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L-*threo*-2,3-HEXODIULOSONO-1,4-LACTONE AS A PRECURSOR FOR OTHER HETEROCYCLIC COMPOUNDS*

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ABSTRACT

Reaction of the 2-(2-phenylhydrazone) (**1**) of the title compound and of that (**2**) of 4-(2-acetoxyethylidene)-4-hydroxy-2,3-dioxobutyro-1,4-lactone with methylhydrazine afforded unexpected, rearranged heterocycles. Their structures were confirmed by their i.r., n.m.r., and mass spectra. In contrast, reaction with 1-methyl-1-phenylhydrazine, or benzoylhydrazine, gave the expected products.

INTRODUCTION

Extended work in the field of saccharide bishydrazones[1–9] has shown that this field is still open for the discovery of new reactions[1–3]. The synthesis of L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(2-phenylhydrazone) (**1**) was achieved[6] in our laboratory by the reaction of L-*threo*-2,3-hexodiulosono-1,4-lactone with 1-acetyl-2-phenylhydrazine in the presence of iodine. With phenylhydrazine, only the D-*erythro* isomer was isolated[10]. Accordingly, the synthesis of the L-*threo* isomer by our method made it available as a starting material, avoiding the known[11] multistep synthesis and opening the way to synthesis of its mixed bishydrazones. Acylation of the L-*threo*- and D-*erythro*-2,3-hexodiulosono-1,4-lactone 2-(2-phenylhydrazone) gave the same olefinic product[6,10], namely, the 2-(2-phenylhydrazone) (**2**) of 4-(2-acetoxyethylidene)-4-hydroxy-2,3-dioxobutyro-1,4-lactone. The reactions of both the hydrazone and its acylated, olefinic derivative with hydrazines were studied, and form the subject of this paper.

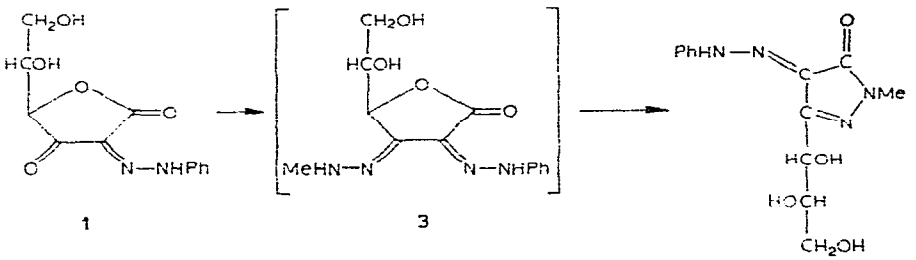
DISCUSSION

L-*threo*-2,3-Hexodiulosono-1,4-lactone 2-(2-phenylhydrazone) (**1**) was prepared by the previously published procedure[6]. Acetylation of **1** with either acetyl chloride in *N*,*N*-dimethylaniline, or acetic anhydride in pyridine, afforded the same acetate (**2**).

*Heterocycles from Carbohydrate Precursors, Part II. For Part I, see E. S. H. El Ashry, *Carbohydr. Res.*, 33 (1974) 178–183.

The behavior of both **1** and **2** towards different hydrazines was studied. Previously, it had been found[3] that, in the carbohydrate series, alkyl- and heterocyclic hydrazines react differently from aryl- and acyl-hydrazines.

Reaction of **1** with methylhydrazine gave a product which, from its elemental analysis and infrared (i.r.) spectrum (carbonyl band at 1660 cm^{-1}, different from the lactone band at 1778–1720 cm^{-1}), was a rearranged product, namely, 3-(L-*threo*-glycerol-1-yl)-1-methyl-4,5-pyrazoledione 4-phenylhydrazone (**4**), and not the expected, mixed bishydrazone (**3**) (see Scheme 1). The n.m.r. spectrum of **4** shows a sharp peak for the CH_3 group at τ 6.68. The multiplet at τ 5.66 can be assigned to



SCHEME 1

H-6 and H-6′, and the multiplet at τ 5.13 to H-5. The signal for H-4 appears as a doublet at τ 4.45, due to the spin–spin interaction with H-5. The phenyl group gives a multiplet pattern at τ 2.75. Further evidence for the structure of **4** came from a study of its mass spectrum (see Fig. 1), which exhibits a hydroxyalkyl fragmentation-pattern similar to that of the pyrazoledione; it shows a strong, molecular-ion peak at *m/e* 292, which is the third largest peak after the base peak. The ion showing the base peak at *m/e* 231 is formed by the α,β-cleavage of the trihydroxypropyl side-chain. Between these two peaks appears a series of peaks due to the loss of water and successive fragmentation of the side chain, at *m/e* 270, 261, and 242. Farther down in the spectrum, after the base peak, is a group of peaks due to further loss therefrom, *e.g.*, at *m/e* 140 due to the loss of PhN from the base peak ion. These are followed by peaks at *m/e* 105 (PhNN), 104 (HNCPh), 93 ($PhNH_2$), 92 (PhNH), 91 (PhN), and 77 (Ph).

The reaction of the olefinic acetate **2** with methylhydrazine was found to be more complicated. Thus, an orange product was obtained whose elemental analysis was quite different from that of the expected, mixed osazone (**5**), and agreed with that calculated for $C_{14}H_{16}N_6O$. It was given structure **6** (see Scheme 2) from the following evidence. (*1*) Its i.r. spectrum had a band at 1640 cm^{-1}, which was assigned to carbonylamide, and the lactone and the acetyl bands had disappeared. This suggested occurrence of a rearrangement that involved the acetyl group, and the opening of the lactone ring with further cyclization with one of the hydrazone residues, to give a product which showed the amide absorption. A similar i.r. spectrum is given by the

pyrazolediones, which show an amide band at 1660 cm^{-1}. (*2*) On attempted acetylation of **6** with acetic anhydride in pyridine, it was isolated unchanged, indicating the absence of hydroxyl groups, confirmed by the absence of hydroxyl absorption from its i.r. spectrum. (*3*) The n.m.r. spectrum of **6** in deuteriochloroform (see Fig. 2)

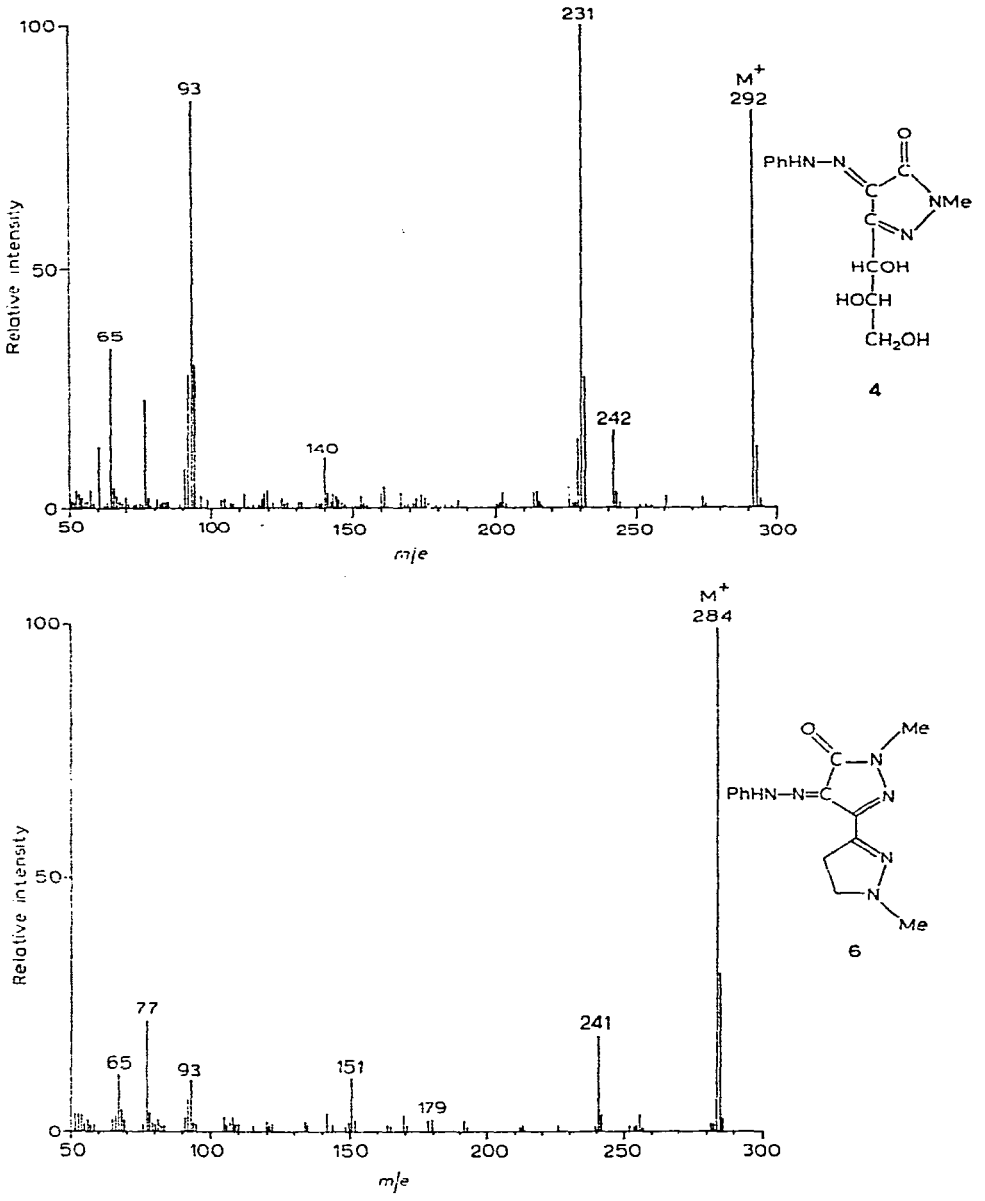
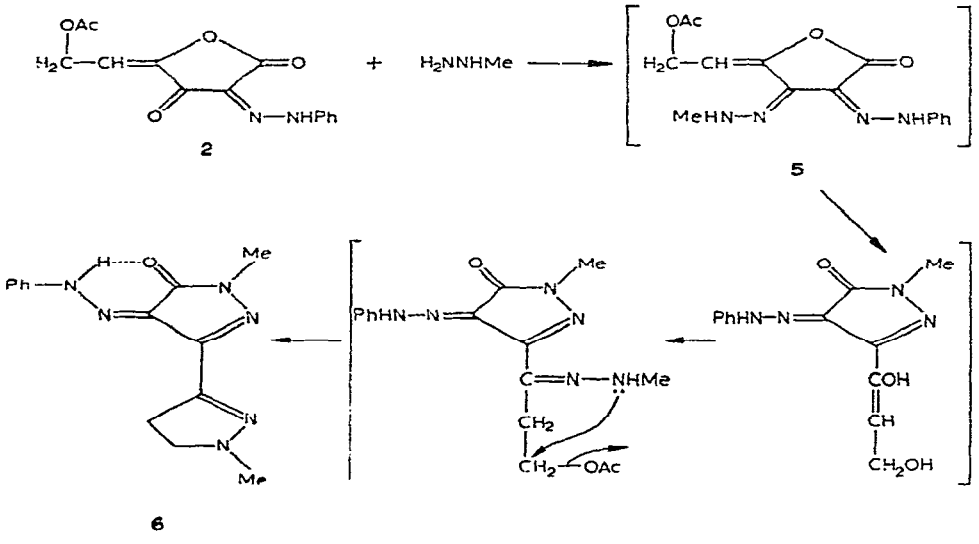


Fig. 1. Mass spectra of 3-(L-*threo*-glycerol-1-yl)-1-methyl-4,5-pyrazoledione 4-phenylhydrazone (**4**) and 1-methyl-3-(1-methylpyrazolin-3-yl)-4,5-pyrazoledione 4-phenylhydrazone (**6**).

showed two two-proton triplets, at τ 7.27 and 6.70, of the two adjacent, methylene groups. Two singlets appeared at τ 6.85 and 6.52, due to two methyl groups. The phenyl group appeared at τ 2.85, and the N–H proton at τ −3.56. (*4*) The mass spectrum of **6** (see Fig. 1) showed a molecular-ion peak at *m/e* 284, which agreed with the molecular weight expected. The presence of peaks at *m/e* 201 and 83 was presumed



SCHEME 2

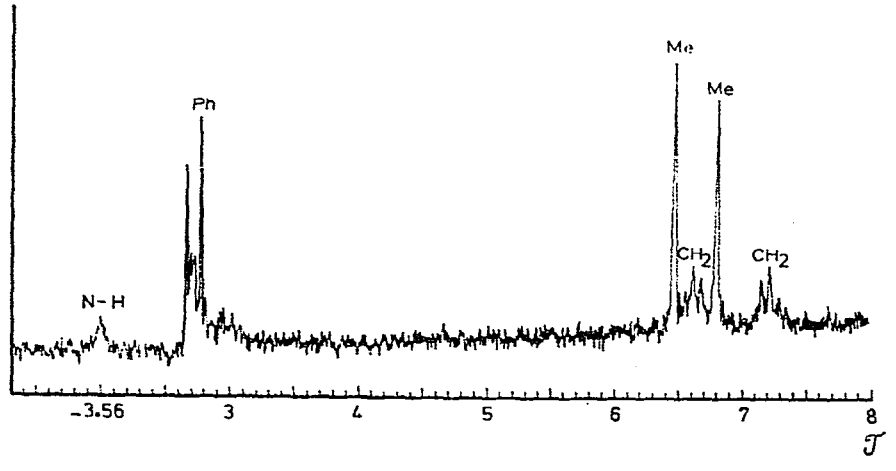
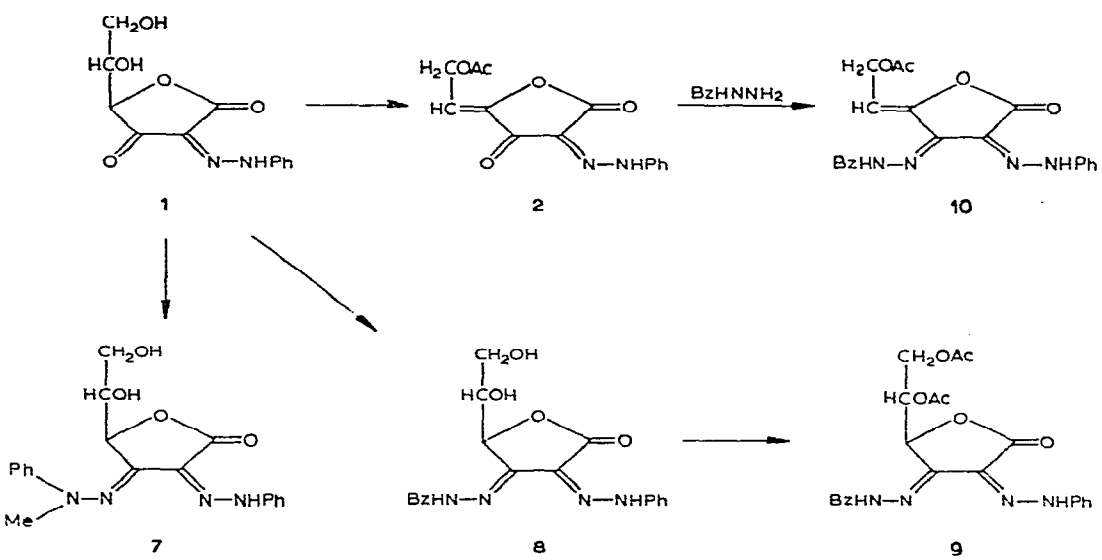


Fig. 2. ^{1}H-N.m.r. spectrum of compound **6**.

due to the cleavage of the molecule into its component heterocycles. In addition, the spectrum showed a major peak at *m/e* 269 due to the splitting of the methyl group, and one peak at *m/e* 253 and another at *m/e* 241, due to further splitting of oxygen and CO, respectively.

From these results, it was concluded that, during the reaction, two moles of methylhydrazine are involved, as shown by the elemental analysis, and the n.m.r. and mass spectra, and that one of the three hydrazone residues is free (not cyclized), as indicated by the n.m.r. spectrum, which revealed only one imino proton. In addition, of the two other hydrazone residues, one is involved in cyclization with the carbonyl group resulting from the opening of the lactone ring, as indicated by the i.r. spectrum, and the other is also involved in cyclization, probably with the acetoxyl group. Therefore, it was deduced that methylhydrazine reacts with **2** as shown in Scheme 2, to give **6**. The imino proton of the hydrazone residue is chelated with the adjacent carbonyl group, as indicated[12–16] by its resonance in the n.m.r. spectrum.

On the other hand, the reaction of asymmetric hydrazines, *e.g.*, 1-methyl-1-phenylhydrazine, with L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(2-phenylhydrazone) (**1**) afforded the expected, corresponding bishydrazone, namely, L-*threo*-2,3-hexodiulosono-1,4-lactone 3-(2-methyl-2-phenylhydrazone) 2-(2-phenylhydrazone) (**7**). This product is obviously unable to undergo the rearrangements already described. Its infrared spectrum showed a lactone band at 1730 cm^{-1}, and a hydroxyl band at 3500 cm^{-1}. Its n.m.r. spectrum showed a three-proton signal at τ 6.55, due to the methyl group. A multiplet for the two phenyl groups appeared at τ 2.95–2.45. Its mass spectrum showed a small, molecular-ion peak at *m/e* 368, in addition to other fragments which supported the structure assigned.



SCHEME 3

The reaction of the phenylhydrazone **1** with benzoylhydrazine gave the corresponding, mixed osazone (**8**). Its i.r. absorption spectrum showed a carbonylamide band at 1660 cm^{-1}, a lactone band at 1725 cm^{-1}, and hydroxyl-group absorption at 3350 cm^{-1}. Acetylation of L-*threo*-2,3-hexodiulosono-1,4-lactone 3-benzoylhydrazone 2-(2-phenylhydrazone) (**8**) with acetic anhydride in pyridine afforded the corresponding diacetate (**9**) (see Scheme 3), and no dehydration product could be isolated. Structure **9** was indicated by the elemental analysis, and the i.r. spectrum, which showed a band at 1730 cm^{-1} corresponding to the *O*-acetyl group, in addition to the lactone band. To confirm that dehydration does not occur during acetylation, the olefinic, mixed osazone **10** was prepared by condensation of the olefinic acetate **2** with benzoylhydrazine, and it was found that the compounds are completely different. The mass spectrum of **9** (see Fig. 3) showed a small, molecular-ion peak at *m/e* 466, followed by peaks at *m/e* 424 (due to the loss of CH_2=CO), at *m/e* 406 (due

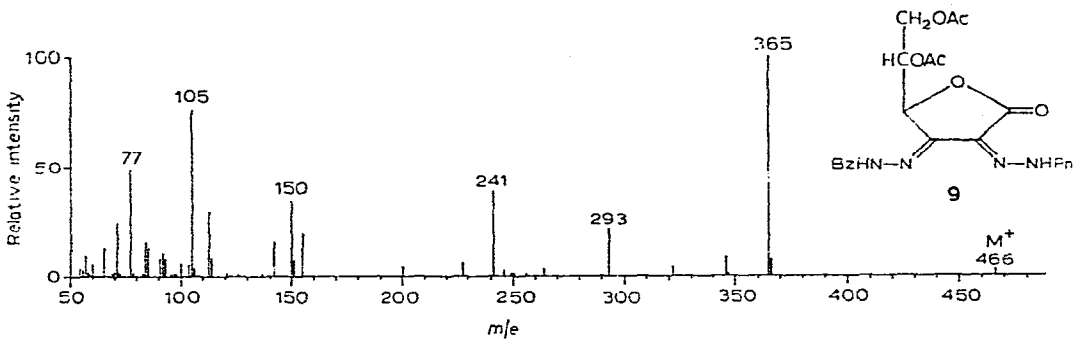


Fig. 3. Mass spectrum of 5 6-di-*O*-acetyl-L-*threo*-2 3-hexodiulosono-1,4-lactone 3-(2-benzoylhydrazone) 2-(2-phenylhydrazone) (**9**).

to the loss of AcOH), the base peak at *m/e* 365 (due to the cleavage between C-5 and C-6, in addition to the loss of CO of the lactone), and other peaks (due to the losses from the side chain), and the common peak at *m/e* 105 due to either PhCO or PhNN. Unlike bis(arylhydrazones) of dehydro-L-ascorbic acid, which are dehydrogenated with such mild oxidants as cupric chloride to the dehydro derivatives[4], the bis(acylhydrazones) underwent decomposition, through complex formation, to give benzoic acid. This reaction was applied to the mixed osazone **8**; it gave 1,2-dibenzoylhydrazine, and no other products could be isolated.

EXPERIMENTAL

General methods. — Unless otherwise indicated, solutions were evaporated under diminished pressure at 40–50°. Melting points were determined with a Kofler-block apparatus, and are uncorrected. I.r. spectra were recorded with Hitachi Model EPT-GS and Unicam SP 200 spectrometers; u.v. and visible spectra, with a Unicam

SP 800 spectrometer; and n.m.r. spectra (for solutions in pyridine-d_5 or chloroform-*d*), with INM 4-H-100 and Varian A-60 spectrometers, with tetramethylsilane as the standard. Chemical shifts are given on the τ scale. Mass spectra were recorded with an M-66 instrument; intensities are given in parentheses, as percentages of the base peak. Microanalyses were performed in the Chemistry Department, Tokyo Institute of Technology, Tokyo, Japan.

L-threo-*2,3-Hexodiulosono-1,4-lactone 2-(2-phenylhydrazone)* (**1**). — Compound **1** was prepared by a modification of the previously published procedure[6] by heating a solution of L-*threo*-2,3-hexodiulosono-1,4-lactone [prepared by the oxidation of L-ascorbic acid (18 g) with iodine] in water (200 ml) with 1-acetyl-2-phenylhydrazine (15 g) for 30 min on a boiling-water bath. The mixture was cooled, kept for a few hours, diluted with cold water, and washed with chloroform. The aqueous layer was nucleated with a few crystals of the monohydrazone **1**, and kept overnight in an evaporating dish, to give a crop of the monohydrazone **1**; after a few days, a second crop had separated. The product was recrystallized from ethanol, to give yellow needles, m.p. 167–170°.

Acetylation of L-threo-*2,3-hexodiulosono-1,4-lactone 2-(2-phenylhydrazone)*[6] (**1**). — A suspension of compound **1** (0.5 g) in *N,N*-dimethylaniline (10 ml) was cooled, and then acetyl chloride (5 ml) was added dropwise. The mixture was kept overnight at room temperature and then poured onto crushed ice, with stirring. The product that separated was filtered off, washed repeatedly with water, and dried. Recrystallization from chloroform–ethanol afforded yellow crystals of **2**, m.p. 130–132°, which, on repeated recrystallization, gave a product of m.p. 160–162°.

3-(L-threo-*Glycerol-1-yl)-1-methyl-4,5-pyrazoledione 4-(2-phenylhydrazone)* (**4**). — A solution of compound **1** (0.5 g) in methanol (50 ml) was treated with methylhydrazine (2 ml). The mixture was boiled for 1 h, and then cooled and concentrated. The product that crystallized was recrystallized from ethanol, to give orange needles of **4**, m.p. 187–188°; ν_{max}^{KBr} 3250 (OH), 1660 (CON), 1595, 1450, 1345, 1260, 760, and 665 cm^{-1}; n.m.r. data (100 MHz, C_5D_5N and D_2O): τ 6.68 (3-proton singlet, CH_3), 5.66 (2-proton multiplet, H-6,6′), 5.13 (1-proton multiplet, H-5), 4.45 (1-proton doublet, H-4), and 2.45–2.95 (5-proton multiplet, Ph); mass-spectral data: 294 (2, M+2), 293 (21, M+1), 292 (83, M), 274 (2, M−H_2O), 261 (2, M−CH_2OH), 243 (3), 242 (16, M−CH_2OH−H_3O), 232 (30), 231 (100, M−$CHOHCH_2OH$), 230 (15), 227 (5), 215 (3), 214 (3, 231−OH), 203 (3, 231−CO), 187 (2, 231−CO–O), 175 (2), 174 (2, 231−CO–CHO), 167 (3), 161 (5), 153 (2), 144 (2), 143 (3), 141 (3), 140 (10), 124 (2), 120 (3), 119 (3, PhNCO), 112 (3), 105 (2, PhNN), 104 (2), 94 (28), 93 (85, $PhNH_2$), 92 (27), 91 (8), 77 (23), 65 (33), 61 (13), 57 (3), and 53 (3).

Anal. Calc. for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.93; H, 5.62; N, 19.45.

1-Methyl-3-(1-methylpyrazolin-3-yl)-4,5-pyrazoledione 4-(2-phenylhydrazone) (**6**). — A solution of compound **2** (0.5 g) in ethanol (20 ml) was treated with methylhydrazine (0.3 ml), and boiled for 10 min. The mixture was cooled, and the product crystallized in dark-orange plates of **6**, m.p. 264–266° (from ethanol); ν_{max}^{KBr} 1640 (CON)

and 1600 cm^{-1} (C=N); n.m.r. data (100 MHz, chloroform-*d*): τ 7.27 (2-proton triplet, methylene group), 6.85 (3-proton singlet, Me), 6.70 (2-proton triplet, methylene group), 6.52 (3-proton singlet, Me), 3.0–2.7 (5-proton multiplet, Ph), and ~3.56 (1-proton, broad singlet, N–H); mass-spectral data: 286 (2, M+2), 285 (32, M+1), 284 (100, M), 283 (1), 269 M−CH_3), 256 (3, M−CO or M−N_2), 255 (1), 252 (1, M−CH_3–OH), 242 (3), 241 (19, M−CH_3–CO), 240 (1), 226 (1, M−2 CH_3–CO), 213, 212, 201, 193, 192 (2, M−CH_3–Ph), 180 (2), 179 (2, M−PhNN), 171, 170 (3), 165, 164 (1), 152 (2), 151 (11), 150 (2), 149, 144 (1), 142 (3), 137, 136 (2), 135 (2), 134 (M−2 CH_3–PhNN), 122 (1), 121, 120 (2), 119 (PhNCO), 115, 110 (1), 109 (1), 108 (2), 107 (1), 106, 105 (3), 95 (1), 94 (1), 93 (10), 92 (6), 91 (3), 83 (1), 82, 81 (2), 80, 79, 78 (4), 77 (22, Ph), 76, 69 (2), 68, 67 (6), 66 (4), 65 (12), 64 (3), 63 (2), 58 (1), 57 (1), 56 (2), 55 (1), 54 (3), 53 (2), 52 (3), 51 (7), 50 (2), 44 (8), 43 (16), 42 (24), 41 (3), 40 (2), 39 (8), 38 (2), and 30 (3).

Anal. Calc. for $C_{14}H_{16}N_6O$: C, 59.14; H, 5.67; N, 29.56. Found: C, 58.86; H, 5.38; N, 29.75.

L-threo-*2,3-Hexodiulosono-1,4-lactone 3-(2-methyl-2-phenylhydrazone) 2-(2-phenylhydrazone)* (**7**). — A solution of compound **1** (0.5 g) in methanol (50 ml) was boiled with 1-methyl-1-phenylhydrazine (2 ml) for 15 min. The mixture was concentrated, and the product was filtered off, and recrystallized from ethanol, to give orange needles of **7**, m.p. 205–207°; ν_{max}^{KBr} 3500 (OH), 1730 (COO), and 1600 cm^{-1} (C=N); n.m.r. data (100 MHz, C_5D_5N and D_2O): τ 6.55 (3-proton singlet, Me), 5.75 (multiplet), 5.15 (multiplet), 3.9 (singlet), and 2.95–2.45 (10-proton multiplet, 2 Ph); mass-spectral data: 368 (11, M^+), 298 (3), 273 (6), 262 (4.6, M−PhNNH), 234 (5), 233 (8, M−PhNNH–CHO), 232 (5), 184 (11), 183 (75, M−PhNNH–Ph–2 H), 182 (59), 169 (6), 155 (6), 141 (5), 136 (3), 128 (5), 121 (16), 114 (9), 107 (6), 106 (13), 94 (11), 93 (100, $PhNH_2$), 92 (19), 78 (6), 77 (25), 76 (6), 66 (71), 65 (29), 54 (6), 52 (8), and 51 (8).

Anal. Calc. for $C_{19}H_{20}N_4O_4$: C, 61.94; H, 5.47; N, 15.21. Found: C, 61.75; H, 5.31; N, 15.31.

L-threo-*2,3-Hexodiulosono-1,4-lactone 3-(2-benzoylhydrazone) 2-(2-phenylhydrazone)* (**8**). — A solution of compound **1** (0.2 g) in ethanol (20 ml) was treated with benzoylhydrazine (0.2 g), and the mixture was boiled under reflux for 30 h. The solution was concentrated, and the precipitated product was filtered off, washed with water, dried, and recrystallized from ethanol, to give yellow needles of **8**, m.p. 228–230°; ν_{max}^{KBr} 3300 (OH), 1725 (COO), 1660 (CON), and 1600 cm^{-1} (C=N).

Anal. Calc. for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.75; N, 14.65. Found: C, 59.52; H, 4.82; N, 14.32.

5,6-Di-O-acetyl-L-threo-*2,3-hexodiulosono-1,4-lactone 3-(2-benzoylhydrazone) 2-(2-phenylhydrazone)* (**9**). — A solution of compound **8** (0.2 g) in dry pyridine (10 ml) was treated with acetic anhydride (4 ml), and kept overnight at room temperature. The mixture was poured onto crushed ice, and the product was filtered off, washed with water, dried, and recrystallized from ethanol, to give yellow needles of **9**, m.p. 182–184°; ν_{max}^{KBr} 1730 (COO and OAc), 1680 (CON), and 1595 cm^{-1} (C=N); mass-

spectral data: 466 (2, M^+), 366 (7), 365 (100, $M-CH_2OAc-CO$), 346 (9, $M-CH_2OAc-CO-H_3O$ or $M-2$ AcOH), 322 (5), 293 (21), 264 (10), 241 (40), 228 (7), 200 (4), 155 (19), 151 (7), 150 (35), 142 (17), 121 (1), 114 (7), 113 (33), 106 (3), 105 (77, PhNN or PhCO), 104 (5), 100 (6), 93 (7), 92 (10), 91 (7), 85 (12), 84 (15), 77 (70), 71 (25), 65 (13), 60 (5), 57 (9), and 53 (4).

Anal. Calc. for $C_{23}H_{22}N_4O_7$: C, 59.22; H, 4.75; N, 12.01. Found: C, 59.22; H, 4.72; N, 12.11.

4-(2-Acetoxyethylidene)-4-hydroxy-2,3-dioxobutyro-*1,4-lactone 3-(2-benzoylhydrazone) 2-(2-phenylhydrazone)*[6] (**10**). — A solution of compound **2** (0.3 g) in ethanol (20 ml) was boiled with benzoylhydrazine (0.2 g) under reflux for 20 h. The mixture was concentrated, and the solid product (**10**) was filtered off, and recrystallized from ethanol, to give yellow needles, m.p. 160–162°; ν_{max}^{KBr} 1740 (COO, OAc), 1675 (CON, C=C), and 1600 cm^{-1} (CN).

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