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HOMOLOGS OF DEHYDRO-L-ASCORBIC ACID PHENYLOSAZONE

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ABSTRACT

The reaction of D-*arabino*-2,3-heptodiulosono-1,4-lactone (**1**) with phenylhydrazine gives two crystalline products, namely, a red bis(hydrazone) (**2a**), which was oxidized to bicyclic compound **4a**, and a yellow pyrazoline (**3a**) which gave an anhydride (**5a**) on treatment with methanolic sulfuric acid. On similar treatment, D-*erythro*-2,3-hexodiulosono-1,4-lactone (**6a**) afforded a pyrazoline (**7a**). Esters of the compounds prepared are described.

INTRODUCTION

The reaction of dehydro-L-ascorbic acid (L-*threo*-2,3-hexodiulosono-1,4-lactone) and its homologs with phenylhydrazine yields varying proportions of a red bis(phenylhydrazone) and a yellow compound which was at first thought to be the bis(hydrazone), but was later given a phenylazo pyrazolinone structure[1]. In continuation of our work[2] on these compounds, we now report on the reaction products of phenylhydrazine with two homologs of dehydro-L-ascorbic acid, namely, D-*arabino*-2,3-heptodiulosono-1,4-lactone (**1**; dehydro-"D-*gluco*-ascorbic" acid) and D-*erythro*-2,3-hexodiulosono-1,4-lactone (**6a**).

DISCUSSION

D-*arabino*-2,3-Heptodiulosono-1,4-lactone (**1**) was found to react with phenylhydrazine to give a mixture of the red bis(phenylhydrazone) **2a** and the yellow pyrazoline[3] **3a**, which were characterized by conversion into acetates **2b** and **3b**, and benzoate **3c**, respectively.

On similar treatment, D-*erythro*-2,3-hexodiulosono-1,4-lactone (**6a**) yielded an amorphous bis(phenylhydrazone) and a crystalline pyrazoline (**7a**) which was converted into the triacetate (**7b**) and tribenzoate (**7c**). The 100-MHz n.m.r. spectra of **7b** and **7c** in deuterochloroform show, in addition to the expected resonances for the side-chain protons*, a signal for one imino proton, at δ13.69 and 13.75 p.p.m., respectively. We therefore assigned to this group of compounds the structure of a

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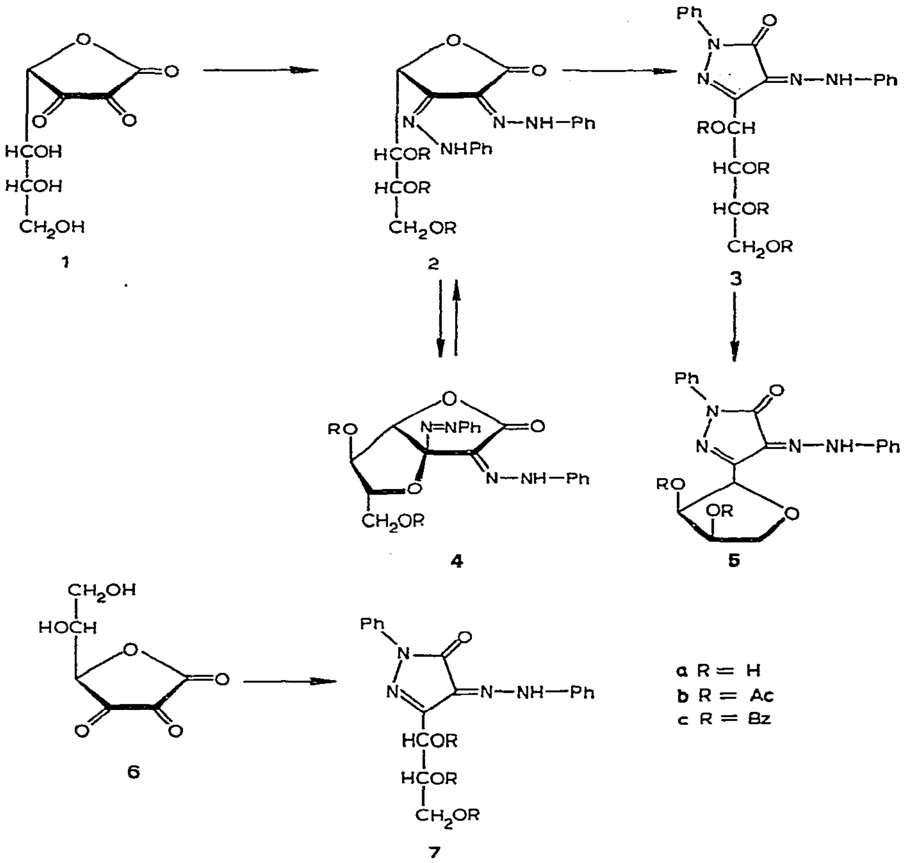
*H. El Khadem, D. Horton, and J. D. Wander, unpublished results.



substituted 3-(hydroxyalkyl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone), instead of the tautomeric, 3-(hydroxyalkyl)-1-phenyl-4-phenylazo-3-pyrazolin-5-one structure previously given.

Like many heterocycles having tetrahydroxybutyl side-chains, compound **3a** readily underwent dehydration on boiling a solution in methanolic sulfuric acid under reflux, and gave anhydride **5a**, which was characterized by conversion into the diacetate **5b**.

As with L-*threo*-2,3-hexodiulosono-1,4-lactone bis(phenylhydrazone), lactone **2a** was oxidized with cupric chloride to the corresponding 3,6-anhydride **4a**, which was converted into the diacetate **4b**, and reduced with stannous chloride to the starting bis(phenylhydrazone) **2a**. With sodium iodide, 7-*O*-*p*-tolylsulfonyl-D-*arabino*-2,3-heptodiulosono-1,4-lactone bis (phenylhydrazone) gave a 7-deoxy-7-iodo derivative which was characterized as its diacetate.

EXPERIMENTAL

D-arabino-*2,3-Heptodiulosono-1,4-lactone 2,3-bis(phenylhydrazone)* (**2a**). — A solution of D-*erythro*-2,3-heptodiulosono-1,4-lactone (dehydro-"D-*gluco*-ascorbic" acid) (2 g) in water (20 ml), phenylhydrazine (5 ml), and a few drops of acetic acid was heated for 40 min on a steam bath. The red bis(phenylhydrazone) **2a** was separated from the more soluble **3a** by fractional recrystallization; yield 0.8 g, crystallized from ethanol in red needles, m.p. 238–239°; $\nu_{\max}^{\mathrm{KBr}}$ 1750 (COO) and 3425 cm^{-1} (OH).

Anal. Calc. for $C_{19}H_{20}N_4O_5$: C, 59.4; H, 5.2; N, 14.6. Found: C, 59.0; H, 5.1; N, 14.9.

Periodate oxidation of **2a**. — A suspension of compound **2a** (14.6 mg) in a solution of sodium metaperiodate (385 mg) in water (20 ml) was kept overnight at room temperature, with occasional shaking, and filtered. The filtrate was diluted to 100 ml, treated with an excess of arsenite, and then back-titrated against iodine solution; periodate consumption, 2.0 moles per mole.

*Tri-O-acetyl-*D-arabino-*2,3-heptodiulosono-1,4-lactone 2,3-bis(phenylhydrazone)* (**2b**). — To a solution of **2a** (0.1 g) in dry pyridine (10 ml) was added acetic anhydride (5 ml), and the solution was kept overnight at room temperature, and poured onto crushed ice. The product that separated was filtered off, washed with water, dried (yield 0.1 g), and recrystallized from ethanol in red needles, m.p. 177–178°; $\nu_{\max}^{\mathrm{KBr}}$ 1720 cm^{-1} (COO and OAc).

Anal. Calc. for $C_{25}H_{26}N_4O_8$: C, 58.8; H, 5.1; N, 11.0. Found: C, 59.0; H, 5.1; N, 10.7.

*7-O-p-Tolylsulfonyl-*D-arabino-*2,3-heptodiulosono-1,4-lactone 2,3-bis(phenylhydrazone)*. — To a solution of compound **2a** (0.1 g) in dry pyridine (10 ml) was added *p*-toluenesulfonyl chloride (0.1 g), and the solution was kept overnight at room temperature. The mixture was poured onto crushed ice, and the product that separated was filtered off, washed repeatedly with water, dried (yield 0.1 g), and recrystallized from chloroform–ethanol; red needles, m.p. 217–219°; $\nu_{\max}^{\mathrm{KBr}}$ 1720 (C=O) and 3450 cm^{-1} (OH).

Anal. Calc. for $C_{26}H_{26}N_4O_7S$: C, 58.0; H, 4.9; N, 10.4. Found: C, 58.4; H, 5.0; N, 10.3.

*Di-O-acetyl-7-deoxy-7-iodo-*D-arabino-*2,3-heptodiulosono-1,4-lactone 2,3-bis-(phenylhydrazone)*. — To a solution of 7-*O-p*-tolylsulfonyl-D-*arabino*-2,3-heptodiulosono-1,4-lactone 2,3-bis(phenylhydrazone) (0.1 g) in dry acetone (5 ml) was added sodium iodide (0.5 g), and the mixture was heated in a sealed tube for 2 h at 100°. After being cooled, the tube was opened, and the contents were filtered; the precipitated sodium *p*-toluenesulfonate was washed with dry acetone. The filtrate and washing were combined, and evaporated to dryness under diminished pressure; the mixture was washed with water (to remove remaining sodium salt), and the insoluble product was dried (yield 0.1 g) and crystallized from chloroform–ethanol; red needles, m.p. 251–252°. A solution of this compound in pyridine (5 ml) and acetic anhydride (2 ml) was kept overnight at room temperature, and then poured onto crushed ice. The product that separated was filtered off, washed with water, dried (yield 50 mg), and recrystallized from ethanol; red, prismatic needles, m.p. 234–235°.

Anal. Calc. for $C_{23}H_{23}IN_4O_6$: C, 47.8; H, 4.0; N, 9.7. Found: C, 48.0; H, 4.1; N, 10.0.

*3,6-Anhydro-3-phenylazo-*D-gluco-*heptulosono-1,4-lactone 2-(phenylhydrazone)* (**4a**). — A solution of **2a** (0.5 g) and cupric chloride (0.5 g) in ethanol (50 ml) was boiled for 10 min under reflux, and concentrated to 20 ml. Hot water was added to the solution to incipient turbidity, and the product that separated was filtered off, washed with water, and dried (yield 0.25 g). It crystallized from ethanol in yellow needles, m.p. 208–210°; ν_{max}^{KBr} 1720 (C=O) and 3400 cm^{-1} (OH).

Anal. Calc. for $C_{19}H_{18}N_4O_5$: C, 59.7; H, 4.8; N, 14.7. Found: C, 59.3; H, 4.9; N, 14.8.

Attempted periodate oxidation of **4a**. — A suspension of **4a** (0.02 g) in a solution of sodium metaperiodate (0.5 g) in water (10 ml) was shaken for 2 days at room temperature; **4a** was recovered unchanged, and no periodate was consumed.

Reduction of **4a**. — To a solution of **4a** (50 mg) in ethanol (10 ml) was added a solution of stannous chloride (0.5 g) in concentrated hydrochloric acid (3 ml), and the suspension was heated for 10 min at 60–70°; by then, the anhydride had dissolved. Hot water was added until the solution became turbid, and the product that separated was filtered off, washed with water, and dried (yield 30 mg). D-*arabino*-2,3-Heptodiulosono-1,4-lactone 2,3-bis(phenylhydrazone) crystallized from ethanol in red needles, m.p. and mixed m.p. 238–239°.

*Di-O-acetyl-3,5-anhydro-3-phenylazo-*D-gluco-*heptulosono-1,4-lactone 2-(phenylhydrazone)* (**4b**). — A solution of **4a** (0.1 g) in dry pyridine (10 ml) and acetic anhydride (5 ml) was kept overnight at room temperature. The mixture was poured onto crushed ice, and the product that separated was filtered off, washed with water, and dried (yield 0.1 g); compound **4b** was recrystallized from ethanol in yellow needles, m.p. 178°; ν_{max}^{KBr} 1735 (CO and OAc) and 3275 cm^{-1} (NH).

Anal. Calc. for $C_{23}H_{22}N_4O_7$: C, 59.2; H, 4.8; N, 12.0. Found: C, 59.0; H, 4.9; N, 11.8.

*1-Phenyl-3-(*D-arabino-*tetrahydroxybutyl)-4,5-pyrazoledione 4-(phenylhydrazone)* (**3a**). — A suspension of **2a** or its triacetate **2b** (0.5 g) in water (50 ml) was heated with 1.5M sodium hydroxide solution (15 ml) for 5 min at 70–80°; by then, the osazone had dissolved. The pH of the resulting solution was adjusted to 6 with acetic acid, and the product that separated was filtered off, washed successively with water and ethanol, and dried. It was recrystallized from chloroform–ethanol in orange needles, m.p. 226°, lit.[3] m.p. 226°; ν_{max}^{KBr} 1650 (CON) and 3375 cm^{-1} (OH).

Periodate oxidation of **3a**. — A suspension of compound **3a** (0.2 g) in a solution of sodium metaperiodate (3 g) in water (200 ml) was kept overnight at room temperature, with occasional shaking, and filtered. The filtrate was diluted to 1 liter with water, treated with an excess of arsenite, and then back-titrated against iodine solution (periodate consumption 3.1 moles per mole). The precipitate afforded the known[2] 3-formyl-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone), m.p. and mixed m.p. 140–141°; lit.[2] m.p. 139–141°.

*1-Phenyl-3-(*D-arabino-*tetraacetoxybutyl)-4,5-pyrazoledione 4-(phenylhydrazone)* (**3b**). — A solution of **3a** (0.1 g) in dry pyridine (5 ml) and acetic anhydride (5 ml) was kept overnight at room temperature. The mixture was poured onto crushed ice, and the product that separated was filtered off, washed with water, and dried (yield 0.1 g). Compound **3b** was recrystallized from ethanol; yellow-orange needles, m.p. 153°; $\nu_{\max}^{\mathrm{KBr}}$ 1660 (CON) and 1750 cm^{-1} (OAc).

Anal. Calc. for $C_{27}H_{28}N_4O_9$: C, 58.7; H, 5.1; N, 10.1. Found: C, 59.1; H, 5.3; N, 10.5.

1-Phenyl-3-[D-arabino-*tetra-(benzoyloxy)butyl]-4,5-pyrazoledione 4-phenylhydrazone)* (**3c**). — A solution of **3a** (0.1 g) in dry pyridine (10 ml) was treated with benzoyl chloride (3 ml) and kept for 2 days at room temperature. The mixture was poured onto crushed ice, and the product that separated was filtered off, washed with water, and dried (yield 0.12 g). Compound **3c** was recrystallized from ethanol in orange needles, m.p. 168°; $\nu_{\max}^{\mathrm{KBr}}$ 1650 (CON) and 1700 cm^{-1} (OBz).

Anal. Calc. for $C_{47}H_{36}N_4O_9$: C, 70.5; H, 4.5; N, 7.0. Found: C, 70.3; H, 4.81; N, 6.6.

1,4-Anhydro-3-(D-arabino-*2,3-dihydroxybutyl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone)* (**5a**). — A solution of compound **3a** (0.1 g) and concentrated sulfuric acid (1 ml) in dry methanol (100 ml) was boiled for 36 h under reflux. The mixture was concentrated to a small volume, and the product that separated was filtered off, washed with water, and dried (yield 0.1 g). Compound **5a** crystallized from chloroform–ethanol in orange needles, m.p. 254–255°.

Anal. Calc. for $C_{19}H_{18}N_4O_4$: C, 62.3; H, 4.9; N, 15.3. Found: C, 62.4; H, 5.1; N, 15.2.

1,4-Anhydro-3-(D-arabino-*2,3-diacetoxybutyl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone)* (**5b**). — A solution of compound **5a** (0.08 g) in dry pyridine (5ml) and acetic anhydride (5 ml) was kept overnight at room temperature. The mixture was poured onto crushed ice, and the product was filtered off, washed with water,and dried (yield 0.08 g). Compound **5b** crystallized from ethanol in orange needles, m.p. 188°.

Anal. Calc. for $C_{23}H_{22}N_4O_6$: C, 61.3; H, 4.9; N, 12.4. Found: 61.0; H, 4.9; N, 12.1.

1-Phenyl-3-(D-erythro-*trihydroxypropyl)-4,5-pyrazoledione 4-(phenylhydrazone)* (**7a**). — To a solution of D-*erythro*-2,3-hexodiulosono-1,4-lactone (10 g) (obtained by air oxidation of the ascorbic acid homolog) in water (200 ml) were added phenylhydrazine (10 ml) and acetic acid (10 ml), and the mixture was heated for 2 h on a steam bath, and cooled. A mixture of the amorphous, red bis(hydrazone) and the crystalline, yellow pyrazoline **7a** separated. It was filtered off and dissolved in warm 2M sodium hydroxide, and the suspension was filtered from some insoluble material. The filtrate was acidified with acetic acid, whereupon **7a** crystallized in yellow needles, m.p. 215°; $\nu_{\max}^{\mathrm{KBr}}$ 1660 (CON) and 3450 cm^{-1} (OH).

Anal. Calc. for $C_{18}H_{18}N_4O_4$: C, 61.0; H, 5.1; N, 15.8. Found: C, 61.3; H, 5.3; N, 15.9.

1-Phenyl-3-(D-erythro-*triacetoxypropyl)-4,5-pyrazoledione 4-(phenylhydrazone)* (**7b**). — Compound **7a** was acetylated with acetic anhydride in pyridine as for the preparation of **3b** from **3a**. The product had m.p. 112°; ν_{max}^{KBr} 1660 (CON) and 1750 cm^{-1} (OAc).

Anal. Calc. for $C_{24}H_{24}N_4O_7$: C, 60.0; H, 5.0; N, 11.7. Found: C, 60.4; H, 5.3; N, 11.5.

1-Phenyl-3-[D-erythro-*tri-(benzoyloxy)propyl*]*-4,5-pyrazoledione 4-(phenylhydrazone* (**7c**). — Benzoylation of compound **7a** with benzoyl chloride in pyridine, with processing as for **3c**, afforded the tribenzoate **7c**, m.p. 193°; ν_{max}^{KBr} 1660 (CON) and 1720 cm^{-1} (OBz).

Anal. Calc. for $C_{39}H_{30}N_4O_7$: C, 70.3; H, 4.5; N, 8.4. Found: C, 70.4; H, 4.7; N, 8.3.

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