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Note

The reaction of 1,1-dibromopinacolone with L-ascorbic acid

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We were interested in preparing an unknown 2,3-acetal (**2**) of L-ascorbic acid. This acetal would contain the 1,3-dioxole ring-system, which was first synthesized by Field[1] in 1961. Synthesis of 5,6-acetals of L-ascorbic acid is straightforward[2], but, because of the acidity of the 2,3-hydroxyl groups, a different approach was necessary for preparing such acetals. In 1945, Vestling prepared the 2,3-diphenacyl derivative of L-ascorbic acid by treating ascorbic acid with phenacyl bromide in aqueous sodium hydrogen carbonate[3]. It appeared reasonable to prepare a 2,3-acetal by treating L-ascorbic acid with a suitable *gem*-dibromide.

However, when ascorbic acid reacted with 1,1-dibromopinacolone, an open-chain compound, 3-*O*-(3,3-dimethyl-2-oxobutyl)ascorbate (**3**) was isolated. The structure assigned to **3** is based on spectral data, pK_a, and elemental analyses. The ^1H-n.m.r. spectrum shows a sharp singlet at 5.3 p.p.m. integrating for two protons. The ^{13}C-n.m.r. spectrum supports the presence of an isolated methylene group and also shows the carbon skeleton of L-ascorbic acid to be intact (Table I). The chemical shifts of the pinacolone portion of the molecule are similar to values reported in the literature. It is difficult to rationalize any structure, other than the pinacolone-alkylated ascorbic acid, which could accommodate a methylene group having no adjacent protons.

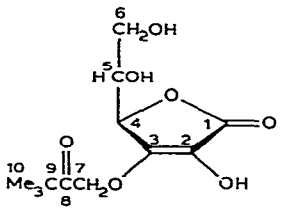
The presence of 3 hydroxyl groups was confirmed by treating **3** with excess benzoyl chloride to give **4**.

The u.v. spectrum of **3** shows one acidic hydroxyl group. In aqueous solution, **3** shows a maximum of 244 nm which shifts to 272 nm in base. The same chromophore in **3** is present in 3-*O*-methyl L-ascorbic acid, whose u.v. spectrum is similar to that of **3** showing a maximum at 245 nm which shifts to 275 nm in basic solution[4]. The 2-methyl ether was not available for comparison. The 2,3-di-methyl ether has a u.v. maximum[5] at 232.5 nm.

The pK_a data confirmed that alkylation was at HO-3. The pK_a of **3** (7.4) was determined by observing the u.v. spectrum in different buffers[6]. The pK_a of 3-*O*-methylascorbate is[7] 7.8. The pK_a of HO-3 of L-ascorbic acid has been measured and was found[8] to be 4.25.

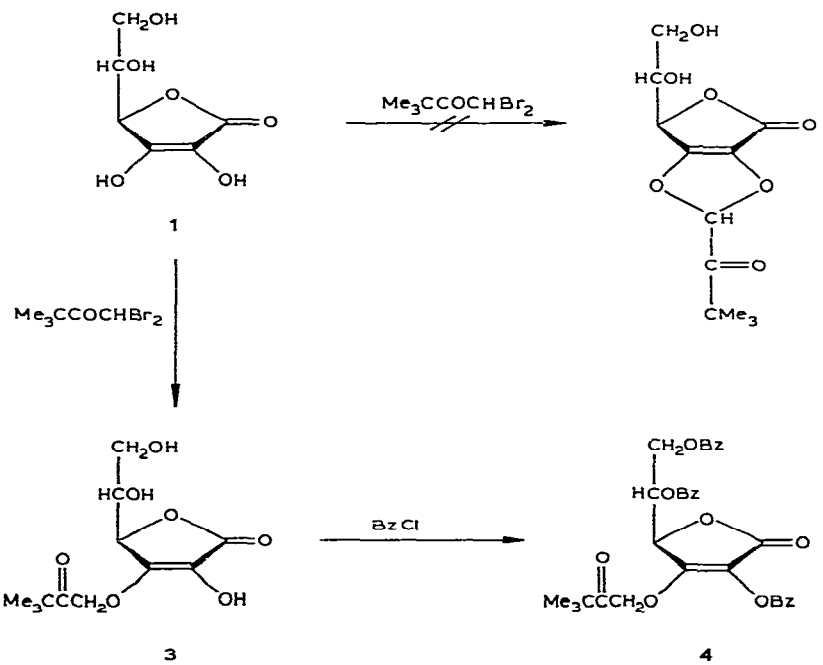
TABLE I

^{13}C-N.M.R. CHEMICAL-SHIFT ASSIGNMENTS



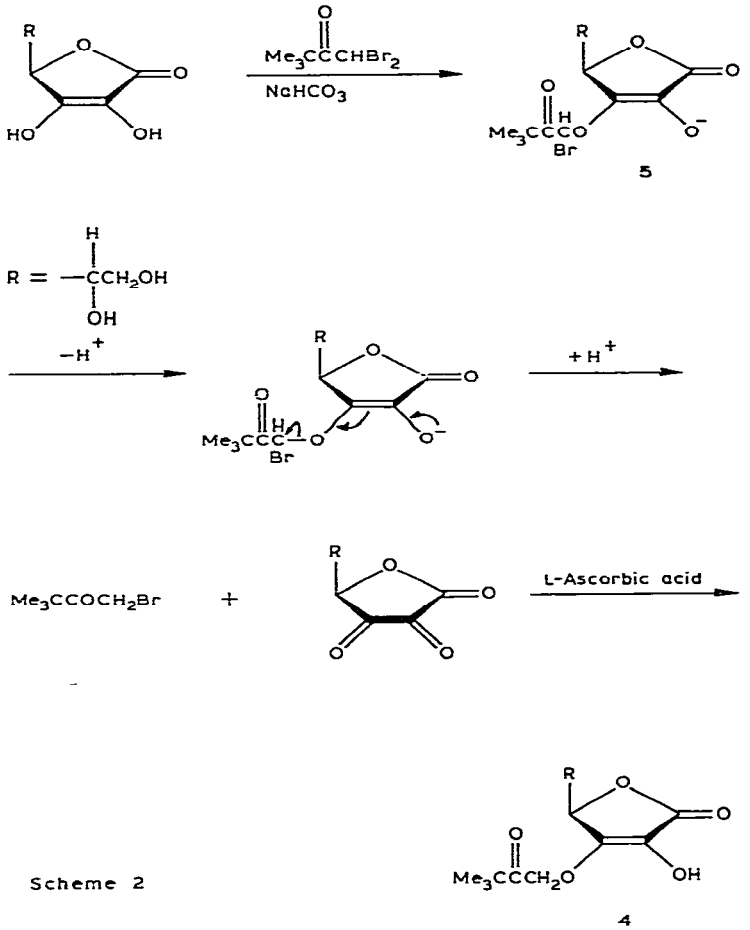
Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*	*C-10*
3-*O*-Methyl-L-ascorbate[7]	174.3	119.5	155.7	76.9	70.0	63.0				
Compound 4[a]	170.1	119.6	149.6	74.6	68.8	61.6	70.8	195.6	42.1	26.0
Pinacolone[9]								212.6	44.2	26.5
	^{13}C-H Coupling Constants (Hz)									
				148 (d)	142 (d)[b]	146 (t)[b]	147 (t)			

[a]Shifts are relative to internal Me_4Si standard. Spectra were obtained from a 25% (w/w) solution of sample in $(CD_3)_2SO$. The splitting pattern of the off-resonance decoupled spectrum of **4** support the chemical-shift assignments. [b]With fine structure.



Scheme 1

Mechanism. — As the product contains no bromine, the mechanism of the reaction must involve a reduction step. The proposed mechanism involves alkylation of L-ascorbic acid by 1,1-dibromopinacolone to give the bromoalkylated intermediate **5** (Scheme 2). This intermediate undergoes an intramolecular redox reaction, generating dehydroascorbic acid and 1-bromopinacolone. As the reaction employed a large excess of L-ascorbic acid, the bromopinacolone alkylates L-ascorbic acid to give the product **4**.



Scheme 2. Proposed mechanism for the formation of 3-*O*-(3,3-dimethyl-2-oxobutyl)-L-ascorbate.

This mechanism is supported by the isolation of 1-bromopinacolone and dehydroascorbic acid, the latter being trapped with *o*-phenylenediamine. Monitoring the reaction by gas chromatography reveals fairly rapid disappearance of 1,1-dibromopinacolone and the appearance of 1-bromopinacolone (Table II). The rapid initial reaction slowed, perhaps because of the increased acidity generated as the reaction proceeded. No significant amount of pinacolone could be found.

TABLE II

GAS-CHROMATOGRAPHIC ANALYSES OF THE REACTION MIXTURE

Time (min)	0.0	0.5	1.0	2.0	6.0	15	30
1-Bromopinacolone[a]	0.0	1.15	1.27	1.25	1.20	0.61	0.15
1,1-Dibromopinacolone[a]	1.68	0.51	0.44	0.41	0.25	0.00	0.00

[a]Concentration in mmol of product and reactant in mixture. No significant amount of pinacolone could be found.

An unidentified compound was detected by g.l.c. in the 15- and 30-min aliquots. It is believed this compound is a hydrolysis product of 1-bromopinacolone. The same compound appears when 1-bromopinacolone is boiled under reflux in aqueous isopropyl alcohol buffered to pH 6.8 with phosphate.

EXPERIMENTAL

General methods. — Melting points were determined on a Thomas–Hoover capillary point apparatus and are uncorrected. ^{1}H-n.m.r. spectra were taken with a Varian EM-306A spectrometer and ^{13}C-n.m.r. spectra with a Varian CFT-20 spectrometer. I.r. spectra were recorded with a Perkin–Elmer 521 and u.v. spectra with a Varian Super Scan 3. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. EM Reagents 0.2-mm silica gel sheets, No. 5717 were used for t.l.c.

3-O-(3,3-Dimethyl-2-oxobutyl)-L-ascorbate (3). — Into a 500-mL round-bottom flask were added 28 g (0.33 mol) of sodium hydrogencarbonate and 250 mL of water. Nitrogen was bubbled through for 30 min and 55 g (0.31 mol) of L-ascorbic acid was added slowly. 1,1-Dibromopinacolone (5.05 g, 20 mmol) was added, followed by 100 mL of isopropyl alcohol. After boiling for 30 min under reflux, the solvent was removed with a rotary evaporatory at a bath temperature of 50°. The last traces of water were azeotroped off with toluene.

The oily residue was extracted with acetone (6 × 100 mL). After the second extraction, the oil solidified. The combined acetone fractions were dried (calcium chloride) and evaporated. The resultant brown oil was dissolved in dry ether, and petroleum ether (b.p. 35–55°) was added until the solution became slightly cloudy. Refrigeration overnight gave 2.0 g (36%) of crude product. T.l.c. (ethyl acetate) showed one major component. Recrystallization from dry ether–petroleum ether and then from ethyl acetate–petroleum ether gave a white solid, m.p. 144.5–146°; ν_{max}^{Nujol} 3415, 3470, 1760, 1710, and 1690 cm^{-1}; $\lambda_{max}^{H_2O}$ 244 nm (ε 8000), λ_{max} (1.0 mM NaOH) 272 nm; n.m.r. (D_2O): δ 1.0 (9 H, s), 3.5–4.2 (3 H, m), 4.55 (DHO), 4.8 (1 H, d), 5.27 (2 H, s); $[\alpha]_D^{20}$ +24.7° (*c* 8.72, ethanol).

Anal. Calc. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.61. Found (average of two determinations): C, 52.59; H, 6.60.

2,5,6-Tri-O-benzoyl-3-O-(3,3-dimethyl-2-oxobutyl)-L-ascorbate (**4**). — Into a 50-mL Erlenmeyer flask were added 0.60 g (22 mmol) of 3-*O*-(3,3-dimethyl-2-butanonyl)-L-ascorbate (**3**), 1.5 g (11 mmol) of benzoyl chloride, and 8 mL of pyridine. After stirring for 2 h in an ice bath, ~25 mL of water was added, whereupon an oil separated, which was washed several times with water, dissolved in ethanol, and then water was added to turbidity. A semi-solid that separated after ~18 h was crystallized from ethanol to give 0.97 g (75% yield) of product, m.p. 108–120°. Recrystallization from 7:1 cyclohexane–ethyl acetate, gave 0.7 g (54%) of product, m.p. 129–130.5°: n.m.r. ($CDCl_3$): δ 0.90 (9 H, s), 4.81 (2 H, d), 5.01 (2 H, s), 5.37 (1 H, d), 5.87 (1 H, m), and 7.3–8.3 (15 H, m): $[\alpha]_D^{20}$ −30° (*c* 0.74, 1:1 ethanol–acetone).

Anal. Calc. for $C_{33}H_{30}O_{10}$: C, 67.57; H, 5.16. Found (average of two determinations): C, 67.34; H, 5.27.

Analyses of the reaction by gas chromatography. — The reaction was performed as just described, except that 1,1-dibromopinacolone and cyclohexanone (internal standard) were dissolved in isopropyl alcohol and added when the temperature reached 85°. Aliquots were removed at timed intervals and cooled in an ice–salt bath. The samples were analyzed by g.l.c as soon as possible in an FM Laboratory Chromatograph. Model 700 programmed from 60–200° at 20°/min on a 6-ft column of 10% SE-30 on Chromosorb W 80 (100 mesh).

Trapping of dehydroascorbic acid with o-phenylenediamine. — To a 500-mL round bottom flask equipped with a magnetic stirrer, condenser, gas inlet tube, and thermometer, was added 100 mL of water. After bubbling nitrogen through for 30 min, 22.0 g (0.125 mol) of L-ascorbic acid and 11.2 g (0.133 mol) of sodium hydrogencarbonate were added. The temperature was raised to 85° and 2.0 g (78 mmol) of 1,1-dibromopinacolone dissolved in 40 mL of isopropyl alcohol was added. The reaction was allowed to proceed for 30 sec and was then quenched by placing the vessel in an ice–salt bath. To prevent basic hydrolysis of dehydroascorbic acid, 10 mL of acetic acid dissolved in 30 mL of dichloromethane was added. Nitrogen was bubbled through the mixture as it was stirred and cooled to 20°.

The organic layer was separated and the aqueous solution extracted with 30 mL of dichloromethane to remove unreacted bromo compounds. The aqueous layer was added to 1.2 g (11 mmol) of *o*-phenylenediamine in 1.0 mL of acetic acid. The mixture was stirred for 90 min at room temperature and then extracted with chloroform (8 × 30 mL). The extract was dried (sodium sulfate) and evaporated to a viscous oil. Acetic acid (5 mL, 0.1M) was added and, after cooling for 4 h in an ice bath, 0.44 g of crude solid was collected. The solid was recrystallized from methanol and then from acetone, m.p. 170–172° (dec.), lit.[7] 177°. T.l.c. (ethyl acetate) showed a trace of unreacted *o*-phenylenediamine in the sample.

Reaction of dehydroascorbic acid with an excess of o-phenylenediamine. — Into a 50-mL Erlenmeyer flask was added 0.20 g (0.91 mmol) of dehydroascorbic acid–methanol complex, 0.50 g (4.6 mmol) of *o*-phenylenediamine, 0.50 g (8.3 mmol) of acetic acid, and 10 mL of water. After stirring for 10 min at room temperature, a solid separated, which was collected after one h and recrystallized from methanol

to give 0.21 g of product, m.p. 175° (dec.), (lit[7] 177°). (The m.p. was sensitive to rate of heating).

Comparison of o-phenylenediamine–dehydroascorbic acid adduct isolated from reaction mixture with adduct synthesized directly. — T.l.c. showed the *o*-phenylenediamine–dehydroascorbic acid adduct obtained by trapping and the adduct synthesized directly to be identical; R_F (ethyl acetate) 0.11, (acetone) 0.67. Mixing one compound with the other did not give a distorted spot.

The m.p. values were sensitive to the rate of heating. Melting points obtained at a "moderate rate" of heating were: synthesized adduct 175° (dec.); trapped adduct 170–172° dec., and mixed adducts 174–175° (dec.). Melting points obtained at a "low rate" of heating were: synthesized adduct 171–172° (dec.), trapped adduct 168–169° (dec.), and mixed adducts 169–170° (dec.).

The u.v. spectra of the two adducts were superposable and showed absorbances at 205, 242, and 300–325 nm with the same relative intensities.

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