid itself. Finally, the experience of others in the reductive cleavage of methyl phenyl ethers suggested the possibility of carrying out partial or total demethylation simultaneously with nuclear reduction.

Accordingly, attempts were made to accomplish ring reduction of trimethyl gallic acid (XLVI) by means of sodium and isoamyl alcohol; the proportions of sodium to (XLVI) being varied from 5.5 atoms to 36.9 atoms per mole of (XLVI). In all of these cases, several products were obtained, but in every case benzenoid reduction and demethylation took place to a great extent. These results are in contrast to those of Semmler (20) who when submitting (XLVI) to the action of sodium and absolute ethanol, isolated as his sole product m-methoxy benzoic acid in unreported yields.

In all of the reductions, substantially constant reaction conditions were maintained: the amount of trimethyl gallic acid used was 0.118 mole, dissolved in one liter of isoamyl alcohol with an initial temperature of 100°, the amount of sodium added being varied. Only the extreme case, where 36.9 atoms of sodium was used, was the initial temperature of the reaction mixture varied and reduced to 50°, so that the exothermic process might be kept under control. Figure 3 summarizes the products isolated.

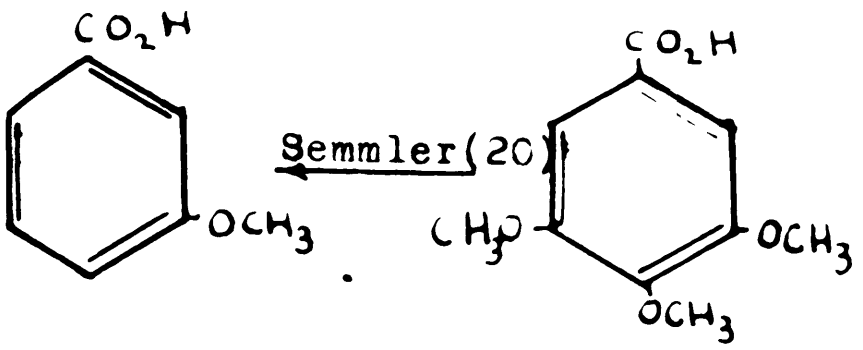
A survey of these products reveals the trend that with increasing amounts of sodium the amounts of hydrogen introduced in the benzene ring are also increased. Thus, for example, under relatively mild conditions two atoms of hydrogen were added to produce compound (LIV), cyclohexanedione 3,5 carboxylic acid, which may be regarded as the dihydro derivative of 3,5 dihydroxy-benzoic acid. Compound (XLVIII), 3-keto cyclohexanecarboxylic

acid which may be similarly expressed as the tetrahydro m-hydroxybenzoic acid, and (LVII) the tetrahydro m-methoxy benzoic acid, were all obtained in reductions employing larger quantities of sodium. Extreme conditions produced a small amount of the hexahydro m-methoxy benzoic acid (LVIII) together with a larger amount of the tetrahydrobenzoic acid (LIII). A similar observation was reported by Birch (24) in the sodium and liquid ammonia reduction of phenol ethers, where dihydro derivatives were obtained as intermediates and continued reduction gave cyclohexene derivatives, as shown in figure 1.

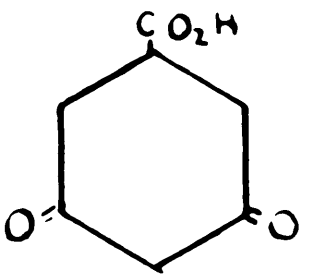
As might be expected, the main technical difficulty in the present work was to separate, assign probable structures to, or to identify the products indicated in Figure 3, and it now seems appropriate to discuss these matters in greater detail.

The Structure of Compound (LIV) $C_7H_8O_4$

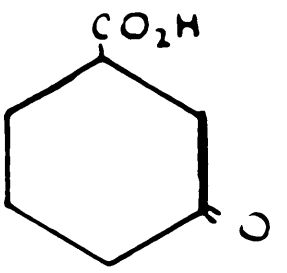
The empirical formula, $C_7H_8O_4$, of the principal product, m.p. 166 -167°, isolated in the reduction of trimethyl gallic acid (XLVI) with 5.5 atoms of sodium indicates the possible structures shown in Figure 4.



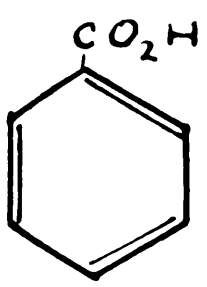
XXI XLVI.



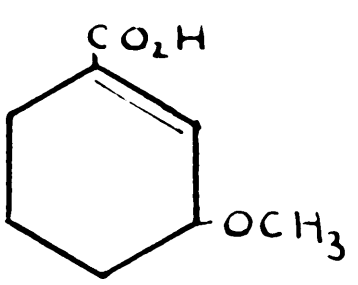
LIV



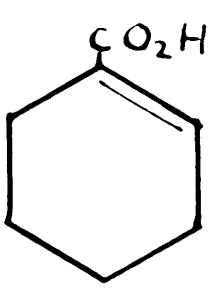
XLVIII



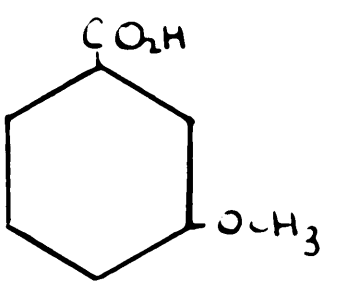
LII



LVII



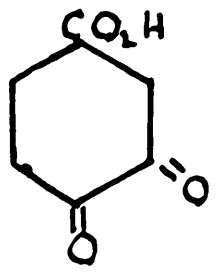
LIII



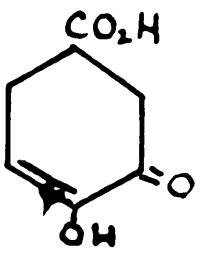
LVIII

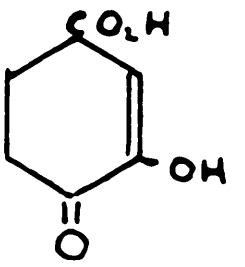
Atoms of sodium Per Mole of XLVI	Products and Yields		
5.5	XLVIII (11-14%)	+ LIV (29-42%)	+ XLVI recovered (16-29%)
11.1	XLVIII (19%)	+ LIV (2%)	
14.8	XLVIII (24%)		
18.4	XLVIII (27-34%)	+ LII (5-13%)	+ LVII (9-15%)
36.9	XLVIII (10%)	+ LIII (14-21%)	+ LVIII (6%)

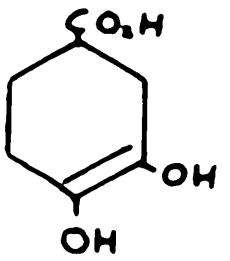
Figure 3 - Products and Yields in the Reduction of Trimethyl Gallic Acid (XLVI).



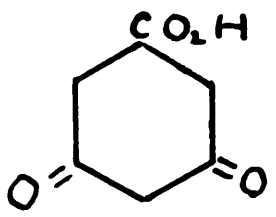
and the enol forms



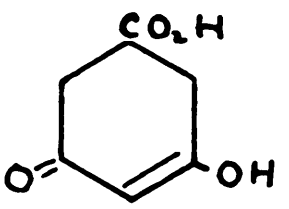


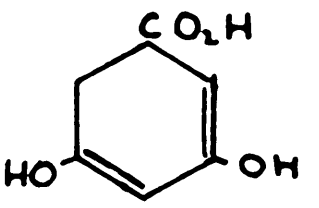


LIX LIXa LIXb LIXc



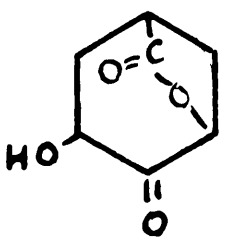
and the enol forms

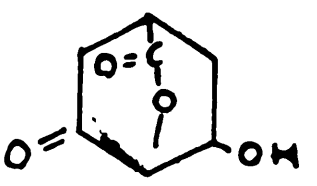




LIV LIVa LIVb

and the possible lactones





LX LXI

Figure 4 - Possible Structures for Compound $C_7H_8O_4$.

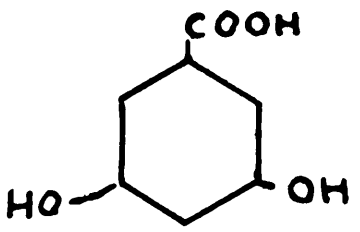
The neutralization equivalents obtained by direct titration with alkali and by boiling with 100 percent excess alkali were substantially the same, thereby indicating a dibasic acid, and ruling out immediately any possible lactone structures such as (LX) and (LXI). Attempts to construct model lactone structures of (LX) and (LXI) by means of Fisher-Hirschfelder-Taylor models also showed that the spatial relationships are completely unfavourable for the formation of the lactone ring.

As between the α diketone structure (LIX) and the β diketone structure (LIV) the latter seems more probable because it is the

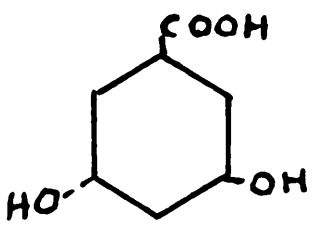
central methoxy group which invariably undergoes cleavage in such compounds as pyrogallol trimethyl ether (XXXIX) (41, 42) or trimethyl gallic acid (XLVI). Furthermore, the sodium and liquid ammonia reduction of pyrogallol trimethyl ether (XXXIX) yields the 2,5 dihydro resorcinol dimethyl ether (XXXII). The same product is obtained with resorcinol dimethyl ether (XXXI) (24). In both cases, cyclohexanedione 1,3 (XXXIII) is the product isolated after hydrolysis with dilute mineral acid. It thus follows that if the central carbon-oxygen bond undergoes fission more easily than the others, then the β diketone structure (LIV) is the more probable one for the empirical formula $C_7H_8O_4$.

The catalytic reduction of this substance over platinum at room temperature introduced four atoms of hydrogen (Figure 2) and a thirty percent yield was obtained of three fractions of white crystalline material, melting at 98 to 101°, 116 to 124° and 116 to 118° respectively, corresponding in empirical formula and neutralization equivalent to the cyclohexanedicl carboxylic acids, $C_7H_{12}O_4$. Neither this product, nor the oily residue absorbed periodic acid to any great extent, even after standing for fourteen hours. Since the absorption of one mole of periodic acid would be diagnostic under these circumstances for one α glycol (142), it may be inferred that no such group is present in the reduced product. The crystalline fractions, unfortunately, could not be further fractionated into sharply melting substances, because the amount available was insufficient for a separation

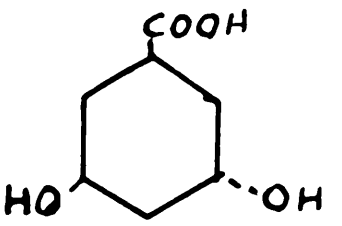
into the three possible cis-trans isomers of cyclohexanediol 3,5 carboxylic acid (LXII).



LXIIa



LXIIb



LXIIc

The negative results for an α glycol group obtained from the periodate oxidation of the reduction product, $C_7H_{12}O_4$, clearly demonstrated that the original unreduced material must be the β diketone (LIV) rather than the α diketone (LIX).

Investigations of the ultraviolet absorption spectra of cyclic β diketones (108, 143), made it possible to carry out a similar study with compound $C_7H_8O_4$. The absorption curves (Figure 5) were kindly provided by Dr. J.E. Currah of the Central Research Laboratories of Canadian Industries Limited at McMasterville, P.Q. Maximum absorption for this compound was found to be 254 mμ and the maximum extinction coefficient was 31,000 (logϵ 4.49). Other workers (108, 143) found that the ultraviolet absorption spectra of cyclic β diketones invariably show a λ max in the region 250 - 300 mμ and logϵ 4 approximately; cyclic α diketones, on the other hand, show an absorption shifted towards the visible region (110). Blout, Eager and Silverman (108) studied the effect of substituents and environment on the spectra of various cyclohexanedione 1,3 derivatives.

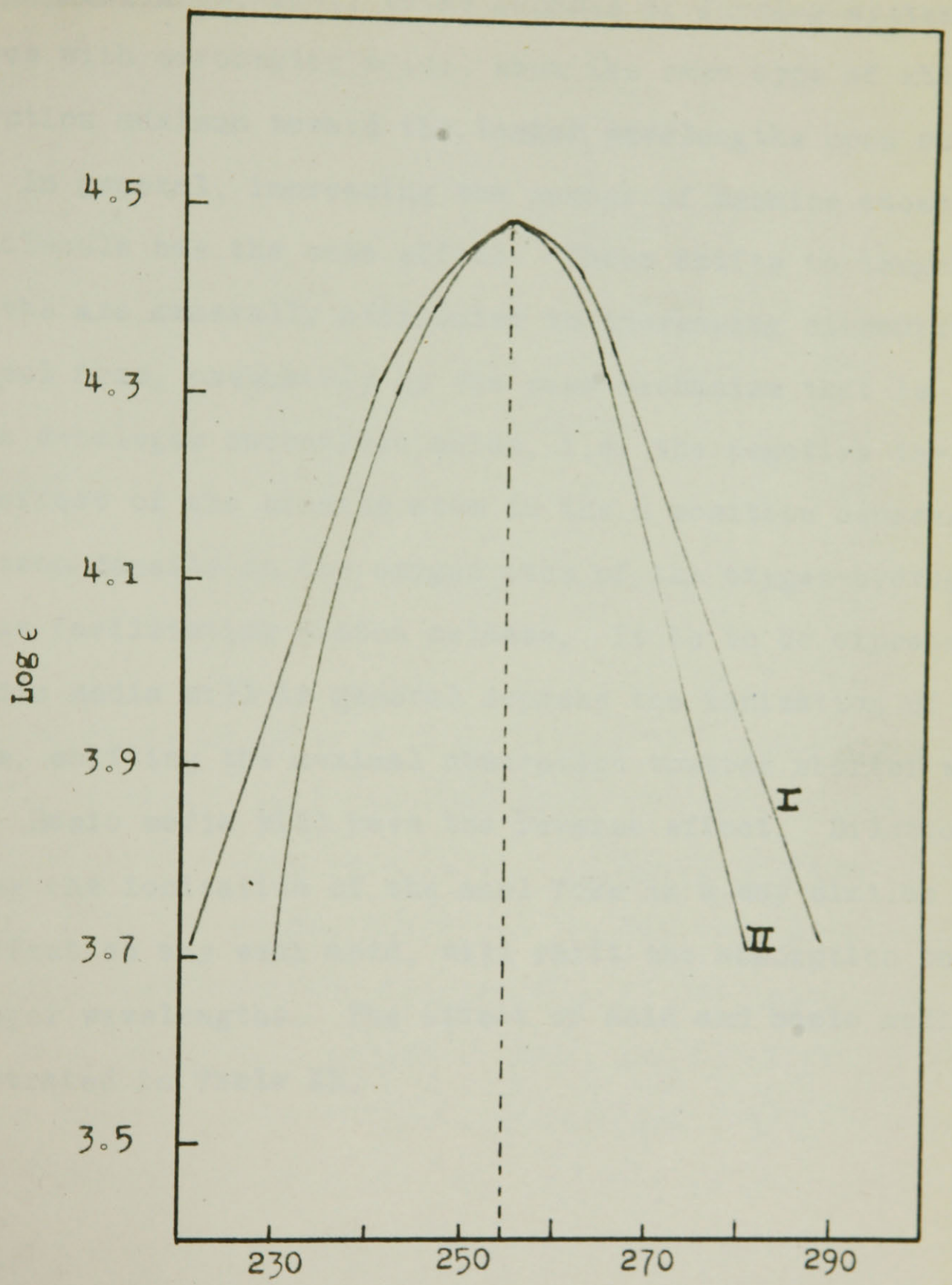


Figure 5 - Ultraviolet Absorption Spectra of Compound $C_7H_8O_4$ in Methanol

I 3.2×10^{-5}M , II 2.2×10^{-5}M

It was noted that all derivatives which are not dibrominated in the two positions, i.e., those capable of forming systems vinylogous with carboxylic acids, show the same type of shift in absorption maximum toward the longer wavelengths upon dilution. In general, increasing the number of bromine atoms in the molecule has the same effect. These shifts to longer wavelengths are generally attributed to increasing dissociation of the enol form, presumably by the same mechanism that is active in α-halogen carboxylic acids, i.e. the negative inductive effect of the bromine atom in the α position decreases the electron density on the oxygen atom of the oxygen-hydrogen link, thus facilitating proton release. It is to be expected that acidic media will in general depress the ionization of the enol form, shifting the maximal absorption towards shorter wavelengths. Basic media will have the reverse effect. Dilution, increasing the ionization of the enol form in a way similar to the effect on any weak acid, will shift the absorption towards longer wavelengths. The effect of acid and basic media are illustrated in Table XX.

TABLE XX

Effect of Basic Acid and Neutral Media on the Ulatraviolet Absorption of Cyclic β Diketones

5×10^{-5} M

Compound	Solvent	max mμ	Log ε
5,5 Dimethyl cyclohexanedione 1,3 (LI)	absolute ethanol	282	4.25 (a)
	acidic abs. ethanol	255	4.23 (a)
	basic abs. ethanol	283	4.43 (a)
cyclohexanedione 1,3 (XXXII)	ethanol	250	4.30 (b)
cyclohexanedione 3,5 carboxylic acid (LIV)	methanol	254	4.49 (c)

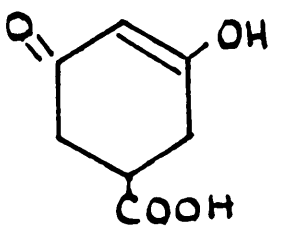
(a) Blout et al (108) (b) Bastron, Davis and Butz (143)

(c) Concentration, 3.2×10^{-5} M.

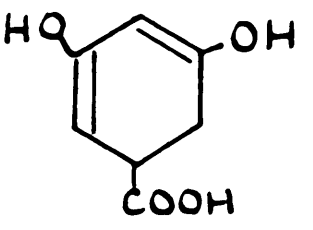
In comparing compound (LIV) with 5,5 dimethyl cyclohexanedione 1,3 (LI), it is seen that in neutral media the enol groups of (LIV) are less dissociated than in (LI). This phenomenon is to be expected from the acidic nature of the carboxylic acid group in (LIV) which depresses the dissociation of the enol form. On the other hand, according to Watson (52), and as already discussed in connection with acetoacetic acid and levulinic acid, the electron releasing character of the carboxyl group may come into play via a positive inductive mechanism to assist the enolization of the second carbonyl group. This possibility offers an explanation for the high log ε (4.49) observed with (LIV) and for the fact that the percent enol, determined titrimetrically, is about 20 percent higher than theoretically required for the enolization of one keto group (Table XVIII). This excessive

result for the enol content of (LIV) may also include an unknown bromination side reaction affecting some other unit in the molecule apart from the double bond.

The acidic nature of cyclic β diketones is ascribable to the fact that upon enolization of one of the hydrogen atoms between the carbonyl groups, a group is formed which has all the properties of, and is vinylogous with, a carboxylic acid. By analogy with the results reported by Blout, Eager and Silverman (108) for 5,5 dimethyl cyclohexanedione 1,3 (LI), the principal forms which are responsible for the light absorption properties of (LIV) are

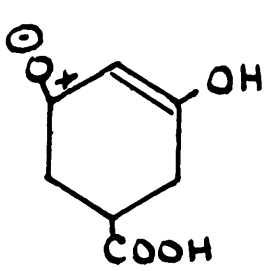


LIVa

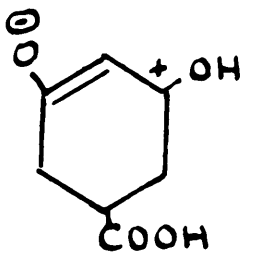


LIVb

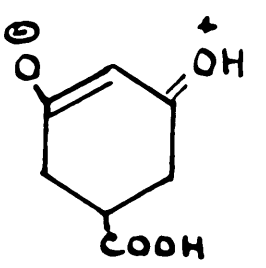
There also may be contributions from forms such as



LIVc

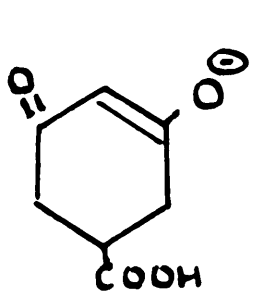


LIVd

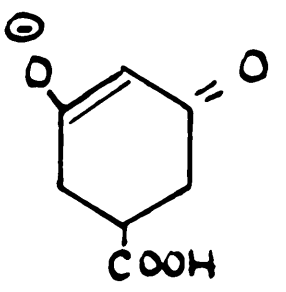


LIVe

and their dissociated or ionic forms



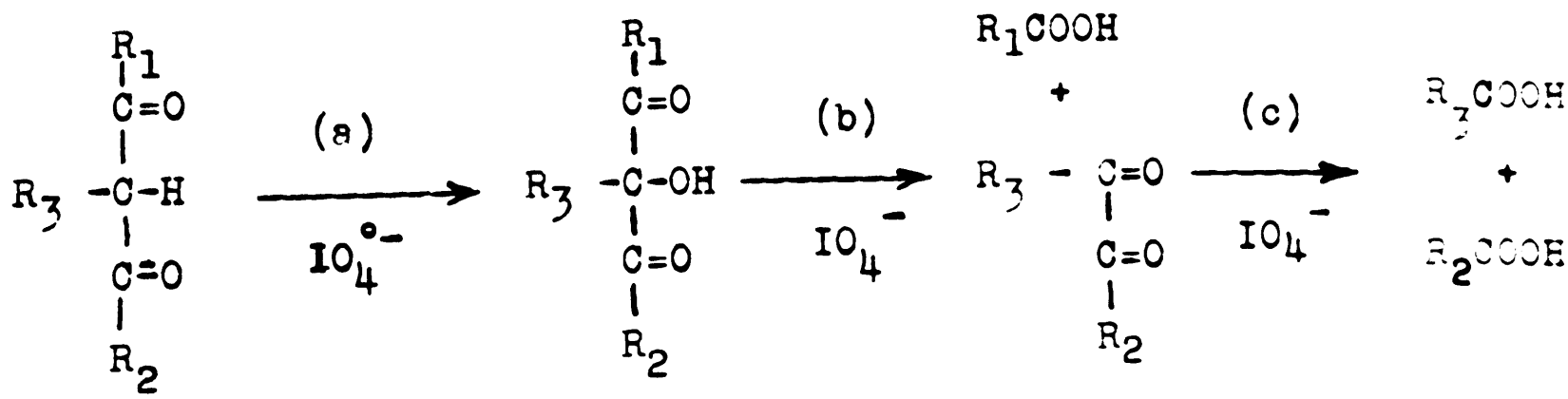
LIVf



LIVg

although the latter pair, (LIVf) (LIVg), would be largely suppressed by the acidic nature of the carboxyl group.

It was anticipated that if compound (LIV) was an α diketone, it would reduce one mole of periodic acid (142) and if a β diketone, no reaction would take place. Experiment proved, however, that (LIV) reduced one mole of periodate rapidly and an additional mole more slowly. This unexpected result led to a study of the reaction between periodate and the known cyclic β diketone, 5,5 dimethylcyclohexanedione 1,3 (LI) which also was found to consume two moles of the oxidant although the second mole was used more rapidly than in (LIV) (Figure 6). It was concluded, therefore, that the absorption of periodate by compound (LIV) was not in contradiction to the cyclic β diketone structure just assigned to it. The anomalous behaviour of the periodate toward these β diketones is probably related to the recent discovery by Huebner, Ames and Bubl (144) that this oxidant is capable of converting an active α-hydrogen to an α-hydroxyl group. The configuration necessary may be shown diagrammatically as follows (144):



The general requirements of the reaction were shown to be:

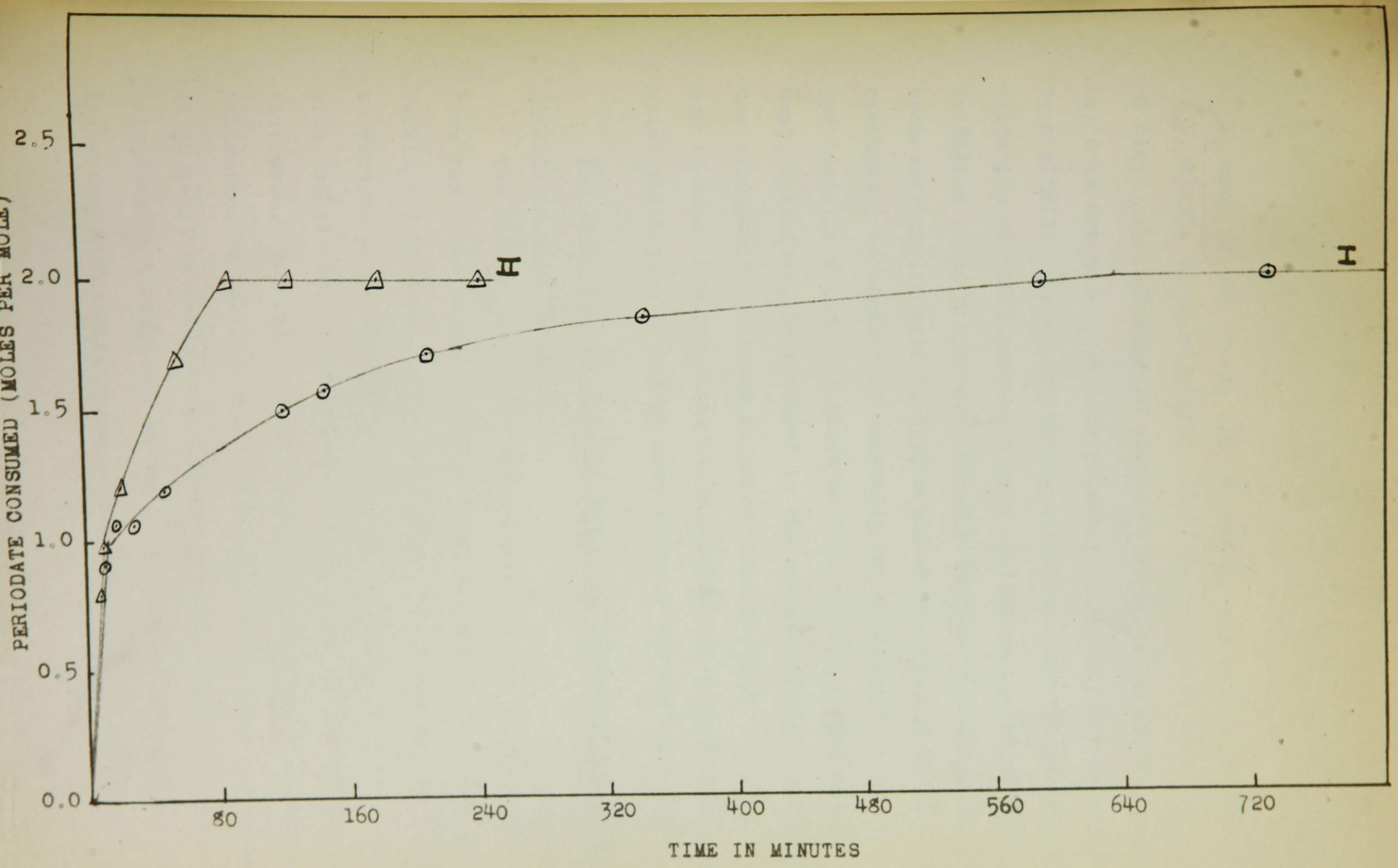


Figure 6 - Periodate Oxidations at pH 4.0

I Compound $C_7H_8O_4$ at 24° (6.05×10^{-3}M IO_4^-)
II 5,5 Dimethylcyclohexanedione 1,3 at 32° (4.82×10^{-3}M IO_4^-)

1) R_1 must be -OH or -H; 2) R_2 and R_3 may be any combination of H, alkyl, OH or -O alkyl; 3) if R_3 is -alkyl and/or R_2 is -O alkyl, the reaction is slow; 4) if R_2 is -O alkyl reaction (c) does not occur; 5) the grouping $-CO-R_2$ may not be replaced by a nitrile without inhibiting oxidation. If the periodate oxidation of (LIV) proceeded by a similar mechanism through oxidation of an α hydrogen, the 3,5 diketone 4 hydroxy cyclohexanecarboxylic acid (LXIII) would be formed, and would presumably be capable of consuming two additional moles of periodate or a total of three moles. Some other mechanism must, therefore, be involved in the case of cyclic β diketones, the elucidation of which requires further study. It is interesting to note, however, that other examples of β dicarbonyl systems exist which consume one or more moles of periodic acid.

The Isolation and Identification of 3-Keto Cyclohexane-Carboxylic Acid (XLVIII).

The ketone, (XLVIII), was isolated as the methyl ester from the other products of the trimethyl gallic acid (XLVI). Perkin and Tattersall (16) have shown that acids act on (XLVIII) to produce condensed and polymerized products, thus esterification with methyl alcohol and mineral acids could not be applied in this case. The methyl ester, therefore, was formed either by instantaneous reaction with diazomethane, avoiding the formation of an ethylene oxide ring with the carbonyl group (77), or by using Purdie's reagents, silver oxide and methyl iodide. Rectification of the diazomethane-produced ester yielded fractions

which gave acceptible values for caroon, hydrogen and methoxyl content, but had variable refractive indices, n_D^{25} 1.4643 to 1.4650, whereas the methyl ester of (XLVIII) prepared oy synthesis has a refractive index, n_D^{20} 1.4640. The methyl ester of (XLVIII) obtained by Purdie's method also yielded fractions varying in refractive index from n_D^{25} 1.4651 to n_D^{25} 1.4720, although these fractions gave acceptible methoxyl values. It became evident, therefore, that rectification alone did not yield the pure methyl 3-keto cyclohexanecarboxylate, but was contaminated by other reaction products of approximately the same chemical composition. In particular, the use of silver oxide at both low and high temperatures brought about unknown changes which were probably of an oxidative nature. These results suggested that a chemical means of separation combined with distillation would be required to yield a product having the proper refractive index as well as proper analytical values. A preliminary purification of the crude methyl esters was, therefore, accomplished by the formation of the sodium bisulphite addition compound, since experiment showed that an authentic sample of the methyl ester of (XLVIII) could be recovered from its bisulphite addition compound in about 75 percent yield. In this way, the methyl ester of (XLVIII) having identical properties as the synthetic product was isolated from the reduction of trimethyl gallic acid (XLVI).

The identification of the methyl ester of (XLVIII) was established by saponification to the crystalline free acid,(XLVIII),

whose melting point, 76°, was not depressed by admixture with an authentic sample, prepared by the oxidation of cis cyclohexanol-3 carboxylic acid (XI). This saponification could not serve, however, to completely characterize the bisulphite extracted fraction because the yield of (XLVIII) on saponification was only about 37 percent. The known semi-carbazone of (XLVIII) was isolated in minor yields (18 to 25%) from the water-soluble part of reduction product, A-1, and was, therefore, rejected as a method for estimating the composition of the reduction product. The p-bromphenacyl ester of (XLVIII), however, was prepared from a synthetic sample of the free acid, (XLVIII), in almost quantitative yields. When this same derivative was formed from the reduction product A-1, a yield of 60 percent was obtained and was undepressed in melting point with an authentic sample. The crude fraction A-1 was, therefore, at least 60 percent 3-keto cyclohexanecarboxylic acid (XLVIII) when prepared by the reduction of trimethyl gallic acid (XLVI) employing 18.4 atoms of sodium per mole of (XLVI). The calculated yield of pure product (XLVIII) present in the total crude reduction products (36 percent) agreed with the yield actually obtained (34 percent) by isolation of (XLVIII) as the methyl ester.

The possible keto-enol tautomerism of (XLVIII), suggested by the known enolization of the open chain analog, levulinic acid, was investigated because the existence of such an equilibrium would indicate how secondary products derivable from

the enol form might also be present in the residual crude product of the sodium reduction. A modified Meyer titration, however, failed to show the presence of appreciable quantities of enol in the reduction product from the reaction employing 18.4 atoms of sodium, or in the p-bromphenacyl ester of (XLVIII). Enolization of an authentic sample of (XLVIII) was attempted in sodium carbonate solution followed by rapid acidification and titration of the enol form with standard "bromide-bromate" solution. This experiment, based on the work of Wolfrom and Lewis (145) and Montgomery and Hudson (146) failed to detect the existence of any keto-enol equilibrium. Numerous methylations with diazomethane, as well as with silver oxide and methyl iodide, failed to yield the enol methyl ether of (XLVIII). Finally, ultraviolet absorption spectra for the ketone (XLVIII) (Figure 7) showed only a very weak absorption ($\log \epsilon$ 1.5) at 284 mμ. Such an absorption is typical of simple non-enolizable ketones; enols, on the other hand, show an intense absorption ($\log \epsilon$ 4.0) in the range 250 to 300 mμ (108). All of these results make it certain that (XLVIII) does not exist in the enol form to any appreciable extent, and differs in this respect from its open chain analog. A possible explanation for this phenomenon is based on the supposition that in the cyclic ketone (XLVIII), the positive inductive effect of the carboxyl group is distributed in parallel between the two branches of the ring, rather than along a single carbon to carbon skeleton as in levulinic acid, resulting in a greatly decreased electron

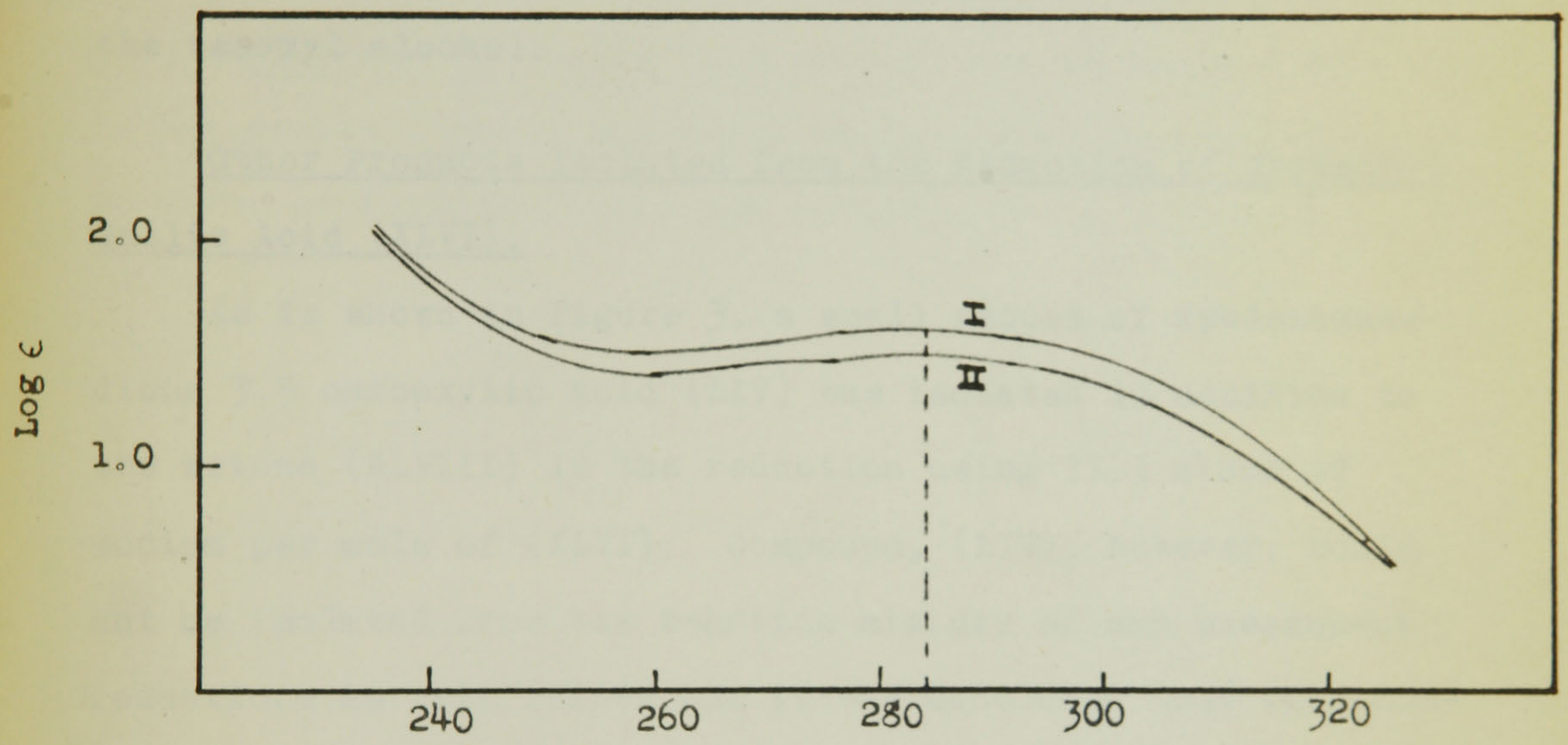


Figure 7 - Ultraviolet Absorption Spectra of 3-Keto Cyclohexane Carboxylic Acid.

I 5.0×10^{-3}M , II 1.0×10^{-2}M

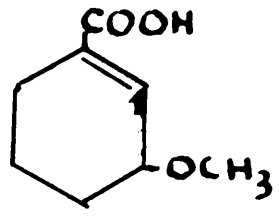
density on the oxygen atom of the keto group. As figure 3 shows, 3-keto cyclohexanecarboxylic acid (XLVIII) was obtained in all the reductions of trimethyl gallic acid attempted, the yield passing through a maximum of about 30 percent of theory when the reduction employed 18.4 atoms of sodium in the isoamyl alcohol.

Other Products Isolated from the Reduction of Trimethyl Gallic Acid (XLVI).

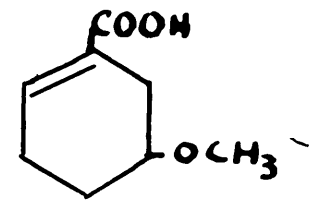
As is shown in Figure 3, a small amount of cyclohexanedione 3,5 carboxylic acid (LIV) was isolated in addition to the ketone (XLVIII) in the reduction using 11.1 atoms of sodium per mole of (XLVI). Compound, (LIV), however, could not be isolated from the reaction mixture of any subsequent reductions in this series and it was concluded that this compound could not survive the extended reduction, but was transformed into other products. The use of 18.4 atoms of sodium, resulted in significant amounts of benzoic acid (LII) (5 to 13%) and of (LVII), $C_8H_{12}O_3$, the latter being isolated as the methyl ester (9 to 15%), which had a methoxyl content of 19 percent. From Table VIII, the methoxyl content of the crude reduction product was calculated to be approximately 4 percent, and assuming that all can be attributed to the compound, $C_8H_{12}O_3$, the yield should be about 19 percent. The difference between this figure and the maximum of 15 percent actually isolated can be accounted for by losses during purification

by fractional distillation.

The structure (LVII) assigned to the compound $C_8H_{12}O_3$ is based in part on elementary analysis, methoxyl content, the molar refraction M_D and the saponification equivalent. Since no instantaneous bromine absorption was noted, it was concluded that the double bond present was in the α β position to the carboxyl group and might be in either of two positions as shown in formula (LVII) and (LVIIa).



LVII



LVIIa

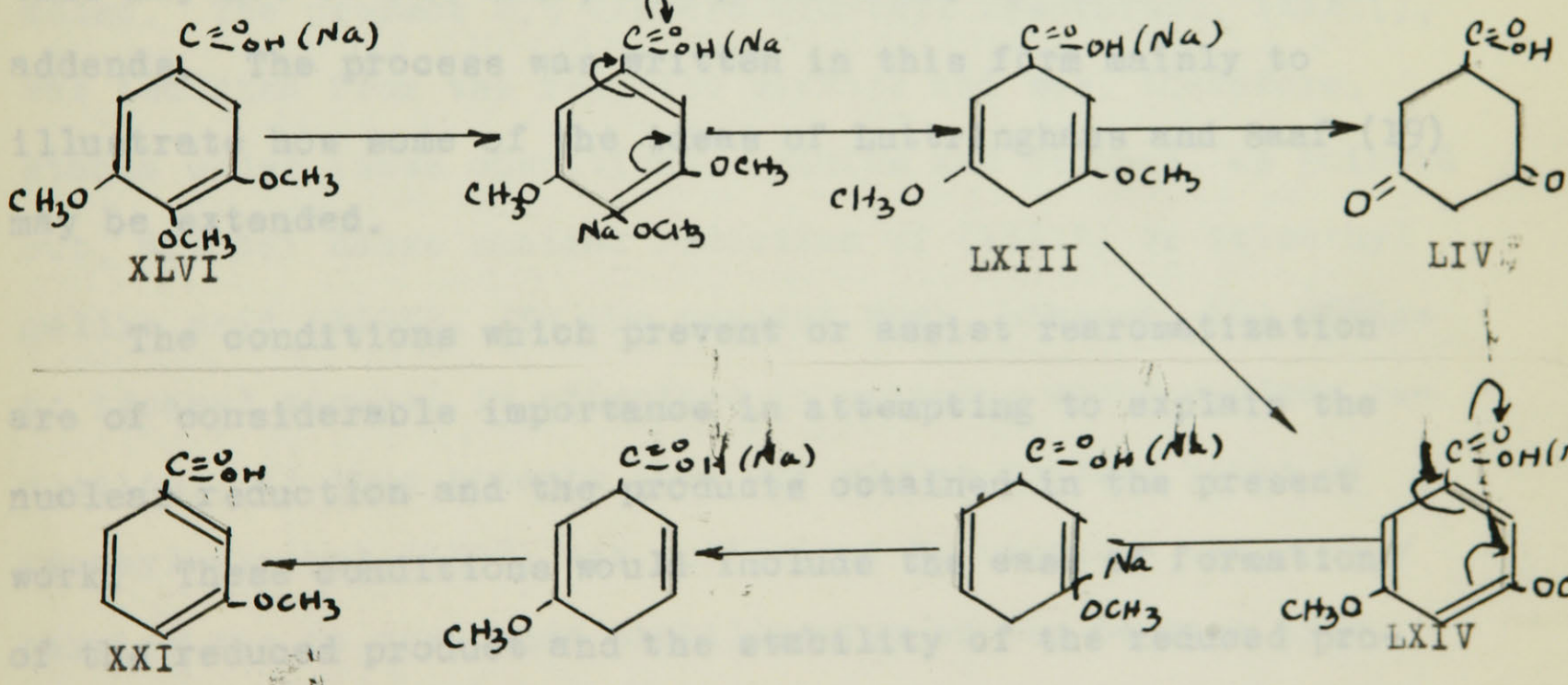
An equilibrium mixture of the forms (LVII) and(LVIIa) is also obviously possible, just as the Δ^1 and Δ^2 tetrahydrobenzoic acids are formed by the sodium-amalgam reduction of benzoic acid (136). In any case, the extended reduction of trimethyl gallic acid with 36.9 atoms of sodium yielded a product, $C_8H_{14}O_3$, (LVIII), the methyl ester of which is identical in chemical composition (elementary analysis, methoxyl content, saponification equivalent) and physical properties (density, refractive index, molar refraction) with synthetic methyl cis-3 methoxy cyclohexanecarboxylic acid (L). Besides identifying product (LVIII), the synthesis of the methyl ester of (LVIII) made it possible to assign structures (LVII) and/or (LVIIa) to compound, $C_8H_{12}O_3$, which must be intermediate to the formation of (LVIII) from

trimethyl gallic acid. In addition to compounds (XLVIII) and (LVIII), the known Δ_1 cyclohexenecarboxylic acid, (LIII), was obtained in 17 percent yield from the reduction product using 36.9 atoms of sodium per mole of (XLVI).

The Course of the Reduction of Trimethyl Gallic Acid (XLVI) with Sodium and Isoamyl Alcohol.

Reference to Figure 3 shows that there is a definite transition from dihydro to tetrahydro products and finally to a small yield of a hexahydro compound as the amount of alkali metal is increased in relation to the trimethyl gallic acid (XLVI) reduced. When a small molar ratio of sodium was employed, the principal product was cyclohexanedione 3,5 carboxylic acid (LIV). The isolation of this substance is clearly analogous to the recovery of resorcinol dimethyl ether with sodium and alcohol (41, 42) and with the further reduction of either of these ethers to the dihydro resorcinol derivative (XXXII) when sodium in liquid ammonia was used (24). Cyclohexanedione 1,3 (XXXIII), readily formed by the mineral acid hydrolysis of the enol methyl ether (XXXII), was the final product when the liquid ammonia reductant was used. These changes were explained in the Introduction by an electronic mechanism suggested by Birch (4, 23, 24) and by Luttringhaus and Saaf (19), and it seems extremely probable that a similar mechanism is also valid for the reduction of trimethyl gallic acid by sodium in isoamyl alcohol. This mechanism assumes that a methoxy group activates the cleavage of a second methoxy group to the greatest extent when the two

groups are ortho to each other. As in the case of pyrogallol trimethyl ether (XXXIX), two such effects are operative in trimethyl gallic acid (XLVI), and it follows that the increased electron density on the central carbon atom facilitates the addition of a proton or cation (Na^+) at this point with a corresponding decrease in electron density in the para position. An easy cleavage of the readily hydrolyzable enolic methyl ether groups in (LXIII)(91) would then give rise to the cyclohexanedione 3,5 carboxylic acid (LIV) actually isolated.



Cleavage of Methyl Ether Groups Of Trimethyl Gallic Acid.

Figure 8

Such a process would be facilitated in the case of trimethyl gallic acid (XLVI) because the presence of the carboxyl para to the central methoxy group would assist the mesomeric effect and transmit it along the carbon to carbon skeleton as shown in Figure 8. The formation of m-methoxy benzoic acid by cleavage of a second methoxyl group is supported by the more recent

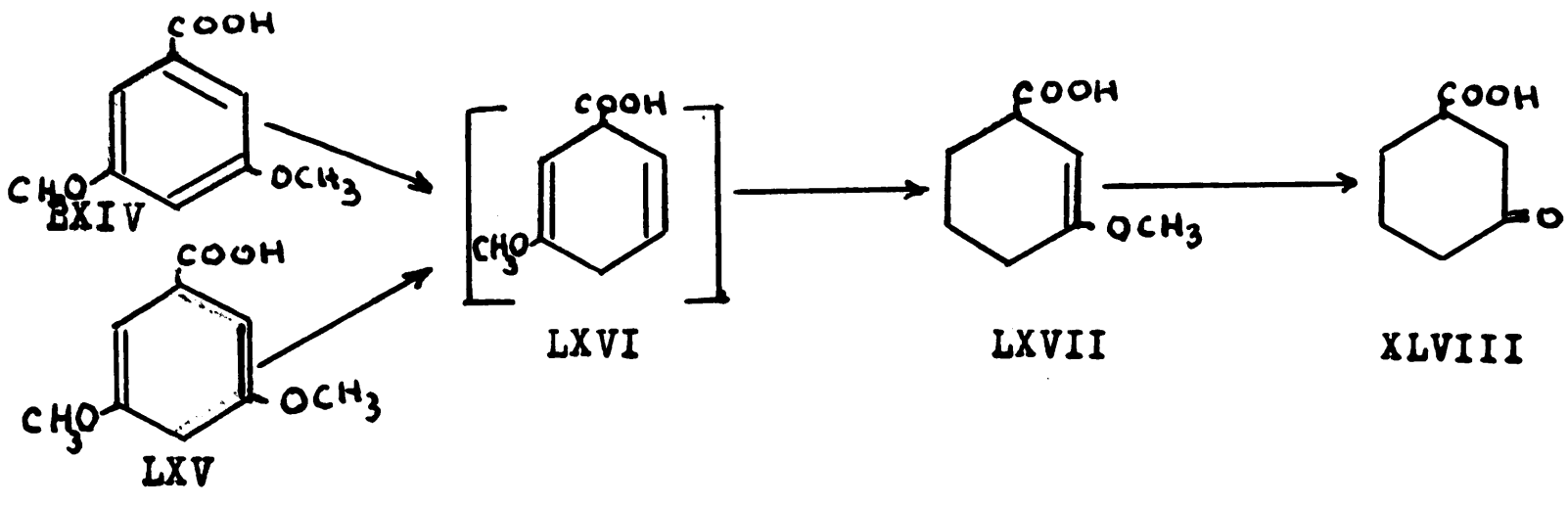
work of Birch (24) who found that m-methoxy groups also activate the cleavage of phenol ethers, although to a lesser extent than when in the ortho position. It seems reasonable, according to this scheme (Figure 8), that this activation, assisted by the electromeric polarisibility of the carboxyl group, absent in pyrogallol trimethyl ether (XXXIX), is sufficient to cause cleavage of a second phenol ether linkage. This mechanism (Figure 8) is written showing sodium atoms attached to the benzene ring but, as discussed in the Introduction (page 26), this may not be the case, and protons may be substituted as addends. The process was written in this form mainly to illustrate how some of the ideas of Luttringhaus and Saaf (19) may be extended.

The conditions which prevent or assist rearomatization are of considerable importance in attempting to explain the nuclear reduction and the products obtained in the present work. These conditions would include the ease of formation of the reduced product and the stability of the reduced product under the reaction conditions. If a given compound is formed with great ease and in good yield because of the very effective action of the reducing agent in promoting the mesomeric process, rearomatization would be hindered because of the facile addition of a proton (or other cation) to the benzene ring, obliterating the resonance stabilization of the nucleus and the resulting aromatic character. The effectiveness of the reducing agent would be dependent on its ability, as pointed

out by Birch (4), to provide both a source of electrons and a ready source of protons for subsequent addition to the resulting carbanions. Furthermore, the more stable the reduced form, the less would be the tendency to revert to an aromatic ring. Apparently the sodium and liquid ammonia reduction, with added alcohol, of pyrogallol trimethyl ether (XXXIX) fulfills all of these requirements because the liquid ammonia reductant is considered a solution of metal cations and solvated electrons (37), and a source of protons the alcohol was added. The product 2,5 dihydro dimethyl resorcinol, (XXXII), was isolated from the reaction mixture and was, therefore, stable under these conditions. Sodium and ethanol, as pointed out, did not cause nuclear reduction of (XXXIX) or trimethyl gallic acid (XLVI). In the present work, however, the change to isoamyl alcohol is effective in bringing about nuclear reduction. It thus appears that the higher boiling point of isoamyl alcohol (130°) was sufficient to overcome the energy barrier due to resonance stabilization of the benzene ring, while that of ethanol (78°) was insufficient. The amount of chemical energy in each case was substantially the same since this energy was provided by the formation of the sodium alkoxide. The intensity factor of the energy (the temperature), however, was different. The increased intensity of energy in the reduction employing isoamyl alcohol may have provided the type of activation energy (or quanta of specific frequency) adequate to overcome the resonance exhibited by (XLVI). This idea is,

of course, purely speculative. It is also possible that the higher temperature of the isoamyl alcohol brought about more efficient heat transfer during the reductions. This latter explanation seems less probable, because, in one experiment only one-third of the amount of sodium was employed with isoamyl alcohol as was used with ethanol, nevertheless, nuclear reduction did take place in the former case, but not in the latter.

The formation of 3-keto cyclohexanecarboxylic acid (XLVIII), may be postulated as arising from either 3,5 dimethoxy benzoic acid (LXIV) and/or the 1,4 dihydro derivative (LXV) through the intermediate 1,4 dihydro m-methoxy benzoic acid (LXVI) in a manner analogous to the formation of cyclohexanone (XL) after hydrolysis of the product of the extended reduction of resorcinol dimethyl ether (XXXI), (24).



The further cleavage of methyl ether groups from (LXIV) would yield m-methoxy benzoic acid (XXI) and benzoic acid (LII), the latter only being actually isolated. This retention of aromaticity

under moderate reaction conditions (18.4 atoms of sodium) may be considered further evidence of the weak influence of the carboxyl group by itself in causing polarization to the Dewar bridge formula for benzene. $\Delta_1$cyclohexenecarooxylic acid (LIII), could have arisen either by the reduction of benzoic acid (LII), or by the ether cleavage of compound (LVII), 3-methoxy Δ_1 cyclohexenecarboxylic acid and/or the isomer, the Δ_6-acid, (LVIIa). Compounds (LVII) and (LVIIa) may have resulted from α,β and β,γ shifts of the olefinic linkage respectively of the enol ether (LXVII), postulated as intermediate in the formation of the ketone, (XLVIII). The reduction of both (LVII) and (LVIIa) would yield the cis 3-methoxy cyclohexanecarboxylic acid, (LVIII), actually isolated, although information is lacking to explain why the cis form alone should be produced.

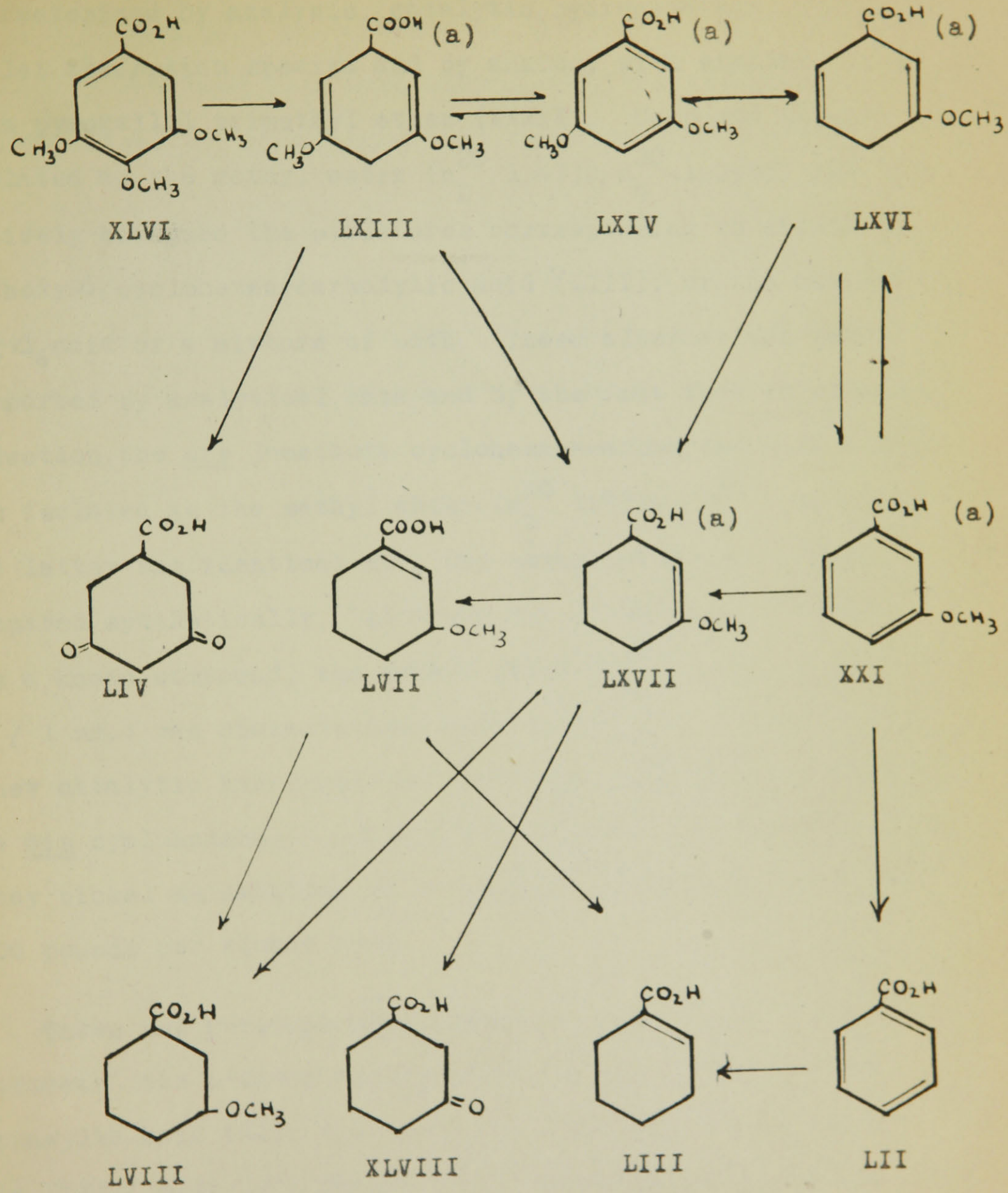
Except in the first reduction of the series, where the overall recovery of pure material was about 70 percent, the average overall yield for these reductions varied from 20 percent to 50 percent (Figure 3). The reasons for these relatively low yields may be attributed to the number and reactivity of the compounds produced. The presence of several products in each case multiplied the problems of isolation and purification with a consequent decrease in the isolated yields of each component, as well as in the overall recovery. All of the products and their supposed intermediates are reactive entities under the conditions of the reduction, having reactive methylene groups

alpha to carboxyl groups and, therefore, under the conditions obtaining, susceptible to the Claisen condensation with another molecule of a carboxylic acid. These reactive methylene groups could also add to olefinic linkages, the latter also being exposed to the possibility of polymerization. In these ways, and doubtless in many more that have not been mentioned, the recovery of single identifiable substances would be drastically curtailed.

SUMMARY

In contrast to the reduction of gallic acid (XLV) where no non-phenolic products could be isolated, the benzenoid nucleus of trimethyl gallic acid (XLVI) was successfully reduced by a chemical agent, sodium and isoamyl alcohol. The course of the reduction, as discovered by the results and discussion in this Thesis, is summarized in Figure 9. Of the compounds shown in Figure 9, (LXIII), (LXIV), (LXVI), (XXI), (LXVII), were not actually isolated but are postulated as intermediate to other reduction products. Of the former (LXIII), (LXVII) are the enol ethers of (LIV) and (XLVIII), respectively, and would not be expected to survive acidification of the crude reduction product. Substance (LXVI) would be hydrogenated far too easily to (LXVII) to be recovered as such. m-Methoxy benzoic acid (XXI), was not isolated, although Semmler (20) using ethanol in his sodium reduction succeeded in doing so. This difference would indicate that under the present conditions (XXI) would undergo nuclear reduction. The fact that 3,5 dimethoxy benzoic acid, (LXIV), was not isolated makes it possible that this step was shortcircuited. It is also possible that future work will show that (LXIV) reduces under these conditions to compounds such as the cyclic β diketone (LIV) and the monoketone (XLVIII).

Several new compounds were isolated during the research. Cyclohexanedione 3,5 carboxylic acid (LIV), m.p. 166 - 167° was



(a) not isolated.

Figure 9 - The Course of the Reduction of Trimethyl Gallic Acid(XLVI).

characterized by analysis, catalytic hydrogenation, ultraviolet absorption spectra and by analogy with similar reductions with pyrogallol trimethyl ether (XXXIX). Compound (LIII), was isolated as the methyl ester (n_D^{20} 1.4770, d_4^{20}-1.0989) and tentatively assigned the structures corresponding to either 3-methoxy Δ_1 cyclohexenecarboxylic acid (LIII), or the corresponding Δ_6 acid or a mixture of both. These alternatives were supported by analytical data and by the fact that on extended reduction the cis 3-methoxy cyclohexanecarboxylic acid (LVIII) was isolated as the methyl ester (n_D^{20} 1.4510, d_4^{20} - 1.0351). The latter was identical with the methyl ester of (LVIII) prepared synthetically. Although the γ keto acid (XLVIII) was a known compound, the methyl ester (n_D^{20} 1.4640, b.p. 76 - 78 / 1 mm.) was characterized apparently for the first time. A new catalytic hydrogenation producing high yields (50%) of the cis cyclohexanol-3 carboxylic acid (XI) was developed using Raney nickel as catalyst at an initial hydrogen pressure of 2000 pounds per square inch.

Three new p-bromphenacyl esters of known compounds were produced: the p-bromphenacyl ester of cis cyclohexanol-3 carboxylic acid (XI), m.p. 136°, of Δ_1 cyclohexenecarooxylic acid (LIII) m.p. 97°, and of 3-keto cyclohexanecarboxylic acid (XLVIII) m.p. 121 - 122°.

Two cyclic β diketones, cyclohexanedione 3,5 carooxylic acid (LIV), and 5,5 dimethyl cyclohexanedione 1,3 (LI) were observed to consume periodate when oxidized at room temperature

and pH 4.0, one mole being absorbed rapidly and an additional mole being consumed much more slowly. It was beyond the scope of this thesis to investigate this reaction any further.

Two standard analytical methods, one determining the bromine number by means of the "bromide-bromate" reagent and the other determining the percent of "enol" form, were modified for the analysis of semi-micro quantities of materials.

CLAIMS TO ORIGINAL RESEARCH

(1) Nuclear reduction of trimethyl gallic acid (XLVI) was successfully accomplished by means of sodium and isoamyl alcohol. The course of the reduction was followed by varying the amount of alkali metal used and noting the products isolated. An electronic mechanism for this reduction was suggested, consistent with other reductions of carbon to carbon multiple bonds and with the nuclear reduction of other phenol ethers.

(2) Gallic acid did not yield any non-phenolic products when the same reductant was used. No reduced substances of any kind could be isolated because of the deep seated degradation that occurred.

(3) The principal products of the reaction with 5.5 atoms of sodium per mole of trimethyl gallic acid (XLVI) was cyclohexanedione 3,5 carboxylic acid (LIV) m.p. 166-167°, with 18.4 atoms of sodium, 3-keto cyclohexanecarboxylic acid (XLVIII) m.p. 76°, with 36.9 atoms of sodium, Δ_4 cyclohexenecarboxylic acid (LIII) m.p. 38-39°.

(4) Several new compounds were isolated during the research. Cyclohexanedione 3,5 carboxylic acid, (LIV), was characterized by analysis, catalytic hydrogenation, ultraviolet absorption spectra and by analogy with similar reductions of pyrogallol trimethyl ether (XXXIX) carried out by other

workers. A substance, having the empirical formula $C_8H_{12}O_3$, was isolated as the methyl ester (n_D^{20} 1.4770, d_4^{20} - 1.0989) and tentatively assigned the structures corresponding to 3-methoxy Δ_1 cyclohexenecarboxylic acid, (LIII), or the corresponding Δ_6 acid or a mixture of both. These alternatives were supported by the fact that on extended reduction the cis 3-methoxy cyclohexanecarboxylic acid (LVIII) was isolated as the methyl ester (n_D^{20} 1.4510, d_4^{20} - 1.0351). The latter was identical with the methyl ester of (LVIII) prepared synthetically. The methyl ester (n_D^{20} 1.4640, b.p. 76 - 78° / 1 mm.) of the known compound 3-keto cyclohexanecarooxylic acid (XLVIII) was character-ized apparently for the first time.

(5) Three new p-bromphenacyl esters of known compounds were prepared: the p-bromphenacyl ester of cis cyclohexanol-3 carboxylic acid (XI), m.p. 136°, of Δ_1 cyclohexenecarooxylic acid (LIII) m.p. 97°, and of 3-keto cyclohexanecarboxylic acid (LVIII) m.p. 121 - 122°.

(6) A new catalytic hydrogenation of m-hydroxy benzoic acid producing a high yield (50%) of cis cyclohexanol-3 carooxylic acid (XI) was developed using Raney nickel as catalyst at an initial hydrogen pressure of 2000 pounds per square inch.

(7) Two cyclic β diketones, cyclohexanedione 3,5 carooxylic acid (LIV) and 5,5 dimethyl cyclohexanedione 1,3 (LI) were observed to consume periodate when oxidized at room temper-

ature and pH 4.0, one mole being absorbed rapidly and an additional mole being consumed much more slowly.

(8) Two standard analytical methods, one determining the bromine number by means of the "bromide-bromate" reagent and the other determining the percent of "enol" form, were modified for the analysis of semi-micro quantities of material.

REFERENCES

1. Campbell and Campbell, Chem. Rev. 31 77-175 (1942).
2. Wooster and Godfrey, J. Am. Chem. Soc. 59 596 (1937).
3. Wooster, U.S. patent 2,182,242 (1939); C.A. 34 1993.
4. Birch, J. Chem. Soc. 1944 430.
5. Kazanskii and Glushnev, J. Gen. Chem. (U.S.S.R.) 8 642 (1938); C.A. 33 1279.
6. Kazanskii and Smirnova, Bull. acad. sci. (URSS) Classe sci. mat. nat., Ser. chim. 1937 547; C.A. 32 2090 (1938).
7. Kazanskii and Glushnev, Bull. acad. sci. (URSS) Classe. sci. mat. nat., Ser. Chem. 1938 1061; C.A. 32 6256.
8. Breteau, Bull. Soc. Chem. (4) 9 729 (1911).
9. Willstatter, Seitz and Bumm, Ber. 61 871 (1928).
10. Meittler, Ber. 39 2933 (1906).
11. Merling, Ann. 278, 28 (1894).
12. Wislicenus, Ber. 27, 358 (1894)
13. Einhorn, Ber. 28 694 (1895).
14. Einhorn, and Willstatter, Ber. 26 2913 (1893), 27 331 (1894).
15. Baudisch, Hibbert and Perkin, J. Chem. Soc. 95 1876 (1909).
16. Perkin and Tattersall, J. Chem. Soc. 91 489 (1907).
17. Durand, Compt. rend. 172 70-1 (1921).
18. Schorigin, Ber. 56 176-86 (1923); ibid, 57 1634-37 (1924); ibid, 57 1627-34 (1924).
19. Luttringhaus and Saaf, Ang. Chem. 51 915-53.
20. Semmler, Ber. 41 1774 (1908).
21. Einhorn. Beilstein, Band X 372 (1927).

22. Freudenberg, Lautsch and Piazolo, Ber. 74 1886 (1941).

23. Birch, J. Chem. Soc. 1946 593.

24. Birch, J. Chem. Soc. 1947 102.

25. Papa and Schwenk, J. Org. Chem. 10 232 (1945).

26. Baeyer, Ann. 269 145 (1892).

27. Willstatter, Seitz and Bumm, Ber. 61 871 (1928).

28. Wooster and Smith, J. Am. Chem. Soc. 53 179 (1931).

29. Geib and Harteck, Ber. 66 1815 (1933).

30. Huckel and Bretschneider, Ann. 540 157 (1939).

31. Wilson, Trans. Electrochem. Soc. 75 353 (1939).

32. Isaacs and Wilson, J. Chem. Soc. 1936 202, ibid, 1936 574; ibid, 1936 810.

33. Conant, Chem. Rev. 3 1 (1926-27).

34. Conant and Cutter, J. Am. Chem. Soc. 48 1016 (1926).

35. Michaelis and Schubert, Chem. Rev. 22 437 (1938).

36. Prins, Rev. trav. Chem. 44 1093 (1925).

37. Burton and Ingold, J. Chem. Soc. 1929 2022.

38. Kraus, J. Am. Chem. Soc. 43 764 (1921).

39. Sartoretto and Sowa, J. Am. Chem. Soc. 59 603 (1937).

40. Weber and Sowa, J. Am. Chem. Soc. 60 94 (1938).

41. Thoms and Siebeling, Ber. 44 2135 (1911).

42. Semmler, Ber. 41 2556 (1908).

43. Lapworth, J. Chem. Soc. 85 30 (1904).

44. Dawson and Ark, J. Chem. Soc. 99 1740 (1911).

45. Dawson, Burton and Ark, J. Chem. Soc. 95 1860 (1909).

46. Dawson and Powis, J. Chem. Soc. 101 1503 (1912).

47. Dawson and Wheatley, J. Chem. Soc. 97 2043 (1910).

48. Hughes and Watson, J. Chem. Soc. 1929 1945.

49. Lowry, J. Chem. Soc. 127 1382 (1925); ibid, 1927 2557.

50. Ingold, Shoppee and Thorpe, J. Chem. Soc. 1926 1490.

51. Baker, J. Chem. Soc. 1928 1583.

52. Watson, Chem. Rev. 7 173 - 201 (1930).

53. Arndt and Martius, Ann. 499 228-87 (1932).

54. Hammett, Physical Organic Chemistry, p. 229-31 (McGraw-Hill, 1940).

55. Remick, Electronic Interpretations of Organic Chemistry p. 375 (Wiley, 1943).

56. Freer, Am. Chem. J. 13 308 (1891).

57. Freer, Am. Chem. J. 15 582 (1893).

58. Freer, Am. Chem. J. 18 552 (1896).

59. Freer, Ann. 293 326 (1896).

60. Freer and Higley, Am. Chem. J. 13 322 (1891).

61. Freer and Lachmann, Am. Chem. J. 19 373 (1897).

62. Denis, Am. Chem. J. 13 308 (1891).

63. Evans and Nicoll, J. Am. Chem. Soc. 47 2739 (1925).

64. Witzemann, J. Am. Chem. Soc. 39 2657 (1917).

65. Knorr, Ber. 44 2767 (1911).

66. Knorr, Rothe and Averbeck, Ber. 44 1135 (1911).

67. Meyer and Schoeller, Ber. 53 1410 (1920).

68. Duffraisse and Moureu, Compt. rend. 180 1946 (1925); Bull. Soc. Chem. 41 1607 (1927).

69. Moureu, Compt. rend. 186 730, 503 (1925); 188 504 (1929).

70. Schiff, Ber. 23 1594 (1890).

71. Bougault and Hemmerle, Compt. rend. 170 1392 (1920).

72. Gault and Weick, Compt. rend. 170 1392 (1920).

73. Schwarzenbach and Felder, Helv. Chem. Acta 27 1701-11 (1944).

74. Henri and Fromageot, Bull. soc. chim. 4, 37 845-53 (1925).

75. Neuberg, Biochem. Zeitschr. 219 165-170 (1930).

76. Kohler and Thompson, J. Am. Chem. Soc. 55 3822 (1933).

77. Arndt, Ozansoy and Ustunyar, Rev. faculte univ. Istanbul (N.S.) 4, (1-2), 83-87 (1939).

78. Meyer, Ber. 45 2843 (1912).

79. Meyer, Ber. 47 826 (1914).

80. Meyer and Wilson, Ber. 47 832, 837 (1914).

81. Sidgewick, J. Chem. Soc. 1925 907.

82. Conant and Thompson, J. Am. Chem. Soc. 54 4044 (1932).

83. Remick, Electronic Interpretations of Organic Chemistry p. 375 (Wiley, 1943).

84. Grignard and Blanchon, Roczniki Chem. 9 547-68 (in French) 568-80 (in Polish) (1929); C.A. 1342^{5} (1930).

85. Grignard and Blanchon, Bull. soc. chem. (4) 49, 23-42 (1931); C.A. 2124^{2} (1931).

86. Arndt and Martius, Rev. faculte univ. Istanbul (N.S.) 4, (1-2) 88-90 (1939).

87. Arndt, Loewe, Ozansoy, Ogut, Arslan, Bagavi, Ber. 71B 1631-40 (1938).

88. Arndt, Loewe, Severge, Turegun, Ber. 71B 1640-4 (1938).

89. Arndt, Loewe and Ozansoy, Ber. 73B 779-82 (1940).

90. Arndt, Loewe and Beyer, Ber. 74B 1460-4 (1941); C.A. 36 5776^{5} (1942).

91. Skrabal and Skrabal, Z. physic. chem. A181 449-68 (1938).

92. Fjader, Acta Chem. Fennica 6B 60-1 (1933); C.A. 28 2345^{7} (1934).

93. Meyer, Ann. 38 212 (1911); Ber. 44 2718 (1911).

94. Cooper and Barnes, Ind. Eng. Chem. (Anal.) 10 379 (1938).

95. Whitmore and George, J. Am. Chem. Soc. 64 1239-42 (1942).

96. Whitmore and Block, J. Am. Chem. Soc. 64 1619-21 (1942).

97. Whitmore and Lewis, J. Am. Chem. Soc. 64 2964-6 (1942).

98. Seidel, Thier, Uber and Dittmer, Ber. 69B 650-3 (1936).

99. Bohme and Fischer, Ber. 76B 106-9 (1943).

100. v. Auwers, J. Am. Chem. Soc. 53 1496-1500 (1931).

101. Michalek and Post, J. Am. Chem. Soc. 54 1963-4 (1932).

102. Hayashi, Bull. Inst. Phys. Chem. Research (Tokyo) 12, 579-588; Sci. Papers Inst. Phys. Chem. Research (Tokyo) 21 69-79 (in English) (1933); C.A. 27 3700^{5} (1933).

103. Milone, Gazz. Chem. ital. 65 339-49 (1935); C.A. 30 82^{5} (1936).

104. Hilbert, Wulf, Hendricks and Liddel, J. Am. Chem. Soc. 58 548-555 (1936).

105. Buswell, Rodebush and Roy, J. Am. Chem. Soc. 59 1767 (1937).

106. Baly and Desch, Z. physic. chem. 55 317 (1906).

107. Hantzsch, Ber. 43 3049 (1910).

108. Blout, Eager and Silverman, J. Am. Chem. Soc. 68 566-571 (1946).

109. Woodward, J. Am. Chem. Soc. 63 1123-1126 (1941).

110. Heywood and Kon, J. Chem. Soc. 1940 713; Gillam, Lynas-Grey, Penfold and Simonsen, ibid, 1941 60.

111. Bastron, Davis and Butz, J. Org. Chem. 8 515-25 (1943).

112. Lewis and Bradstreet, Ind. Eng. Chem. (Anal.) 12 337 (1940).

113. Lewis and Bradstreet, Ind. Eng. Chem. (Anal.) 16 617 (1944).

114. Niederl and Niederl, Micromethods of Quantitative Organic Analysis, p. 66 (2nd. ed. Wiley, 1946).

115. Schneider, Qualitative Organic Microanalysis, p. 161 (Wiley, 1946).

116. Lieff, Ph.D. Thesis, McGill University (1938).

117. Kohler, Stone and Fuson, J. Am. Chem. Soc. 49 3181 (1927).

118. v. Auwers and Eisenlohr, Ber. 43 806 (1910), as quoted in Gilman, "Organic Chemistry, An Advanced Treatise", p. 1751 (Wiley, 1943).

119. Clark, Ind. Eng. Chem. (Anal.) 10 677 (1938).

120. Viebock and co-workers, Ber. 63 2818, 3207 (1930).

121. Niederl and Niederl, Micromethods of Quantitative Organic Analysis, p. 101 (2nd. ed. Wiley, 1946).

122. Stepanow, Ber. 39 4056 (1906).

123. Kamm, Qualitative Organic Analysis, p. 199 (Wiley, 1932).

124. Adams and Voorhees, Organic Syntheses, Coll. Vol. I, p. 61 (2nd. ed. Wiley, 1944).

125. Graebe and Martz, Ann. 340, 219 (1905).

126. Mauthner, Organic Syntheses, Coll. Vol.I, 537 (Wiley, 1941).

127. Offermann, Ann. 280 5-61 (1894).

128. Huntress and Mulliken, Identification of Pure Organic Compounds (Wiley, 1941).

129. Arndt, Organic Syntheses, Vol XV, 3, (Wiley, 1935).

130. Langley, Organic Syntheses, Coll. Vol.I 127 (Wiley, 1941).

131. Bower and Cooke, Ind. Eng. Chem. (Anal.) 15 290 (1943).

132. Fleury and Lange, J. pharm. chim. (8) 17, 107, 196 (1933).

133. Chattaway, J. Chem. Soc. 1937 2495-6.

134. Dobson, Ferns and Perkin, J. Chem. Soc. 1909, 2015.

135. Purdie and Irvine, J. Chem. Soc. 1904 1058.

136. Boorman and Linstead, J. Chem. Soc. 1935, 258.

137. Linstead, J. Chem. Soc. 1927, 355-62.

138. Allen, Abell and Normington, Organic Syntheses, Coll. Vol. I, p. 205 (2nd. ed. Wiley, 1944).

140. Shriner and Fuson, Identification of Organic Compounds, p. 132 (2nd. ed. Wiley, 1946).

141. Lucas, J. Am. Chem. Soc. 48 1832 (1926); ibid, 51 2718 (1929); quoted in Remick, Electronic Interpretations of Organic Chemistry, p. 30 (Wiley, 1943).

142. Jackson, Organic Reactions, Vol. II p. 341 (Wiley, 1944).

143. Bastron, Davis and Butz, J. Org. Chem. 8 515-25 (1943).

144. Huebner, Ames and Bubl, J. Am. Chem. Soc. 68 1621 (1946).

145. Wolfrom and Lewis, J. Am. Chem. Soc. 50 837-54 (1928).

146. Montgomery and Hudson, J. Am. Chem. Soc. 52 2101-6 (1930).

147. Christian, Ph.D. Thesis, McGill University (1946).

148. Gogek, Ph.D. Thesis, McGill University (1946).

149. Dixon, Ph.D. Thesis, McGill University (1947).