A Novel Degradation Pathway of L-Ascorbic Acid under Non-oxidative Conditions[1]

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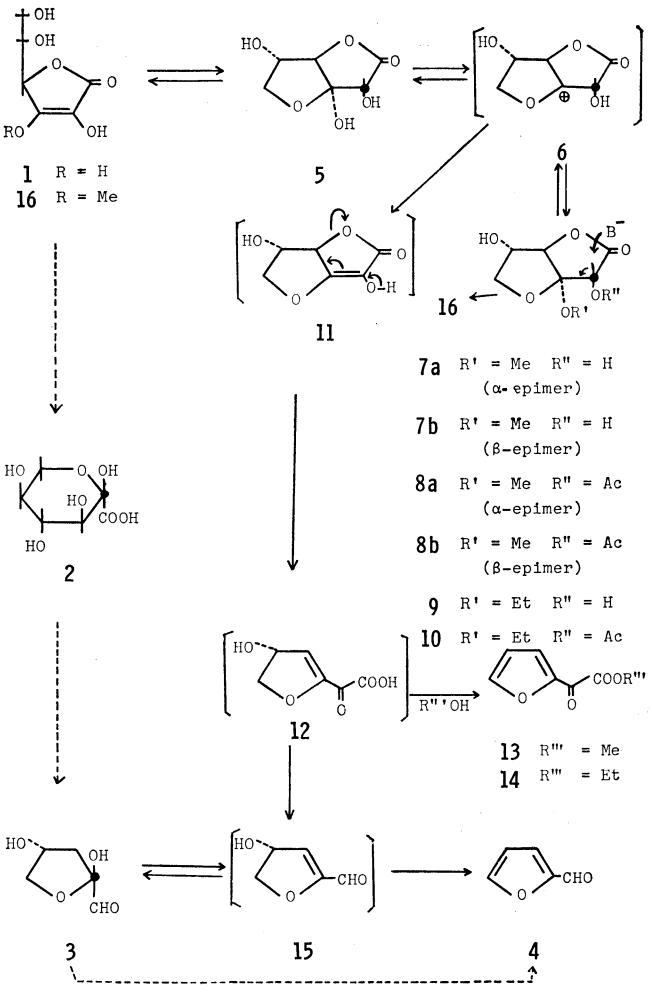
The degradation of L-ascorbic acid (**1**) in methanol was studied in the presence of boron trifluoride-etherate under non-oxidative conditions. Two epimeric compounds containing an acetal group (**7a** and **7b**) were isolated as the intermediates and 2-methoxalylfuran (**13**) the final product. From the result, the degradation pathway of **1** in methanol was proposed to be **1**→**7**→**13**. By analogy with the proposed pathway, one in an aqueous acid was also presented.

It is well known that L-ascorbic acid (**1**) decomposes to 2-furaldehyde (**4**) and carbon dioxide in aqueous acids under non-oxidative conditions.[2,3] Many extensive studies have been reported on the mechanism of this degradation reaction.[3-9] From the kinetic point of view, Regna and Caldwell[5] and Yamamoto and Yamamoto[3] have concluded that the degradation does not proceed *via* L-xylo-2-hexulosonic acid (**2**),[2] the hydrolyzed product of **1**, as an intermediate. Several pathways have been proposed in which that conclusion was expanded.[6,7] However, no experimental proofs on their proposed pathways have been provided. On the other hand recently, Kurata and Sakurai[9] have succeeded in the first isolation of an intermediate, 3-deoxy-L-2-pentosulose (**3**), and proposed a novel pathway of **1**→**2**→**3**→**4**.

Although the isolation of **3** was very important, their conclusion as to the degradation pathway seemed to be in conflict with the kinetic results from which a possible pathway of the degradation can be presented as (**2**→)**1**→**3**→**4**. This disagreement in the interpretation of the role of **3** prompted us to study the degradation of **1**. For the purpose, the degradation of **1** in methanol containing boron trifluoride-etherate was studied as a model reaction.

When **1** in methanol was refluxed in the presence of boron trifluoride for about 10—15 hr, three spots appeared in the tlc, though some of the starting material, **1**, remained unchanged. From the product, **7a**, **7b**, and 2-methoxalylfuran (**13**)[8] were successfully isolated by means of preparative thin-layer chromatography. Compounds **7a** and **7b** had correct analyses for **1** plus one mole of methanol minus one mole of water.



They showed the characteristic bands due to hydroxyl and γ-lactone groups in the IR spectra. Their acetylation gave diacetates, **8a** from **7a** and **8b** from **7b**, which showed the absence of a hydroxyl group in the IR spectra and a singlet due to one methoxy group in the NMR. By the deacetylation of **8a** with a potassium carbonate solution, **7a** was recovered; further, small amounts of **7b** and 3-*O*-methyl-L-ascorbic acid (**16**)[10] were detected. A similar result was obtained for the deacetylation of **8b**, which gave **7b** as the major product and **7a** and **16** as minor products. Therefore,

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8) K. Goshima, N. Maezono, and K. Tokuyama, This Bulletin, **45**, 3692 (1972).
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10) W. N. Haworth, E. L. Hirst, and F. Smith, *J. Chem. Soc.*, **1934**, 1556.

Table 1. Chemical shifts and coupling constants

Compound	Solvent	Chemical shift (τ)						Coupling constant (Hz)			
		H_2	H_4	H_5	H_6	$H_{6'}$	MeO	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
8a	$CDCl_3$	4.27	5.25	4.79	5.28	5.50	6.62	0.5	7.0	5.0	10.0
	C_6D_6	4.28	5.27	5.01	5.88	6.27	6.87				
8b	$CDCl_3$	5.20	5.02	4.37	5.49	6.01	6.62	0.5	7.0	5.0	10.0
	C_6D_6	5.23	5.12	4.93	5.95	6.43	6.93				
10	$CDCl_2$	4.29	5.21	4.78	5.45	6.01					
	C_6D_6	4.29	5.49	5.95	5.75	6.20					

7a and **7b** must be epimers to each other.

The formation of **16** was interesting; it occurred by the further reactions of **7a** and **7b**, initially formed by the deacetylation, with the base employed. The fact that the alkaline treatment of **7a** easily afforded **16** supports this idea and suggests that the position of the methoxy group of **7** corresponds to the C_3-position of **1**. Therefore, the structures of **7a** and **7b** were determined to be the acetal derivatives of **1**, as is shown in the chart.

The structures were confirmed by the NMR spectra, the data of which are reported in Table 1. In the NMR spectrum of **8a** in chloroform-*d* at 60 MHz, three singlets due to one methoxy and two acetoxy groups, a singlet due to H_2 and signals appearing as the pattern of an ABXY system due to H_6, H_6', H_5, and H_4 were observed. The NMR spectrum of **8b** was similarly assigned.

The easy exchange of the methoxy group of **7a** with an ethoxy group also supported the idea of the existence of an acetal group in **7**. When **7a** in ethanol was refluxed in the presence of boron trifluoride, the ethoxy analog of **7a** (**9**) and 2-ethoxalylfuran (**14**) were obtained. The structure of **9** was determined by its conversion into its diacetate (**10**), whose NMR spectrum was assigned in a way similar to that used for **8a** (see Table 1). The structure of **14** was established from the IR and mass spectra, which are quite similar to those of **4**[11] and **13**.[8] Another compound was detected on the tlc. It was considered to be the ethoxy analog of **7b**, but an attempt of its isolation was unsuccessful because of its limited amount.

We will now describe how the epimeric structures of **7a** and **7b** were determined. It is quite natural to consider that the configuration of the 3-methoxy group should be α, since a *cis*-form is more stable in bicyclo-[3.3.0]octanes.[12] Therefore, **7a** should be the C_2-epimer of **7b**. In the acid treatment of **1**, the yield of **7a** was always higher than that of **7b**. Further, in the acid-catalyzed epimerization of **7**, the yield of **7a** was always higher, too. These facts demonstrate that **7a** is a stable epimer. Therefore, the configuartion of the 2-hydroxyl group of **7a** must be α, since the compound with the OH-*exo* configuration to the tetrahydrofuran ring is more stable than that with the OH-*endo* configuration, from the stereochemical point of view.

The CD curves for **7a** and **7b** in UV spectral region have peaks at 236 and 231 nm, respectively. The positive Cotton effect of **7a** suggests that the β-atom of the lactone exists above the lactone plane and the negative one of **7b** suggests the opposite conformation.[13,14] On the other hand, their diacetates, **8a** and **8b**, show a positive Cotton effect. The difference in conformations of the lactone ring between **7b** and the other compounds supported the above-described epimeric structures. The conformation of **7b** must be affected by the presence of a hydrogen bond between the 2-hydroxy group and the oxygen atom of the tetrahydrofuran ring; the presence of the hydrogen bond cannot be considered in the cases of the other compounds. When the hydrogen bond of **7b** disappears upon the acetylation of the 2-hydroxy group, the conformation may be effected to be transformed a conformation similar to the others; that is, the sign of the Cotton effect in **8b** was in accord with those of **7a** and **8a**. The presence of the hydrogen bond in **7b** was also evidenced by the IR spectrum in chloroform.

When **1** was treated in methanol containing boron trifluoride, the spots of **7a** and **7b** appeared on the tlc at the initial stages of the reaction, and then there appeared **13**, which increased at the expense of **7**. Therefore, the reaction was concluded to proceed *via* the pathway of **1**→**7**→**13**. This apthway was further supported by the fact that the acid treatment of **7** afforded **13**. In this treatment, a small amount of **1** was also detected, so the presence of an equilibrium between **1** and **7** was confirmed.

In conclusion, on the basis of the above results, the acid-catalyzed degradation of **1** in methanol may be said to proceed *via* the pathway of **1**→**5**→**6**→**11**→**12**→**13** as is shown in the chart. By analogy with this conclusion, the possible pathway of the degradation of **1** in water can be proposed to be **1**→**5**→**6**→**11**→**12**→**15**→**4**, as is shown in the chart. The interesting intermediate, **3**, reported by Kurata and Sakurai[9] can reasonably be explained as the hydrate of a possible intermediate, **15**.

Experimental

All the melting points were recorded on a Kofler block and have not been corrected. The NMR spectra were taken with a Varian A-60-A spectrometer, using tetramethylsilane as the internal reference; the data are reported in

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12) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, **1936**, 611.
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14) A. F. Beecham, *ibid.*, **1968**, 2355, 3591.

Table 1. Thin-layer chromatography was performed on a silica-gel plate using acetone and chloroform [5: 5, v/v (Solvent A) and 6: 4, v/v (Solvent B)] as the solvent for both detection and preparation. The separated materials were developed with either iodine vapor or UV light. The R_f-values are shown in Table 2. In the case of preparative thin-layer chromatography (ptc), the developed zones were extracted with acetone. The evaporation of the acetone under reduced pressure gave the materials.

Table 2. R_f-values of products

Compound	Solvent A	Solvent B
1	0.13—0.18	
7a	0.50—0.59	0.48—0.49
7b	0.53—0.63	—0.57
13	0.84—0.91	0.28—0.40
16	—0.20	

Reaction of L-*Ascorbic Acid (1) in the Presence of Boron Trifluoride-etherate.* (i) A solution of **1** (5.0 g) in absolute methanol (100 ml) containing boron trifluoride-etherate (5 ml) was refluxed for 10 hr and neutralized with triethylamine (7.5 ml), and then the solvent was removed. The preparative thin-layer chromatography of the residue with Solvent A afforded a mixture syrup of **7a** and **7b** (1.20 g) and crystals of **13** (0.3 g). The further ptc of the mixture syrup with Solvent B yielded **7a** (449 mg) and **7b** (169 mg) in pure states.

7a: mp 167—169°C. $[\alpha]_D^{26}$ +2.7 (*c* 1.031, methanol). CD (methanol) $[\phi]_{251}$ 0, $[\phi]_{226}$ +1351. $IR_{cm^{-1}}^{Nujol}$ 3480, 3390 (OH), 1790 (γ-lactone). Found: C, 44.24; H, 5.42%. Calcd for $C_7H_{10}O_6$: C, 44.21; H, 5.30%. **7b**: mp 94—95°C. $[\alpha]_D^{21.5}$ +73.9 (*c* 1.016, methanol), CD (methanol) $[\phi]_{257}$ 0, $[\phi]_{231}$ −1698, $IR_{cm^{-1}}^{Nujol}$ 3360, 3160 (OH), 1780 (γ-lactone). $IR_{cm^{-1}}^{CHCl_3}$ 3607 (free OH), 3578 (bonded OH). Found: C, 44.47; H, 5.19%. Calcd for $C_7H_{10}O_6$: C, 44.21; H, 5.30%.

(ii) A solution of **1** (2.0 g) in methanol (40 ml) containing boron trifluoride-etherate (2 ml) was refluxed for 15 hr and neutralized with triethylamine, and then the solvent was removed. The residue was washed with acetone. The remaining crystals (702 mg) were identified as **1**. The repeated preparative thin-layer chromatography of the acetone-soluble part with Solvents A and B afforded **1** (377 mg), **7a** (275 mg), **7b** (82 mg), and **13** (103 mg).

Reaction of **7a**. *1) Acetylation*: To a solution of **7a** (4.0 g) in pyridine (20 ml) we added acetic anhydride (20 ml) under cooling, after which the solution was left in a refrigerator overnight. The solution was evaporated to dryness and the residue was recrystallized from ether and petroleum ether. The acetate of **7a** (**8a**) was thus obtained. The yield was 5.68 g. Mp 105—106°C. $[\alpha]_D^{21}$ +58.9 (*c* 1.025, chloroform). CD (methanol) $[\phi]_{250}$ 0, $[\phi]_{216}$ +9100. $IR_{cm^{-1}}^{Nujol}$ 1806, 1740 (C–O), $IR_{cm^{-1}}^{CCl_4}$ 1820, 1760 (C=O). Found: C, 48.37; H, 5.18%. Calcd for $C_{11}H_{14}O_8$: C, 48.18; H, 5.15%.

2) Deacetylation of **8a**: To a solution of **8a** (600 mg) in methanol (12 ml) we added a solution of potassium carbonate (600 mg) in water (3 ml). The solution was left at room temperature for 1 hr, neutralized with Amberlite IR-120 (H^+) (25 ml), and then evaporated to dryness. The preparative thin-layer chromatography of the residue with Solvent B afforded **7a** (373 mg), **7b** (39 mg), and **16** (44 mg).

3) Base-catalyzed Reaction: A solution of potassium carbonate (700 mg) in water (3.5 ml) was added to a solution of **7a** (700 mg) in methanol (14 mg). The solution was allowed to stand at room temperature for 2.5 hr, neutralized with Amberlite IR 120 (H^+) (25 ml), and then evaporated to dryness. The preparative thin-layer chromatography of the residue with Solvent B afforded **7a** (499 mg), **7b** (57 mg), and **16** (67 mg).

4) Acid-catalyzed Reaction: (i) Methanol as a solvent: A solution of **7a** (700 mg) in absolute methanol (14 ml) containing boron trifluoride-etherate (0.7 ml) was refluxed for 15 hr, neutralized with triethylamine (0.5 ml), and then evaporated to dryness. The preparative thin-layer chromatography of the residue with Solvent A afforded **1** (105 mg), **7a** (349 mg), **7b** (22 mg), and **13** (118 mg).

(ii) Ethanol as a solvent: A solution of **7a** (1.0 g) in absolute alcohol (20 ml) containing boron trifluoride-etherate (1.0 ml) was refluxed for 6 hr. The solution was neutralized with triethylamine (1 ml) and then the solvent was removed. The preparative thin-layer chromatography of the residue with a mixture of acetone and chloroform (6: 4, v/v) afforded **1** (47 mg, R_f 0.06), **9** (493 mg, R_f 0.46), and **7a** (211 mg, R_f 0.85). **9**: Mp 144—145.5°C. $[\alpha]_D^{21}$ −2.5 (*c* 1.021, methanol). $IR_{cm^{-1}}^{Nujol}$ 3570, 3450 (OH), 1815 (C=O). Found: C, 47.33; H, 5.96%. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.92%. **14**: Mp 29—29.5°C. $IR_{cm^{-1}}^{CCl_4}$ 1735, 1677 (C=O), C=C), 886 (furan).[15] Found: C, 56.39; H, 4.85%. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80%.

Compound **9** was acetylated in a way similar to that used in the acetylation of **7a**. The acetate of **9** (**10**): syrup. $[\alpha]_D^{20}$ +48.2 (*c* 0.901, chloroform). IR $_{cm^{-1}}^{CCl_4}$ 1815, 5757. Found: C, 50.00; H, 5.60%. Calcd for $C_{12}H_{12}O_8$: C, 50.02; H, 5.61%.

Reaction of **7b**. *1) Acetylation*: Acetic anhydride (5 ml) was added to a solution of **7b** (1.0 g) in pyridine (5 ml) under cooling. The solution was left overnight in a refrigerator and then evaporated to dryness. The recrystallization of the residue from acetone and ether gave **8b** (1.2 g). Mp 98.5—100°C. $[\alpha]_D^{26}$ +155.8 (*c* 1.053, chloroform). CD (methanol) $[\phi]_{265}$ 0, $[\phi]_{223}$ +4824, $[\phi]_{205}$ +2396. IR $_{cm^{-1}}^{Nujol}$ 1788, 1750 (C=O). IR $_{cm^{-1}}^{CCl_4}$ 1810, 1760 (C=O). Found: C, 47.99; H, 5.34%. Calcd for $C_{11}H_{14}O_8$: C, 48.18; H, 5.15%.

2) Deacetylation of **8b**: A solution of potassium carbonate (1.0 g) in water (5 ml) was added to a solution of **8b** (1.0 g) in methanol (20 ml). The mixture was allowed to stand at room temperature for 1 hr and then neutralized with Amberlite IR 120 (H^+) (40 ml). After the removal of the solvent, the residue was fractionated by ptc (Solvent A) to give 128 mg of **7a**, 261 mg of **7b**, and 20 mg of **16**.

3) Acid-catalyzed Reaction: A solution of **7b** (700 mg) in absolute methanol (14 ml) containing boron trifluoride-etherate (0.7 ml) was refluxed for 15 hr and then worked up in a way similar to that used for **7a** (Reaction of **7a**, *4*). L-Ascorbic acid **1** (157 mg), **7a** (98 mg), **7b** (85 mg, and **13** (74 mg) were thus obtained.

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