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SYNTHESIS AND REACTIONS OF SOME HYDRAZONES OF DEHYDRO-L-ASCORBIC ACID*

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ABSTRACT

L-*threo*-2,3-Hexodiulosono-1,4-lactone 2-(3-chlorophenylhydrazone) and 4-(2-acetoxyethylidene)-4-hydroxy-2,3-dioxobutano-1,4-lactone 2-(3-chlorophenylhydrazone) were prepared. The two geometric isomers of the corresponding bis(hydrazone) underwent an intramolecular rearrangement to 1-(3-chlorophenyl)-3-(L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(3-chlorophenylhydrazone), which gave a tri-*O*-acetyl derivative upon acetylation and the anticipated formyl derivative upon periodate oxidation. Oxidation of the bis(hydrazone) with cupric chloride afforded the bicyclic compound 3,6-anhydro-3-*C*-(3-chlorophenylazo)-L-*xylo*-2-hexulosono-1,4-lactone 2-(3-chlorophenylhydrazone), whose acetylation afforded the mono-*O*-acetyl derivative.

INTRODUCTION

The synthetic potentiality of hydrazines and hydrazones in the synthesis of heterocyclic compounds attracted attention to the utility of their carbohydrate derivatives as precursors for heterocyclic compounds[2]. The carbohydrate moieties in such types of heterocycle may either remain[3–10] or be modified[4–12]. In some reactions, all of the chiral centers of the carbohydrate molecules may be employed in building the heterocyclic ring[13–19], and, consequently, the resulting molecules will have no chirality. Alternatively, synthesis of the latter type of heterocyclic compound can be achieved by degradation of the carbohydrate residue after formation of the heterocyclic ring.[2] In this connection, the synthesis of some hydrazones of L-ascorbic acid was achieved, and some reactions thereof are described in this report.

RESULTS AND DISCUSSION

The carbohydrate precursor required for the preparation of the aforemen-

*Heterocycles from Carbohydrate Precursors, Part XXV. For Part XXIV, see ref. 1. The Scope of the Reactions of Hydrazines and Hydrazones, Part XV. For Part XIV, see ref. 1.

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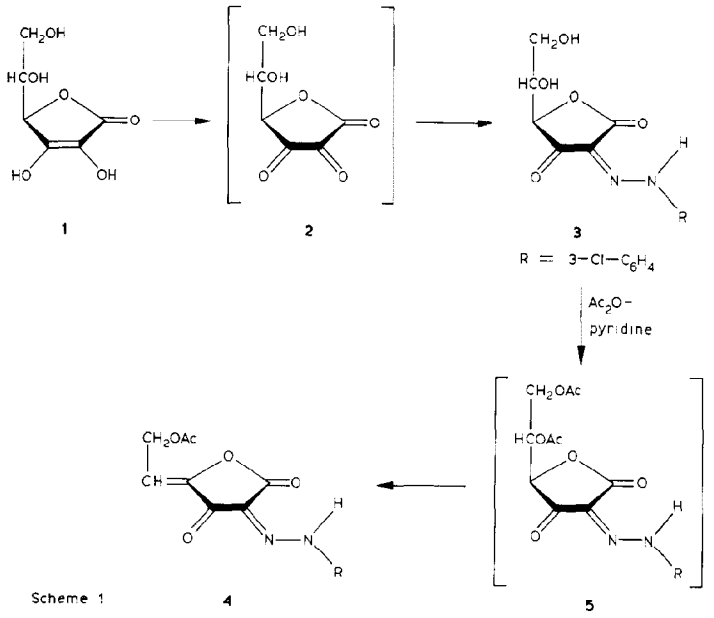
tioned hydrazones was L-*threo*-2,3-hexodiulosono-1,4-lactone (**2**), which was prepared by the oxidation of L-ascorbic acid (**1**) in aqueous or alcoholic solution. The solution of **2** was used directly, without isolation, for the preparation of the hydrazones in order to avoid complications arising from severe or long treatment of such a labile molecule.

It has been shown in this laboratory that the controlled reactions of L-*threo*-2,3-hexodiulosono-1,4-lactone (**2**) with *p*-substituted phenylhydrazines afford the corresponding monohydrazones. On the other hand, similar reaction using phenylhydrazine gave the bis(hydrazone), not the corresponding monohydrazone, despite numerous trials under conditions milder than those used for the *p*-substituted analogs. Consequently, it became of interest to ascertain the behavior of other substituted phenylhydrazines in this reaction, to explore whether they can afford monohydrazones or not. Thus, when an aqueous solution of **2** was treated with 1 molar equivalent of (3-chlorophenyl)hydrazine at room temperature, it afforded a yellow, crystalline product, identified as L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(3-chlorophenylhydrazone) (**3**). Further reaction of **3** with (3-chlorophenyl)hydrazine gave the corresponding bis(hydrazone) **6**, which exists in two crystalline forms isolated[20]. It should be noted that this is the first example of the isolation of two isomers of an L-ascorbic acid bis(hydrazone), despite the presence of such isomerism in solution. Consequently, it became interesting to study their reactions.

The structure of **3** was confirmed from its elemental analysis, as well as its spectra. Thus, its combustion analysis agreed with the molecular formula $C_{12}H_{11}ClN_2O_5$, indicating that the product corresponded to the consumption of only one molecule of the hydrazine per molecule in this reaction. The infrared (i.r.) spectrum of **3** showed two types of band in the carbonyl-frequency region, one at 1770 cm^{-1} (due to the lactone carbonyl) and the other at 1680 cm^{-1} (due to the 3-carbonyl).

When L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(3-chlorophenylhydrazone) was subjected to acetylation using acetic anhydride in pyridine, a product was obtained whose structure was found to be the optically inactive alkenic compound **4**. Its elemental analysis agreed with the molecular formula $C_{14}H_{11}ClN_2O_5$. Its i.r. spectrum showed bands at 1670 (due to CO and C=C), 1730 (OAc) and 1800 cm^{-1} (lactone carbonyl). The ^{1}H-n.m.r. spectrum of **4** showed the presence of one acetyl group, at δ 2.12, a doublet of two-proton intensity at δ 4.87 (J 6 Hz) attributed to the methylene group, and a triplet of one-proton intensity, at δ 6.0, assigned to the adjacent proton. The imino proton appeared at δ 12.67. These data indicated clearly that acetylation of **3** afforded **4**, which may be formed as a result of simultaneous acetylation to the di-*O*-acetyl compound **5**, which readily eliminated a molecule of acetic acid to give **4**.

It has been shown that compounds possessing a pyrazoledione ring are of potential, chemotherapeutic interest[18]. Consequently, compounds having various substituents on that ring had been prepared[2]. Thus, when the bis(3-chlorophenylhydrazone) (**6**) of L-*threo*-2,3-hexodiulosono-1,4-lactone was heated with a



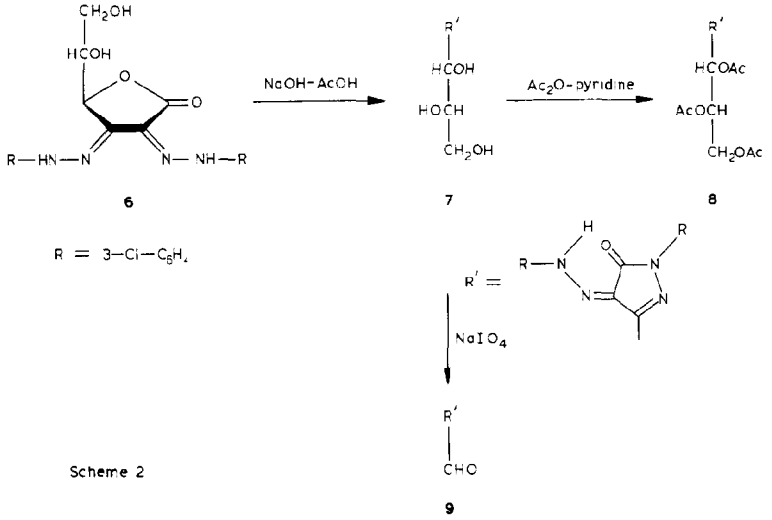
Scheme 1

solution of sodium hydroxide, followed by acidification with acetic acid, it rearranged to 1-(3-chlorophenyl)-3-(L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(3-chlorophenylhydrazone). Both geometric isomers of **6** afforded **7**.

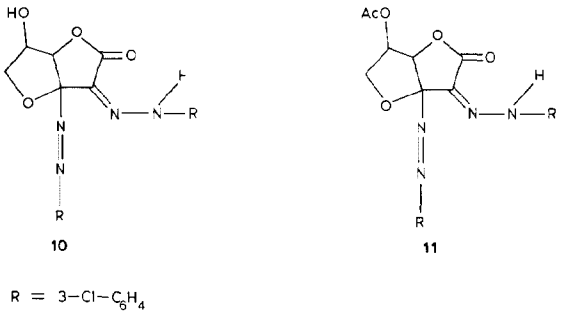
Periodate oxidation of **7** gave 1-(3-chlorophenyl)-3-formyl-4,5-pyrazoledione 4-(3-chlorophenylhydrazone) (**9**). The structure of the aldehyde was confirmed by its i.r. spectrum, which showed two bands in the carbonyl frequency region, one at 1670 cm^{-1} (due to OCN) and the other at 1700 cm^{-1} (due to the CHO group).

Acetylation of the glycerolyl side-chain of **7** with acetic anhydride in pyridine yielded 1-(3-chlorophenyl)-3-(1,2,3-tri-*O*-acetyl-L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(3-chlorophenylhydrazone) (**8**). Its i.r. spectrum showed bands at 1760 cm^{-1} (due to OAc) and at 1680 cm^{-1} (due to OCN). The ^{1}H-n.m.r. spectrum of **8** showed the presence of three acetyl groups, as two singlets, of six- and three-proton intensity, at δ 2.13 and 2.23, respectively. The signals for H-3 and H-3′ of the glycerolyl side-chain appeared as two quartets, at δ 4.47 and 4.27, respectively. The smaller coupling ($J_{2,3}$ 4 and $J_{2,3'}$ 6 Hz) was due to coupling with H-2, and the larger coupling ($J_{3,3'}$ 12 Hz) in each quartet was due to geminal coupling. The signal for H-2 appeared as a quartet, at δ 5.80, of one-proton intensity, and that for H-1 appeared as a doublet at δ 6.23 ($J_{1,2}$ 6 Hz). The signals for the aromatic protons appeared at δ 7.3–7.9, and that for the imino proton, at δ 13.3. The rather downfield shift of the imino-proton signal indicated its involvement in hydrogen bonding with the adjacent carbonyl group.

It is known[21] that the bis(arylhydrazone) of such 1,2-dicarbonyl compounds as glyoxal, phenylglyoxal, and benzil, as well as sugar bis(hydrazones), can be con-



Scheme 2



verted into triazoles by the action of such oxidizing salts as cupric chloride. Different behavior was noted when the bis(arylhydrazones) of L-*threo*-2,3-hexodiulosono-1,4-lactone were subjected to the same conditions, the 3,6-anhydro-3-(arylazo)-L-*xylo*-2-hexulosono-1,4-lactone 2-(arylhydrazones) being obtained. When **6** was boiled with an ethanolic solution of cupric chloride, **10** was obtained as a yellow, crystalline compound. Its structure was deduced from its mode of preparation, as well as from its spectral data. Its i.r. spectrum showed a band at 1740 cm^{-1} (due to the carbonyl of the lactone), in addition to bands at 3360 (due to NH) and 3460 cm^{-1} (due to the hydroxyl group).

Acetylation of **10** afforded the acetyl derivative **11**, whose ^{1}H-n.m.r. spectrum showed the presence of only one acetyl group, as a singlet at δ 2.05, indicating the presence of one hydroxyl group in its precursor. Moreover, the spectrum showed a two-proton multiplet at δ 4.30, corresponding to the C-6 methylene group, a one-proton doublet at δ 5.25 (due to H-4), and a one-proton quartet at δ 5.40 (due to H-5), in addition to an eight-proton multiplet at δ 7.0–7.9 due to aromatic protons, and a one-proton singlet at δ 12.0 due to the NH. The downfield

shift of the quartet due to H-5, compared with the doublet for H-4, could be attributed to the attachment of an acyloxy group to C-5.

EXPERIMENTAL

General methods. — Melting points were determined with a Meltemp apparatus having a 76-mm immersion thermometer, and are uncorrected. Microanalyses were made in the Unit of Microanalysis, Faculty of Science, Cairo University, Cairo, Egypt. T.l.c. was performed on Baker-Flex silica gel B-F plates. Infrared spectra were recorded with a Unicam SP 1025 spectrometer. ^{1}H-N.m.r. spectra were recorded with a Varian EM-390 spectrometer for solutions in chloroform-*d* or dimethyl sulfoxide-d_6, with tetramethylsilane (Me_4Si) as the internal or external reference, respectively. The spectra are reported with chemical shifts downfield from Me_4Si.

L-threo-*2,3-Hexodiulosono-1,4-lactone 2-(3-chlorophenylhydrazone)* (**3**). — A cold solution of L-*threo*-2,3-hexodiulosono-1,4-lactone [obtained by the oxidation of L-ascorbic acid (1.76 g, 0.01 mol)] in water (50 mL) was treated with a solution of (3-chlorophenyl)hydrazine hydrochloride (1.79 g, 0.01 mol) in ethanol (25 mL), sodium acetate (0.8 g, 0.01 mol), and a few drops of glacial acetic acid. The cooled mixture was stirred for 10 min, and then kept overnight at room temperature, whereupon yellow, crystalline product had separated out. The product was filtered off, successively washed with water, ethanol, and ether, dried, and recrystallized from ethanol, to afford yellow crystals (1.7 g, 57% yield); m.p. 186°; ν_{max}^{KBr} 3415 (OH), 3123 (NH), 1770 (OCO), and 1680 cm^{-1} (CO).

Anal. Calc. for $C_{12}H_{11}ClN_2O_5$: C, 48.3; H, 3.7; N, 9.4. Found: C, 48.4; H, 3.7; N, 9.1.

Reaction of L-threo-*2,3-hexodiulosono-1,4-lactone 2-(3-chlorophenylhydrazone) with 3-(chlorophenyl)hydrazine.* — A solution of **3** (0.9 g, 3.0 mmol) in ethanol (10 mL) was treated with (3-chlorophenyl)hydrazine hydrochloride (1.2 g, 3.4 mmol), sodium acetate (0.3 g, 3.7 mmol), and a few drops of acetic acid. The mixture was boiled for 30 min under reflux on a steam-bath, and then diluted with hot water to incipient turbidity. It was allowed to cool, whereupon a red product separated out that, on fractional recrystallization, afforded the two forms of L-*threo*-2,3-hexodiulosono-1,4-lactone 2,3-bis(3-chlorophenylhydrazone). The products were identical (m.p. and infrared spectra) with authentic samples[20].

4-(2-Acetoxyethylidene)-4-hydroxy-2,3-dioxobutano-1,4-lactone 2-(3-chlorophenylhydrazone) (**4**). — (*a*) A solution of compound **3** (0.2 g, 0.67 mmol) in dry pyridine (3 mL) was cooled, treated with acetic anhydride (3 mL), kept overnight at room temperature, and then poured onto crushed ice. The product that separated out was filtered off, successively washed with a dilute solution of sodium hydrogencarbonate, and water, and recrystallized from ethanol, to give yellow plates (0.2 g, 67% yield); m.p. 148°; ν_{max}^{KBr} 1800 (OCO), 1730 (OAc), and 1670 cm^{-1} (C=C and CO); ^{1}H-n.m.r. ($CDCl_3$): δ 12.67 (s, 1 H, NH), 7.2–7.7 (m, 4 H, aroma-

tic protons), 6.0 (t, 1 H, *J* 6 Hz, =CH-), 4.67 (d, 2 H, CH_2O), and 2.12 (s, 3 H, CH_3CO).

Anal. Calc. for $C_{14}H_{11}ClN_2O_5$: C, 52.1; H, 3.4; N, 8.7. Found: C, 51.6; H, 3.7; N, 8.8.

(*b*) A suspension of compound **3** (0.1 g) in acetic anhydride (5 mL) was boiled under reflux on a boiling-water bath, cooled, and then poured onto crushed ice. The product that separated out was filtered off, and washed with water. It was recrystallized from ethanol, to give yellow crystals (0.065 g, 60% yield); m.p. 148° (alone, or admixed with the product prepared by method *a*).

Action of alkali on L-threo-*2,3-hexodiulosono-1,4-lactone 2-(3-chlorophenylhydrazone).* — Compound **3** (0.1 g) was dissolved in 2M sodium hydroxide solution (5 mL), and the base was then neutralized with acetic acid. The product that separated out was filtered off, washed with water, and recrystallized from ethanol, giving yellow crystals identical with the starting material.

*1-(3-Chlorophenyl)-3-(*L-threo-*glycerol-1-yl)-4,5-pyrazoledione 4-(3-chlorophenylhydrazone)* (**7**). — A suspension of compound **6** (1.0 g, 2.4 mmol) in water (25 mL) was treated with 2M sodium hydroxide solution (30 mL), and the mixture was heated for 30 min at 80°, whereby the bis(hydrazone) dissolved completely. The pH of the resulting solution was adjusted to 6 with glacial acetic acid, and the product that separated out was filtered off, washed several times with water and then ethanol, dried, and recrystallized from ethanol, to give orange crystals (0.7 g, 70% yield); m.p. 220°; ν_{max}^{KBr} 3440 (OH), 1670 (OCN), and 1600 cm^{-1} (C=N).

Anal. Calc. for $C_{18}H_{16}Cl_2N_4O_4$: C, 51.1; H, 3.8; N, 13.2. Found: C, 51.0; H, 4.0; N, 13.2.

*1-(3-Chlorophenyl)-3-(1,2,3-tri-*O-*acetyl-*L-threo-*glycerol-1-yl)-4,5-pyrazoledione 4-(3-chlorophenylhydrazone)* (**8**). — A cold solution of compound **7** (1.0 g, 2.4 mmol) in dry pyridine (5 mL) was treated with acetic anhydride (5 mL), and the mixture was kept for 24 h at room temperature, and poured onto crushed ice. The product that separated out was filtered off, successively washed with a dilute solution of sodium hydrogencarbonate, water, and ethanol, and recrystallized from ethanol, giving orange crystals (0.8 g, 67% yield); m.p. 151°; ν_{max}^{KBr} 1760 (OAc) and 1670 cm^{-1} (OCN); ^{1}H-n.m.r. ($CDCl_3$): δ 7.1–7.9 (m, 8 H, aromatic), 6.23 (d, 1 H, $J_{1,2}$ 6 Hz, H-1), 5.8 (m, 1 H, H-2), 4.47 (q, 1 H, $J_{2,3}$ 4, $J_{3,3'}$ 12 Hz, H-3), 4.27 (q, 1 H, $J_{2,3'}$ 6 Hz, H-3'), 2.23 (s, 3 H, CH_3CO), and 2.13 (s, 6 H, 2 CH_3CO).

Anal. Calc. for $C_{24}H_{22}Cl_2N_4O_7$: C, 52.5; H, 4.0; N, 10.2. Found: C, 52.2; H, 4.1; N, 10.2.

1-(3-Chlorophenyl)-3-formyl-4,5-pyrazoledione 4-(3-chlorophenylhydrazone) (**9**). — A suspension of compound **7** (0.4 g, 1 mmol) in water (50 mL) was treated with a solution of sodium metaperiodate (0.5 g, 2.2 mmol) in distilled water (50 mL). The mixture was stirred for 1 h, and then kept overnight in the dark at room temperature. The product was filtered off, and recrystallized from ethanol, to give orange needles (0.2 g, 59% yield); m.p. 175°; ν_{max}^{KBr} 1700 (CHO) and 1670 cm^{-1} (OCN).

Anal. Calc. for $C_{16}H_{10}Cl_2N_4O_2$: C, 53.2; H, 2.8; N, 15.5. Found: C, 53.0; H, 2.9; N, 15.1.

3,6-Anhydro-3-C-(3-chlorophenylazo)-L-xylo-*2-hexulosono-1,4-lactone 2-(3-chlorophenylhydrazone)* (**10**). — A suspension of compound **6** (1.0 g) and cupric chloride (2.0 g) in ethanol (20 mL) was heated for 30 min on a boiling-water bath, diluted with hot water, and then cooled. The precipitated product was filtered off, successively washed with water, ethanol, and ether, dried, and recrystallized from ethanol, to give yellow crystals (0.8 g, 80% yield); m.p. 113°; ν_{max}^{KBr} 3460 (OH), 3360 (NH), and 1740 cm^{-1} (OCO).

Anal. Calc. for $C_{18}H_{14}Cl_2N_4O_4$: C, 51.3; H, 3.4; N, 13.3. Found: C, 51.0; H, 3.9; N, 13.3.

5-O-Acetyl-3,6-anhydro-3-C-(3-chlorophenylazo)-L-xylo-*2-hexulosono-1,4-lactone 2-(3-chlorophenylhydrazone)* (**11**). — A cold solution of compound **10** (0.2 g) in dry pyridine (3 mL) was treated with acetic anhydride (3 mL). The mixture was kept overnight at room temperature, and then poured onto crushed ice, and the product that separated out was filtered off, washed successively with a dilute solution of sodium hydrogencarbonate, water, and alcohol, and recrystallized from ethanol, to give yellow needles (0.15 g; 68% yield); m.p. 145°; ν_{max}^{KBr} 1760 (OAc) and 1740 cm^{-1} (OCO); ^{1}H-n.m.r. ($CDCl_3$): δ 12.0 (s, 1 H, NH), 7.0–7.9 (m, 8 H, aromatic), 5.4 (m, 1 H, H-5), 5.25 (d, 1 H, $J_{4,5}$ <1 Hz, H-4), 4.3 (m, 2 H, H-6,6′), and 2.05 (s, 3 H, CH_3CO).

Anal. Calc. for $C_{20}H_{16}Cl_2N_4O_5$: C, 51.9; H, 3.5; N, 12.1. Found: C, 51.7; H, 3.3; N, 12.2.

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