

The properties of eighteen substituted vinyl alkyl barbituric acids, prepared by one of the three condensation procedures, and the yields of purified products, are recorded in Table I. The yields of nitriles formed as by-products are given as a rough indication of the amount of alcoholysis which occurred in each case. The nitriles were distilled and had relatively constant boiling points, but the amounts available in most cases did not permit the careful fractionation necessary to obtain pure samples for analysis.

Ozonizations.—The barbituric acids designated by footnotes (g) and (h), Table I, were ozonized by the procedure previously used for (1-methylpropenyl) alkyl barbituric acids.³ The volatile aldehydes produced on the decomposition of the ozonides were identified by converting them to the 2,4-dinitrophenylhydrazones, whose melting points are recorded in the footnotes. Traces of formaldehyde detectable by color tests also were formed in the ozonizations but, as pointed out previously,³ this does not necessarily indicate the presence of traces of the isomeric compounds in which the substituted vinyl group has the structure $\text{CH}_2=\text{C}(\text{R})-$, since even saturated barbituric acids give traces of formaldehyde on ozonization.

Quantitative Reductions.—Samples of methyl, ethyl and propyl (1-methyl-1-butenyl) barbituric acids (the first three compounds in Table I) were dissolved in alcohol and reduced with hydrogen in the presence of a palladinized charcoal catalyst. In each case one molar equivalent of hydrogen was absorbed, within experimental error. The catalyst was separated by filtration and the reduction product purified by one or two crystallizations. The methyl derivative gave 5-methyl-5-(1-methylbutyl)-barbituric acid,⁴ m. p. 179–180°. The ethyl derivative gave 5-ethyl-5-(1-methylbutyl)-barbituric acid,⁴ m. p. and mixed m. p. with a known sample 129–130°. The propyl derivative gave 5-propyl-5-(1-methylbutyl)-barbituric acid,⁴ m. p. 85–87°.

Pharmacological Data

The results of preliminary pharmacological

(4) Volwiler and Tabern, *ibid.*, **56**, 1139 (1934).

tests made on the new substituted vinyl barbituric acids are recorded in Table II. The (1-methyl-1-butenyl) and (1-ethylpropenyl) derivatives are effective hypnotics which have high therapeutic ratios. In both of these groups of compounds the substituted vinyl group contains five carbon atoms. The majority of the remaining compounds, in which the substituted vinyl groups have six and seven carbon atoms, have somewhat lower therapeutic ratios. The compounds containing a (1-methyl-1-butenyl) group, with the exception of the methyl derivative, are effective in practically the same dosage when administered orally to white mice as when administered intraperitoneally. This indicates unusually efficient absorption of the (1-methyl-1-butenyl) compounds following administration by mouth. The presence of two branches in the chain of the substituted vinyl group appears to be undesirable, since both of the (1,3-dimethyl-1-butenyl) compounds produced convulsions, and the ethyl derivative had no narcotic action whatever.

Summary

A number of 5-(dialkylvinyl)-5-alkyl barbituric acids have been prepared by condensing substituted vinyl alkyl cyanoacetic esters with urea or guanidine, and hydrolyzing the resulting imino barbituric acids. Several of the barbituric acids, particularly those in which the substituted vinyl group contains five carbon atoms, are effective hypnotics with high therapeutic ratios.

BRYN MAWR, PENNSYLVANIA

RECEIVED JANUARY 20, 1939

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

The Action of Barium Hydroxide on the Monobasic Sugar Acids. · III

BY FRED W. UPSON, WILLIAM K. NOYCE AND WALTER D. ALBERT

This paper is a continuation of the work of Bonnett and Upson¹ and Albert and Upson,² and presents the results of a quantitative study of the products resulting from the action of barium hydroxide on several aldonic acids at a temperature of 140° for twenty-four hours. The compounds studied were glycolic acid, *dl*-erythronic acid, α -*d*-glucoheptonic acid, *l*-rhammonic acid and α -*l*-rhamnohexonic acid. We now have in-

formation concerning the alkali decomposition of aldonic acids containing from two to seven carbon atoms including two methyl aldonic acids and also glycolic acid.

Experimental

Materials.—The various materials used in this study either were prepared in this Laboratory by known methods or obtained from commercial sources. The *dl*-erythronic lactone was supplied by Dr. J. W. E. Glattfeld of the University of Chicago. The different substances were purified where necessary. Analysis, specific rotation

(1) Bonnett and Upson, *THIS JOURNAL*, **55**, 1245 (1933).

(2) Albert and Upson, *ibid.*, **57**, 132 (1935).

and melting point were determined in each case to establish purity of each compound.

Procedure.—The apparatus and methods used were substantially those described by Albert and Upson.² The acid to be treated was dissolved, together with four equivalents of barium hydroxide, in sufficient water to make a four normal solution of the alkali. From 10 to 82 g. of the acid was used depending on the amount available. The reaction mixture was heated in a round-bottomed flask to expel air, the flask was tightly stoppered and heated in a small autoclave for twenty-four hours at a temperature of 140°. The general procedure as outlined in a previous paper² in this series was followed for the determination of carbon dioxide, oxalic, formic, acetic and lactic acids. Oxalic acid and carbon dioxide were found in the residue as barium salts. After removal of the solid residue, the barium ion was removed from the filtrate by means of sulfuric acid and the resulting solution evaporated *in vacuo*. The free organic acids were then subjected to several distillations *in vacuo*, which resulted in separation into a *volatile* and a *non-volatile* fraction. Previous experiments³ have shown that the volatile fraction consists in the main of formic and acetic acids with traces of lactic acid.

The total acidity and the acidity due to formic acid were determined by the method of Evans and Haas,⁴ and the difference calculated as acetic acid. The usual qualitative tests for the latter were made.

The non-volatile acids were dissolved in water and separated into two portions by continuous extraction with ether for forty-eight hours according to the method originally devised by Evans, Edgar and Hoff.⁵ The lactic acid in the ether fraction was determined in the usual way as the zinc salt. After complete removal of the zinc lactate there remained in each experiment a small amount of acid gums, which, except in the case of glucoheptonic acid, did not admit of identification.

From the non-volatile acid fraction not extracted by ether, there was obtained likewise only a small amount of acid gums in each experiment. Again, except in the case of glucoheptonic acid these did not admit of identification.

Carbon dioxide formed from the various acids was determined in each case by a separate procedure using the methods described by Albert and Upson.²

Glycolic Acid.—The experiment showed that glycolic acid remains unaffected by alkali treatment at 140°. Eighty-six per cent. of the original material was recovered at the end of the experiment as unchanged glycolic acid.

The remaining four compounds, *dl*-erythronic, glucoheptonic, rhammonic and rhamnohexonic acids were subjected to alkali decomposition and the resulting compounds were determined according to the general methods outlined above. Except in the case of glucoheptonic acid the only products identified were carbonic, formic, acetic, oxalic and lactic acids. The results are collected in Table I. For ease of comparison the results of Albert and Upson² on gluconic, arabonic and glyceric acids have been included.

Glucoheptonic acid was the only compound studied which yielded identifiable products in addition to those

TABLE I
Per cent. of original carbon returned

Acid used	Car- bonic	For- mic	Acetic	Oxalic	Lac- tic	Total	% Total as lactic
Erythronic	Trace	8.8	10.5	6.1	39.6	65.0	60.0
Glucoheptonic	1.7	1.6	5.5	6.2	32.5	47.5	68.5
Rhamnohexonic	Trace	1.7	9.9	3.6	40.5	55.7	72.5
Rhammonic	0.8	6.6	8.5	Trace	44.5	60.4	74.0
Gluconic ²	1.92	3.28	1.97	1.49	65.2	73.9	88.0
Arabonic ²	2.58	1.92	6.36	5.7	59.9	76.5	81.0
Glyceric ²	5.09	8.93	3.20	4.0	65.2	86.4	75.0

listed above. The ether soluble portion, after the removal of lactic acid, yielded a small amount of acid gums which were converted to the brucine salt in the usual manner. From this, by recrystallization from alcohol, there was obtained a salt of m. p. 157–159° and $[\alpha]_D^{25} -34^\circ$. These are the constants given by Nef⁶ for the brucine salt of *d*-threo-1,3,4-trihydroxyvaleric acid. From the original ether insoluble acids there was isolated a small amount of brucine *l*-glycerate of m. p. 221–222° and $[\alpha]_D^{25} -24^\circ$.

Discussion

Since glycolic acid after alkali treatment according to the method described in this paper is recovered to the extent of 86%, we may conclude that it is not formed either as an intermediate or an end-product in the alkaline decomposition of sugar acids.

The remaining four acids studied in this research all give relatively large amounts of lactic acid. The amounts vary from 32.5% of the original carbon in the case of glucoheptonic to 44.5% in the case of rhammonic acid. However, these figures are considerably lower than the corresponding figures obtained by Albert and Upson² for gluconic, arabonic and glyceric acids, which were 65.2, 60 and 65.2% lactic acid, respectively. On the basis of moles per mole of original compound none of the four acids in this series gives as much as one mole of lactic acid although rhamnohexonic acid gives approximately this value (0.95 mole). In the case of all acids studied lactic acid accounts for the larger part of the decomposition products identified. The lactic acid in terms of total carbon identified varies from 60% in the case of erythronic to 88% in the case of gluconic acid.

In the previous paper² it was pointed out that gluconic and arabonic acids yield relatively much higher amounts of lactic acid than do the corresponding sugars studied by Evans⁸ and his students. Gluconic acid gives two and one-half times

(6) Nef, *Ann.*, **376**, 46 (1910).

(7) Anderson, *Am. Chem. J.*, **42**, 407 (1909).

(8) (a) Evans and O'Donnell, *This Journal*, **50**, 2551 (1928);

(b) Evans, Edgar and Hoff, *ibid.*, **48**, 2703 (1926); (c) Evans and Conway, *ibid.*, **52**, 3680 (1930).

(3) Albert and Upson, *This Journal*, **57**, 132 (1935).

(4) Evans and Haas, *ibid.*, **48**, 2703 (1926).

(5) Evans, Edgar and Hoff, *ibid.*, **48**, 2665 (1926).

as much lactic acid as glucose, and arabonic acid gives almost six times as much lactic acid as does arabinose. Even more striking is a comparison of glyceric acid with glyceric aldehyde. Evans and Haas⁴ obtained by the action of alkali on the latter compound a maximum yield of 4% lactic acid, whereas the results of Albert and Upson² show that glyceric acid is converted into lactic acid to the extent of 65%.

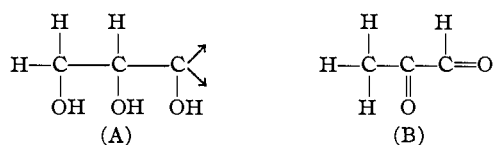
A similar situation is found in comparing rhamnose and rhammonic acid. Whereas Evans⁹ obtained a maximum yield of 27% lactic from rhamnose, our results indicate a formation of 45.5% lactic acid from rhammonic acid. Nef¹⁰ makes the statement, recently checked by Evans¹¹ that erythrose does not give any lactic acid. Erythronic acid on the other hand is converted into lactic to the extent of 40% as shown in Table I. Results on the aldoses corresponding to the remaining two acids studied by us are not available.

Theoretical Discussion

Any attempt to devise a mechanism to account for the decomposition reactions which occur in the experiments described in this paper must take into account this difference in behavior of aldoses and aldonic acids toward alkalies. The aldoses are much the more sensitive to alkali treatment and give in addition to the well-known products larger amounts of saccharinic acids and tarry material, which cannot be identified. This latter probably results from splitting of the carbon chain into various active aldehyde forms which in part undergo condensation reactions similar to that which yields "aldehyde resin."

The theory of the enediol first proposed by Wohl and Neuberg¹² was applied by Nef¹³ and his students to explain saccharinic acid formation and the various decomposition reactions which occur as the result of the action of alkalies on the common aldoses and ketoses. More recently the same theory has been used by Evans¹⁴ and his students to explain the results of their extensive experiments on the mechanism of carbohydrate oxidation. This theory assumes the presence of 1,2,-2,3-, and 3,4-enediols in alkaline solutions of the various aldoses and ketoses. These enediols

are postulated as intermediate products in the rearrangement reactions leading to saccharinic acid formation,¹⁵ as well as those reactions which result in the various cleavage products both in the presence and absence of oxidizing agents. Thus according to this theory a 1,2-enediol of glucose may result in the formation of a C₅ saccharinic acid and formic acid or, if an oxidizing agent is present, in formic or carbonic acids and arabonic acid. The 3,4-enediol is thought to be the forerunner of lactic acid. This enediol is assumed to break into two C₃ fragments (A) which may be looked upon as the active form of glyceric aldehyde. The action of alkali on this converts it first into pyruvic aldehyde (B) and then into



lactic acid. Evans has demonstrated by definite experiments that pyruvic aldehyde is intermediate in the formation of lactic acid.^{14,15}

The conclusion to be drawn from our experiments is that lactic acid cannot be formed entirely through cleavage of the 3,4-enediol, since in our experiments larger amounts of lactic acid are formed than can be accounted for on the basis of this theory. Evans^{15b} obtained 25% of lactic acid from glucose at 50° with 4 *N* alkali whereas in the experiments of Albert and Upson³ 65% of lactic acid was obtained from gluconic acid.¹⁶ Glucose may break into two molecules of the active form of glyceric aldehyde neither of which can be converted quantitatively to lactic

(15) (a) Evans and Benoy, *ibid.*, **47**, 3086 (1925); (b) Evans, Edgar and Hoff, *ibid.*, **48**, 2675 (1926).

(16) The comparison of the results herein reported with those of Evans and his students has been criticized by one reviewer because of the different conditions employed in the two sets of experiments. This criticism we believe is more apparent than real. We have selected for comparison 4 *N* concentration of alkali, and 50° temperature in Evans' experiments for definite reasons. This is the concentration of alkali used in our experiments. Numerous experiments in this Laboratory have shown that results in this type of work are little affected by the nature of the alkali but are dependent primarily on the concentration of alkali used.

The temperature of 50° in Evans' experiments was chosen for comparison because at this temperature in the case of glucose,^{3a} arabinose^{9b} and rhamnose,⁹ maximum return of lactic acid was obtained. In the case of the four sugars cited, glucose and rhamnose gave less lactic acid at 75 than at 50°; arabinose gave practically the same amount, and glyceric aldehyde,⁴ which was studied only at two temperatures, gave less lactic at 50° than at 25°. Furthermore, in one experiment,² in this Laboratory, with glucose and 4 *N* barium hydroxide at 140° slightly less lactic acid was obtained than in the experiments of Evans at 50°.^{3a} Therefore the conclusion seems justified that the higher temperature and different alkali employed in our experiments does not account for the larger amounts of lactic acid obtained from the aldonic acids.

(9) Nadeau, Newlin and Evans, *THIS JOURNAL*, **55**, 495 (1933).

(10) Nef, *Ann.*, **376**, 40 (1907).

(11) Evans, private communication.

(12) Wohl and Neuberg, *Ber.*, **33**, 3099 (1900).

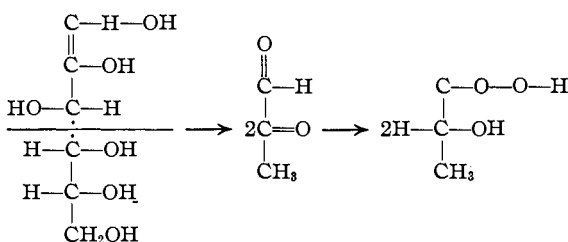
(13) Nef, *Ann.*, **335**, 394 (1904); **357**, 214 (1907); **376**, 1 (1910); **403**, 204 (1914).

(14) See *THIS JOURNAL*, **55**, 4957 (1933), for bibliography.

acid in the light of Evans' results.⁸ The presence of the carboxyl group in place of the aldehyde group must change the course of the reaction. Probably the presence of the carboxyl group tends to stabilize the fragment to which it is attached so that it is converted by a process involving intermolecular oxidation-reduction into lactic acid.

The theory proposed by Otto Schmidt¹⁷ makes use of the theory of enediols but explains the breaking of the carbon chain as follows. "The double bond strengthens the single bond following and weakens the next following. This alternation of strong and weak single bonds goes through the whole molecule with decreasing energy ('double bond rule')." The theory of Schmidt is in harmony with modern concepts of bond strength as developed by the experimental methods of physical chemistry. Carbon-carbon double bonds require nearly twice the energy of single bonds to break them.¹⁸

If this theory is applied to explain the formation of lactic acid from glucose we must assume that the 1,2-enediol causes rupture of the molecule in the 3,4-position giving two fragments, as pointed out by Schmidt, which change under the influence of the alkali into two molecules of pyruvic aldehyde and then into lactic acid.



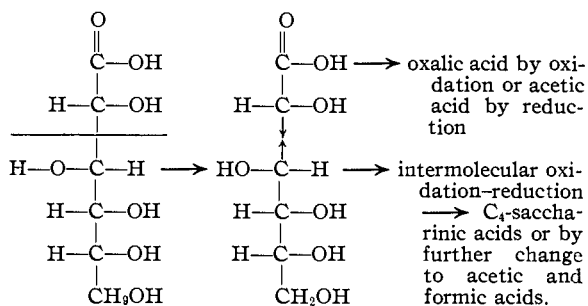
According to the "double bond rule" the point of rupture of the molecule depends on the positions of the enediol; 1,2-enediols cause rupture in the 3,4-position, 2,3-enediols in the 4,5-position and 3,4-enediols either in the 1,2- or the 5,6-position. Schmidt's theory differs from that of Nef and Evans essentially in the manner in which the molecule undergoes cleavage under the influence of the various enediols.

In addition to enediol formation in the various positions, followed by subsequent splitting of the

(17) Otto Schmidt, *Chem. Rev.*, **17**, 139 (1935).

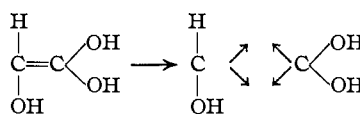
(18) Evans [*J. Org. Chem.*, **1**, 6 (1936)] has pointed out the difficulty of reconciling the Nef enediolic theory of scission of carbohydrate molecules with the theories of Schmidt. We incline to the second possibility suggested by Evans, namely, that alkali scission in the presence of and in the absence of oxidizing agents may be two different processes.

second single bond in the chain we may assume according to the Schmidt theory that the carbon-oxygen double bond of the carboxyl group influences also breaking of the carbon chain, in this case at the 2,3-bond, as follows



This cleavage in the 2,3-position best accounts for the formation of oxalic acid which was formed in limited amount from all acids studied with the exception of rhammonic and glycolic acids. No oxalic acid has been found as the result of the alkali treatment of the aldoses.

A crucial test of the Schmidt theory would seem to be found in the results with glycolic acid. Glycolic acid does not give lactic acid, nor does it undergo cleavage to any extent. According to the theory of Nef, glycolic acid should undergo cleavage at the 1,2-enediol to give carbonic acid.

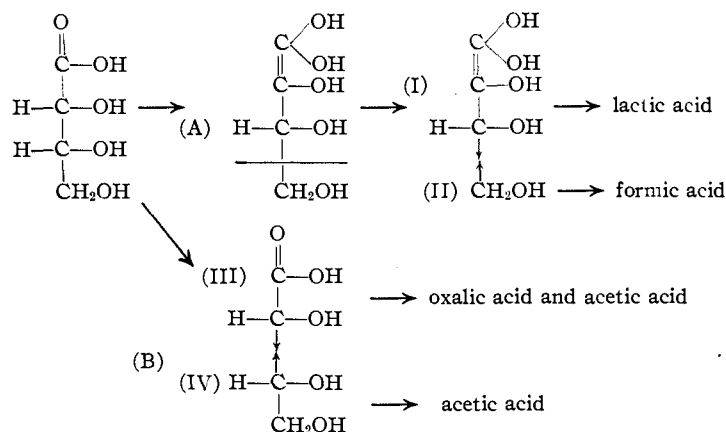


This does not occur. Glycolic acid is remarkably stable toward alkali at 140°. No cleavage products were obtained and 86% of the original acid was recovered in our experiments. Since there are but two carbon atoms in glycolic acid the "double bond rule" of Schmidt does not apply and since no cleavage products are obtained we must conclude that fragmentation of the enediol does not occur.

It should be emphasized that of the eight acids studied five do not give appreciable amounts of carbonic acid, and only one, glyceric acid, gives as much as 5%. It has long been known that the carboxyl group does bring about 1,2-enolization. If the 1,2-enediol were capable of cleavage we should expect relatively much larger quantities of carbonic acid than were obtained from any of the aldonic acids studied.

Erythronic acid, it seems to us, also furnishes a test of the "double bond rule" of Schmidt. This acid gives no carbonic acid but does give

40% lactic acid with considerable amounts of formic, oxalic and acetic acids. Erythrose, according to Nef,¹⁰ gives no lactic acid and this has been confirmed by Evans.¹¹ Therefore the more stable carboxyl group causes erythronic acid to undergo a type of cleavage which does not occur with erythrose. Erythronic acid must undergo cleavage in two ways as pictured below.



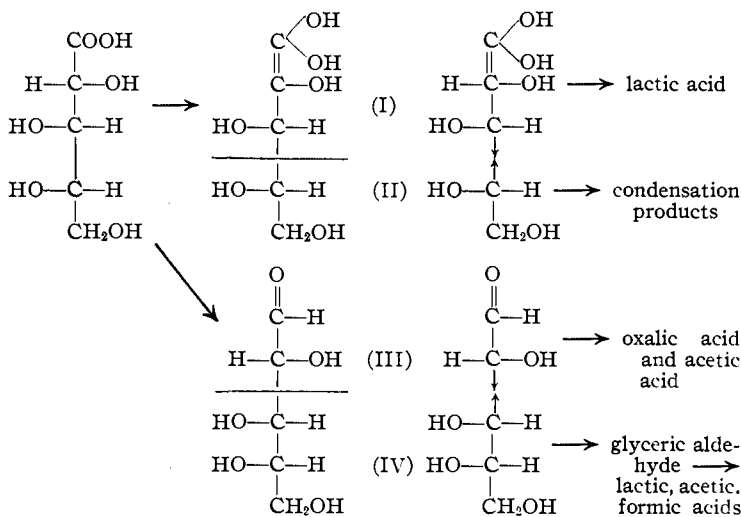
Cleavage according to process (A) must occur to the greater extent since lactic acid is the chief product. This cleavage occurs in the 3,4-position under the influence of the 1,2-enediol. Cleavage in the 2,3-position according to process (B) occurs under the influence of the double bond oxygen of the carboxyl group and probably ex-

amounts of formic, oxalic and acetic acids formed from fragments II, III and IV by the oxidation process are roughly equivalent to the lactic acid formed by the reduction process from fragment (I).

Arabonic acid according to the double bond rule may undergo the series of changes pictured below, both type (A) and type (B) cleavage taking place. The former leads to fragments I and II and the latter to fragments III and IV. Fragment (I) must be the chief source of lactic acid although small amounts may come from fragment (IV). Fragment (III) must be the source of the oxalic acid as pointed out above. All these changes occur as the result of intermolecular oxidation-reduction processes. Fragment IV by one step is converted to glyceric aldehyde which as Evans and Haas⁴ have shown would then be converted to lactic, acetic and formic acids in small amounts. Frag-

ment II above is converted to glycolic aldehyde and then into various condensation products, which probably accounts for the 24% carbon not identified. The above mechanism accounts qualitatively for all the products which were identified.

Gluconic acid may undergo cleavage as pictured below (X).



plains the formation of oxalic acid from all the aldonic acids studied. The various end-products then are formed as the result of intermolecular oxidation-reduction processes. A calculation in the case of erythronic acid shows that the

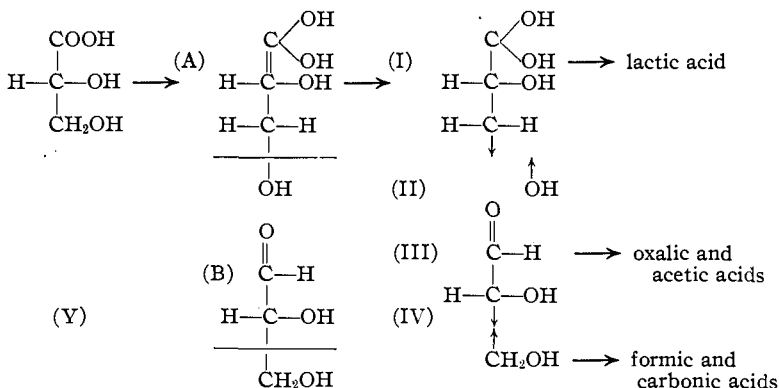
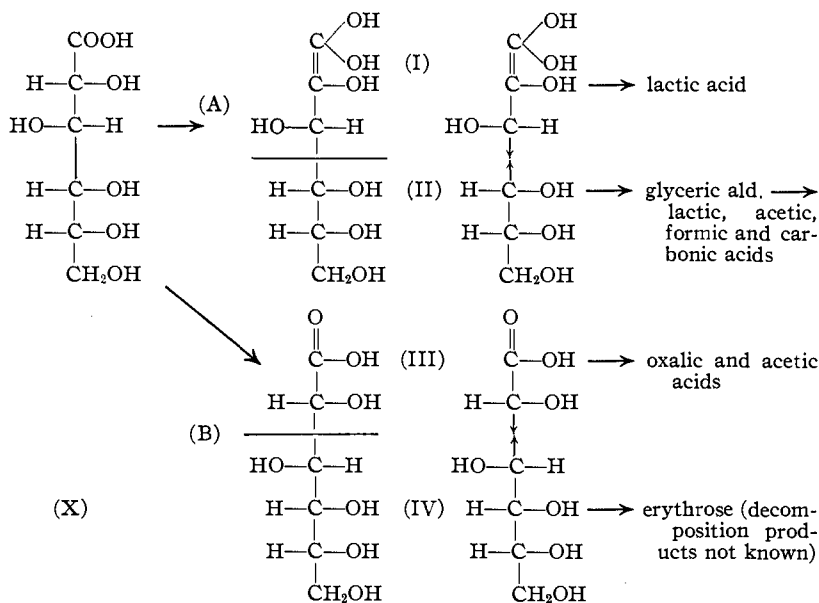
amounts of formic, oxalic and acetic acids formed from fragments II, III and IV by the oxidation process are roughly equivalent to the lactic acid formed by the reduction process from fragment (I).

Cleavage must occur mainly according to process (A) since fragments I and II account for the chief products formed. Process (B) occurs only to a limited extent since only 1.5% of the original carbon is converted to oxalic acid.

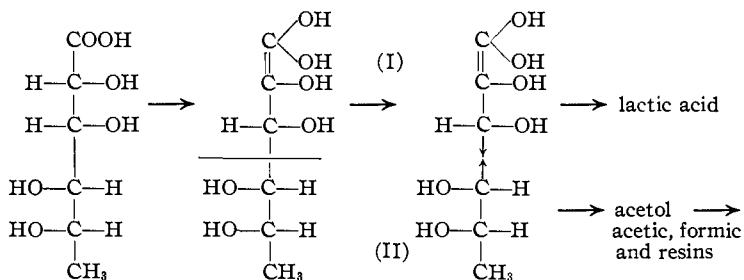
Glyceric acid also must undergo fragmentation in two different ways as shown below (Y).

The intermolecular oxidation-reduction reactions which may occur between the different fragments account qualitatively for the different products identified. Glyceric acid is the only substance studied which gives significant amounts of carbonic acid and it also gives the largest amount of formic acid.

Rhamnonic acid does not yield identifiable amounts of oxalic acid and only traces of carbonic acid. Since lactic acid is the chief product and



is formed in considerably greater amount than from rhamnose as shown by Evans,⁹ it follows that rhamnonic acid reacts primarily according to process (A).



Fragment II by one step oxidation probably is converted to lactic aldehyde and then into acetol,⁹ which in part may be converted into formic and acetic acids but also into resinous material.¹⁹ Rhamnonic acid gave the largest amount of a

(19) Nef, *Ann.*, **335**, 254 (1904).

dark resinous material of any of the acids studied.

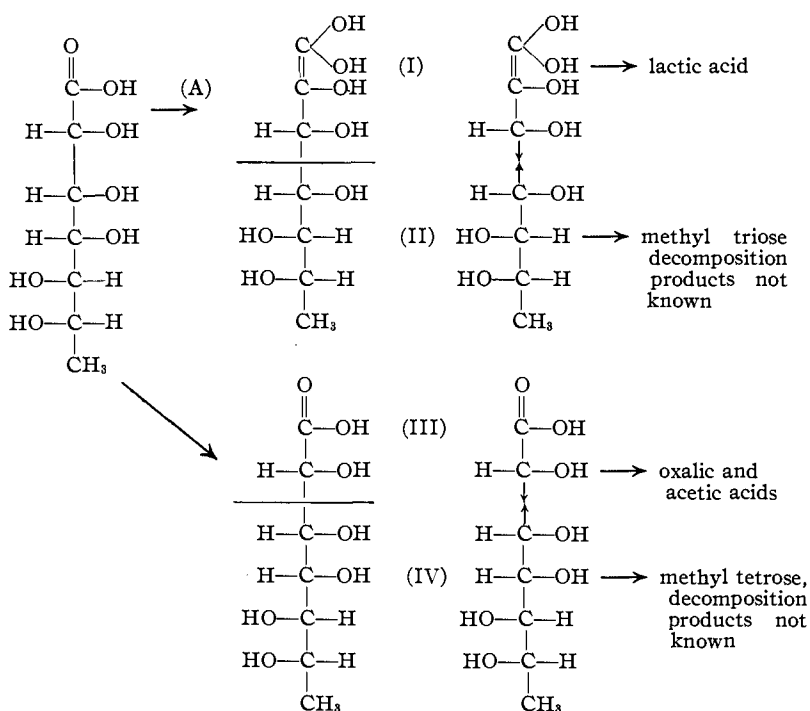
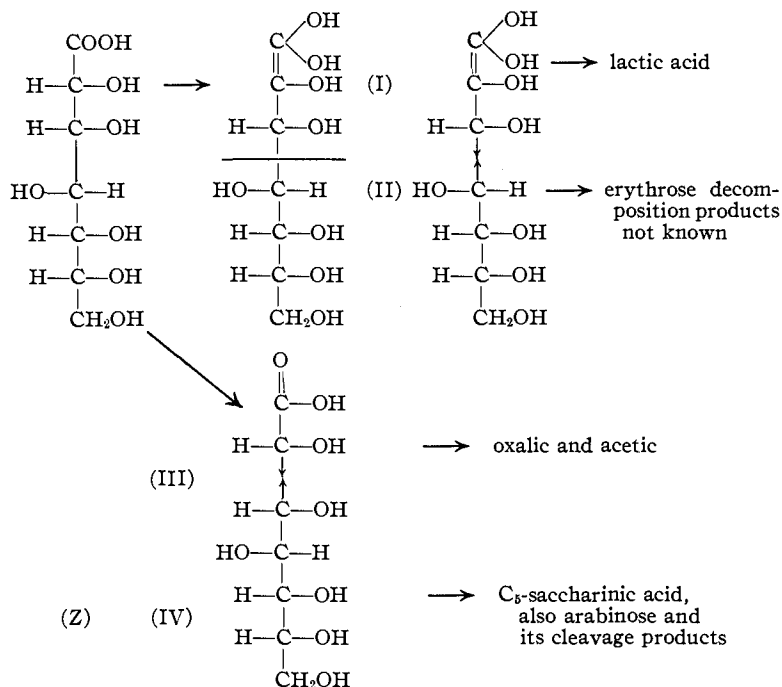
Glucoheptonic and rhamnohexonic acids yield a lower percentage of carbon return than any of the other acids studied. This is because in each case two of the fragments contain four and five carbon acids which may react like the corresponding sugars, giving less amounts of identifiable products. Glucoheptonic acid gives but 32.5% lactic (0.76 mole). The isolation of a C₅-saccharinic acid, 2,4,5-trihydroxyvaleric acid, among the decomposition products is significant and also indicates fragmentation in the 2,3-position.

The two types of cleavage are indicated below (Z).

As with the other aldonic acids cleavage must occur at two points in the carbon chain. Fragments (I) and (II) are formed through cleavage at the 3,4-bond under the influence of the 1,2-enediol and fragment (I) accounts in part for the lactic acid. Fragment (III) from cleavage of the 2,3-bond accounts for the oxalic acid and fragment (IV) by a one step oxidation may give arabinose whose products of decomposition are known. This is the source of the C₅-saccharinic acid mentioned above. Qualitative evidence for the formation of glycerinic acid was obtained. This could be formed from fragment I by a one step reduction.

Rhamnohexonic acid formed almost no carbonic and formic acids but did give a considerable amount of acetic acid, some oxalic and almost one mole (0.95) of lactic acid.

The cleavage therefore occurs mainly according to process (A) at the 3,4-bond with the four carbon fragment (II) undergoing further decomposition. As in the case of the other acids fragment (I) must be the source of the lactic acid and fragment (III) of the oxalic acid and part of the acetic



acids. Fragments (II) and (IV) may be converted to the corresponding aldoses by a one step oxidation and of course will undergo further cleavage. The methyl tetrose from fragment (IV) could form, by a 2,3-fragmentation, lactic aldehyde which Evans⁹ has postulated would be converted in part into acetol.

In conclusion it seems desirable to emphasize once more that the final products are formed through fragmentation of the original carbon chains of the aldonic acids followed by intermolecular oxidation-reduction processes occurring between the fragments. For example, the two carbon fragment (III) postulated as one of the intermediate substances may by a two-step oxidation be converted into oxalic acid or by a one-step reduction into acetic acid, the oxidation or the reduction as the case may be occurring at the expense of other fragments. Probably the three carbon fragment (I) which must be the precursor of lactic acid is the most important oxidizing agent. These processes are not unlike the Cannizzaro reaction by means of which benzaldehyde is converted to benzyl alcohol and benzoic acid.

It should be noted also as emphasized many times by Nef and by Evans that carbohydrate research of this type is greatly handicapped by the lack of adequate methods for separating and identifying the various decomposition products. With the exception of carbonic, formic, oxalic and lactic acids none of the possible products admit of quantitative separation. The various saccharinic acids containing from four to six carbon atoms which must always be formed are difficult of detection and in no case may be separated in anything like a quantitative yield. These are the reasons why it is possible to account for only 50 to 85% of the original carbon in our experiments. Evans in his work on the aldose and ketose sugars is able to account for even less of the carbon because the compounds yield much larger amounts of the saccharinic acids.

Summary

1. The results of the reaction of 4 *N* alkali at a temperature of 140° on five aldonic acids are recorded.

2. The results with three other acids from a previous paper have been included for comparison.

3. Lactic acid is the chief product formed from all aldonic acids studied except glycolic acid.

4. The "double bond rule" of Schmidt seems to offer an adequate explanation of the results.

LINCOLN, NEBRASKA

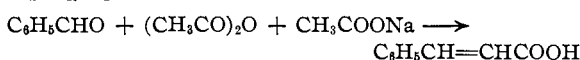
RECEIVED SEPTEMBER 15, 1938

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

Condensations Brought about by Bases. V. The Condensation of the Anhydride with the Aldehyde in the Perkin Synthesis¹

BY DAVID S. BRESLOW AND CHARLES R. HAUSER

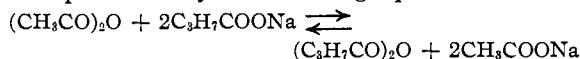
Perkin² assumed that in the reaction that bears his name



the anhydride condenses with the aldehyde, the sodium acetate serving merely as a catalyst. As support for this view he showed that cinnamic acid is formed also when benzaldehyde is heated with acetic anhydride at 180° in the presence of other salts, for example, sodium butyrate.

Fittig³ soon contested this view; he considered that the salt, and not the anhydride, condenses. In support of his view, Fittig⁴ showed that when benzaldehyde is heated with acetic anhydride and sodium butyrate at 100°, instead of 180°, ethylcinnamic acid is the main product. He showed further that, as the temperature is raised, relatively less ethylcinnamic acid is formed and relatively more cinnamic acid; at 150°, he obtained half as much ethylcinnamic acid as cinnamic acid, while at 180°, he obtained only one-tenth as much ethylcinnamic acid, the reaction yielding almost entirely cinnamic acid as Perkin had reported.

Fittig explained these results on the assumption that at the higher temperatures (but not at 100°) acetic anhydride and sodium butyrate are converted by double decomposition into butyric anhydride and sodium acetate, the latter then condensing with the aldehyde to give cinnamic acid. The anhydride-salt exchange may be represented by the following equation



(1) This work was supported in part by a grant from the Duke University Research Council.

(2) See especially, Perkin, *J. Chem. Soc.*, **31**, 389 (1877).

(3) See especially, Fittig, *Ber.*, **14**, 1824 (1881); *Ann.*, **227**, 48 (1885).

(4) See Fittig and Stocum, *ibid.*, **227**, 53 (1885).

Michael⁵ and others showed that this anhydride-salt exchange does actually occur, but that it takes place even at 100°; in fact, at this temperature the exchange proceeds to a greater extent⁶ (*i. e.*, the equilibrium of the exchange is further on the side of butyric anhydride and sodium acetate) than at 180°. Michael⁵ showed also that, like the experiment with acetic anhydride and sodium butyrate at 100°, benzaldehyde with butyric anhydride and sodium acetate at this temperature gives mainly ethylcinnamic acid.

A consideration of the products formed and of the equilibrium of the anhydride-salt exchange at various temperatures led Michael to support Perkin's view that the anhydride condenses. Fittig's view, however, received apparent confirmation from the work of Stuart,⁷ who reported that a mixture of benzaldehyde, acetic anhydride and sodium malonate at room temperature evolves carbon dioxide and gives cinnamic acid. Since malonic acid is incapable of forming an anhydride, it would appear that the salt (sodium malonate) condenses.

(5) Michael, *J. prakt. Chem.*, **60**, 364 (1899); *Ber.*, **34**, 918 (1901). See also Tiemann and Kraaz, *ibid.*, **15**, 2061 (1882).

(6) It has been shown⁸ that at 100° the equilibrium is far on the side of the salt of the stronger acid, *i. e.*, on the side of sodium acetate and butyric anhydride; in fact, Michael obtained butyric anhydride in good yield from acetic anhydride and sodium butyrate at 100°. At 180°, however, because of the greater volatility of acetic anhydride, the equilibrium is shifted somewhat toward acetic anhydride and sodium butyrate. Michael assumed that at this temperature the equilibrium was mostly on the side of acetic anhydride and sodium butyrate, and he showed that when sodium acetate and butyric anhydride were heated at 180°, acetic anhydride distilled off. We have observed that, on heating sodium acetate with butyric anhydride at 180°, acetic anhydride soon refluxes in the mixture. Although the position of equilibrium is not known, there is no doubt that it is further on the side of butyric anhydride and sodium acetate at 100° than at 180°.

(7) Stuart, *J. Chem. Soc.*, **43**, 403 (1883); see also Fittig, *Ber.*, **16**, 1436 (1883).