597. Studies on Uronic Acid Materials. Part VII.[1] The Kinetics and Mechanism of the Decarboxylation of Uronic Acids.

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Mechanisms for the decarboxylation of uronic acids in mineral acid solution are discussed with reference to the dependence of the rate of decarboxylation on the uronic acid concentration and on the Hammett acidity function. The experimental values of the Arrhenius activation energies and the entropies of activation are compared with those for other reactions of known mechanism; in consequence, an S_E2 decarboxylation mechanism, which explains both the kinetic results and the nature of the products, is proposed.

THE significance, in structural studies, of the possible decarboxylation of uronic acids in hot aqueous solutions has been discussed,[2] and the first-order rate constants for the acidic decarboxylation of glucuronic acid, labelled with ^{14}C at the carboxyl group, have been published.[3]

Although decarboxylation mechanisms for many carboxylic acids have been established,[4] the acidic decarboxylation of uronic acids clearly proceeds by a multi-step process [3] and none of the decarboxylation mechanisms [5,6] proposed to date has explained all the facts. This paper presents the results of studies which were undertaken in order to extend previous knowledge of the decarboxylation mechanism.

EXPERIMENTAL AND RESULTS

Origin of Samples.—The purity and origin of the samples of D(+)-galacturonic acid monohydrate, D(+)-glucurone, alginic acid, trigalacturonic acid, and calcium L-sorburonate (calcium 5-keto-D-gluconate) have been described.[2] 2-Keto-L-galactonic acid and calcium 2-keto-D-gluconate were kindly provided by Dr. W. W. Reid. L(−)-Ascorbic acid (B.D.H. Ltd.) gave 1·0 mol. of carbon dioxide after 2·5 hr. in refluxing 19% w/w aqueous hydrochloric acid.[3,7] " AnalaR " mineral acids were used, the appropriate dilutions being made with conductivity-grade distilled water.

Kinetic Measurements.—Anderson's decarboxylation apparatus [7] was used; the modifications facilitating reproducible kinetic measurements have been described.[2,3]

Order of Reaction with Respect to Uronic Acid Concentration.—The rate of decarboxylation of widely different weights of galacturonic acid monohydrate (30·0 mg., 322 mg., 999 mg.) in boiling 3·8% w/w aqueous hydrochloric acid was investigated. The averaged results, obtained from duplicate runs for each weight, are shown in Table 1. Since the molar yield is independent of the sample weight, the rate-constant is of the first order with respect to the uronic acid concentration; calculation, by Guggenheim's method,[8] gives $k_1 = 4{\cdot}03 \times 10^{-5}$ sec.$^{-1}$.

Dependence of the Reaction Rate on Temperature.—Samples (30·0 mg.) of galacturonic acid monohydrate were decarboxylated in 3·8% w/w aqueous hydrochloric acid, the temperature being maintained, in successive runs, at 103°, 100°, and 90°. Table 2 shows the values found for the first-order rate-constant. The graph of log k_1 against $1/T$ is shown in Fig. 1 (curve a), from which the values shown in Table 2 for the Arrhenius activation energy (E_A) and for the unimolecular Arrhenius factor A_1 ($k_1 = A_1 \exp - E_A/\boldsymbol{R}T$) were calculated.

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[1] Part VI, Anderson and Herbich, *J.*, 1963, 1.

[2] Anderson, Bews, Garbutt, and King, *J.*, 1961, 5230.

[3] Anderson and Garbutt, *Talanta*, 1961, **8**, 605.

[4] Henecka, in Houben-Weyl's " Methoden der Organische Chemie," Georg Thieme Verlag, Stuttgart, 4th edn., 1952, Vol. VIII, Part 3, p. 484.

[5] Isbell, *J. Res. Nat. Bur. Standards*, 1944, **33**, 45; Huber and Deuel, *Helv. Chim. Acta*, 1951, **34**, 853; Zweifel and Deuel, *ibid.*, 1956, **39**, 662; Taylor, Fowler, McGee, and Kenyon, *J. Amer. Chem. Soc.*, 1947, **69**, 342; Machida, *Bull. Faculty Textile Fibres, Kyoto Univ.*, 1955, **1**, 59.

[6] Stutz and Deuel, *Helv. Chim. Acta*, 1958, **41**, 1722.

[7] Anderson, *Talanta*, 1959, **2**, 73.

[8] Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

TABLE 1.

The decarboxylation of galacturonic acid monohydrate in boiling 3·8% w/w hydrochloric acid. (Results expressed as % moles of carbon dioxide per mole of uronic acid.) (*a*) 30·0, (*b*) 322·2, (*c*) 999·3 mg. of uronic acid.

	Carbon dioxide (% mole/mole)		
Time (sec.)	(*a*)	(*b*)	(*c*)
2000	7·9	8·0	8·2
4000	15·0	15·2	15·7
6000	21·0	21·3	22·0
10,000	32·5	33·1	34·0
15,000	46·2	46·7	48·1
20,000	57·4	58·3	60·1
30,000	98·2	99·8	102·9

TABLE 2.

Rate-constants, k_1 (10^{-4} sec.$^{-1}$), Arrhenius activation energies (E_A), and entropies of activation ($\Delta S^‡$) for the decarboxylation of various uronic acids.

	Temp.					E		
Compound in 3·8% w/w HCl	112°	103°	100°	95°	90°	(kcal. mole^{-1})	log A_1	ΔS‡ (e.u.)
D(+)-Galacturonic acid monohydrate	—	0·40	0·31	—	0·12	25·5	10·43	−13·4
	Temp.							
Compound in 19% w/w HCl	112°	105°	100°	95°	90°			
D(+)-Galacturonic acid monohydrate	12·0	5·7	3·6	2·2	1·3	27·9	12·9	−5·2
D(+)-Glucurone	6·5	3·7	2·6	1·6	1·0	23·8	10·34	−17·1
Trigalacturonic acid	13·0	6·6	3·8	2·8	1·7	28·0	13·08	−4·6
Alginic acid	4·6	2·4	1·5	0·99	0·57	26·5	11·73	−10·7
Ca L-sorburonate	37·0	21·0	13·0	8·2	5·0	26·4	11·57	−11·5
2-Keto-L-galactonic acid	6·8	3·6	2·7	1·6	—	23·8	10·34	−17·1
Ca 2-keto-D-gluconate	8·1	4·2	2·9	1·9	—	27·1	12·30	−8·1
Ascorbic acid	10·0	4·6	2·8	1·7	1·2	26·1	12·34	−7·9
					Mean	26·1		−10·6

The experiments were repeated for galacturonic acid monohydrate (30·0 mg.) in 19% w/w aqueous hydrochloric acid at 112°, 105°, 100°, 95°, and 90°. The values obtained for k_1 are shown in Table 2; plotting log k_1 against $1/T$ gave line (b) in Fig. 1, from which the values for E_A and A_1 shown in Table 2 were calculated. The close agreement in the values of E_A given by the 3·8% and the 19% acid indicates that the same decarboxylation mechanism probably operates at both these acid concentrations.

Similar experiments in the 19% acid were then conducted for glucurone, trigalacturonic acid, alginic acid, calcium L-sorburonate, 2-keto-L-galactonic acid, calcium 2-keto-D-gluconate, and ascorbic acid. The results for k_1, E_A, and A_1 are shown in Table 2, the plots of log k_1 against $1/T$ being shown in Fig. 1 (curves c—h). The values for E_A are in good agreement with those previously found,[9] by different methods, for the 2-keto-acids and for ascorbic acid.

Calculation of the Entropy of Activation, $\Delta S^‡$.—A correlation has been found [10] between the entropy of activation and reaction mechanism, the values of $\Delta S^‡$ varying between +5 and +9 e.u. for *A*-1 mechanisms, and between −20 and −25 e.u. for *A*-2 mechanisms.[10] Values for $\Delta S^‡$ can be found from the Eyring equation, $\Delta S^‡ = 2{\cdot}303\boldsymbol{R} \log (A_2 h/e\boldsymbol{k}T)$, where $\boldsymbol{k}$ is Boltzmann's constant. (For substitution in this expression, our values for A_1 were corrected to bimolecular values for the appropriate acid concentrations, the units for A_2 then being l. mole^{-1} sec.$^{-1}$.) The values obtained for $\Delta S^‡$ are shown in Table 2; values approximately 1 unit less negative are obtained when the activity of the mineral acid solution is taken into account.

Dependence of Reaction Rate on the Mineral Acid Concentration.—First-order rate constants were obtained for the decarboxylation of uronic acids in boiling aqueous mineral acids of various concentrations. The values obtained were corrected to 100° (on the basis of the observed reflux temperatures and the activation energies already obtained from Fig. 1). These

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[9] Regna and Caldwell, *J. Amer. Chem. Soc.*, 1944, **66**, 246.

[10] Long, Prichard, and Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 2362.

corrected values are shown in Table 3; Fig. 2 shows that they have a linear dependence[11] on the Hammett acidity function, H_0, when the values quoted for $-H_0$ at 25° by Long and Paul[12] are used. This suggests[12] that the reaction follows either an A-1 or an A-S_E2 mechanism. Values of the gradient (S') of the lines in Fig. 2 are shown in Table 3. (For $-H_0$ values greater than ~0·5, the plots of molarity against H_0 at various temperatures are parallel;[13] the values of H_0 at 25° may therefore be used for values observed at other temperatures, only the intercept on the ordinate of Fig. 2 being altered.)

As shown in Fig. 2, the rate constants for the decarboxylation of galacturonic acid in sulphuric and hydrochloric acid are identical over a limited range of H_0 values. Above a certain concentration, however, the plot for sulphuric acid tends to a limiting value (Fig. 2), suggesting that a change in mechanism occurs. A similar effect has been reported[14] for aromatic carboxylic acids and also for galacturonic acid in phosphoric acid media.

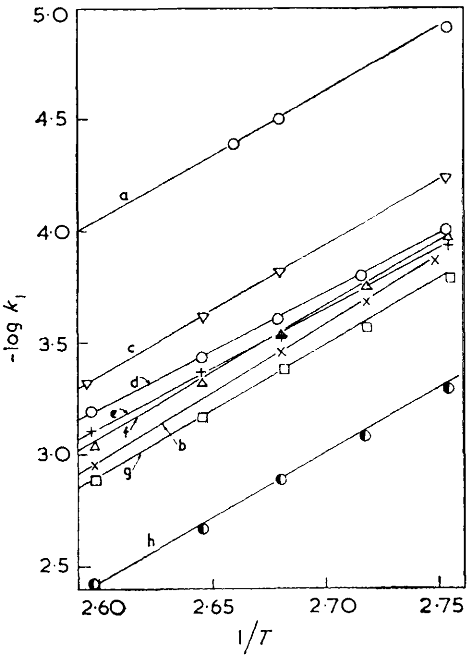

FIG. 1. Plots of log k_1 against $1/T$.

Galacturonic acid monohydrate (a) in 3·8% w/w HCl and (b) in 19% w/w HCl. c, Alginic acid. d, Glucuronic and 2-keto-L-galactonic acid. e, Calcium 2-keto-D-gluconate. f, Ascorbic acid. g, Trigalacturonic acid. h, Calcium 5-keto-D-gluconate. (c—h) in 19% w/w HCl.

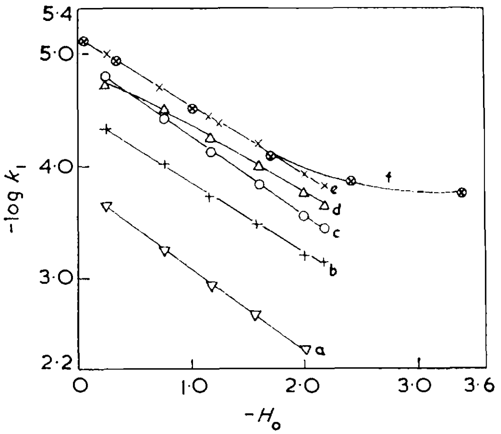

FIG. 2. Plots of log k_1 against the Hammett acidity function, H_0.

a, Calcium 5-keto-D-gluconate. b, Trigalacturonic acid. c, D(+)-Glucurone and 2-keto-L-galactonic acid. d, Alginic acid. e, D(+)-Galacturonic acid monohydrate in HCl. f, D(+)-Galacturonic acid monohydrate in H_2SO_4.

The Effect of Solvation of Hydrogen Ions on the Kinetics.—Various workers[12] have extended the Zucker–Hammett hypothesis[11] to include the effect of solvation of hydrogen ions on reaction kinetics and mechanism. It has been suggested[15] that four water molecules are involved in proton solvation in acidic solution. For a decarboxylation reaction, Pedersen[16] obtained a linear relation between log k_1 and ($-H_0$ + 4 log a_{H_2O}), where a_{H_2O} is the activity of the water. In a similar approach, Bunnett[17] plotted (log k_1 + H_0) against log a_{H_2O}, suggesting that if the slope w of this plot is zero or less than unity, then water molecules are

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[11] Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791.

[12] Long and Paul, *Chem. Rev.*, 1957, **57**, 935.

[13] Gel'bstein, Shcheglova, and Temkin, *Zhur. neorg. Khim.*, 1956, **1**, 282.

[14] Schubert, *J. Amer. Chem. Soc.*, 1949, **71**, 2639.

[15] Leisten, *Chem. and Ind.*, 1959, 397.

[16] Pedersen, *Acta Chem. Scand.*, 1960, **14**, 1448.

[17] Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956, 4968, 4973, 4978.

TABLE 3.

Values of the first-order rate-constants (as log k_1) for the decarboxylation of some uronic acids in mineral acids at 100°,

	Log k at the following Hammett acidity functions (H_0):							Slope
Uronic acid in HCl	−2·15	−2·01	−1·57	−1·22	−1·16	−0·74	−0·24	S'
D(+)-Glucurone	−3·47	−3·58	−3·84	−4·09	−4·13	−4·45	−4·78	−0·70
D(+)-Galacturonic acid monohydrate	−3·82	−3·92	−4·19	−4·40	−4·45	−4·66	−4·99	−0·61
Trigalacturonic acid	−3·17	−3·21	−3·48	—	−3·76	−4·02	−4·34	−0·62
Alginic acid	−3·66	−3·76	−4·00	—	−4·25	−4·51	−4·76	−0·60
Ca L-sorburonate	—	−2·35	−2·67	—	−2·97	−3·26	−3·65	−0·73

	Log k at the following Hammett acidity functions (H_0):						Slope
Uronic acid in H_2SO_4	−3·38	−2·41	−1·72	−1·01	−0·31	0·02	S'
D(+)-Galacturonic acid monohydrate	−3·75	−3·86	−4·10	−4·49	−4·93	−5·11	−0·61

not involved in the reaction; for $w \approx +2$, water acts as a nucleophile; for $w \approx +5$ to $+7$, water acts as a proton-transfer agent. Bunnett's values [17] of log a_{H_2O} were therefore used in conjunction with the results in Table 3 to obtain the typical, slightly curved, Bunnett plots shown in Fig. 3 (data in Table 4). In hydrochloric acid, the limiting slopes vary between

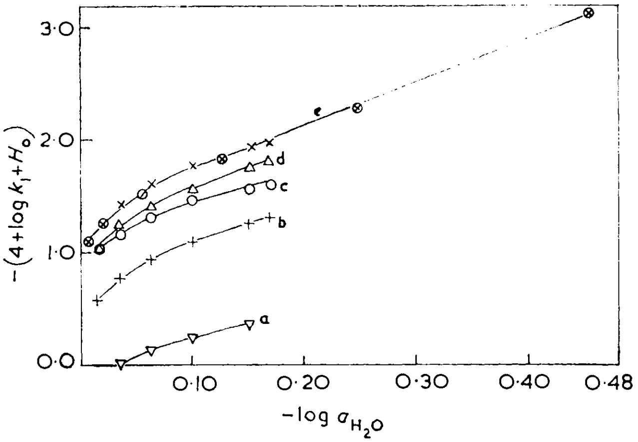

FIG. 3. Bunnett plots of $-\log a_{H_2O}$ against $-(4 + \log k_1 + H_0)$.

a, Calcium 5-keto-D-gluconate. b, Trigalacturonic acid. c, D(+)-Glucurone. d, Alginic acid. e, D(+)-Galacturonic acid monohydrate in HCl. f, D(+)-Galacturonic acid monohydrate in H_2SO_4.

TABLE 4.

Values of $(4 + \log k_1 + H_0)$ and log a_{H_2O} for the decarboxylation of some uronic acids.

In hydrochloric acid at 100°.

$-\log a_{H_2O}$	0·169	0·152	0·102	0·069	0·064	0·036	0·016	
$-H_0$	2·15	2·01	1·57	1·22	1·16	0·74	0·24	Slope
Uronic acid			$-(4 + \log k_1 + H_0)$					(w)
D(+)-Glucurone	1·60	1·56	1·43	1·33	1·30	1·17	1·02	+2·5
D(+)-Galacturonic acid monohydrate	1·97	1·93	1·76	1·62	1·60	1·43	1·23	+2·8
Trigalacturonic acid	1·29	1·24	1·09	—	0·92	0·76	0·57	+3·0
Alginic acid	1·79	1·75	1·57	—	1·40	1·23	1·02	+3·5
Ca L-sorburonate	—	0·36	0·24	—	0·12	0·01	−0·13	+2·5

In sulphuric acid at 100°.

$-\log a_{H_2O}$	0·455	0·249	0·128	0·056	0·020	0·008	
$-H_0$	3·38	2·41	1·72	1·01	0·31	0·02	Slope
			$-(4 + \log k_1 + H_0)$				(w)
D(+)-Galacturonic acid monohydrate	3·13	2·27	1·82	1·50	1·24	1·09	+4·0

+2·5 and +3·5 (mean +2·9), suggesting that water is acting as a nucleophile; in sulphuric acid, the value of *w* is more positive, as is generally found.[17] Bunnett[17] also plotted $\Delta S^{\ddagger}$ against *w*: the average values of *w* and of $\Delta S^{\ddagger}$ from Table 2 (−10·6 e.u.) agree well with Bunnett's correlations.

DISCUSSION

The kinetic results show that the acidic decarboxylation of uronic acids is bimolecular, depending on the first power of both the uronic acid and the mineral acid concentration. The dependence of log k_1 on the Hammett acidity function suggests that the decarboxylation follows either an *A*-1 or an A-S_E2 course:[12] the entropies of activation are not sufficiently negative to be correlated with values previously reported[10,18] for *A*-2 reactions.

An S_E2 mechanism was proposed[19] for the decarboxylation of polycyclic carboxylic acids, and further examples have been reported;[14,20] the kinetic data published for some of these are listed in Table 5, together with values calculated for $\Delta S^{\ddagger}$ (with the aid of bimolecular *A* factors computed from the unimolecular values given in the references cited). The variation in $\Delta S^{\ddagger}$ (from +0·7 to −25·2; mean = −11·2) for these S_E2 reactions is greater than the variation in $\Delta S^{\ddagger}$ found (see Table 2) for the uronic acid decarboxylations studied (−4·6 to −17·1; mean −10·6); in the present state of knowledge, the observed kinetics are therefore compatible with the results expected from an A-S_E2 reaction.

TABLE 5.

Activation energies (E_A) and entropies of activation ($\Delta S^{\ddagger}$) for established A-S_E2 decarboxylation reactions.

	Acid used			
Acid decarboxylated		concn. % w/w	E_A (kcal. mole^{-1})	$\Delta S^{\ddagger}$ (cal. °c^{-1} mole^{-1})
Mesitoic acid (ref. 14)	H_2SO_4	83·3	27·4	+0·7
2,4,6-Trimethoxybenzoic acid (ref. 19)	$HClO_4$	10·3	18·4	−13·6
	$HClO_4$	59·7	20·6	−6·5
$Me_3Si{\cdot}[CH_2]_2{\cdot}CO_2H$ (ref. 20*a*)	H_2SO_4	90	20·5	−12·0
$Me_3Si{\cdot}[CH_2]_3{\cdot}CO_2H$ (ref. 20*a*)	H_2SO_4	90	19·3	−19·7
2,4,6-Trihydroxybenzoic acid (ref. 20*c*)	HCl	0·44	15·2	−25·2
2,4,6-Trihydroxybenzoic acid anion (ref. 20*c*)	HCl	0·44	21·5	−1·1

Open-chain Formation as the Initial Step of the Reaction Mechanism.—The activation energy (~17 kcal. mole^{-1}) for the mutarotation of simple sugars,[21] the kinetics of which may be explained by regarding ring-opening as the rate-controlling step, is considerably less than that for uronic acid decarboxylations (mean value from Table 2 = 26·1 kcal. mole^{-1}). A further indication that ring-opening is not rate-controlling in uronic acid decarboxylation is given by the similar reaction kinetics given by keto-aldonic acids, uronic acids, and lactones.

The acid hydrolysis of various glucopyranosides is believed to occur[22] *via* a closed-ring carbonium ion intermediate; the slowest rate reported for this reaction is, however, much faster than that of the fastest uronic acid decarboxylation. Furthermore, for uronic acid decarboxylations the rate dependence on the Hammett acidity function is the same in both hydrochloric and sulphuric acid, which have different ionic strengths, and this indicates that the formation of a carbonium ion intermediate is unlikely to be the rate-determining step.

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[18] Rabinovitch and Winkler, *Canad. J. Res.*, 1942, **20**, *B*, 73.

[19] Schenkel and Schenkel-Rudin, *Helv. Chim. Acta*, 1948, **31**, 514.

[20] (*a*) Schubert, Zahler, and Robins, *J. Amer. Chem. Soc.*, 1955, **77**, 2293; (*b*) Schorr, Freiser, and Speier, *ibid.*, 1955, **77**, 547; (*c*) Brown, Hammick, and Scholefield, *J.*, 1950, 778; (*d*) Brown, Elliott, and Hammick, *J.*, 1951, 1384.

[21] Isbell and Pigman, *J. Res. Nat. Bur. Stand.*, 1937, **18**, 141.

[22] Banks, Meinwald, Rhind-Tutt, Sheft, and Vernon, *J.*, 1961, 3240.

There is considerable evidence [23] that sugars exist mainly in the straight-chain ene-diol form in widely different acid concentrations, the activation energy for the polarographic reduction of the straight-chain form being 20—25 kcal. mole^{-1}.[24] In the absence of direct evidence to the contrary, it appears to be a reasonable assumption that uronic acids, in acidic solution, also exist in the straight-chain ene-diol form, the formation of which is not rate-determining.

Significance of the Reaction Products.—Any proposed mechanism must explain the formation of the products observed under differing experimental conditions. Decarboxylation of galacturonic acid in concentrated sulphuric acid yields 5-formylfuroic acid; [25] 100 mole % of carbon dioxide, 32 mole % of furfuraldehyde, and 19 mole % of reductic acid were isolated [6] after decarboxylation in 3·5N-hydrochloric acid for 4 hours. Significant amounts of pentoses have not been isolated from the acidic solutions used to decarboxylate uronic acids.[6,26] The activation energy for the formation of furfuraldehyde from xylose in mineral acid is 14 kcal. mole^{-1}, with a slightly positive entropy of activation [27]—values which differ widely from those found for uronic acid decarboxylations. Further, the yield of furfuraldehyde from uronic acids is considerably less than that isolable from pentoses; [6,28] different mechanisms are therefore strongly indicated, although both may involve the formation of ene-diol intermediates.

After consideration of the kinetic results and other evidence which has been discussed, a reaction pathway which appears to explain the known facts is presented in the chart.

Proposed Reaction Mechanism.—Structures (I—III) are in equilibrium; the formation of (II) and (III) is unlikely to be rate-determining, since similar kinetics were observed for ring structures and linear chains. In general, the attack of a proton on a hydroxyl group will be fast: although elimination of water from (III) could be rate-determining, an A-S_E2 reaction, as indicated by the kinetics, would not result. Consideration shows that proton attack on the 4-hydroxyl group is required to explain the formation of the observed products. Elimination of water from (III) may be *cis* (galacturonic acid) or *trans* (glucuronic, mannuronic acid), so that the observed small differences in activation energy and entropy of activation would be expected to occur. Further elimination of water from (IV) leads to (V), which can either cyclise directly to give 5-formylfuroic acid (VI), or can give an intermediate (VII), which was readily decarboxylated.[29] Proton attack on (V) may be the rate-determining A-S_E2 reaction. The acid (VI) will be preferentially formed in concentrated sulphuric acid, where the change in bisulphate ion concentration may become important; this is consistent with the limiting value observed for log k_1 at high sulphuric acid concentrations (Fig. 2). Lower concentrations of mineral acid will favour the rapid formation of the material (VII) which on decarboxylation gives either (VIII) or (XI).

The observed production of reductic acid (XIII) requires the formation of a carbon–carbon bond to be explained, and the mechanism proposed should also explain the non-formation of reductic acid from pentoses. It is suggested that the necessary carbon–carbon bond formation occurs when (VII) gives rise to (XI) upon decarboxylation, and not as the result of cyclisation between an aldehydic and a hydroxyl group, as has been suggested.[6] Cyclisation of (VII) to (XI) is clearly less favourable than the formation of (VIII) from (VII) by the normal βγ-unsaturated decarboxylation mechanism, and it can be deduced, from the relative yields of the products (X) and (XIII) reported, that the rate of formation of (VIII) from (VII) is about three times that of formation of (XI) from (VII); under

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[23] Singh, Dean, and Cantor, *J. Amer. Chem. Soc.*, 1948, **70**, 517; Pacsu and Hiller, *ibid.*, p. 523; Wolfrom, Schuetz, and Cavalieri, *ibid.*, 1949, **71**, 3518.

[24] Overend, Peacocke, and Smith, *J.*, 1961, 3487.

[25] Stutz and Deuel, *Helv. Chim. Acta*, 1956, **39**, 2126.

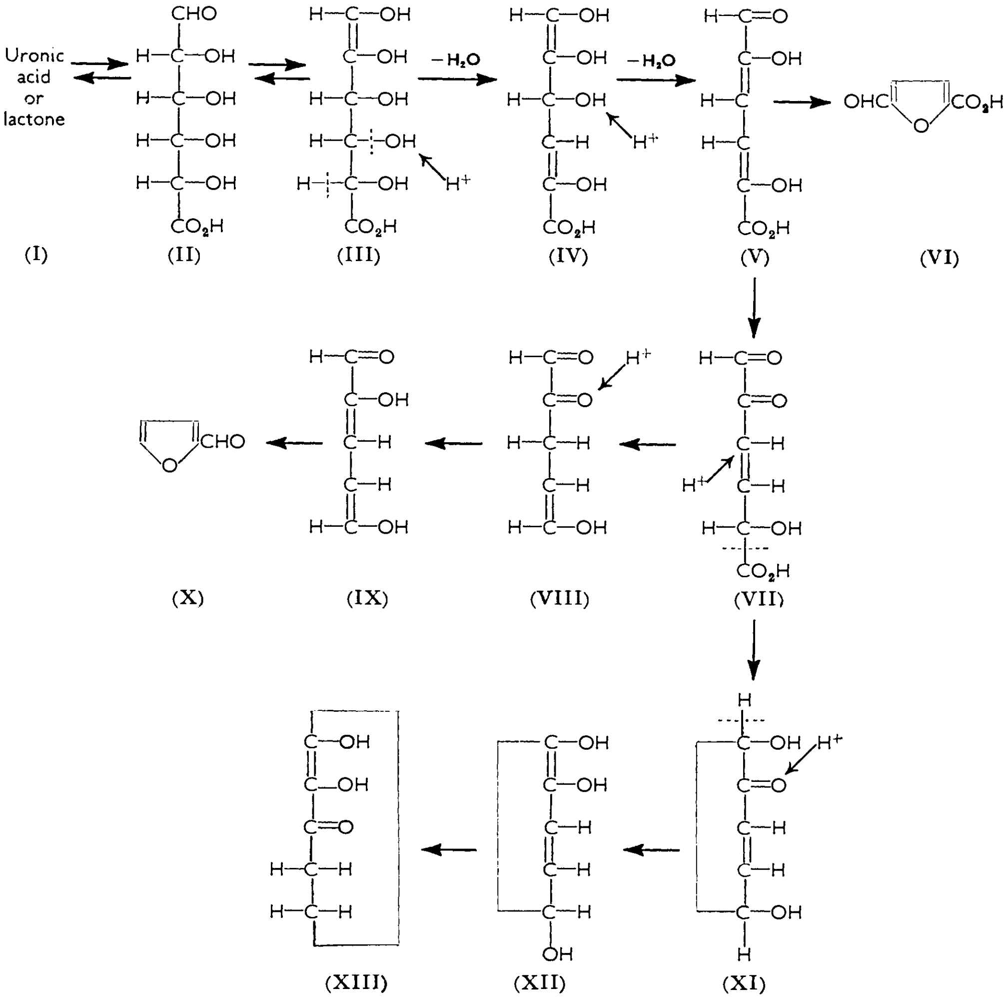
[26] Franken, *Biochem. Z.*, 1933, **257**, 245.

[27] Dunlop and Peters, " The Furans," Reinhold Publ. Corp., New York, 1953, p. 292.

[28] Reichstein and Oppenauer, *Helv. Chim. Acta*, 1933, **16**, 988.

[29] Arnold, Elmer, and Dodson, *J. Amer. Chem. Soc.*, 1950, **72**, 4359.

mildly dehydrating conditions the yield of (XIII) increases[6] relative to that of (X). In the formation of furfuraldehyde, cyclisation of structures prior to (IX) would involve sterically strained systems.



We thank Professor E. L. Hirst, C.B.E., F.R.S., for his interest and advice, and are grateful to Professor F. A. Long and Dr. B. C. Challis (Cornell University, U.S.A.) for helpful discussion (with S. G.). We thank the Department of Scientific and Industrial Research for the award of a maintenance grant (to S. G.).

Department of Chemistry, University of Edinburgh. [*Received, November 21st,* 1962.]