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SOME STUDIES ON DEHYDRO-D-ASCORBIC ACID 2-(PHENYLHYDRAZONE)

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ABSTRACT

Reaction of hydroxylamine with D-*erythro*-2,3-hexodiulosono-1,4-lactone 2-(phenylhydrazone) (**2**) gave the 3-oxime 2-(phenylhydrazone) (**3**). On boiling with acetic anhydride, **3** gave 4-(D-*erythro*-2,3-diacetoxy-1-hydroxypropyl)-2-phenyl-1,2,3-triazole-5-carboxylic acid 5,1′-lactone. Compound **3** was also converted into the related, unacetylated 2-(*p*-bromophenyl)triazole with bromine. Treatment of **2** with boiling acetic anhydride gave an optically inactive, olefinic compound, assigned the structure 4-(2-acetoxyethylidene)-4-hydroxy-2,3-dioxobutano-1,4-lactone 2-(phenylhydrazone). The 2-(phenylhydrazone) **2** gave the corresponding 2,3-bis(phenylhydrazone) on condensation with phenylhydrazine.

DISCUSSION

In previous publications, we dealt with reactions of dehydro-L-ascorbic acid phenylhydrazones[1–3] and analogs[4]. We now describe the synthesis and some reactions of dehydro-D-ascorbic acid 2-mono(phenylhydrazone) [D-*erythro*-2,3-hexodiulosono-1,4-lactone 2-(phenylhydrazone)] (**2**). The latter was prepared by applying the procedure used by Micheel and Mittag[5] for the synthesis of its 5-epimer, L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(phenylhydrazone) (**12**). The infrared absorption spectrum of **2** showed two carbonyl absorptions, at 1735 and 1670 cm^{-1}, due to the lactone group and the ketone group, respectively. The mass spectrum of **2** showed the molecular-ion peak at *m/e* 264, followed by a peak at *m/e* 246 resulting from the elimination of a molecule of water from the side chain. The fragment at *m/e* 204 is due to the loss of the side chain, and that at *m/e* 127 is due the loss of the side chain together with the phenyl group. The spectrum showed fragments at *m/e* 118 $(C{=}N\text{-}NH\text{-}Ph)^+$, 105 $(PhNN)^+$, 92 $(PhNH)^+$, and 77 (Ph).

When compound **2** was treated with hydroxylamine, D-*erythro*-2,3-hexodiulosono-1,4-lactone 3-oxime 2-(phenylhydrazone) (**3**) was obtained. Dehydrative cyclization and concomitant acetylation of **3** with boiling acetic anhydride gave 4-(D-*erythro*-2,3-diacetoxy-1-hydroxypropyl)-2-phenyl-1,2,3-triazole-5-carboxylic

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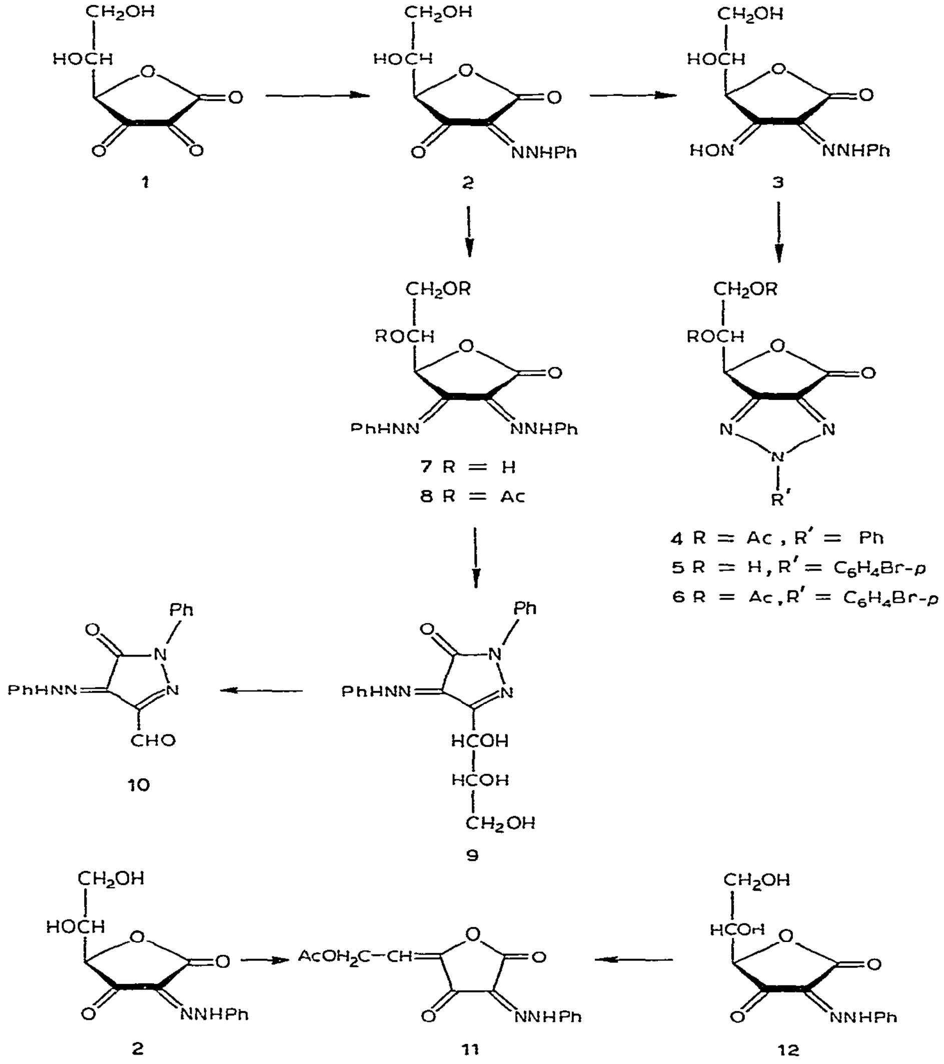
acid 5,1′-lactone (**4**); this reaction is similar to that conducted[6] on the 5-epimer of **3**. The n.m.r. spectrum of **4** showed two *O*-acetyl protons at δ 2.05 and 2.17, two protons centered at δ 4.8 (due to the methylene group at C-6), a multiplet at δ 5.2 assigned to the C-5 methine proton, and a doublet at δ 5.7 (*J* 4 Hz) due to the C-4 methine proton. The protons of the phenyl group appeared at δ 7.5–8.2.

Treatment of compound **3** with bromine-water caused its cyclization, to give 2-(*p*-bromophenyl)-4-(D-*erythro*-1,2,3-trihydroxypropyl)-1,2,3-triazole-5-carboxylic acid 5,1′-lactone (**5**). Acetylation of **5** with boiling acetic anhydride afforded the diacetate **6**; the same product was obtained by reaction of **4** with bromine-water.

When treated with phenylhydrazine, compound **2** was converted into the red bis(phenylhydrazone) (**7**). Reaction of **7** with hydrazine hydrate, or alkali, followed



by acidification, gave 3-(D-*erythro*-glycerol-1-yl)-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**9**). Compound **9** was, presumably, formed through opening of the lactone ring and nucleophilic attack of the imino nitrogen atom of the hydrazone residue at C-3 on the carbonyl group at C-1. Periodate oxidation of **9** resulted in the consumption of two moles of the oxidant per mole, and the formation of 3-formyl-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**10**). The infrared spectrum of **10** showed a band at 1700 cm^{-1} due to the aldehyde group.

Acetylation of **2** with boiling acetic anhydride, or with cold acetic anhydride and pyridine, caused simultaneous dehydration and formation of an optically inactive, olefinic compound (**11**). The n.m.r. spectrum of **11** in chloroform-*d* (see Fig. 1) showed one *O*-acetyl group signal at δ 2.07, a doublet at δ 4.93 (geminal coupling, 4 Hz) due to the 6-methylene group, and a triplet (one-proton intensity) at δ 5.91 (J 5 Hz) assigned to H-5. The protons on the phenyl ring appeared at δ 7.5–8.2, and the imino proton, at δ 12.1. El Khadem and El Ashry[7] showed that acetylation of L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(phenylhydrazone) (**12**) affords the same olefinic compound (**11**), but reported its melting point to be 157–161°. We repeated the acetylation of **12**, but isolated a product, m.p. 132–134°, that did not depress the m.p. of the product isolated from the 5-epimer **2**. The isolation of compound **11** from both the D-*erythro* and L-*threo* compounds (**2** and **12**) is in agreement with the structure proposed for **11**, namely, 4-(2-acetoxyethylidene)-4-hydroxy-2,3-dioxobutano-1,4-lactone 2-(phenylhydrazone).

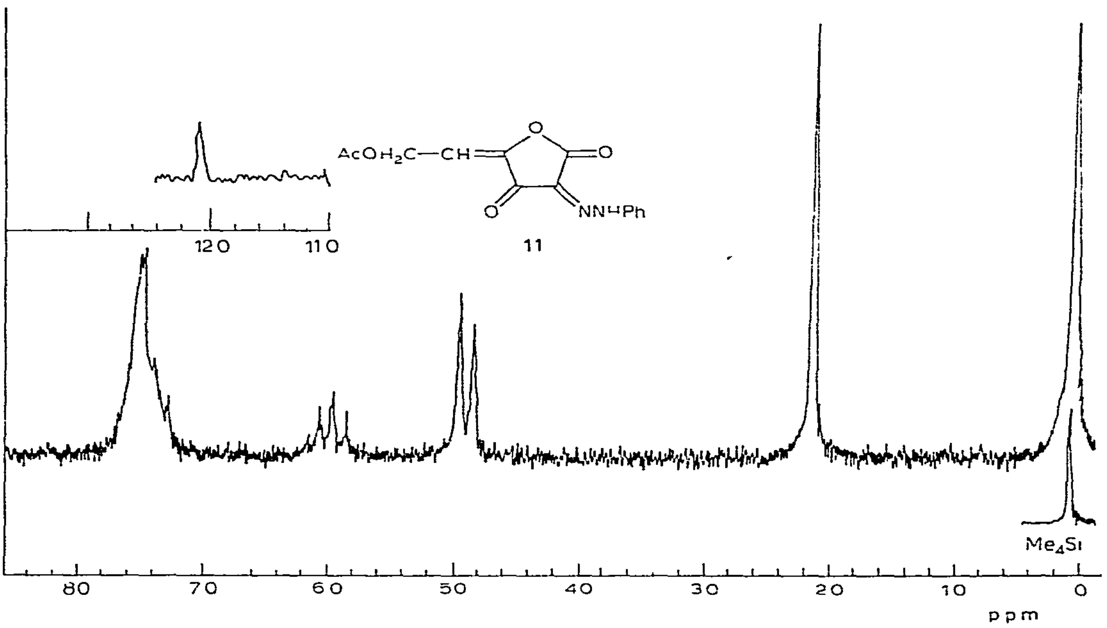


Fig. 1. N.m r. spectrum of **11**.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler block and are uncorrected. I.r. and u.v. spectra were recorded with Unicam Sp-200 and Unicam Sp-800 instruments. Microanalyses were made in the Microanalytical Laboratory, Cairo University. N.m.r. spectra were recorded with a Varian 60 instrument, and mass spectra with a Varian M 60 spectrometer.

D-erythro-*2,3-Hexodiulosono-1,4-lactone 2-(phenylhydrazone)* (**2**). — A solution of dehydro-isoascorbic acid ("dehydro-D-araboascorbic acid"), obtained by oxidizing a solution of isoascorbic acid (20 g) in water (300 ml), was treated with 1-acetyl-2-phenylhydrazine (20 g) and a few drops of acetic acid, and the mixture was heated on a steam bath for 2 h and then kept for four weeks at room temperature; compound **2** crystallized out, and was filtered off, washed successively with water, ethanol, and ether, and dried (yield 3 g). It was recrystallized from ethanol, to give yellow needles, m.p. 168–170°; ν_{max}^{Nujol} 1735 (lactone C=O) and 1670 cm^{-1} (C=O); λ_{max}^{EtOH} 208 (sh), 235, 354 (sh), and 395 nm (log ε 3.81, 3.99, 3.85, and 4.21); λ_{min}^{EtOH} 290 nm (log ε 3.30). It is soluble in chloroform, acetone, or 1,4-dioxane, sparingly soluble in methanol or ethanol, and insoluble in water.

Anal. Calc. for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.58; N, 10.60. Found: C, 54.62; H, 4.56; N, 10.83.

D-erythro-*2,3-Hexodiulosono-1,4-lactone 3-oxime 2-(phenylhydrazone)* (3). — A solution of **2** (1 g) in ethanol (50 ml) was treated with hydroxylamine hydrochloride (1 g) and sodium acetate (1 g), and the mixture was boiled under reflux for 2 h, cooled, and concentrated; the solid that separated out was filtered off, successively washed with water, ethanol, and ether, and dried (yield 0.4 g). Compound 3 crystallized from ethanol in yellow needles, m.p. 207–208°; ν_{max}^{Nujol} 3350 (OH) 1735 (lactone C=O), and 1620 cm^{-1} (C=N); λ_{max}^{EtOH} 226, 284, and 386 nm (log ε 4.18, 3.84, and 4.36); λ_{min}^{EtOH} 260 and 310 nm (log ε 3.50 and 3.46).

Anal. Calc. for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.90; H, 4.89; N, 15.34.

*4-(*D-erythro-*2,3-Diacetoxy-1-hydroxypropyl)-2-phenyl-1,2,3-triazole-5-carboxylic acid 5,1'-lactone* (4). — (*a*). A suspension of compound 3 (1 g) in acetic anhydride (10 ml) was boiled under reflux for 1 h. The mixture was then cooled, and poured onto crushed ice, and the product that separated was filtered off, washed successively with water and ethanol, and dried (yield 0.7 g). Compound **4** was recrystallized from ethanol, to give colorless needles, m.p. 91–92°; ν_{max}^{Nujol} 1780 (lactone C=O and OAc) and 1600 cm^{-1} (C=N); λ_{max}^{EtOH} 217 and 282 nm (log ε 3.64 and 4.11); λ_{min}^{EtOH} 235 nm (log ε 3.15). It is soluble in acetone, benzene, chloroform, or ether, sparingly soluble in methanol or ethanol, and insoluble in water.

Anal. Calc. for $C_{16}H_{15}N_3O_6$: C, 55.65; H, 4.38; N, 12.38. Found: C, 55.42; H, 4.60; N, 12.10.

(*b*). A solution of compound 3 (0.1 g) in dry pyridine (10 ml) was treated with acetic anhydride (5 ml), and kept for 24 h at room temperature. The mixture was poured onto crushed ice, and the product was filtered off and dried (yield 80 mg). Compound **4** was recrystallized from ethanol, to give colorless needles, m.p. 91–92°, alone or mixed with the product from (*a*). The two products had identical i.r. and n.m.r. spectra.

*2-(*p*-Bromophenyl)-4-(*D*-*erythro*-1,2,3-trihydroxypropyl)-1,2,3-triazole-5-carboxylic acid 5,1'-lactone* (**5**). — A suspension of compound **3** (1 g) in water (20 ml) was treated portionwise with bromine (2 ml) in water (10 ml), with stirring. Stirring was continued for 3 h at room temperature, and then the excess of bromine was removed by passing a stream of air through the mixture. The product was filtered off, successively washed with water, ethanol, and ether, and dried (yield 0.5 g). Compound **5** was recrystallized from ethanol, to give colorless needles, m.p. 158–159°; ν_{max}^{Nujol} 3450 (OH) and 1725 cm^{-1} (lactone C=O).

Anal. Calc. for $C_{12}H_{10}BrN_3O_4$: C, 42.37; H, 2.96; Br, 23.49; N, 12.35. Found: C, 42.21; H, 3.00; Br, 23.52; N, 12.51.

*2-(*p*-Bromophenyl)-4-(*D*-*erythro*-2,3-diacetoxy-1-hydroxypropyl)-1,2,3-triazole-5-carboxylic acid 5,1'-lactone* (**6**). — A suspension of compound **4** (0.2 g) in water (10 ml) was treated portionwise with bromine (0.5 ml) in water (10 ml) with stirring, and processed as for **5**. The product was obtained in a gelatinous form; ν_{max}^{Nujol} 1730 cm^{-1} (lactone C=O + OAc).

Anal. Calc. for $C_{16}H_{14}BrN_3O_6$: C, 45.30; H, 3.33; N, 9.91. Found: C, 45.58; H, 3.62; N, 10.01.

D-*erythro*-*2,3-Hexodiulosono-1,4-lactone 2,3-bis(phenylhydrazone)* (**7**). — A solution of compound **2** (0.5 g) in ethanol (50 ml) was treated with phenylhydrazine (1 ml) and a few drops of acetic acid, and the mixture was heated for 30 min on a steam bath and then allowed to cool to room temperature. The product was filtered off, washed successively with water, ethanol, and ether, and dried (yield 0.4 g). Compound **7** was recrystallized from chloroform–ethanol, to give red needles, m.p. 181–182°; ν_{max}^{Nujol} 3450 (OH) and 1720 cm^{-1} (lactone C=O); λ_{max}^{EtOH} 208, 261, 352, and 442 nm (log ε 4.00, 4.11, 4 25, and 4.20); λ_{min}^{EtOH} 222, 322, and 380 nm (log ε 3.81, 3.70, and 3.89).

Anal. Calc. for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found. C, 61.20, H, 5.31; N, 15.52.

*5,6-Di-O-acetyl-*D*-*erythro*-2,3-hexodiulosono-1,4-lactone 2,3-bis(phenylhydrazone)* (**8**). — A solution of compound **7** (0.1 g) in acetic anhydride (10 ml) was boiled under reflux for 1 h. The mixture was poured onto crushed ice, and the product that separated out was filtered off, successively washed with water and ethanol, and dried (yield 0.1 g). Recrystallization from ethanol gave compound **8** as red needles, m.p. 159–160°; ν_{max}^{Nujol} 1725 cm^{-1} (lactone C=O and OAc); λ_{max}^{EtOH} 207, 256, 282, 355, and 445 nm (log ε 4.02, 4.11, 4.21, 3.98, and 4.21); λ_{min}^{EtOH} 221, 320, and 380 nm (log ε 3.97, 3.89, and 4.00).

Anal. Calc. for $C_{22}H_{22}N_4O_6$: C, 60.27; H, 5.06; N, 12.78. Found· C, 60.31; H, 5.00; N, 12.41.

*3-(*D*-*erythro*-Glycerol-1-yl)-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone)*

(9). — A suspension of compound **7** (1 g) in water (50 ml) was treated with hydrazine hydrate (4 ml), and boiled under reflux until complete dissolution occurred (20 min). The solution was acidified with acetic acid, and the resulting solid was filtered off, successively washed with water and ethanol, and dried (yield 0.8 g). Recrystallization from chloroform–ethanol gave **9** as orange needles, m.p. 215–216°; ν_{max}^{Nujol} 3450 (OH) and 1660 cm^{-1} (CON); λ_{max}^{EtOH} 208, 252, and 402 nm (log ε 4.21, 4.41, and 4.31); λ_{min}^{EtOH} 220 and 300 nm (log ε 4.20 and 3.64).

Anal. Calc. for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 60.91; H, 4.93; N, 15.56.

3-Formyl-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone) **(10)**. — A suspension of compound **9** (0.5 g) in water (20 ml) was treated with a solution of sodium metaperiodate (1.5 g) in water (10 ml), and the mixture was kept overnight at room temperature, with shaking. The resulting solid was filtered off, successively washed with water and ethanol, and dried (yield 0.3 g). Recrystallization from ethanol gave compound **10** as orange prisms, m.p. 140–141° (lit.[8] m.p. 139–141°).

4-(2-Acetoxyethylidene)-4-hydroxy-2,3-dioxobutano-1,4-lactone 2-(phenylhydrazone) **(11)**. — (*a*). A suspension of compound **2** (0.1 g) in acetic anhydride (10 ml) was boiled under reflux for 1 h, cooled, and poured onto crushed ice; the product was filtered off, successively washed with water and ethanol, and dried (yield 0.1 g). Recrystallization from ethanol gave compound **11** as golden-yellow plates, m.p. 132–134°, (lit.[7] m.p. 158–161°); ν_{max}^{Nujol} 1780 (lactone C=O) and 1730 cm^{-1} (OAc); λ_{max}^{EtOH} 232, 270 (sh), and 405 nm (log ε 4.01, 4.11, and 4.30); λ_{min}^{EtOH} 315 nm (log ε 3.88).

Anal. Calc. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.53; H, 4.20; N, 9.91.

(*b*). A solution of compound **2** (0.1 g) in dry pyridine (10 ml) was treated with acetic anhydride (10 ml), and the mixture was kept overnight at room temperature, and poured onto crushed ice; the solid that separated was filtered off, successively washed with water and ethanol, and dried (yield 0.1 g). Compound **11** was recrystallized from ethanol, to give golden-yellow plates, m.p. 132–134°, alone or mixed with the product from (*a*). The two products had identical i.r. and n.m.r. spectra.

(*c*). A solution of compound **12** (0.2 g) and acetic anhydride (10 ml) was boiled under reflux for 1 h. The mixture was poured onto crushed ice, and the product that separated was filtered off, successively washed with water and ethanol, and dried (yield 0.18 g). Compound **11** was recrystallized from ethanol, to give golden-yellow plates, m.p. 132–134°, alone or mixed with the product from (*a*) or (*b*). The products from (*a*), (*b*), and (*c*) had the same i.r. and n.m.r. spectra.

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