ous acetic acid using platinum oxide catalyst at 50 atm. and 120–140° to a mixture of L-galactonic and D-altronic acids, which were isolated as the cadmium and calcium salts, respectively.

The authors hydrogenated 100 g. of the normal calcium 5-keto-L-galactonate by suspending it in about one liter of water in a stainless steel, high-pressure autoclave containing about 10 g. of Raney nickel catalyst. The reduction was carried out by slowly heating the mixture to 80° under 2300 lb. pressure. At the end of the hydrogenation period the nickel was removed by filtration. The filtrate showed no reduction of Fehling solution, indicating a fully hydrogenated mixture of the calcium salts of L-galactonic and D-altronic acids. The hot solution after removal of the nickel catalyst was concentrated under diminished pressure to about 200 cc. It was allowed to stand several days after which 45 g. of calcium L-galactonate was obtained. The solution was evaporated further and 2 g. more of calcium L-galactonate was gained.

The mother liquor containing chiefly calcium D-altronate could not be made to crystallize readily. Seeds were finally obtained by keeping a few cc. of the solution on a watch glass in an evacuated desiccator over barium oxide for several days. These were then used to inoculate the original solution and with the aid of stirring, 32 g. of calcium D-altronate·$3^1/_2H_2O$ was finally obtained. One recrystallization from water yielded pure calcium D-altronate·$3^1/_2H_2O$ which was identified by its analysis and its mutarotation in *N* hydrochloric acid. Table I shows the observations on the rotation of the salt made by the authors and the corresponding values obtained by Richtmyer, Hann and Hudson[7] for this compound prepared from sedoheptulose.

TABLE I

MUTAROTATION OF CALCIUM D-ALTRONATE·$3^1/_2H_2O$ IN *N* HCl (*c*, 3) AT 20°

Time, min.	$[\alpha]^{20}D$ from sedoheptulose	$[\alpha]^{20}D$ from 5-keto-L-galactonic acid
5	+11.5	+11.8
10	13.8	14.0
15	15.9	16.0
20	17.3	18.0
30	19.6	20.4
45	21.9	22.0
60	23.1	23.2
90	24.2	24.3
Constant	24.8	25.0

By concentrating the mother liquor and cautiously adding methanol, 9.2 g. more of the salt was gained. From 100 g. of the normal calcium 5-keto-L-galactonate·$5H_2O$, a total of 47 g. of calcium L-galactonate·$5H_2O$ and 41.2 g. of calcium D-altronate·$3^1/_2H_2O$ was obtained.

The separation of calcium L-galactonate from calcium D-altronate was relatively simple before seeds of the latter salt were obtained. But as we worked with these calcium salts in the laboratory, we found it increasingly more difficult to effect the fractionation of the calcium salts. Hence, recourse was made to separating their cadmium salts. This was readily done by removing the calcium ions from the mixture following the high pressure hydrogenation. The solution of the free acids was heated and neutralized with a suspension of freshly precipitated cadmium hydroxide. The separation of the cadmium salts was effected as described above for the calcium salts.

Acknowledgment.—One of the authors (P. P. R.) wishes to express his indebtedness to Dr. Richard Pasternack, with whom he collaborated in a separate investigation during which was developed the convenient method of isolating D-galacturonic acid by means of precipitation as its sodium calcium salt.

Summary

A new preparation for large quantities of D-altronic acid is reported and two intermediate products, sodium calcium D-galacturonate hexahydrate and calcium 5-keto-L-galactonate pentahydrate, are described.

BROOKLYN, N. Y. RECEIVED JULY 23, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Kinetics of Transformation of 2-Ketopolyhydroxy Acids

BY PETER P. REGNA[1] AND B. P. CALDWELL

Ohle[2] and Maurer and Schiedt[3] were first to show that weak alkaline agents and alkoxides convert methyl 2-keto-D-gluconate into D-araboascorbic acid. Reichstein[4] recognized that this procedure was general for the rearrangements of 2-keto-3,4-dihydroxy acids and utilized the reaction for the enolization and lactonization of its isomer methyl 2-keto-L-gulonate into L-ascorbic acid (vitamin C). In addition he showed that hydrochloric acid can also bring about this transformation, but that the continued action of the hydrochloric acid results in decomposition of the L-ascorbic acid.

In the course of previous work, one of the authors had noted marked differences in the effect of hydrochloric acid on the rates of rearrangement of the isomers of 2-ketogluconic and 2-ketogulonic acids although similar intramolecular processes are involved. This observation led the present investigators to study the rates of the transformation of a series of 2-ketohydroxy acids into their ascorbic acid analogs and the rates at which the corresponding ascorbic acid analogs decompose.

Prefatory experiments showed the action of hydrochloric acid on L-ascorbic acid to be essentially a constant pseudo-unimolecular or first-order reaction. An analytical examination of the end product corroborated the observations of Hirst[5] and his collaborators, who showed that when ascorbic acid is heated with 12% hydro-

(1) This paper is constructed from a thesis presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, June, 1942. Present address: Chas. Pfizer & Co., Inc., Brooklyn, New York.

(2) Ohle, *Angew. Chem.*, **46**, 399 (1933).

(3) Maurer and Schiedt, *Ber.*, **66**, 1054 (1933).

(4) Reichstein and Grüssner, *Helv. Chim. Acta*, **17**, 311 (1934).

(5) Herbert, Hirst, Percival, Reynolds and Smith, *J. Chem. Soc.*, 1270 (1933).

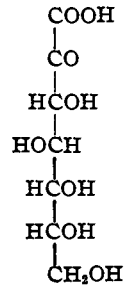
chloric acid furfural, confirmed as the phloroglucide, is readily obtained. In addition, long heating with hydrochloric acid tends to polymerize the furfural. Hence, the consecutive reactions involved in the complete process can be formulated thus

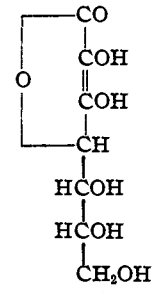
$$K \xrightarrow[(1)]{k_1} A \xrightarrow[(2)]{k_2} F \xrightarrow[(3)]{k_3} P \qquad (1)$$

where K is a 2-ketohydroxy acid, A is the corresponding ascorbic acid analog, F is the furfural formed by the decomposition of the ascorbic acid and P is the polymerized furfural. However, we are here concerned only with the first two steps. Inasmuch as a precise method is unavailable for determining the concentration of the 2-keto acid during the rearrangement, it was necessary to measure the velocities of reactions (1) and (2) independently. Such a procedure is justified by the fact that both reactions are carried out in the presence of a high concentration of hydrochloric acid.

These measurements were made by titrating portions of each reaction mixture with a standard iodine solution of approximately 0.025 *N*. This gives a quantitative indication of the ascorbic acid present in each flask at that moment, since iodine oxidizes ascorbic acid to its first oxidation product, dehydroascorbic acid.[6]

After preliminary experiments, the temperatures 59.9 and 69.9° were chosen, since the rearrangements are nearly complete within a reasonable time. Reaction rates were measured on the following pairs of acids: 2-keto-D-gluconic and D-araboascorbic acids, 2-keto-L-gulonic and L-ascorbic acids, 2-keto-D-galactonic and D-ascorbic acids, 2-keto-D-glucoheptonic (I) and D-glucoascorbic acids (II) and 2-keto-D-galactoheptonic (III) and D-galactoascorbic acids (IV).


(I)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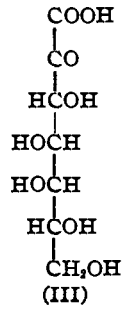
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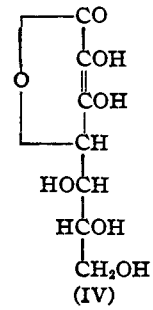
(IV)

The two particular 2-ketoheptonic acids (I) and (III) were expressly chosen in this study for their relative differences of structure. The hydroxy groups on carbon atoms 3 and 4 of both molecules are in *trans* position while the hydroxy groups on carbon atoms 5 and 6 are in *cis* position in (I) and in *trans* position in (III). Thus as a result of the identity of arrangement of substituents on the first four carbon atoms, the ascorbic acid analogs have their ring closures on the same side of the molecule.

Experimental

Apparatus and Method.—Exactly 5 *M* hydrochloric acid solutions were prepared by weighing the required amount of a previously determined stock solution in calibrated 500-ml. flasks. Stock solutions were stored in all-glass apparatus and were prepared as needed by diluting C. P. analyzed hydrochloric acid to approximately 6 *M*. Just before each kinetic run a portion of the stock solution was weighed and titrated with standard sodium hydroxide. The theoretical amount of 2-keto acid to make a 0.0500 *M* solution was weighed out and dissolved in distilled water at 20°. This solution was then quickly transferred to the flask containing the hydrochloric acid at 20°, and rapidly shaken to ensure thorough mixing. The flask was then filled exactly to the mark with distilled water, attached to its air-tight connections and the temperature rapidly raised in a steam-bath to within 0.5° of that of the thermostat. It was necessary to use thick-walled flasks to withstand the internal pressure developed during the rise in temperature. The flask was continuously shaken during its immersion in the steam-bath which usually required less than three minutes, and was then quickly submerged in the constant temperature bath. In this way thermal equilibrium between solution and thermostat was quickly reached, and it was possible to withdraw the first sample soon after the addition of the 2-keto acid. The same technique was employed in handling the ascorbic acid analogs and several portions were withdrawn from the reaction mixture as soon as equilibrium was attained, thus establishing the zero reading with considerable certainty.

Each calibrated 500-ml. flask carried a two-hole stopper, through one opening of which a fine capillary (1.5 mm.) glass tube reached 5 mm. from the bottom of the flask and led to an automatic pipet. The capillary tubes and the pipets were covered with cloth, asbestos and rubber tape to insulate the solutions against temperature drop when withdrawing samples. Through the second hole in the stopper passed a short glass tube to a source of purified nitrogen. The nitrogen was maintained at a slight positive pressure over the solution and served to force the hydrochloric acid into the capillary tube and into the two-way pipet.

Two automatic pipets were used for withdrawing samples from the reaction mixtures. These pipets were calibrated at the two temperatures of the experiments, 59.9 and 69.9° by making eight determinations of the amount of standardized 5 *M* hydrochloric acid delivered by each pipet.

The thermostat was equipped with a good mechanical stirrer mounted independent of the bath. A "merc-to-merc" thermo-regulator, when once set, maintained the temperature inside the reaction flasks within ±0.02° during the whole series of runs at the particular temperature. The general procedure for measuring the rate was as follows: the reactions were observed by iodine titrations of the ascorbic acid present in each flask. During a run the iodine solution was frequently standardized against a purified sample of the ascorbic acid analog. Three ml. of a 0.5% solution of starch was used as an indicator and was added just before the stoichiometric point was reached. At frequent intervals the automatic pipets were flushed

(6) Hirst, *Chemistry & Industry*, **52**, 221 (1933).

with a part of the solution which then was used to locate the approximate end-point before being discarded. However, before this titration was made the pipets were filled a second time and drained, and this portion reserved for the precise titration. Samples of the reactions were arrested by draining the solutions into 75 ml. of water containing crushed ice. The time was taken as that of half drainage of the pipet.

Materials.—The crystalline, free 2-keto acids were used whenever possible. When, however, the crystalline acids were not available, the free acids were liberated from their purified salts. The absence of cations was established by ashing a portion of the acid solution, whereupon weighed portions were titrated with standard sodium hydroxide before being used for the kinetic studies. All the ascorbic acid analogs were crystalline substances and were used only after several recrystallizations. The preparations of 2-keto-D-gluconic, 2-keto-D-galactonic, 2-keto-D-glucoheptonic, 2-keto-D-galactoheptonic, D-ascorbic, D-glucoascorbic and D-galactoascorbic acids have been the subject of a preceding communication.[7]

D-Araboascorbic Acid.—This ascorbic acid was prepared, from methyl 2-keto-D-gluconate by the method of Maurer and Schiedt.[3] It showed $[\alpha]^{20}D$ −17.7° (c, 10 in water), m. p. 168°, and titration with standard iodine 99.7%.

2-Keto-L-gulonic Acid.—Prepared by the method of Reichstein and Grüssner[4]; m. p. 170–171°; $[\alpha]^{20}D$ −48.8° (c, 1.0 in water).

L-Ascorbic Acid.—This was obtained by the rearrangement of methyl 2-keto-L-gulonate as proposed by Pasternack and Regna.[8] The methyl ester[3] (41.6 g.) was dissolved in 200 ml. of water and to this solution was added 2.13 g. of magnesium powder. To the cooled solution 12 g. of oxalic acid dihydrate was added and the magnesium oxalate filtered off. The filtrate was evaporated to dryness *in vacuo* and the crystalline residue was taken up with hot methanol, treated with norite and filtered. On concentrating the filtrate *in vacuo* the L-ascorbic acid crystallized readily. After two recrystallizations from methanol, it showed $[\alpha]^{20}D$ +23°, m. p. 191–192°, and titration with iodine, 99.5%.

Rate Calculations

Inasmuch as the rates by iodine titers show the reactions to be of the first order, preliminary experiments which varied the concentration of the solvent showed the rates to be proportional to the concentration of the hydrochloric acid. However, the solvent is in such large excess (100:1) over the solute that the first-order rates are to be expected. Since the reaction of 2-ketohydroxy acid (K) to furfural (F) is a consecutive process of the first order, it can be generalized into the equation

$$\mathrm{K} \xrightarrow[(1)]{k_1} \mathrm{A} \xrightarrow[(2)]{k_2} \mathrm{F} \qquad (2)$$

where (A) is the intermediate ascorbic acid. Since the concentration of ascorbic acid c_A decreases during the course of the reaction by an amount equivalent to c_F, we will have then $c_A - c_F = c_B$ as the amount of ascorbic acid present at time t. Hence

$$c_0 = c_K + c_B + c_F \qquad (3)$$

where c_0 is the initial molecular concentration of the 2-ketohydroxy acid.

The velocity constants k_2 which evaluate the rates of decomposition of the ascorbic acid analogs were determined independently for each acid and calculated simply by the first order equation

$$k_2 = \frac{1}{t} \ln \frac{c_A}{c_A - c_F} \qquad (4)$$

where c_A is the initial concentration of the ascorbic acid, and c_F is the decrease after a lapse of time, t.

The rates of transformations, k_1, of the 2-ketohydroxy acids into their ascorbic acid analogs were calculated from the equation[9]

$$c_A - c_F = c_B = c_0 \left(\frac{k_1}{k_2 - k_1} e^{-k_1 t} - \frac{k_1}{k_2 - k_1} e^{-k_2 t} \right) \qquad (5)$$

where c_B is equal to the amount of ascorbic acid present at any time t, and is the only constituent which was measured at progressive times, t. Equation 5, however, was rewritten and solved in the following form

$$\frac{\log \left(e^{-k_2 t} - \frac{c_B(k_1 - k_2)}{c_0 k_1} \right)}{t \log e} = -k_1 \qquad (6)$$

The value of k_1 was obtained by an iteration process. For example, on substituting an approximate value of k_1 in the left side of equation 6 when the values of c_B and t are taken from some one observation, we gained a value of k_1 usually better than the one which was assumed. This new value was again substituted in the left side of equation 6 and a second value for k_1 was obtained. This process was repeated until convergence was reached, *i. e.*, until the value satisfied the equation. Equation (6), however, converges only if $k_1 > k_2$; for the alternative case, namely, when $k_1 < k_2$, the equation was solved by writing it in the form

$$\frac{c_B k_2}{c_B + c_0(e^{-k_1 t} - e^{-k_2 t})} = k_1 \qquad (7)$$

Reaction Rates.—All the values of k_1 in the ensuing tables have been calculated by the iteration process using equation (5) in the form of equation (6) or (7) depending upon the values of k_1 relative to those of k_2. However, due to the nature of these equations the velocity constants k_1 have been calculated for each experiment as far as the maximum value of c_B.

The decomposition of the ascorbic acid analogs was found to be pseudo-unimolecular in hydrochloric acid solution by application of Equation (4). The best average values of the velocity constant k_2 by the method of least squares was obtained from the logarithm of the iodine titers of the ascorbic acid remaining in the reaction mixtures *vs.* time plot, to the nearest tenth of a minute. For purposes of brevity only the data for a typical run are presented in Tables I and II. In Table I is given the progress and calculation of the transformation of 2-keto-L-gulonic acid into the corresponding L-ascorbic acid at 59.9°, and Table II records the data for the decomposition of L-ascorbic acid at 59.9°.

(7) Regna and Caldwell, THIS JOURNAL, 66, 243 (1944).

(8) Pasternack and Regna, U. S. Patent 2,165,184, July 4, 1939.

(9) Hitchcock and Robinson, "Differential Equations," John Wiley & Sons, Inc., New York, N. Y., 1936, p. 59.

TABLE I

RATE CALCULATIONS FOR THE TRANSFORMATION OF 2-KETO-L-GULONIC ACID INTO L-ASCORBIC ACID AT 59.9°

Time, min.	Volume, ml., V_∞ = 42.17	$e^{-k_2 t}$	$k_1 \times 10^3$ min.$^{-1}$
43.6	4.28	0.97884	
77.6	7.42	.96262	2.55
114.7	10.32	.94528	2.53
166.0	13.45	.92178	2.44
208.7	16.58	.90268	2.57
278.3	19.89	.87236	2.55
361.9	22.73	.83730	2.50
442.3	25.11	.80492	2.55
480.9	25.98	.78980	2.56
516.8	26.41	.77602	2.53
556.1	27.14	.76120	2.56
602.7	27.56	.74398	2.53
658.0	27.98	.72407	2.53
742.8	28.30	.69457	2.51
770.7	28.04	.68495	2.41[a]
802.1	27.82	.67445	2.34[a]
843.8	27.65	.66080	2.27[a]
1436.6	19.48	Average	2.53
1548.8	17.94		
1576.1	17.50		
1601.1	16.95		
1635.0	16.40		
1688.2	16.00		
1760.4	15.20		
1840.1	14.58		
1944.0	13.96		
2887.5	9.05		
2930.5	8.80		

[a] Omitted in averaging.

TABLE II

THE DECOMPOSITION OF L-ASCORBIC ACID INTO FURFURAL AT 59.9°

Time, min.	Volume, ml., V_t	Log V_0/V_t	$k_2 \times 10^4$ min.$^{-1}$
0	V_0 = 42.02		
34.2	41.29	0.00656	4.41[a]
89.1	40.21	.01913	4.95[a]
113.8	39.81	.02347	4.75
146.7	39.20	.03017	4.74
172.0	38.72	.03556	4.76
237.2	37.53	.04901	4.76
272.8	36.92	.05620	4.75
309.5	36.26	.06403	4.77
382.6	34.92	.08039	4.84
427.3	34.06	.09122	4.91
467.6	33.42	.09945	4.90
505.5	32.83	.10719	4.88
539.6	32.20	.11560	4.93
579.1	31.77	.12144	4.83
642.7	30.90	.13350	4.92
683.0	30.10	.14489	4.89
720.0	29.40	.15511	4.96
773.8	28.84	.16347	4.87
810.3	28.15	.17398	4.95
1459.6	20.48	.31213	4.93
1517.4	19.89	.32483	4.93
1570.4	19.36	0.33752	4.95
1599.0	19.10	.34243	4.93
1715.0	18.02	.36339	4.88
1811.4	17.31	.38516	4.89
1907.9	16.46	.40703	4.91
		Av. by L. S.	4.91
2678.1	10.02	.61955	5.30[a]
2887.0	9.01	.66854	5.30[a]
2963.6	8.71	.68344	5.31[a]

[a] Omitted in averaging.

Column 2 in Table I gives the actual values of c_B in terms of the number of ml. of standard iodine solution at the times indicated in column 1. V_∞ is the theoretical volume of iodine which the original amount of 2-ketohydroxy acid would have required if it were quantitatively transformed into its ascorbic acid analog.

In Table II, V_0 is the ml. of iodine at $t = 0$ for the ascorbic acid. This is the reading obtained immediately after the flask was submerged into the thermostat and connected to the automatic pipet. V_t is the ml. of iodine which the remaining ascorbic acid required at time t. Tables III and IV give a summary of the average values of k_1 and k_2 for the other 2-keto acids at the temperatures of the experiments.

TABLE III

THE RATES OF THE TRANSFORMATIONS OF 0.05 *M* 2-KETOHYDROXY ACIDS INTO THEIR CORRESPONDING ASCORBIC ACID ANALOGS AT 59.9 AND 69.9°, IN 5 *M* HYDROCHLORIC ACID

2-Keto acids	k_1 min.$^{-1}$ at 59.9°	k_1 min.$^{-1}$ at 69.9°	E, kcal./mole
L-Gulonic	0.00253	0.00820	26.7
D-Gluconic	.000566	.00186	27.0
D-Galactonic	.000654	.00208	26.3
D-Glucoheptonic	.000478	.00164	28.0
D-Galactoheptonic	.000207	.000704	27.7

TABLE IV

THE RATES OF THE DECOMPOSITIONS OF 0.05 *M* ASCORBIC ACID ANALOGS IN 5 *M* HYDROCHLORIC ACID

Acids	k_2 min.$^{-1}$ at 59.9°	k_2 min.$^{-1}$ at 69.9°	E, kcal./mole
L-Ascorbic	0.000491	0.00141	23.9
D-Araboascorbic	.00162	.00388	19.9
D-Glucoascorbic	.000920	.00279	25.2
D-Galactoascorbic	.00329	.00943	23.9

In some cases there was evidence of slowly drifting k_1 values for the 2-keto acid rearrangements and this may be due to a portion of the keto acids decomposing without first going through the ascorbic acid rearrangement. This is quite small, however, because there was usually no darkening of the solutions due to furfural formation during the first six hours of the kinetic studies until an appreciable amount of ascorbic acid had already formed. The iodine titrations during the rearrangement of the 2-ketohexonic acids behaved more or less normally. Yet, in a number of cases the 2-ketoheptonic acids acted erratically and the

experiments had to be discarded because there was no increased iodine consumption, but rather periods of stationary iodine readings followed by sharp increases of iodine consumption.

The k_2 values for the decomposition of the ascorbic acids exclude any effects due to the presence of the parent substances, namely, the 2-keto acids. However, the maximum amounts of all the ascorbic acids calculated by the equation

$$c_{B\,(max.)} = c_0 \left(\frac{k_2}{k_1}\right)^{\frac{k_2}{k_1 - k_2}} \qquad (8)$$

agree with the maxima obtained from the graphs when the volumes of the iodine titers were plotted against the times of the transformations of the 2-ketohydroxy acids. These results are given in Table V.

TABLE V

OBSERVED AND CALCULATED VALUES OF THE MAXIMUM YIELDS OF ASCORBIC ACIDS FROM 2-KETOHYDROXY ACIDS

Acid	Temp., °C.	Calcd., %	Observed, %
2-Keto-L-gulonic	59.9	67.5	67.6
	69.9	69.4	69.9
2-Keto-D-gluconic	59.9	20.5	20.8
	69.9	24.3	24.4
2-Keto-D-galactonic	59.9	42.1	41.7
	69.9	44.3	42.5
2-Keto-D-glucoheptonic	59.9	25.4	27.7
	69.9	27.6	28.2
2-Keto-D-galactoheptonic	59.9	6.3	6.1
	69.9	5.2	7.3

Activation Energy.—From the values of k_1 and k_2 obtained at the two temperatures, the energies of activation were determined in the usual way using the Arrhenius equation, and are shown in Columns 4 of Tables III and IV. The energies of activation of the 2-keto acids in the six and seven carbon series show a variance of not more than 1.7 kcal./mole, although their reaction velocities vary widely. This would indicate that essentially the same intramolecular mechanism is involved for all of the acids. However, this cannot be wholly the case since the two seven carbon 2-keto acids which we have studied possess the same arrangement of atoms with respect to the first four groups of the molecules. Were the same intramolecular mechanism involved we should expect their rates of transformations into their corresponding ascorbic acids to be very nearly the same, inasmuch as only the first four groups enter into the rearrangement. Yet, the specific rate constants have a 2.3/1 ratio. The only structural explanation for this wide difference lies in the *cis–trans* arrangement of the groups in the parts of the molecule which do not enter into the rearrangement.

A similar condition exists in the six carbon 2-ketoaldonic series. Although 2-ketogulonic and -gluconic acids have identical structures on all but the last two carbon atoms, this alteration accounts for more than a fourfold difference in their rates of transformation.

In the case of 2-ketogalactonic acid with *cis* arrangement of the hydroxy groups on carbon atoms 3 and 4 and 2-ketogluconic with the same hydroxy groups in *trans* position there result almost equal rates of rearrangement. These observations strongly suggest that the groups in the molecules which do not enter into the enolization and lactonization materially affect the rate of transformation.

Summary

1. The kinetics of the consecutive reactions of five 2-ketopolyhydroxy acids and the decomposition of their ascorbic acid analogs have been studied at 59.9° and 69.9° in 5 *M* hydrochloric acid.

2. The rates of rearrangement of 2-ketopolyhydroxy acids into their ascorbic acid analogs are affected by the groups on the carbon atoms outside the lactone ring.

3. The rate constants of the decomposition of the ascorbic acids are greater for molecules which exhibit *cis* arrangement of the hydrogen atoms on carbon atoms 4 and 5 than for those which have *trans* arrangement of the hydrogen atoms.

4. A method is given for calculating rate constants in a reaction A → B → C where only B can be experimentally determined.

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