

Summary

1. The reactions of various Grignard reagents with γ -chloropropyl *p*-toluenesulfonate have been studied.

2. Conditions have been described which make this a useful synthetic reaction in converting RX to $R(CH_2)_3Cl$.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

THE MECHANISM OF CARBOHYDRATE OXIDATION. VIII. THE ACTION OF POTASSIUM HYDROXIDE ON FRUCTOSE

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It has been shown that temperature and concentration of alkali are experimental factors which exert a marked influence on the quantity of reaction products which may be obtained when glucose, fructose, mannose and galactose are oxidized with potassium permanganate in aqueous solutions of potassium hydroxide.¹ A quantitative study of the reaction products obtained by the action of aqueous solutions of potassium hydroxide on glucose and galactose under definitely chosen conditions of temperature and concentration of the base, and in the absence of potassium permanganate, shows that the equilibrated reacting system is one that is easily disturbed by a change in one or both of these experimental factors.² By reason of the fact that fructose in alkaline solutions is converted, in part, to glucose,³ it became of much interest to know whether this ketohexose would show the same general behavior toward potassium hydroxide as that observed for the aldohexose by Evans, Edgar and Hoff.^{2a} To determine this point was the first objective in these experiments.

When fructose-3,4-enediol is ruptured at the double bond, two molecules of the active form of glyceric aldehyde should be formed.⁴ Hence, it follows that in those alkaline solutions of the hexoses in which the equilibrium between the enediols has been shifted largely to the 3,4-form, the action of the alkali on the carbohydrate should involve the same general mechanism as that observed by Hass,⁵ and Cornthwaite and one of us⁶ concerning the behavior of glyceric aldehyde and dihydroxy-acetone

¹ (a) Evans, Buehler, Looker, Crawford and Holl, *THIS JOURNAL*, **47**, 3085 (1925); (b) Evans and Buehler, *ibid.*, **47**, 3098 (1925).

² (a) Evans, Edgar and Hoff, *ibid.*, **48**, 2665 (1926); see (b) Amick, *J. Phys. Chem.*, **31**, 1473-7 (1927); (c) Wolfrom with Lewis, *THIS JOURNAL*, **50**, 838 (1928).

³ (a) De Bruyn and van Ekenstein, *Rec. trav. chim.*, **14**, 156 (1895); (b) **14**, 203 (1895); (c) **15**, 92 (1896); (d) **16**, 257 (1897); (e) **16**, 262 (1897); (f) **16**, 274 (1897); (g) **19**, 1 (1900); (h) **27**, 1 (1908).

⁴ Ref. 1a, p. 3093.

⁵ Evans and Hass, *THIS JOURNAL*, **48**, 2703 (1926).

⁶ Evans and Cornthwaite, *ibid.*, **50**, 486 (1928).

in aqueous solutions of potassium hydroxide. To establish this predicted similarity of behavior was the second objective in this study.

Experimental Part

Treatment of Fructose with Potassium Hydroxide.—The general methods which have been developed in this Laboratory in a similar study on glucose and galactose² were employed in these experiments. To 4.5 g. of *d,l*-fructose contained in a 135-cc. round-bottomed flask, was added 50 cc. of standard potassium hydroxide solution at the temperature of the thermostat. Complete solution was hastened by energetic shaking. The flasks were tightly closed with rubber stoppers and then were agitated for forty-eight hours in a thermostat kept at 25, 50 or 75°. At the end of this period, the flasks were immersed in a freezing mixture for a few minutes, after which the reaction mixtures were treated with equal volumes of standardized phosphoric acid solution of such strength that the resulting solution was neutral. The concentrations of all reacting materials were such that a direct comparison of the experimental results obtained could be made with those of similar work previously published from this Laboratory.

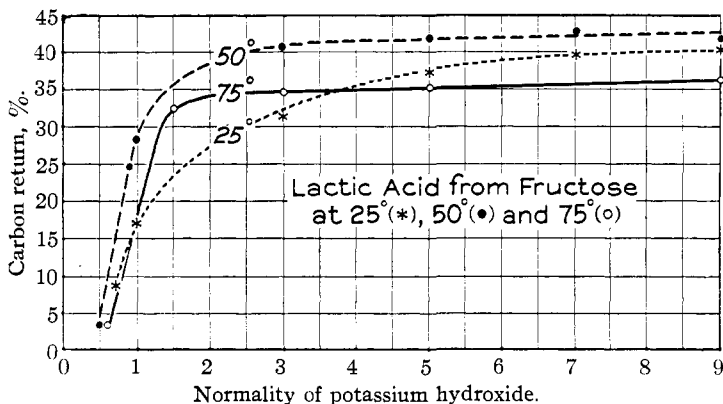


Fig. 1.

Methods of Analysis.—The methods used in the detection and determination of certain reaction products were the same in every detail as those previously described in previous reports on glucose, galactose,² glyceric aldehyde⁵ and dihydroxy-acetone.⁶

Pyruvic Aldehyde Osazone.—In the determination of pyruvic aldehyde, samples were made to contain 4.5 g. of fructose in a mixture of 50 cc. of potassium hydroxide solution, 35 cc. of 95% alcohol and 10 cc. of phenylhydrazine in a 125-cc. round-bottomed flask. The temperature of this mixture when the fructose was added was that chosen for the thermostat for that particular experiment. At the end of forty-eight hours, the yellow osazone was filtered, washed with 10 cc. of 30% alcohol and dried at 65° *in vacuo*.

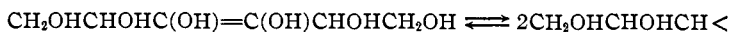
Experimental Data.—The quantitative data obtained in these experiments are shown graphically in Figs. 1, 2, 3, 4, 5 and 6.

Theoretical Part

In a previous report from this Laboratory it was pointed out that certain compounds which were formed by the action of potassium hydroxide on glucose and galactose might be regarded as having been derived from these carbohydrates through the intermediate formation of the isomeric hexose-

1,2-, -2,3- and -3,4-enediols,² and that the amounts of these reaction products were functions of both the temperature and the concentration of the base. This point of view is further confirmed in the following discussion of our experimental data.

3,4-Enediol. (a) **Lactic Acid.**—It has been repeatedly pointed out that the hexose-3,4-enediol in solutions of sufficient alkali concentration will rupture at the double bond, thus giving rise to two molecules of the active form of glyceric aldehyde. This change is shown by the following equation



Under the conditions of these experiments this active glyceric aldehyde may be converted into pyruvic aldehyde, which in turn, is changed into

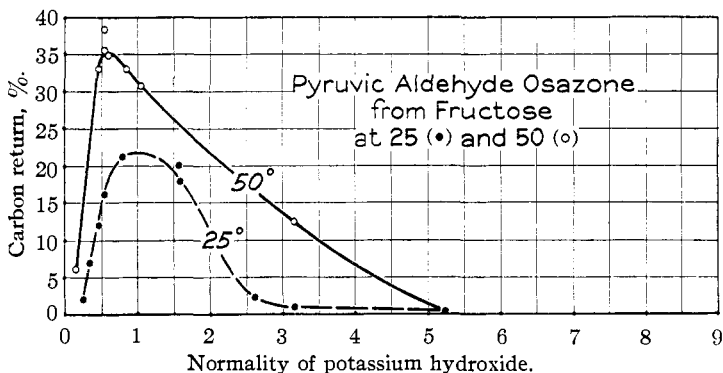


Fig. 2.

lactic acid. Cornthwaite and one of us⁶ have recently shown that the behavior of dihydroxy-acetone and glyceric aldehyde in alkaline solutions is similar to that of aldo- and ketohexoses under similar conditions, that is, these trioses are in equilibrium with their common enediol in the following way



Since the amounts of lactic acid formed by the action of potassium hydroxide on these two trioses depend on the temperature and the alkali concentration, then it follows that the amounts of lactic acid obtained from a hexose such as fructose and glucose should also show a similar relation to these two experimental factors. That this is true is clearly shown by a comparison of our Fig. 1 with Fig. 1 of Evans and Cornthwaite. This is equally true for glucose.⁷ At 75°, tar formation took place very rapidly, thus causing a decrease in the lactic acid yields. No examination of these tars was made for any possible saccharinic acids.

(b) **Pyruvic Aldehyde.**—Since the amounts of pyruvic aldehyde ob-

⁷ Ref. 2a, p. 2670.

tained from dihydroxy-acetone and glyceric aldehyde depend on the temperature and the alkali concentration, and since the common triose enediol is regarded as an intermediate compound in lactic acid formation, then it follows that the amounts of pyruvic aldehyde obtained from the glyceric aldehyde resulting from the rupture of fructose-3,4-enediol under similar conditions should also show this same general relation to the two variable experimental factors. That this is true may be seen by a comparison of our Fig. 2 and Fig. 2 of Evans and Cornthwaite. This is also true for glucose.⁸ It is a very noteworthy fact that the maximum yield of pyruvic aldehyde at a given temperature occurs at approximately the same normality for fructose as that observed for glyceric aldehyde

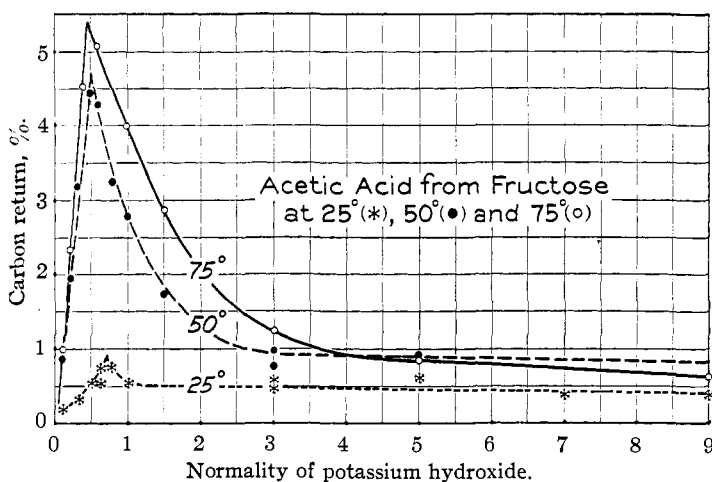


Fig. 3.

and dihydroxy-acetone; that is, approximately 0.5 *N* at 50° and approximately 1.0 *N* at 25°. Evans, Edgar and Hoff made the same observation with reference to galactose when this carbohydrate was submitted to exactly the same conditions as the above sugars. In this connection attention should be directed particularly to the fact that the amount of pyruvic aldehyde at the point of maximum yield is different for each carbohydrate studied. This difference at the maxima may be accounted for in the following way. (1) It is well known that glucose, mannose and fructose form equilibria at low alkali concentrations which are qualitatively the same but not quantitatively so.³ Hence, it would follow that the concentration of the triose formed by the rupture of the fructose-3,4-enediol would be different from that obtained from either glucose or mannose. The equilibrium arising from the interaction of glyceric aldehyde and potassium hydroxide is also not quantitatively identical with that

⁸ Ref. 2, p. 2671.

obtained with dihydroxy-acetone at the lower alkali concentrations. (2). The maximum yields of pyruvic aldehyde are always found to be at approximately the same alkali normality as that at which lactic acid formation is first observed. This seems to indicate that pyruvic aldehyde will undergo the benzilic acid rearrangement at only very definite conditions of temperature and hydroxyl-ion concentration, regardless of the concentration of the pyruvic aldehyde. Owing to the fact that the concentration of the glyceric aldehyde obtained from the hexoses must depend on the state of the sugar-alkali equilibrium and the fact that the conversion to lactic acid will only take place under definite conditions, then it is to be expected that the amounts of pyruvic aldehyde obtained at the maxima will be different for the various carbohydrates. On this basis one can safely predict that the maximum point for pyruvic aldehyde from glucose will be different from that of fructose, when the aldohexose is subjected to the same conditions as those employed in these experiments.

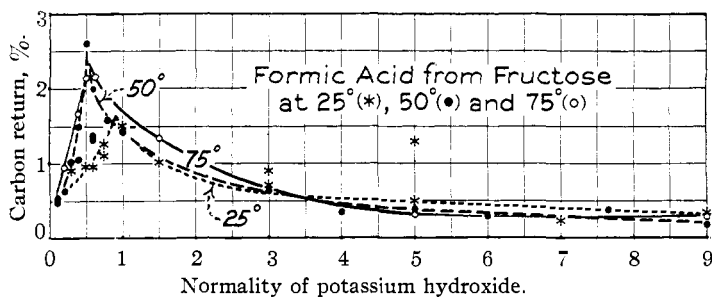


Fig. 4.

(c) **Acetic and Formic Acids.**—It has been shown previously that the acetic acid and a portion of the formic acid derived from the action of potassium hydroxide on glucose and galactose arise from the action of the alkali upon the decomposition products obtained from pyruvic aldehyde in accordance with the following equation: $\text{CH}_3\text{COCHO} \rightarrow \text{CH}_3\text{CHO} + \text{CO}$. When the velocity of the conversion of pyruvic aldehyde to lactic acid becomes greater than that of this decomposition, then it is clear that the yields of these two acids must thereafter diminish. Since this is true for glyceric aldehyde⁹ and dihydroxy-acetone,¹⁰ it should also be true for fructose, as is shown in our Figs. 3 and 4. The same general fact was observed previously in the case of both glucose and galactose.

Production Relation of Lactic, Acetic and Formic Acids and Pyruvic Aldehyde.—From the above discussion it is clear that the yields of lactic and acetic acids, pyruvic aldehyde and a portion of the formic acid must

⁹ Ref. 5, p. 2711.

¹⁰ Ref. 6, pp. 490, 491.

be closely related, since these compounds are derived from the glyceric aldehyde obtained through the rupture of the fructose-3,4-enediol. This interdependence of the yields of these reaction products is shown in Figs. 5 and 6. A comparison of these two sets of data will show in a very marked

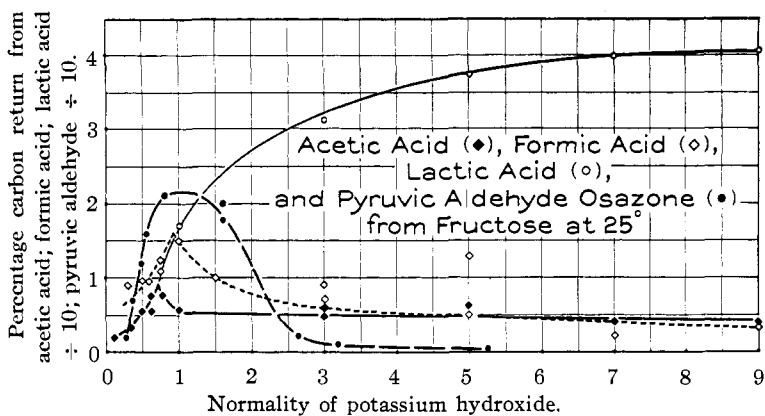


Fig. 5.

manner the effect of temperature on the general reaction. The same general relation has been shown to be true for dihydroxy-acetone at 50° and may be seen to be true for glyceric aldehyde¹¹ by a comparison of the appropriate data. The practically identical character of this interde-

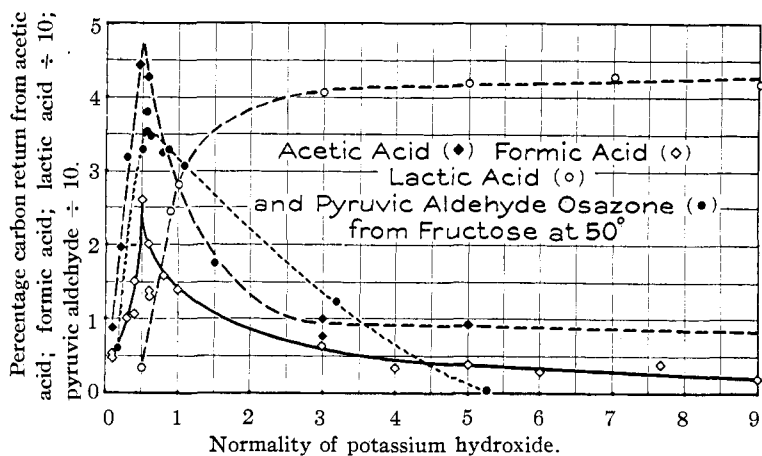


Fig. 6.

pendence in the yields of these compounds seems to be very convincing evidence for the proposed general mechanism of the reaction of the hexoses and potassium hydroxide which involves the formation of glyceric aldehyde through a rupture of the hexose-3,4-enediol.

¹¹ Ref. 6, p. 490.

1,2-Enediol. Formic Acid.—All that was previously reported with reference to the glucose-1,2-enediol being a possible source of formic acid in the reaction of potassium hydroxide on glucose, must be equally true for the reaction of the same alkali on fructose, because in both cases the same general relation exists between the amounts of the formic acid obtained and the experimental conditions of temperature and alkali concentration. That this is true may be seen by a comparison of our Fig. 4 with Fig. 4 of Evans, Edgar and Hoff. In this connection it should be noted that the maxima at 50 and 75° occur at a lower alkali normality than at 25°.

Summary

1. The action of aqueous solutions of potassium hydroxide of various concentrations on fructose was studied at 25, 50 and 75° for the purpose of ascertaining whether the character and the amounts of the reaction products obtained under these conditions were in harmony with the commonly accepted views with reference to the presence of equilibrated systems of certain isomeric hexoses and enediols in such solutions. These equilibrated systems should be disturbed by such experimental conditions as temperature and concentration of alkali.

2. Since glucose is one of the carbohydrates formed from fructose in alkaline solutions, then these two hexoses should show the same general relationship to the experimental factors of temperature and concentration of alkali. Our general results show that this is true.

3. If the hexose-3,4-enediols in alkaline solutions of appropriate concentration rupture at the double bond to form two molecules of glyceric aldehyde, then the reaction products obtained from fructose should be the same as those obtained from glyceric aldehyde under similar conditions, and they should bear the same general relationship to each other and to the variable experimental conditions. Our experimental data bearing on the formation of lactic, acetic and formic acids and also the production of pyruvic aldehyde are in harmony with this statement.

4. The maximum yields of pyruvic aldehyde occur at approximately the same alkali normality as that at which appreciable amounts of lactic acid were first observed. This maximum point for pyruvic aldehyde production from fructose at 25° was approximately 1 *N* and at 50° 0.5 *N*. This is also true for glyceric aldehyde, dihydroxy-acetone and galactose.

5. The difference in the maximum yields of pyruvic aldehyde from fructose and glucose should be different by reason of the difference in the concentration of the glyceric aldehyde in each case, which is due in turn to the fact that equilibria in the case of each carbohydrate are not quantitatively identical.

6. Maximum yields of acetic and formic acids are also obtained with fructose as has been observed for glucose. The quantitative differences

are probably due to the differences in the equilibrium conditions noted above.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

**CYCLOPENTYL ALKYL ACETIC ACIDS AND
OMEGA-CYCLOPENTYLETHYL ALKYL ACETIC ACIDS AND
THEIR BACTERICIDAL ACTION TOWARD B. LEPRÆ. XI¹**

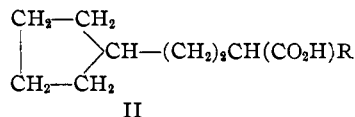
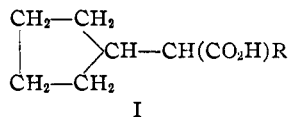
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In previous papers six different isomeric series of acids containing cyclohexyl groups, $C_6H_{11}(CH_2)_xCO_2H$, $C_6H_{11}CH(CO_2H)R$, $C_6H_{11}CH_2CH(CO_2H)R$, $C_6H_{11}(CH_2)_2CH(CO_2H)R$, $C_6H_{11}(CH_2)_3CH(CO_2H)R$, $C_6H_{11}(CH_2)_4CH(CO_2H)R$, have been prepared and have been shown to contain members highly bactericidal *in vitro* to *B. Lepræ*. Those acids with the carboxyl group at the end of the chain were not nearly as effective as the isomers with the carboxyl near the ring. This is a very fortunate circumstance since the latter are much more readily prepared and it is, therefore, possible to make a study of the effect of analogous structures with comparative ease. Acids containing a cyclopentyl group in place of the cyclohexyl group are of interest, not only because they make possible a comparison of the effect of the cyclopentyl and cyclohexyl groups upon the bactericidal activity, but because a cyclopentyl group is present in the dihydrochaulmoogric and dihydrohydnocarpic acids, and the cyclopentenyl group is present in the chaulmoogric and hydnocarpic acids.

In this research two series of acids, cyclopentyl alkyl acetic acids (I) and β -cyclopentylethyl alkyl acetic acids (II) have been prepared,



where R in (I) was *n*-heptyl to *n*-undecyl and R in (II) was ethyl to *n*-octyl. The bacteriological results are given in Tables I and II.

¹ For previous articles in this field see (a) Shriner and Adams, *THIS JOURNAL*, **47**, 2727 (1925); (b) Noller with Adams, *ibid.*, **48**, 1074 (1926); (c) **48**, 1080 (1926); (d) Hiers with Adams, *ibid.*, **48**, 1089 (1926); (e) Van Dyke and Adams, *ibid.*, **48**, 2393 (1926); (f) Sacks with Adams, *ibid.*, **48**, 2395 (1926); (g) Hiers with Adams, *ibid.*, **48**, 2385 (1926); (h) Adams, Stanley, Ford and Peterson, *ibid.*, **49**, 2934 (1927); (i) Arvin with Adams, *ibid.*, **49**, 2940 (1927); (j) Adams, Stanley, and Stearns, *ibid.*, **50**, 1475 (1928).

² This communication is an abstract of a portion of the thesis submitted by G. R. Yohe in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.