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Note

Reactions of 2,3-diamino-2,3-dideoxy-L-ascorbic acid

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Dehydro-L-ascorbic acid (L-*threo*-2,3-hexodiulosono-1,4-lactone), obtained by mild oxidation of L-ascorbic acid, is considered an excellent precursor for the synthesis of many nitrogen heterocycles[1–6] through its reaction with hydrazines or diamines. In this connection, the synthesis of pyrazine and imidazoline derivatives of dehydro-L-ascorbic acid, starting from the title compound, is described.

Catalytic hydrogenation of dehydro-L-ascorbic acid bis(phenylhydrazone) [L-*threo*-2,3-hexodiulosono-1,4-lactone 2,3-bis(phenylhydrazone)] (**1**) with hydrogen in the presence of palladium-on-charcoal has been found to yield 2,3-diamino-2,3-dideoxy-L-ascorbic acid[7,8] (**2**). Treatment of **2** with phenyl- or with naphthalen-2-ylglyoxal afforded a crystalline, bicyclic pyrazine derivative designated 2-arylpyrazine-5-(L-*threo*-glycerol-1-yl)-6-carboxylic acid 6,5[1]-lactone (**3** and **4**). The infrared spectra of compounds **3** and **4** showed the lactone carbonyl band at 1780 cm^{-1}, and the hydroxyl band at 3460 and 3450 cm^{-1}, respectively, and there was no NH absorption. The mass spectrum of compound **3** (see Fig. 1) showed the molecular-ion peak (which is the base peak) at *m/z* 272 in agreement with structure **3**. This was followed by a peak at *m/z* 254 resulting from the elimination of a molecule of water from the side chain, and a fragment at *m/z* 211 due to the loss of the side chain.

Although the interaction of the phenyl dicarbonyl compound and diamine **2** might be anticipated to afford two products (**3**, R^1 = Ph, R^2 = H) and (**3**, R^1 = H, and R^2 = Ph), according to whether the aldehyde group reacts with the 2- or the 3-amino group, such a mixture was not observed. It seems that the amino group on C-2 (being the least deactivated by the lactone carbonyl group) reacts with the (more active) aldehyde group, giving compounds **3** and **4** (R^1 = aryl, and R^2 = H).

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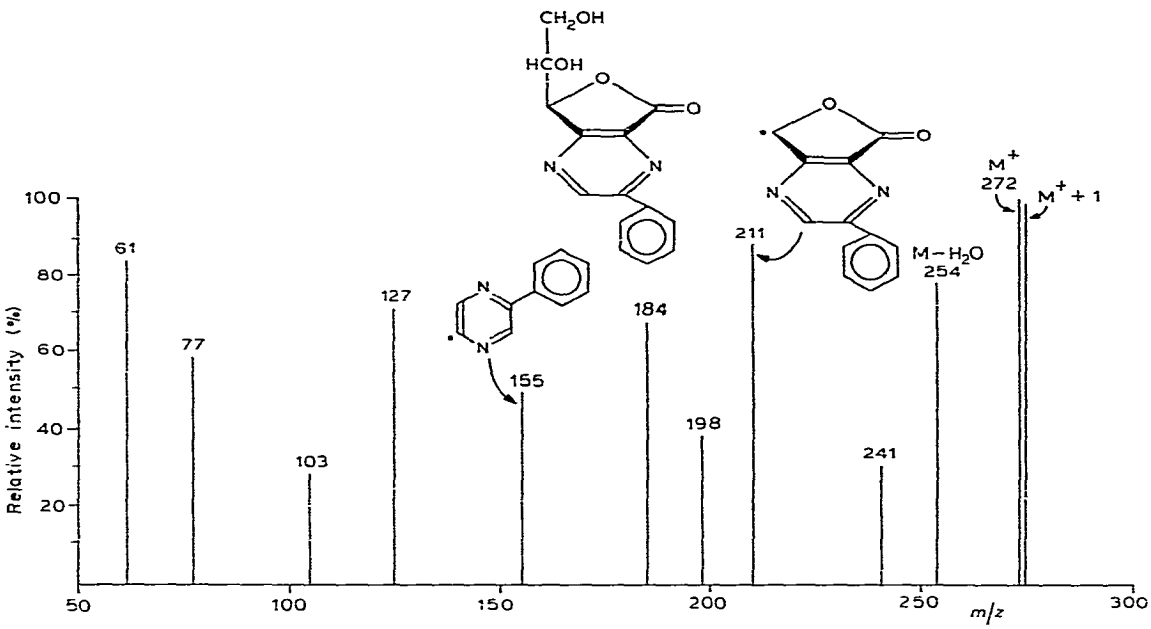


Fig. 1. Mass spectrum of compound 3.

Acetylation of compounds **3** and **4** with boiling acetic anhydride or with acetic anhydride–pyridine, gave 2-arylpyrazine-5-(L-*threo*-2,3-di-*O*-diacetylglycerol-1-yl)-6-carboxylic acid 6,5[1]-lactone (**5** and **6**). The i.r. spectra showed the lactone carbonyl group at 1780 cm^{-1}, and the ester band at 1740 cm^{-1}. The n.m.r. spectrum of compound **6** in chloroform-*d* showed two singlets, of three-proton intensity each, at δ 1.89 and 2.12 (two acetyl groups), two protons centered at δ 4.56 (due to the methylene group at C-3), a multiplet at δ 5.73 assigned to the C-2 methine proton, a doublet at δ 5.89 (J 1.5 Hz) due to the C-1 methine proton, and a singlet at δ 7.26 (due to the heterocyclic proton). The protons of the naphthalenyl group appeared at δ 7.57–8.69 as a multiplet.

Reaction of the diamine **2** with benzaldehyde afforded bicyclic 2-arylimidazolines[8]; we have now extended this reaction to substituted benzaldehydes, as well as to some heterocyclic aldehydes, to give compounds **7** (see Table I). The infrared spectra of compounds **7** showed the OH band at 3500–3400 cm^{-1}, the NH band at 3200–3100 cm^{-1}, and the lactone carbonyl band at 1710–1700 cm^{-1}. Acetylation of compounds **7** with acetic anhydride–pyridine afforded di-*O*-acetyl derivatives (**8**) that failed to crystallize, but that gave correct elemental analyses after purification by preparative t.l.c. The n.m.r. spectra of the acetates showed two distinct *O*-acetyl groups between δ 2.0 and 2.2, in addition to the expected protons (see Table II).

On reaction of diamine **2** with anhydrous formic acid, it did not give the imidazole (**11**) expected, but, instead, gave the diformyl derivative (**9**), on the basis of elemental analysis, and i.r.- and mass-spectral data. Compound **9** showed carbonyl

TABLE I

MICROANALYTICAL AND I.R. DATA FOR IMIDAZOLINE DERIVATIVES (7)

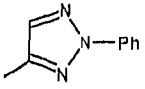
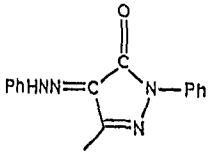
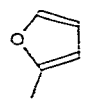
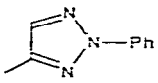
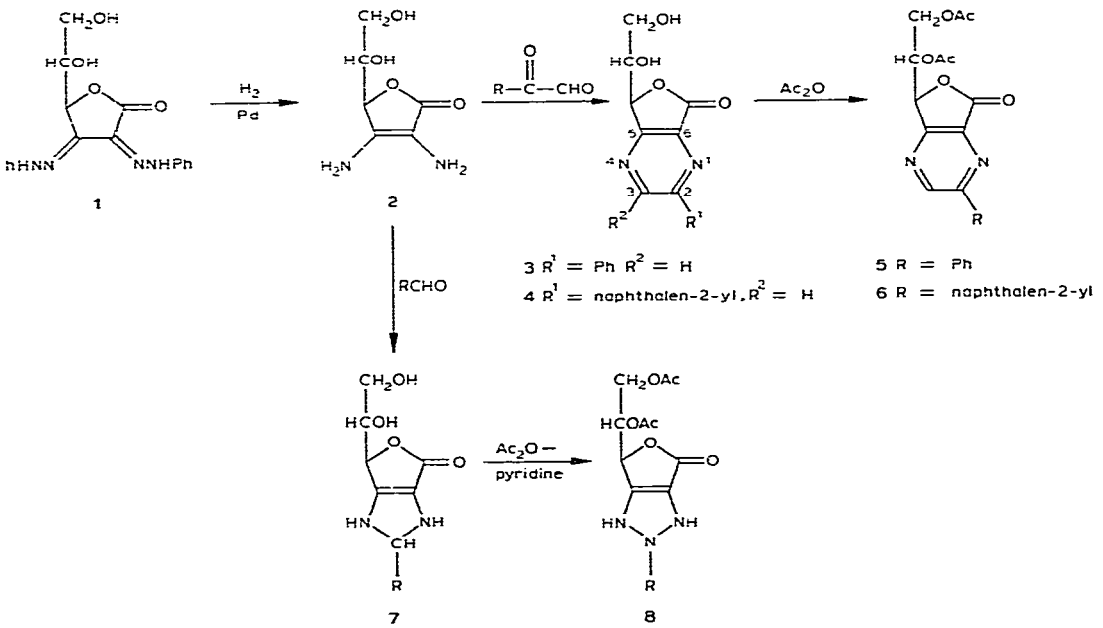
R	*M.p.* *(degrees)*	*Yield* *(%)*	*Molecular formula*	*Analyses*				*ν (cm⁻¹)*		
				C	*H*	*Hal.*	*N*	*CO*	*NH*	*OH*
C_6H_4Br-*p*	228–230	84	$C_{13}H_{13}BrN_2O_4$	Calc.: 45.77	3.84	23.42	8.20	1700	3200	3450
				Found: 45.61	3.99	23.10	8.22			
C_6H_4OMe-*p*	220–222	85	$C_{14}H_{16}N_2O_5$	Calc.: 57.53	5.51		9.57	1710	3250	3450
				Found: 57.16	5.50		9.42			
$C_6H_4CH_3$-*p*	221–223	80	$C_{14}H_{16}N_2O_4$	Calc.: 60.86	5.84		10.14	1700	3200	3430
				Found: 60.43	5.81		10.13			
$C_6H_4NO_2$-*o*	254–256	78	$C_{13}H_{13}N_3O_6$	Calc.: 50.81	4.23		13.68	1710	3180	3450
				Found: 50.79	4.36		13.59			
2-Pyridyl	241–243	66	$C_{12}H_{13}N_3O_4$	Calc.: 54.75	4.98		15.95	1700	3200	3430
				Found: 54.38	3.71		15.69			
2-Furyl	217–219	80	$C_{11}H_{12}N_2O_5$	Calc.: 52.28	4.80		11.11	1700	3220	3450
				Found: 52.35	4.89		11.04			
	228–230	72	$C_{15}H_{15}N_5O_4$	Calc.: 54.71	4.59		21.27	1700	3210	3450
				Found: 54.58	5.07		21.39			
	200–202	76	$C_{22}H_{20}N_6O_5$	Calc.: 58.92	4.50		18.74	1700	3200	3400
				Found: 58.60	4.80		18.51			

TABLE II

MICROANALYTICAL, N.M.R., AND I.R. DATA FOR ACETATES (8)

R	Molecular formula	Analyses	C	H	N	δ (p.p.m.) O-Acetyl	ν (cm⁻¹) NH	OAc	CO
	$C_{15}H_{16}N_2O_7$	Calc.:	53.57	4.79	8.32	2.02, 2.16	3150	1740	1700
		Found:	53.32	4.46	8.68				
	$C_{19}H_{19}N_5O_6$	Calc.:	55.21	4.63	16.93	2.04, 2.18	3180	1740	1700
		Found:	55.36	4.21	16.60				



absorption at 1700 cm^{-1} (lactone) and hydroxyl absorption at 3450 cm^{-1}, in addition to an NH band at 3180 cm^{-1}. Its elemental analysis agreed with the molecular formula $C_8H_{10}N_2O_6$. The mass spectrum of **9** (see Fig. 2) showed a strong, molecular-ion peak at *m/z* 230, followed by a peak at *m/z* 202 due to elimination of CO. The spectrum also showed a strong peak at *m/z* 174 due to the elimination of 2 CO.

Acetylation of compound **9** with acetic anhydride–pyridine afforded a di-*O*-acetyl derivative assigned as 5,6-di-*O*-acetyl-2,3-dideoxy-2,3-diformamido-L-ascorbic acid (**10**). The n.m.r. spectrum of **10** in chloroform-*d* showed two singlets, of three-

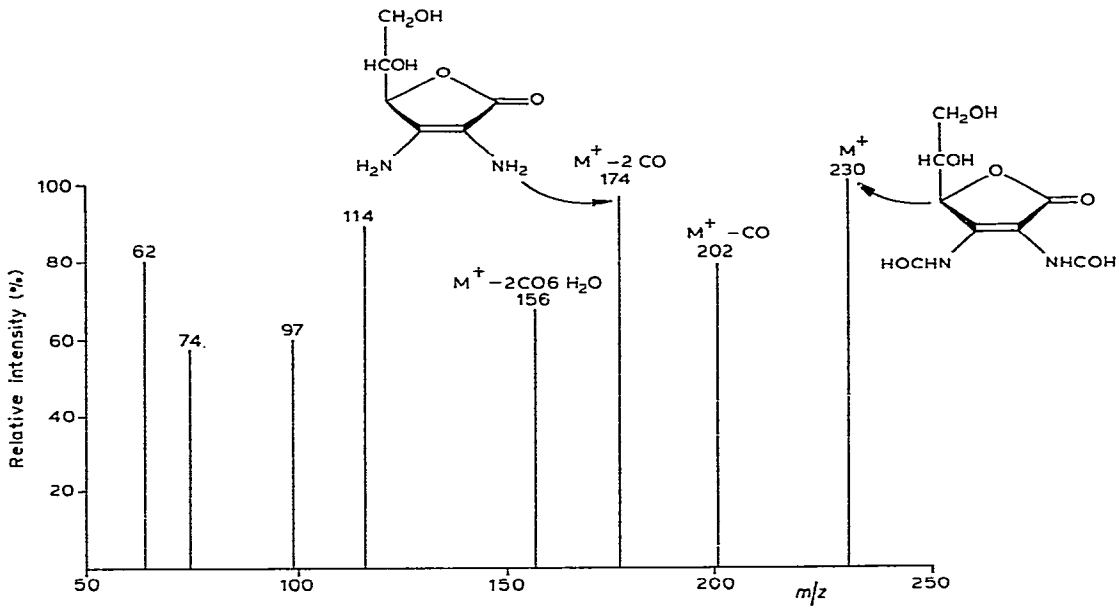
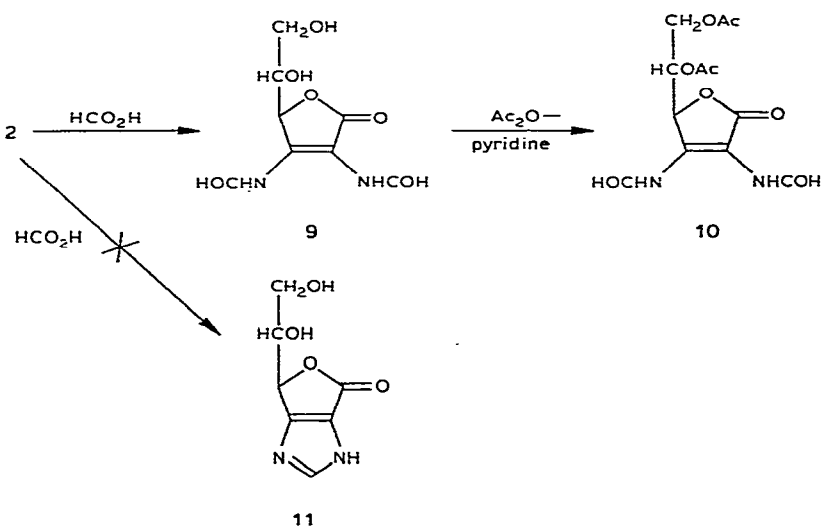


Fig. 2. Mass spectrum of compound 9.

proton intensity, at δ 2.06 and 2.12 (due to two acetyl groups), a two-proton multiplet, at δ 4.42, for a methylene group (C-6), a one-proton multiplet at δ 5.0 (H-5), and a one-proton doublet at δ 5.56 (H-4). In addition, there were two singlets, each of one-proton intensity, at δ 5.92 and 6.12 (2 NH), and two singlets at δ 7.5 and 7.8 (2 formyl protons).



EXPERIMENTAL

General methods. — Melting points were determined with a Kofler-block apparatus and are uncorrected. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt, and in the Service Central d'Analyse du CNRS FRANCE. I.r. spectra were recorded with a Unicam sp. 1025 spectrophotometer for potassium bromide pellets. N.m.r. spectra were recorded with Perkin–Elmer R 12B and CAMECA 250-MHz n.m.r. spectrometers, and mass spectra with an LKB model 2091 mass spectrometer.

*2,3-Diamino-2,3-dideoxy-*L*-ascorbic acid* (**2**). — L-*threo*-2,3-Hexodiulosono-1,4-lactone 2,3-bis(phenylhydrazone)[9–11] (3.54 g, 0.01 mol) was dissolved in absolute ethanol (300 mL) and hydrogenated in the presence of 10% palladium-on-charcoal catalyst (1 g) until no more hydrogen was absorbed. The suspension was filtered, and the filtrate evaporated to dryness under diminished pressure. Water (50 mL) was added, and the solution was washed with ether (3 × 40 mL), to remove aniline, and evaporated under diminished pressure to a thin syrup which was dissolved in ethanol (10 mL), treated with 1:1 dry ether–petroleum ether (100 mL), and kept overnight at 0°. The rose-colored solid that separated out was filtered off, washed with ethanol, and dried. It was recrystallized from ethanol, to give faintly colored prisms, m.p. 138–140° (lit.[8] m.p. 138–140°).

5-(L-threo-*Glycerol-1-yl)-2-phenylpyrazine-6-carboxylic acid 6,5*^{1}*-lactone* (**3**). — A solution of compound **2** (1.74 g, 0.01 mol) in ethanol (30 mL) and phenylglyoxal hydrate (1.52 g, 0.01 mol) in ethanol (30 mL) containing acetic acid (6 mL) was boiled under reflux for 3 h, and concentrated to a small volume. The solid that separated on cooling was filtered off, washed with ethanol and ether, and dried (yield 1.2 g). Compound **3** was recrystallized from ethanol, to give faintly colored prisms, m.p. 189–191°; ν_{max}^{KBr} 3450 (OH) and 1780 cm^{-1} (lactone C=O).

Anal. Calc. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.63; H, 4.43; N, 10.24.

5-(L-threo-*Glycerol-1-yl)-2-naphthalen-2-ylpyrazine-6-carboxylic acid 6,5*^{1}*-lactone* (**4**). — A solution of compound **2** (1.74 g, 0.01 mol) in ethanol (40 mL) and naphthalen-2-ylglyoxal hydrate (2.01 g, 0.01 mol) in ethanol (50 mL) containing glacial acetic acid (6 mL) was boiled under reflux for 10 h. The solid that separated on cooling was filtered off, washed with ethanol and ether, and dried (yield 1.1 g). Compound **4** was recrystallized from ethanol to give colorless prisms, m.p. 224–225°; ν_{max}^{KBr} 3460 (OH) and 1780 cm^{-1} (lactone C=O). It was soluble in acetone, sparingly soluble in methanol or ethanol, and insoluble in water.

Anal. Calc. for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.64; H, 4.35; N, 8.44.

5-(L-threo-*2,3-Di-*O*-acetylglycerol-1-yl)-2-phenylpyrazine-6-carboxylic acid 6,5*^{1}*-lactone* (**5**). — A solution of compound **3** (0.1 g) in dry pyridine (1 mL) was treated with acetic anhydride (5 mL), and kept overnight at room temperature.

The mixture was then poured onto crushed ice. Compound **5** was obtained as a syrup; ν_{max}^{KBr} 1780 (lactone C=O) and 1740 cm^{-1} (OAc).

Anal. Calc. for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.52; N, 7.85. Found: C, 60.36; H, 4.32; N, 7.71.

*5-(*L-threo-*2,3-Di-*O-*acetylglycerol-1-yl)-2-naphthalen-2-ylpyrazine-6-carboxylic acid 6,5*^{1}*-lactone* (**6**). — A suspension of compound **4** (0.1 g) in acetic anhydride (10 mL) was boiled under reflux for 30 min. The mixture was poured onto crushed ice, and the solid that separated out was filtered off, washed with water and ethanol, and dried (yield 60 mg). Compound **6** was recrystallized from ethanol to give colorless needles, m.p. 162–164°; ν_{max}^{KBr} 1780 (lactone C=O) and 1740 cm^{-1} (OAc).

Anal. Calc. for $C_{22}H_{18}N_2O_6$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.56; H, 4.37; N, 6.77.

Imidazolines (**7**). — A solution of compound **2** (0.04 mol) and the substituted benzaldehyde (0.04 mol) in 1:1 ethanol–water containing a few drops of acetic acid was boiled for 1 h on a steam bath. The solid that separated out on cooling was filtered off, washed successively with water, ethanol, and ether, and dried; each product was recrystallized from ethanol, to give pale-yellow needles (except for the product from *o*-nitrobenzaldehyde, which was red, and for the product from the pyrazolone aldehyde, which was orange). Melting points, yields, formulas, analyses, and infrared data are listed in Table I.

Acetylation of the imidazoline derivatives. — A solution of each imidazoline (**7**; 0.1 g) in dry pyridine (10 mL) was treated with acetic anhydride (5 mL), kept overnight at room temperature, and the mixture poured onto crushed ice. The resulting solution was evaporated under diminished pressure to a thin syrup, which was dissolved in chloroform (30 mL), and the solution washed with dilute sodium hydrogencarbonate, and evaporated. Samples of the acetates (**8**) for analysis were obtained as syrups by preparative t.l.c. on silica gel with 3:1 cyclohexane–methanol as the eluant. Molecular formulas, microanalyses, and n.m.r. and i.r. data are listed in Table II.

*2,3-Dideoxy-2,3-diformamido-*L-*ascorbic acid* (**9**). — A solution of compound **2** (174 mg, 1 mmol) in anhydrous formic acid (10 mL) was heated for 4 h at 100°, and evaporated under diminished pressure to a thin syrup that crystallized on adding ethanol. The solid that separated out was filtered off, washed with ethanol, and ether, and dried (yield 150 mg, 65%). Compound **9** crystallized from ethanol in colorless prisms, m.p. 201–203°; ν_{max}^{KBr} 3450 (OH), 3150 (NH), and 1700 cm^{-1} (lactone).

Anal. Calc. for $C_8H_{10}N_2O_6$: C, 41.74; H, 4.37; N, 12.16. Found: C, 41.52; H, 4.80; N, 12.70.

*5,6-Di-*O*-acetyl-2,3-dideoxy-2,3-diformamido-*L-*ascorbic acid* (**10**). — A solution of compound **9** (0.1 g) in dry pyridine (10 mL) was treated with acetic anhydride (5 mL), kept overnight at room temperature, and the mixture poured onto crushed ice. Compound **10** was obtained as a syrup; ν_{max}^{KBr} 3150 (NH), 1740 (OAc), and 1700 cm^{-1} (lactone C=O).

Anal. Calc. for $C_{12}H_{14}N_2O_8$: C, 45.85; H, 4.49; N, 8.91. Found: C, 46.02; H, 4.71; N, 9.37.

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