Studies On Dehydro-L-ascorbic Acid and Dehydro-D-isoascorbic Acid Hydrazones†

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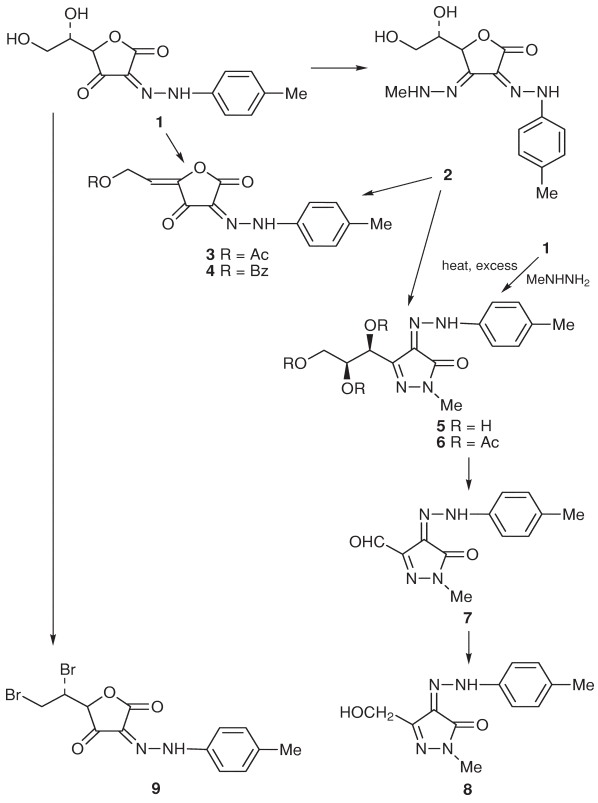
2-Arylhydrazones of dehydro-L-ascorbic acid and its analogues are established as precursors for the synthesis of various heterocyclic compounds including triazoles, pyrazoles, imidazoles and isoxazoles;[1–6] many of these compounds show great chemotherapeutic effects.

Treatment of L-*threo*-2,3-hexodiulosono-1,4-lactone-2-(*p*-tolylhydrazone) (**1**) with methylhydrazine afforded the bis-hydrazone **2** (Scheme 1). The IR spectrum showed the lactone band at 1740 cm^{-1}. Acetylation of **2** did not give the expected di-O-acetyl derivative but instead elimination of acetic acid and hydrolysis of the methylhydrazone moiety took place to give **3** as confirmed by its microanalytical, IR and ^1H NMR data. Compound **3** was also obtained by treatment of **1** with Ac_2O and pyridine. Similarly benzoylation of **1** afforded **4**. Treatment of **2** with hydrazine hydrate followed by acidification gave the pyrazolinedione **5** through opening of the lactone ring followed by internal nucleophilic attack on the carbonyl group. The IR spectrum of **5** showed the amide band at 1655 cm^{-1}. Compound **5** was also obtained from **1** by heating with excess methylhydrazine. Acetylation of **5** afforded the tri-*O*-acetyl derivative **6**. Periodate oxidation of **5** resulted in the consumption of 2 moles of the oxidant and formation of the aldehyde **7** whose IR spectrum showed the aldehyde carbonyl at 1700 cm^{-1}. Sodium tetrahydroborate reduction of **7** gave the corresponding 3-hydroxymethyl derivative **8**. Treatment of **1** with HBr/AcOH gave the dibromo derivative **9**. Similar treatment of the mono-arylhydrazones **10** and **11** with HBr/AcOH afforded the corresponding dibromo derivatives **12** and **13**. Their IR spectra showed the lactone and C2-carbonyl groups and the disappearance of the hydroxy groups (Scheme 2).

The mass spectrum of **12** showed the molecular ion peak (also the base peak) at *m/z* 392, 390 and 388 (1 : 2 : 1). Condensation of **12** with *p*-nitrophenyl-hydrazine semicarbazide and thiosemicarbazide afforded compounds **14**, **15** and **16**, respectively. Condensation of **11** with hydroxylamine afforded the corresponding oxime **17**. Careful treatment of **17** with NaOH followed by acidification resulted in the formation of the isoxazoline-dione **18** whose IR spectrum revealed a carbonyl band at 1731 cm^{-1}. The reaction of L-*threo*-2,3-hexodiulosono-1,4-lactone (**19**) and *m*-bromophenylhydrazine gave the *m*-bromophenyl-hydrazone **20** (Scheme 2). Its IR spectrum showed the lactone band at 1750 cm^{-1} besides the C3-carbonyl band at 1675 cm^{-1}. On treatment with hydroxylamine hydrochloride, **20** gave the 2-hydrazono-3-hydroxyimino derivative **21**. Dehydrative cyclization of **21** with Ac_2O afforded the furano-triazole derivative **22** whose ^1H NMR spectrum showed the two OAc groups at δ 2.0 and 2.1. Upon treatment of **22** with concentrated ammonia in methanol, deacetylation occurred concurrently with opening of the lactone ring to afford the triazole-4-carboxamide derivative **23** whose IR spectrum showed the amide band at 1666 cm^{-1} in addition to the hydroxy band at 3412 cm^{-1}.



Scheme 1

Experimental

Melting points were recorded on a Total (Buchi) apparatus and are uncorrected. IR (KBr) spectra were recorded on a 580 B Perkin Elmer IR spectrometer. The ^1H NMR spectra were recorded on a Varian EM-390, 90 MHz NMR spectrometer using TMS as the standard. Chemical shifts (δ) are given in ppm. Elemental analyses agreed with the assigned structures.

L-threo-2,3-*Hexodiulosono*-1,4-*lactone*-2-p-*tolylhydrazone*-3-*methyl-hydrazone* (**2**).—A solution of **1** (1 g, 3.59 mmol) in ethanol (30 ml) was refluxed for 2 h with methylhydrazine (1 ml) and AcOH (3 ml). The mixture was then concentrated and cooled. The separated product (0.95 g, 86%) was recrystallized from ethanol to give red needles, mp 188–190 °C; ν_{max}/cm^{-1} 3400 (OH) and 1740 (lactone C=O).

5-(2-*Acetoxyethylidene*)*tetrahydrofurantrione* 3-p-*Tolylhydrazone* (**3**).—A solution of **1** or **2** (0.1 g) in dry pyridine (10 ml) was treated with Ac_2O (5 ml), kept overnight at room temp. and then poured onto crushed ice. The separated solid (92 and 81%, respectively) was recrystallized from ethanol to give yellow needles; mp 173–174 °C; ν_{max}/cm^{-1} 1780 (lactone C=O) and 1730 ester (C=O); δ_H ($CDCl_3$) 2.1 (s, 3 H, OAc), 2.33 (s, 3 H, CH_3-*p*), 4.77 (d, 2 H, H-2), 5.82 (m, 1 H, H-1), 7.0–7.5 (m, 4 H, Ar-H) and 12.7 (s, 1 H, NH).

5-(2-*Benzoyloxyethylidene*)*tetrahydrofurantrione* 3-p-*Tolylhydrazone* (**4**).—A solution of **1** (0.1 g, 0.36 mmol) in dry pyridine (10 ml) was treated with BzCl (0.2 ml) as mentioned above (0.1 g, 76%). It was recrystallized from ethanol to give yellow needles; mp

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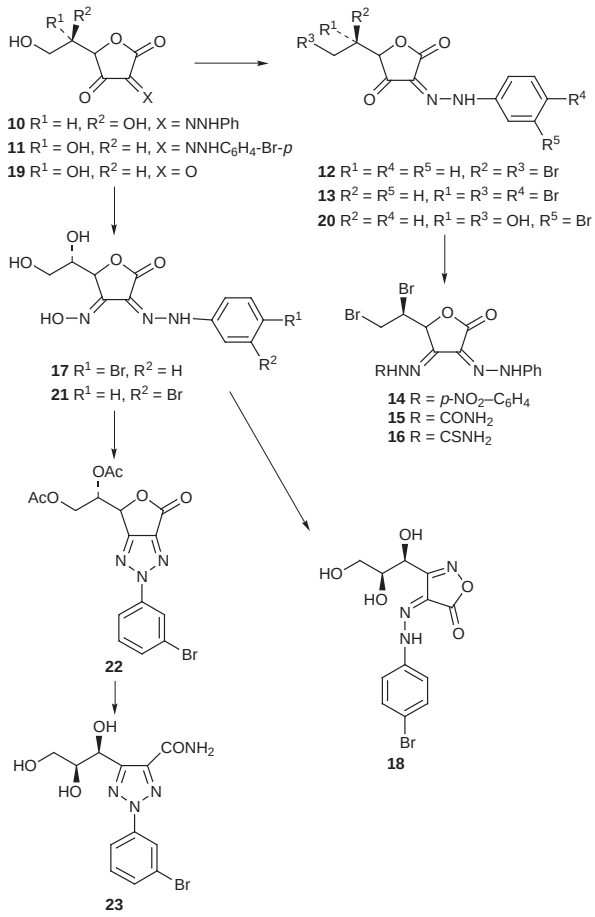
† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme 2

158–159 °C; ν_{max}/cm^{-1} 1760 (lactone C=O) and 1719 (ester C=O); δ_H ([$^2H_6$]DMSO) 2.3 (s, 3 H, CH_3-*p*), 5.03 (d, 2 H, H-2), 6.06 (m, 1 H, H-1), 7.1–8.0 (m, 9 H, Ar-H) and 12.73 (s, 1 H, NH).

3-(L-threo-Glycerol-1-*yl*)-1-*methyl*-4,5-*pyrazolindione* 4-p-*Tolylhydrazone* (**5**).—(A) A solution of **2** (0.5 g, 63 mmol) in ethanol (20 ml) was refluxed for 1 h with hydrazine hydrate (1 ml). The mixture was concentrated and then allowed to cool. The product (0.2 g, 40%) was recrystallized from ethanol to give yellow needles; mp 163–165 °C; ν_{max}/cm^{-1} 3300 (OH) and 1655 (OCN); (B) A solution of **1** (1 g, 3.5 mmol) in ethanol (50 ml) was refluxed for 10 h with methylhydrazine (10 ml). The product (0.5 g, 45%) was identical with that obtained by method A.

1-*Methyl*-3-(1,2,3-*tri*-*O*-*acetyl*-L-threo-*glycerol*-1-*yl*)-4,5-*pyrazolindione* 4-p-*Tolylhydrazone* (**6**).—Acetylation of **5**, as mentioned in the synthesis of **3**, gave **6** as a syrup which was purified by column chromatography (silica gel) eluted with ethyl acetate–methanol (9:1 v/v) (0.13 g, 70%); ν_{max}/cm^{-1} 1745 (ester C=O) and 1653 (OCN); δ_H ($CDCl_3$) 2.00 (s, 6 H, 2OAc) 2.1 (s, 3 H, OAc), 2.33 (s, 3 H, CH_3-*p*), 3.33 (s, 3 H, N-CH_3), 4.18 (m, 2 H, H-3), 5.66 (m, 1 H, H-2), 6.1 (d, 1 H, H-1), 7.0–8.0 (m, 4 H, Ar-H) and 13.55 (s, 1 H, NH).

3-*Carboxaldehyde*-1-*methyl*-4,5-*pyrazolindione* 4-p-*Tolylhydrazone* (**7**).—A suspension of **5** (0.1 g, 0.33 mmol) in water (10 ml) was stirred for 6 h at room temperature with sodium metaperiodate (0.2 g, 0.93 mmol) in water (5 ml). The resulting solid (65 mg; 82%) was recrystallized from ethanol as red needles; mp 135–136 °C; ν_{max}/cm^{-1} 1700 (CHO), 1650 (OCN) and 1600 (C=N).

1-*Methyl*-3-*hydroxymethyl*-4,5-*pyrazolinedione* 4-p-*Tolylhydrazone* (**8**).—A solution of **7** (0.1 g; 0.41 mmol) in methanol (10 ml) was stirred with a solution of sodium tetrahydroborate (0.1 g, 2.6 mmol) in water (10 ml) that was added in small portions. The solution was acidified with AcOH (1 ml) and the separated solid (60 mg, 59.5%) was recrystallized from ethanol as yellow crystals; mp 117–118 °C; ν_{max}/cm^{-1} 3450 (OH) and 1650 (OCN).

Dibromo Derivatives **9**, **12** *and* **13**.—A suspension of the monohydrazones **1**, **10**[8] or **11**[9] (1 g) in 30% HBr in AcOH (30 ml) was stirred for 24 h at room temp. and then poured on to water (100 ml). Compounds **9**, **12** and **13** (71–81%) were recrystallized from chloroform–ethanol (1:1 v/v) to give yellow prisms, mp 168–169, 160–161 and 159–160 °C respectively. The IR spectra revealed the lactone C=O at 1772–1740 and the C3–O at 1696–1680 cm^{-1}; δ_H for **12** ($CDCl_3$) 4.1 (m, 2 H, H-6), 4.86 (m, 1 H, H-5), 5.72 (d, 1 H, H-4), 7.1–7.72 (m, 5 H, Ph) and 9.32 (s, 1 H, NH).

Condensation Products of 5,6-*Dibromo*-5,6-*dideoxy*-D-erythro-2,3-*hexodiulosono*-1,4-*lactone*-2-*phenylhydrazone* (**14**–**16**).—A solution of **12** (0.1 g, 0.25 mmol) in ethanol (20 ml) was refluxed for 6 h with *p*-nitrophenylhydrazine, semicarbazide hydrochloride and sodium acetate or thiosemicarbazide in the presence of a catalytic amount of AcOH (yield 62–87%). Compounds **14**, **15** and **16** were recrystallized from ethanol; mp 159–160, 172–174 and 159–160 °C, respectively. The IR spectra revealed the lactone C=O at 1738–1730 cm^{-1}.

L-threo-2,3-*Hexodiulosono*-1,4-*lactone*-2-p-*bromophenylhydrazone*-3-*oxime* (**17**).—A solution of **11** (1 g, 2 mmol) in ethanol (30 ml) was refluxed for 3 h with hydroxylamine hydrochloride (1 g, 14.4 mmol), sodium acetate (1.2 g; 14.6 mmol) and acetic acid (5 ml); water (50 ml) was added and the mixture left to cool. The separated solid (0.85 g, 81.7%) was recrystallized from ethanol to give yellow needles; mp 209–210 °C; ν_{max}/cm^{-1} 3400 (OH) and 1730 (lactone C=O).

3-(L-threo-*Glycerol*-1-*yl*)-4,5-*isoxazoinedione*-4-p-*bromophenylhydrazone* (**18**).—A suspension of **17** (0.5 g, 1.4 mmol) in water (10 ml) was heated with 10% NaOH (20 ml) to 80 °C, cooled, made neutral with AcOH and kept overnight at room temp. The product AcOH (0.3 g, 60%) was recrystallized from ethanol–water (1:1 v/v) to give pale yellow needles; mp 128–130 °C; ν_{max}/cm^{-1} 3368 (OH) and 1731 (lactone C=O).

L-threo-2,3-*Hexodiulosono*-1,4-*lactone*-2-m-*bromophenylhydrazone* (**20**).—A solution of **19** in 50 ml of a water–ethanol mixture (1 : 1 v/v), obtained by oxidation of L-ascorbic acid (7.2 g, 28.4 mmol) with iodine (7.2 g, 28.4 mmol) in ethanol (20 ml), was treated with *m*-bromophenylhydrazine hydrochloride (1 g, 4.47 mmol) and sodium acetate (1 g, 12.1 mmol) at room temp. The separated solid (2 g, 20%) was recrystallized from ethanol, giving orange needles; mp 156–157 °C; ν_{max}/cm^{-1} 3450 (OH), 3118 (NH), 1750 (lactone C=O) and 1675 (C3=O).

L-threo-2,3-*Hexodiulosono*-1,4-*lactone*-2-m-*bromophenylhydrazone*-3-*oxime* (**21**).—Obtained from **20** as mentioned in the synthesis of **17**; (0.8 g, 77%); mp 209–210 °C; ν_{max}/cm^{-1} 3362 (OH), 3134 (NH), 1735 (lactone C=O).

2-*Acetyloxy*-1-[5-(3-*bromophenyl*)-3-*oxohydrofurano*[3,4-d]1,2,3-*tri*-*triazolyl*]*ethyl Acetate* (**22**).—Obtained by acetylation of **21** as mentioned in the synthesis of **3**; (0.1 g, 85%); mp 99–100 °C; ν_{max}/cm^{-1} 1780 (lactone C=O) and 1745 (ester C=O); δ_H ($CDCl_3$): 2.04 and 2.1 (2 s, 6 H, 2 OAc), 4.45 (m, 2 H, CH_2), 5, 52 (q, 1 H, H-1), 5.86 (d, 1 H, H-6) and 7.5–7.87 (m, 4 H, Ar-H).

2-m-*Bromophenyl*-5-*carboxamide*-4-(L-threo-*glycerol*-1-*yl*)-1,2,3-*triazole* (**23**).—A solution of **22** (0.1 g, 0.24 mmol) in methanol (10 ml) was treated with conc. NH_3 (5 ml), left overnight at room temp., concentrated under reduced pressure and the separated solid (30 mg, 84%) recrystallized from ethanol as colourless needles, mp 165–166 °C; ν_{max}/cm^{-1} 3412 (OH), 3126 (NH) and 1666 (OCN).

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