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INTERPRETATION OF SOME REACTIONS IN THE CARBOHYDRATE FIELD IN TERMS OF CONSECUTIVE ELECTRON DISPLACEMENT

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ABSTRACT

An attempt has been made to show how the concept of consecutive electron displacement that has been developed in recent years may be used for the interpretation of certain reactions in the carbohydrate field. The viewpoint in general is that the peculiar properties of systems involving double bonds may be explained by the migration of electron pairs in the molecule from points of high electron density to points of lower electron density, with the addition and elimination of ions. A number of apparently unrelated complex reactions of the carbohydrates are considered and it is shown that the formation of the products may be explained by a few simple reactions involving shifts of electron pairs; these include enolization, de-enolization and double decomposition. Mechanisms are presented for the formation of the four classes of saccharinic acids from the 1,2-, the 2,3-, and the 3,4-enediols, for the formation of diacetylkojic acid from acetylglucosone, for the formation of unsaturated lactones from hydroxy acids, for the conversion of triacetylglucal to diacetylpsudoglucal, for the conversion of tetramethyl-1,2-glucosene to ω -methoxymethylfurfural, and for the formation of furfural and levulinic acid.

CONTENTS

	Page
I. Introduction.....	45
II. Formation of saccharinic acids by the action of alkali on sugars.....	47
III. Formation of diacetylkojic acid from acetylated glucosone hydrate.....	50
IV. Formation of unsaturated lactones from hydroxy acids.....	51
V. Conversion of triacetylglucal to diacetylpsudoglucal.....	52
VI. Conversion of pseudoglucal to isoglucal and protoglucal.....	53
VII. Conversion of tetramethyl-1,2-glucosene to ω -methoxymethylfurfural.....	54
VIII. Formation of furfural from trimethylpentoses.....	55
IX. Formation of levulinic acid from ω -hydroxymethylfurfural and from 2-desoxypentoses.....	57
X. References.....	59

I. INTRODUCTION

The development of physical organic chemistry in recent years has led to a type of organic chemistry in which reactions are represented in terms of the changes in the electronic structure of the reacting substances. Classical organic chemistry has thus been amplified, and an insight has been gained into the forces causing and controlling reactions. Although the fundamental principles of this approach to organic chemistry have been presented in a number of texts [1, 2, 3],¹ application in the field of carbohydrate chemistry has not been exten-

¹ Figures in brackets indicate the literature references at the end of this paper.

the formation of an activated complex between the base (usually a hydroxyl ion) and the hydrogen of the carbon adjacent to the carbonyl group, or at the end of a conjugated double-bond system. A flow of electrons in the activated complex, from the carbon-hydrogen bond to the carbon-carbon bond and from the carbonyl carbon to the oxygen, yields a resonating enolic ion. This ion picks up a proton from the environment and thereby forms either the enol- or the keto-tautomer. In case the system contains conjugated double bonds, the slightly polarized hydrogen attached to the carbon at the end of the conjugated chain combines with the base and enolization takes place as represented by equation 2.

De-enolization (ketonization) ordinarily takes place by ionization of the enolic hydrogen accompanied by a flow of electrons to the adjacent carbon, or if the enol contains a conjugated double-bond system, to the carbon at the end of the double-bond system. Electrical neutrality is maintained by the addition of a proton, or by elimination of a group carrying the excess electrons. The first process is the reverse of enolization, the second process is represented by equation 3, in which X is a group such as OH, Cl, OCH₃, OAc, etc., attached to the carbon adjacent to the enolic grouping, or to the carbon at the end of a conjugated double-bond system. Elimination of negative groups may also take place by displacement as represented in equation 4, or in some cases with the formation of heterocyclic rings, as in equations 5 and 6.

Changes of the type represented by the equations involve consecutive electron displacements with the addition and elimination of ions. The reaction mechanisms are similar to mechanisms which have been postulated by Hauser in fundamental studies relating to elimination and rearrangement reactions [4]. In a previous publication [5] the present author discussed briefly the alkaline cleavage of certain glycosides, the formation of benzene derivatives from ketoinositols, and the production of furfural from glycoseens. Limitations of space, however, did not permit full development of the subject, and consideration of many other important reactions.

II. FORMATION OF SACCHARINIC ACIDS BY THE ACTION OF ALKALI ON SUGARS

For many years the conversion of reducing sugars to saccharinic acids by the action of strong bases has been the subject of much speculation and considerable research. Recently an excellent review of the reactions resulting in saccharinic acids, and the work which led to the assignment of structures to the various saccharinic acids was published by Evans [6]. In the hexose series the saccharinic acids have been classified in four groups [7, 8]:

1. Metasaccharinic acids, CH₂OH.CHOH.CHOH.CH₂.CHOH.COOH.

2. Saccharinic acids CH₂OH.CHOH.CHOH. $\overset{\text{COOH}}{\text{COH}}$.CH₂.

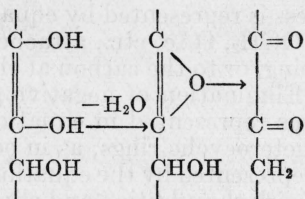
3. Isosaccharinic acids CH₂OH.CHOH.CH₂. $\overset{\text{COOH}}{\text{COH}}$.CH₂OH.

4. Parasaccharinic acids CH₂OH.CHOH. $\overset{\text{COOH}}{\text{COH}}$.CH₂CH₂OH.

On account of the complex character of the substances, the idea was promoted early that they might be formed by recondensation of degradation products of the sugar molecule, such as lactic acid and

glyceraldehyde. This process would not be restricted to the formation of saccharinic acids containing the same number of carbons as the parent sugar; hence one would expect to obtain 6-carbon saccharinic acids from the lower sugars as well as from the hexoses. Since this is not the case, the hypothesis has been generally discarded.

Nef [7] postulated a progressive migration of the carbonyl group along the carbon chain with the formation of 2- and 3-ketohexoses. He assumed that these ketoses, by internal oxidation and reduction, form desoxydiketo compounds, which undergo benzilic acid rearrangements. According to Nef's concept, the desoxydiketo compounds were formed through intermediate methylenic compounds containing an active bivalent carbon atom. In the light of our present knowledge, Nef's mechanism for the production of the diketo compounds seems improbable, but his concept of the occurrence of a benzilic acid rearrangement is nevertheless acceptable. Benoy and Evans [9] suggested the following mechanism for the formation of the desoxydiketo compounds from enediols:



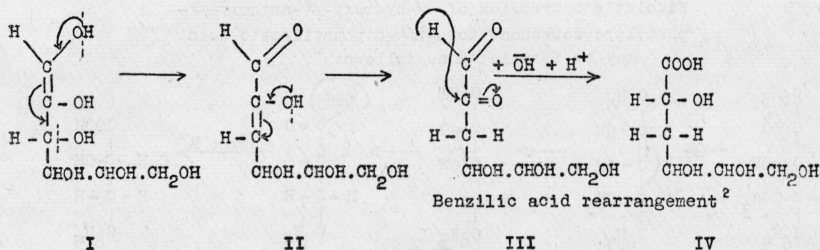
They consider the saccharinic acids to be derived from the 1,2-enediols, the isosaccharinic from the 3,4-enediols, and the parasaccharinic and metasaccharinic acids from the 2,3-enediols.

Nicolet [10] observed that α -hydroxy- β -methoxy- β -phenylpropio-phenone, on treatment with alkali, gives α , β -diphenyllactic acid. He noted that the reaction requires elimination of the methoxyl attached to the beta carbon and stated that the reaction made a revision of Nef's theory of saccharinic acid formation necessary. Elimination of a methoxyl (or of a hydroxyl) on the carbon beta to a carbonyl group might take place directly by elimination of the elements of methyl alcohol (or water) from adjacent carbon atoms, or indirectly through enolization and a reaction of the type represented by equation 3, page 46. The latter course seems the more probable and is used in the equations for saccharinic acid formation, although it is recognized that either course might be followed.

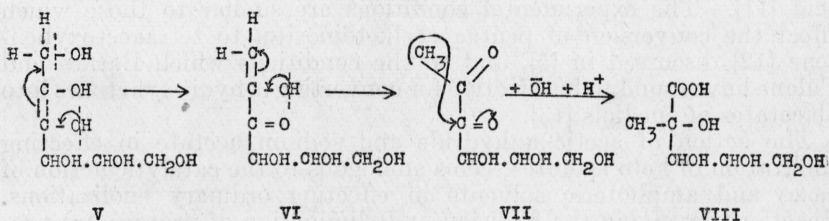
The formation of the various saccharinic acids from the several enediols may be explained in accordance with the concept of consecutive electron displacement, by the following reactions: 1. Ionization of a hydrogen of the enediol followed by elimination of a hydroxyl by a reaction of the type represented by equation 3, page 46. 2. Ketonization with the formation of a desoxydiketo compound. 3. A rearrangement of the benzilic acid type, giving the saccharinic acid. The benzilic acid rearrangement, originally suggested by Nef, involves a shift of a group with its binding electrons from one carbon to another, and differs fundamentally from the consecutive electron displacements characteristic of most of the reactions considered here. Presumably it takes place through an intermediate ion formed either by addition of a hydroxyl, or by loss of a proton from the hydrated carbonyl group. The mechanism for reactions of the benzilic acid type (see footnote 2) is discussed in references [1, 2, 3, 4]. It may be ob-

served by inspection of the accompanying formulas that metasaccharinic acids are represented as derived from the 1,2-enediols, parasaccharinic acids from the 3,4-enediols, and saccharinic and isosaccharinic acids from the 2,3-enediols. These correlations are at variance with those heretofore postulated. Reactions of the type outlined in the formulas may be used to account for the formation of saccharinic acids from other sugars and for the formation of lactic acid from glyceraldehyde through the intermediate methylglyoxal.

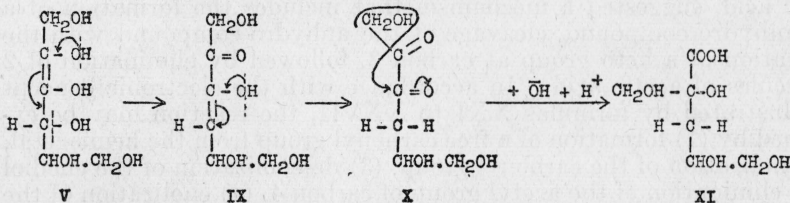
Formation of metasaccharinic acids from
hexose 1,2-enediols



Formation of saccharinic acids from
hexose 2,3-enediols

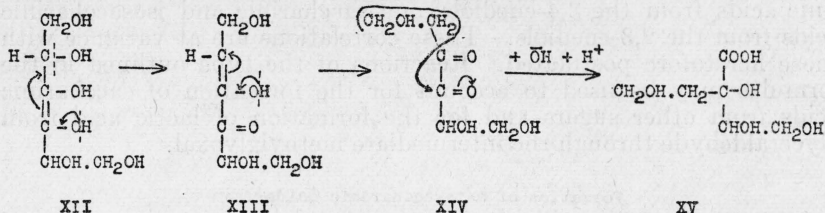


Formation of isosaccharinic acids from
hexose 2,3-enediols.

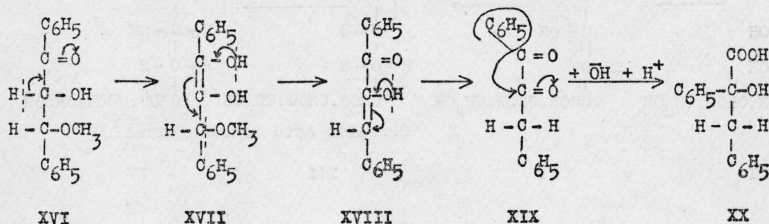


² In the benzilic acid rearrangement reported here, the hydrate and its ion, supposedly formed as intermediates in the reaction, are not given.

Formation of parasaccharinic acids from
hexose 3,4-enediols



Nicolet's conversion of α -hydroxy- β -methoxy- β -phenylpropio-phenone to α , β -diphenyllactic acid may be formulated as follows:



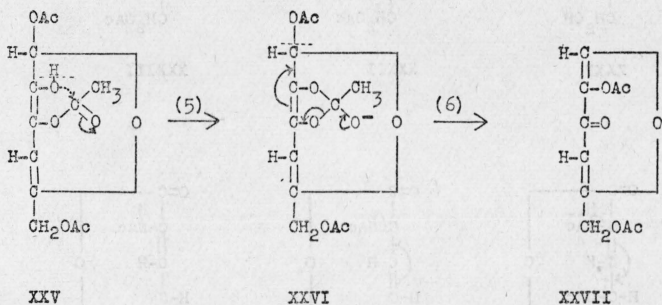
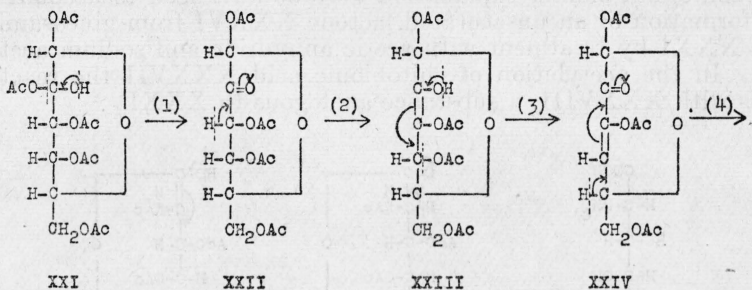
III. FORMATION OF DIACETYLKOJIC ACID FROM ACETYLATED GLUCOSONE HYDRATE

When tetraacetylglucosone hydrate is treated with acetic anhydride and either sodium acetate or pyridine, it is converted to diacetylkojic acid [11]. The experimental conditions are similar to those which effect the conversion of pentaacetylketoinositol to tetraacetoxybenzene [12] discussed in [5], and to the conditions which Barnes and Tulane have found to be effective for converting α -hydroxyketones into diacetates of enediols [13].

The action of acetic anhydride and sodium acetate in effecting enolization of keto acetates seems analogous to the catalytic action of bases and amphoteric solvents in effecting ordinary enolizations. Reactions involving the addition and elimination of protons are promoted by substances capable of donating and accepting protons, whereas reactions involving the addition and elimination of acetate ions seem to be promoted by substances capable of supplying and accepting acetate ions.

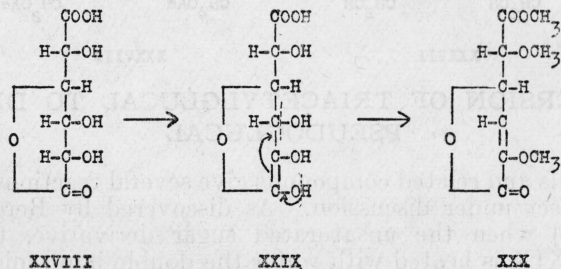
Maurer, who discovered the reaction leading to the formation of kojic acid, suggested a mechanism that includes the formation of a 2,3-anhydro compound, cleavage of the anhydro compound with the formation of a keto group at carbon 3, followed by elimination of 2 molecules of acetic acid. In accordance with the electronic concept as illustrated by formulas XXI to XXVII, the reaction may be explained by (1) formation of a free carbonyl group from the hemiacetal, (2) enolization of the carbonyl group, (3) de-enolization of the enediol with elimination of the acetyl group of carbon 4, (4) enolization of the resulting compound through the conjugated double bond, (5) and (6) migration of the acetyl group of carbon 3 to carbon 2 by means of an

intermediate complex of the orthoester type, with elimination of a proton and an acetate ion. The product would then be diacetylkojic acid, the substance obtained experimentally by Maurer. Many examples of the migration of acetyl groups in partially acetylated carbohydrates are reported in the chemical literature [14].



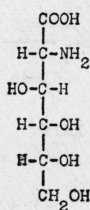
IV. FORMATION OF UNSATURATED LACTONES FROM HYDROXY ACIDS

As pointed out by Kiliani [15], Rehorst [16], and others, the lactones of mannosaccharic and saccharic acids are peculiar in that they give a series of reactions not in accord with the simple lactone structure XXVIII. The lactones react with hydrogen cyanide, combine with iodine and give other reactions indicative of an unsaturated structure. To explain the existence of lactone salts differing from those of the corresponding acids, Haworth [17] proposed an enolic structure. The capacity of carboxylic acids, lactones, and esters to form enolic intermediates provides a means for forming unsaturated derivatives

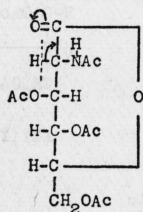


of diverse character by processes of consecutive electron displacement. The formation of the unsaturated ester XXX by methylation of the monolactone of saccharic acid XXVIII and the formation of the dimethylester of dimethoxymuconic acid [18] were considered briefly in [5].

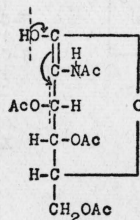
A somewhat similar explanation may be advanced to account for the formation of an unsaturated lactone XXXVI from glucosaminic acid XXXI by treatment with acetic anhydride and sodium acetate [19]. In the acetylation of chitobionic acid XXXVII the reaction stops with XXXVIII, a substance analogous to XXXIV.



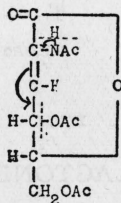
XXXI



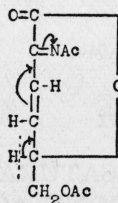
XXXII



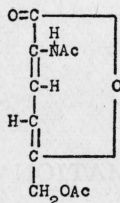
XXXIII



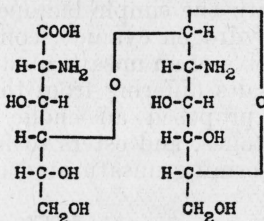
XXXIV



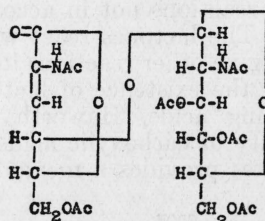
XXXV



XXXVI



XXXVII

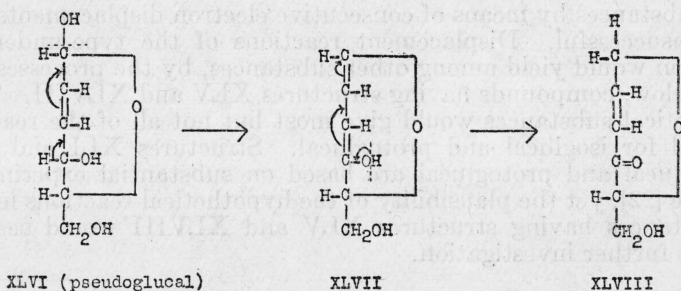
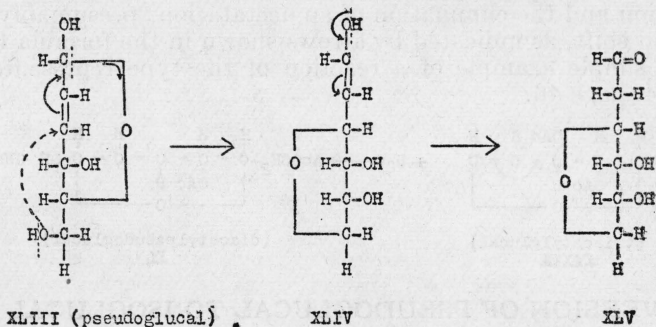


XXXVIII

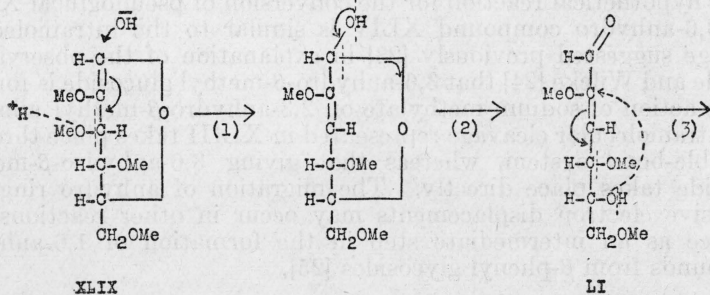
V. CONVERSION OF TRIACETYLGLUCAL TO DIACETYL-PSEUDOGUCAL

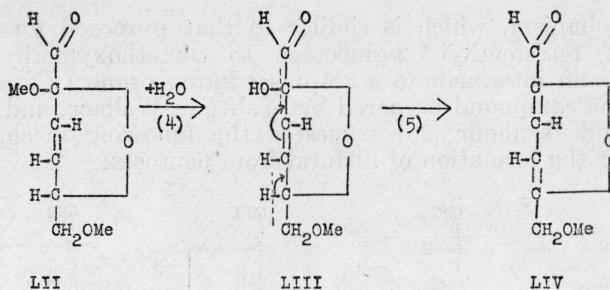
The glycals and related compounds give several reactions of interest to the subject under discussion. As discovered by Bergmann and Schotte [20] when the unsaturated sugar derivative, triacetyl-*D*-glucal, XXXIX is heated with water the double bond migrates from

HYPOTHETICAL REACTIONS OF PSEUDOGLUCAL

VII. CONVERSION OF TETRAMETHYL-1,2-GLUCOSEN TO ω -METHOXYMETHYLFURFURAL

Recently Wolfrom, Wallace, and Metcalf [26] made the very interesting observation that tetramethyl-1,2-glucoseen, XLIX on mild treatment with acid yields ω -methoxymethylfurfural LIV with the intermediate production of a 3,4-unsaturated osone LIII. The formation of the latter substance may be explained by the series of successive electron displacements outlined below. Presumably, the driving force of the reaction is the combination of the methoxyl groups with hydrogen ions to form methyl alcohol.

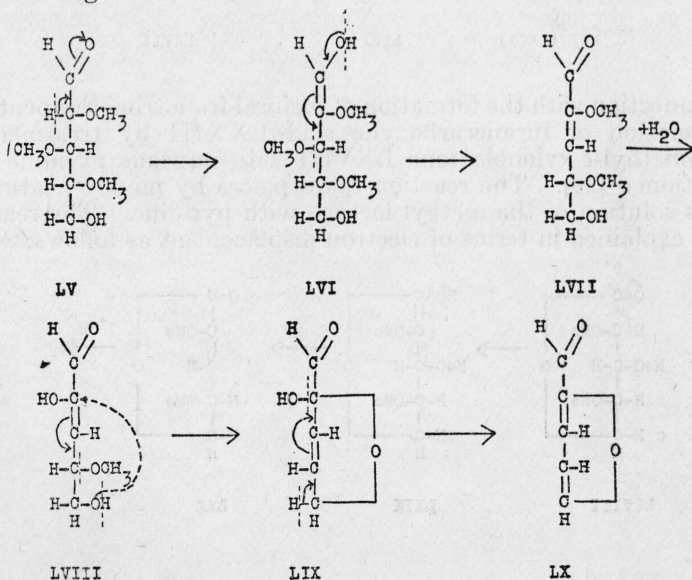




Step (1) is a reaction analogous to the formation of diacetylpsuedoglucal from triacetylglucal, (2) gives the open-chain modification, (3) is a reaction of the type represented by equation 6, page 46, in which the oxygen of carbon 5 provides the entering group, (4) gives rise to the 3,4-unsaturated osone isolated by Wolfrom, Wallace, and Metcalf, and (5) depicts its conversion to ω -methoxymethylfurfural. Hydrolysis of compound LII to the 3,4-unsaturated osone is shown as preceding the formation of ω -methoxymethylfurfural LIV. The latter substance might be formed directly from LII by elimination of the hydrogen of carbon 5 and the methoxyl of carbon 2, with the requisite electron shift.

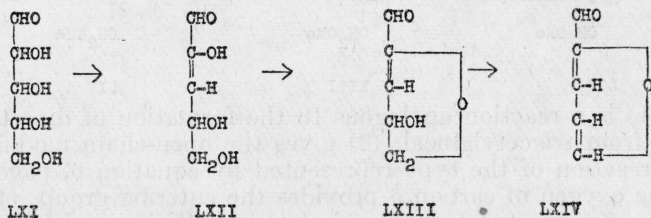
VIII. FORMATION OF FURFURAL FROM TRIMETHYLPENTOSSES

Several years ago Neher and Lewis [27] observed that when a trimethylpentose LV, represented here in the open-chain form is treated first with alkali and then with acid, furfural LX is formed even at room temperature, and suggested that the methylated enediol LVI produced by the action of the alkali on the methylpentose is the precursor of the furfural. In accordance with the concept of consecutive electron displacement, the reaction may be represented in the following manner:

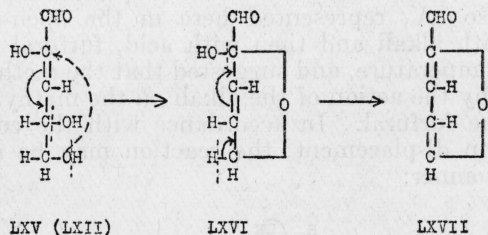


The mechanism, which is similar to that proposed for the conversion of tetramethyl-1,2-glucoseen to ω -methoxymethylfurfural, includes as an intermediate a 3,4-unsaturated osone LIX analogous to LIII, the compound prepared by Wolfrom, Wallace, and Metcalf.

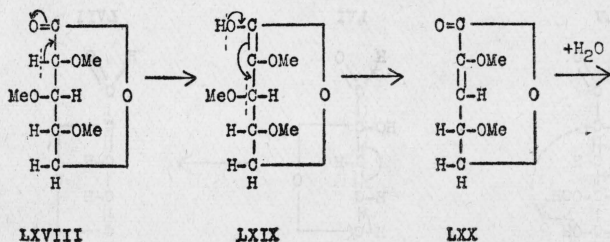
Hurd and Isenhour [28] suggested the following mechanism to account for the formation of furfural from pentoses:

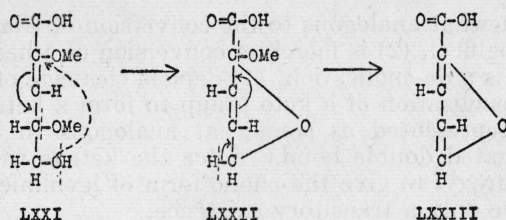


Compound LXII corresponds to the methylated compound, LVII. In accordance with general principles employed here, LXII, on ring closure, would yield the 3,4-unsaturated compound LXVI in place of the 2,3-unsaturated compound LXIII suggested by Hurd and Isenhour. Furfural, LXVII, would result from the changes indicated by the arrows in formula LXVI. The driving force of the reaction would appear to be removal of hydroxyl groups through combination with hydrogen ions derived from the acid catalyst.



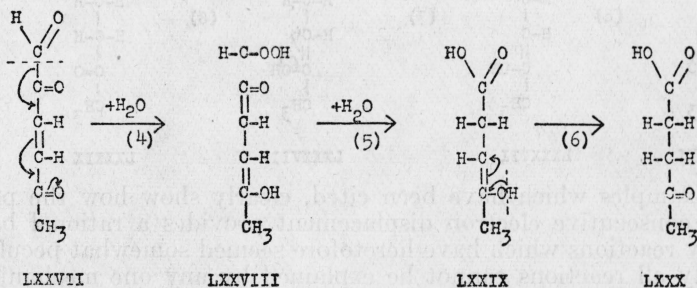
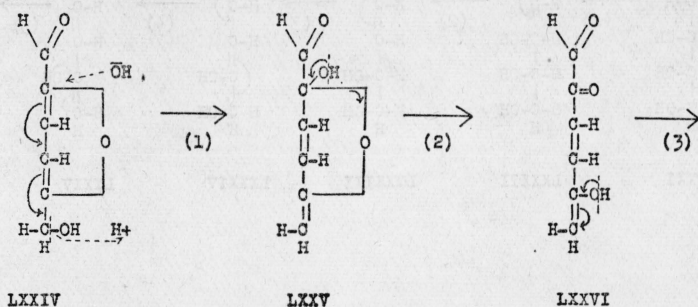
In connection with the formation of furfural from trimethylpentoses, the formation of furancarboxylic acid LXXIII by treatment of 2,3,4-trimethyl- δ -xylonolactone LXVIII with aqueous pyridine may be mentioned [29]. The reaction takes place by merely heating an aqueous solution of the methyl lactone with pyridine. The reaction may be explained in terms of electron displacement as follows:





IX. FORMATION OF LEVULINIC ACID FROM ω -HYDROXY-METHYLFURFURAL AND FROM 2-DESOXYPENTOSE

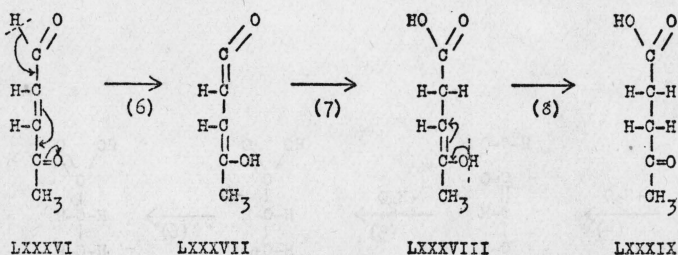
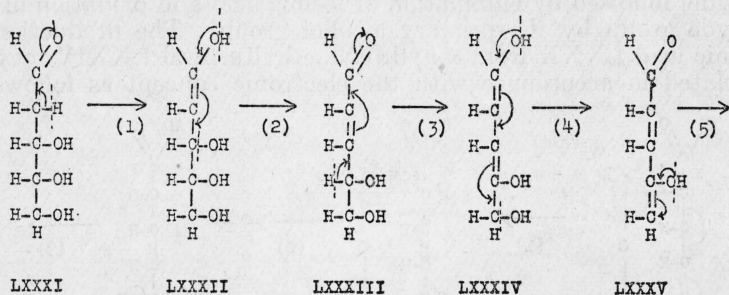
When hexoses are boiled with aqueous acid ω -hydroxymethylfurfural is formed and ultimately converted to levulinic acid.³ Considerable work has been conducted with the object of clarifying the mechanism for the formation of levulinic acid [30]. According to Pummerer, Guyot and Birkofer [30a] the reaction involves opening of the furane ring with the formation of 2,5-dioxo-6-hydroxycaproic aldehyde, followed by elimination of formic acid and oxidation of the aldehyde group by the primary alcohol group. The production of levulinic acid LXXX from ω -hydroxymethylfurfural LXXIV may be formulated in accordance with the electronic concept as follows:



³ A bibliography on levulinic acid has been prepared by the A. E. Staley Manufacturing Co., Decatur Ill.

Step (1) is somewhat analogous to the conversion of triacetylglucal to diacetylpsuedoglucal, (2) is merely a conversion of a hemiacetal to an aldehyde, (3) is a de-enolization, (4) depicts cleavage of a carbon-carbon bond by enolization of a keto group to form a ketene derivative, a process represented as somewhat analogous to enolization through a conjugated double bond. Since the ketene would add a proton and a hydroxyl to give the enolic form of levulinic acid, step (5), it would have only a transitory existence.

Levene and Mori have observed the production of levulinic acid from 2-desoxypentoses [31]; an explanation similar to that given above may be advanced to account for this reaction, formulas LXXXI to LXXXIX. Step 6 is noteworthy as it represents enolization of a keto group through the hydrogen of an aldehyde, a step somewhat analogous to (4) in the preceding process. The existence of LXXXVII as a chemical entity would seem questionable and hence this compound is considered merely as a transition state between the aldehyde and the acid. The transition might follow a free radical course similar to the mechanism of the Cannizzaro reaction.



The examples which have been cited, clearly show how the principle of consecutive electron displacement provides a rational basis for many reactions which have heretofore seemed somewhat peculiar. Naturally all reactions cannot be explained by any one mechanism. Possibly some of the reactions described here may be found in the future to follow other mechanisms, but nevertheless the concept of consecutive electron displacement seems to provide a very useful means for correlating existing knowledge and for stimulating further investigation.

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