*Carbohydrate Research*, 59 (1977) 141–149


# REACTIONS OF THE 3-OXIME 2-PHENYLHYDRAZONE AND MIXED BISHYDRAZONES OF DEHYDRO-L-ASCORBIC ACID: CONVERSION INTO SUBSTITUTED TRIAZOLES AND PYRAZOLINEDIONES

MOHAMED EL SEKILY, SOHILA MANCY, IBRAHIM EL KHOLY, EL SAYED H. EL ASHRY,
*Department of Chemistry, Faculty of Science, Alexandria University, Alexandria (Egypt)*

HASSAN S. EL KHADEM, AND DAVID L. SWARTZ
*Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan 49931 (U. S. A.)*

(Received February 28th, 1977; accepted for publication, March 26th, 1977)

ABSTRACT

L-*threo*-2,3-Hexodiulosono-1,4-lactone 2-phenylhydrazone (**1**) reacted with hydroxylamine to give the 3-oxime 2-phenylhydrazone (**2**). On boiling with acetic anhydride, **2** was dehydrated to 4-[L-*threo*-2,3-diacetoxy-(1-hydroxypropyl)]-2-phenyl-1,2,3-triazole-5-carboxylic acid lactone (**3**), which was converted into 2-phenyl-4-(L-*threo*-1,2,3-trihydroxypropyl)-1,2,3-triazole-5-carboxamide (**4**) with liquid ammonia. The structure of compound **4** was confirmed by acetylation to 2-phenyl-4-(L-*threo*-1,2,3-triacetoxypropyl)-1,2,3-triazole-5-carboxamide (**5**), and by periodate oxidation followed by reduction, to give 4-(hydroxymethyl)-2-phenyl-1,2,3-triazole-5-carboxamide (**6**). Treatment of compound **1** with aryl- or aroyl-hydrazines afforded mixed bishydrazones (**7**–**14**), which were acetylated to **15**-**21**, and treated with hydrazine to give pyrazolinediones **22** and **23**.

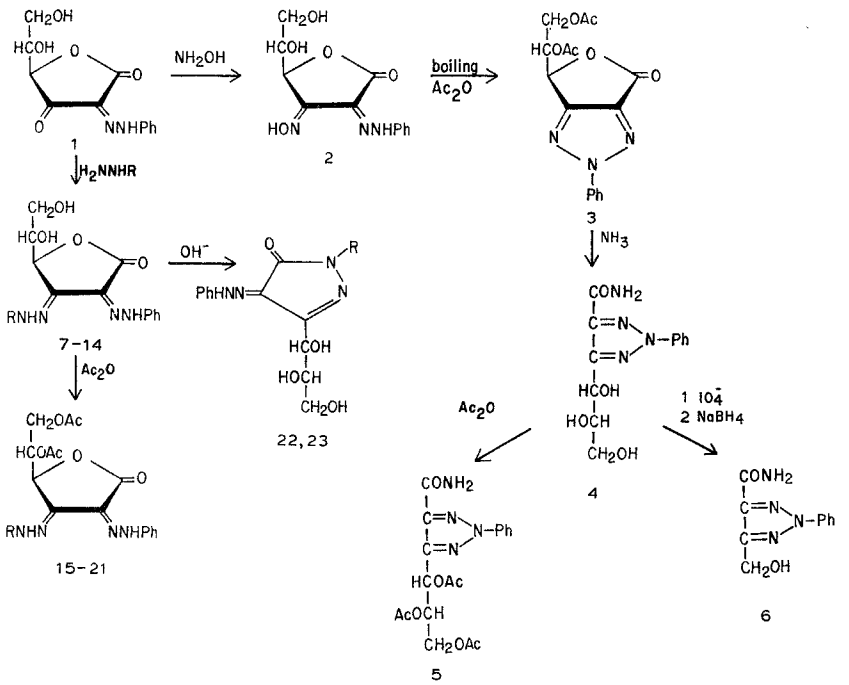
## INTRODUCTION

Many of the reactions of dehydro-L-ascorbic acid bishydrazones (L-*threo*-2,3-hexodiulosono-1,4-lactone bishydrazones) differ from those of the sugar osazones (glycosulose 1,2-bishydrazones). The former readily undergo cyclizations involving either nucleophilic attack of a hydrazone nitrogen atom on the 1-carbonyl group, or attack of a hydroxyl group on the hydrazone residue. Thus, for example, oxidation of the dehydro-L-ascorbic acid bishydrazones yields bicyclic azo compounds[1,2], whereas, the glycosulose osazones yield triazoles[3]. Other differences have been discussed[4,5].

The present work deals with the synthetic application of a monophenylhydrazone of dehydro-L-ascorbic acid, namely, L-*threo*-2,3-hexodiulosono-1,4-lactone 2-phenylhydrazone, by way of its conversion into a hydrazone oxime and into mixed bishydrazones. The first compound yielded hitherto unprepared triazole derivatives of dehydro-L-ascorbic acid.

DISCUSSION

Dehydro-L-ascorbic acid 2-phenylhydrazone (L-*threo*-2,3-hexodiulosono-1,4-lactone 2-phenylhydrazone) (**1**), which was first prepared by Micheel and Hesse[6] and then by one of us[7], is a compound of great synthetic potential. It can react with a variety of carbonyl reagents, such as hydroxylamine, to give a hydrazone oxime, and with substituted hydrazines to give mixed bishydrazones.




When compound **1** was treated with hydroxylamine, L-*threo*-2,3-hexodiulosono-1,4-lactone 3-oxime 2-phenylhydrazone (**2**) was obtained. Boiling of compound **2** with acetic anhydride resulted in acetylation of the hydroxyl groups on C-5 and C-6, and elimination of a molecule of water from the hydrazone residue and the hydroxylamino group, to form 4-[L-*threo*-2,3-diacetoxy-(1-hydroxypropyl)]-2-phenyl-1,2,3-triazole-5-carboxylic acid lactone (**3**). Compound **3** is the first triazole derivative of dehydro-L-ascorbic acid. Its structure was verified by n.m.r. spectroscopy, which showed two acetyl groups at $\delta$ 2.0 and 2.1. The ABX system of the methylene group involving C-6 was centered at $\delta$ 4.5, followed by a multiplet at $\delta$ 5.6 assigned to the methine proton on C-5. A doublet at $\delta$ 5.9 ($J$ 6 Hz) was assigned to the methine proton on C-4. The protons of the phenyl group appeared at $\delta$ 7.57 and 8.2. No protons appeared in the offset region of the spectrum.

The mass spectrum of compound **3** also confirmed the presence of the triazole

ring. It showed a small molecular peak at *m/e* 345, and a base peak at *m/e* 200 due to the loss of the diacetoxyethyl side-chain from triazole **3** (see Fig. 1).

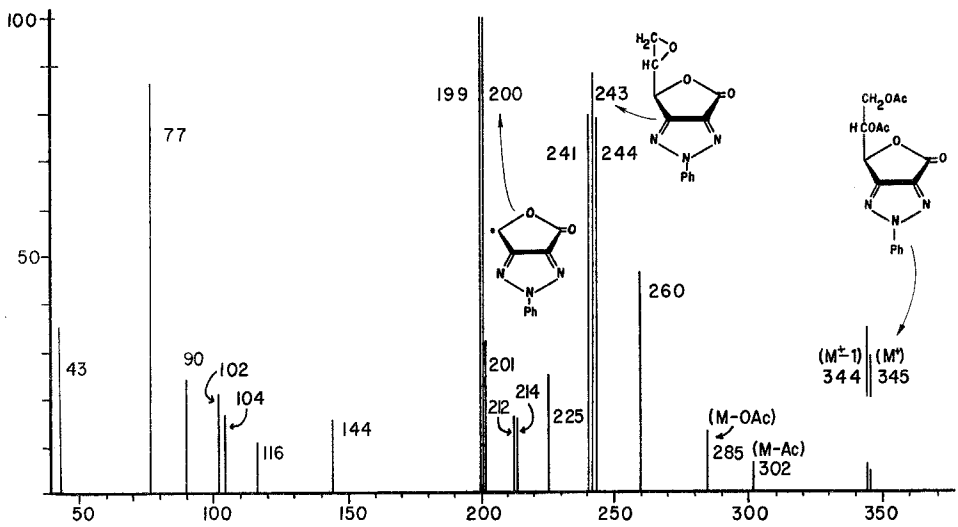



Fig. 1. Mass spectrum of compound **3**.

Upon treatment of triazole **3** with liquid ammonia, deacetylation occurred concurrently with opening of the lactone ring, to afford 2-phenyl-4-(L-*threo*-1,2,3-trihydroxypropyl)-1,2,3-triazole-5-carboxamide (**4**). Acetylation of compound **4** gave a triacetate designated 2-phenyl-4-(L-*threo*-1,2,3-triacetoxypropyl)-1,2,3-triazole-5-carboxamide (**5**). Periodate oxidation of compound **4**, followed by borohydride reduction, afforded 4-(hydroxymethyl)-2-phenyl-1,2,3-triazole-5-carboxamide (**6**).

When the mono(phenylhydrazone) of dehydro-L-ascorbic acid (**1**) was treated with aryl- and aroyl-hydrazines, it yielded mixed 3-(arylhydrazone) 2-(phenylhydrazone) derivatives (**7–9**) and 3-(aroylhydrazone) 2-(phenylhydrazone) derivatives (**10–14**), respectively (see Table I). On acetylation with acetic anhydride in pyridine, these compounds gave diacetates **15–21** (see Table II). When the L-*threo*-2,3-hexodiulosono-1,4-lactone 3-(arylhydrazone) 2-(phenylhydrazone)s (**8, 9**) were treated with hydrazine hydrate, or with alkali, and then acidified, their lactone ring was opened, and a nucleophilic attack of the nitrogen atom of the hydrazone residues on the 1-carbonyl group occurred, yielding 1-aryl-3-(L-*threo*-glycerol-1-yl)-4,5-pyrazolinedione 4-(phenylhydrazone)s (**22, 23**) (see Table III). The structure of these compounds was based on that of similar compounds prepared[2,8].

The hydrazone oxime **2** and the mixed aroylhydrazone phenylhydrazones (**10–14**) were yellow, whereas the mixed 3-arylhydrazone 2-phenylhydrazones (**7–9**) were red. The triazoles **3–6** were colorless, and the pyrazolinediones **22** and **23** had an orange color. The u.v.- and i.r.-spectral data for compounds **7–23** are given in Table IV.

TABLE I

L-*threo*-2,3-HEXODIULOSONO-1,4-LACTONE 2,3-BIS(HYDRAZONE)S (**7–14**)

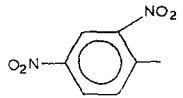
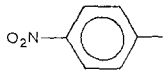
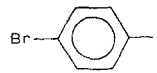
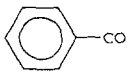
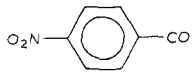
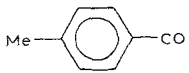
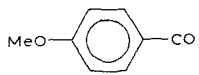
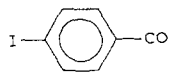
| *Compound* | *R* | *M.p.* (*degrees*) | *Yield* (%) | *Formula* | | *Analysis* | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | *C* | *H* | *N* |
| **7** |  | 205–206 | 76 | $C_{18}H_{16}N_6O_8$ | Calc. | 48.65 | 3.63 | 18.81 |
| | | | | | Found | 48.72 | 3.52 | 18.76 |
| **8** |  | 256–258 | 72 | $C_{18}H_{17}N_5O_6$ | Calc. | 54.13 | 4.29 | 17.54 |
| | | | | | Found | 54.32 | 4.16 | 17.42 |
| **9** |  | 248–249 | 78 | $C_{18}H_{17}BrN_4O_4$ | Calc. | 49.90 | 3.96 | 12.93 |
| | | | | | Found | 49.81 | 3.80 | 12.79 |
| **10**[9] |  | 230–232 | 62 | $C_{19}H_{18}N_4O_5$ | Calc. | 59.78 | 4.75 | 14.65 |
| | | | | | Found | 59.58 | 4.59 | 14.42 |
| **11** |  | 218–220 | 64 | $C_{19}H_{17}N_5O_7$ | Calc. | 53.39 | 4.99 | 16.39 |
| | | | | | Found | 53.46 | 4.26 | 16.54 |
| **12** |  | 204–205 | 60 | $C_{20}H_{20}N_5O_5$ | Calc. | 60.60 | 5.09 | 14.14 |
| | | | | | Found | 60.73 | 5.23 | 14.58 |
| **13** |  | 180–210 | 61 | $C_{20}H_{20}N_4O_6$ | Calc. | 58.28 | 4.39 | 13.58 |
| | | | | | Found | 58.46 | 4.52 | 13.79 |
| **14** |  | 208–210 | 34 | $C_{19}H_{17}IN_4O_5$ | Calc. | 44.89 | 3.37 | 11.02 |
| | | | | | Found | 44.72 | 3.12 | 10.83 |

TABLE II

5,6-DI-*O*-ACETYL-L-*threo*-2,3-HEXODIULOSONO-1,4-LACTONE 2,3-BIS(HYDRAZONE)S (**15–21**)

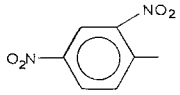
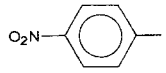
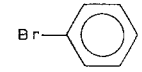
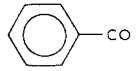
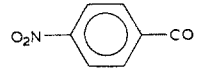
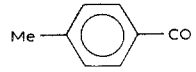
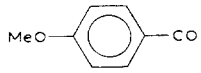
| *Compound* | *R* | *M.p.* (*degrees*) | *Yield* (%) | *Formula* | | *Analysis* | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | *C* | *H* | *N* |
| **15** |  | 148–149 | 92 | $C_{22}H_{20}N_6O_{10}$ | Calc. | 50.00 | 3.83 | 15.91 |
| | | | | | Found | 50.12 | 3.92 | 15.76 |
| **16** |  | 194–195 | 84 | $C_{22}H_{21}N_5O_8$ | Calc. | 54.66 | 4.38 | 14.49 |
| | | | | | Found | 54.48 | 4.46 | 14.32 |
| **17** |  | 200–201 | 82 | $C_{22}H_{21}BrN_4O_6$ | Calc. | 51.07 | 4.09 | 10.83 |
| | | | | | Found | 51.22 | 4.26 | 10.74 |
| **18**[9] |  | 183–185 | 68 | $C_{23}H_{22}N_4O_7$ | Calc. | 59.22 | 4.75 | 12.01 |
| | | | | | Found | 59.01 | 4.62 | 11.84 |
| **19** |  | 133–135 | 64 | $C_{23}H_{21}N_4O_9$ | Calc. | 54.01 | 4.14 | 13.69 |
| | | | | | Found | 53.84 | 4.01 | 13.51 |
| **20** |  | 190–192 | 51 | $C_{24}H_{24}N_4O_7$ | Calc. | 59.99 | 5.04 | 11.66 |
| | | | | | Found: | 59.72 | 4.84 | 11.46 |
| **21** |  | 130–131 | 70 | $C_{24}H_{24}N_4O_8$ | Calc. | 58.06 | 4.87 | 11.29 |
| | | | | | Found | 58.12 | 4.53 | — |

TABLE III

1-ARYL-3-(L-*threo*-GLYCEROL-1-YL)-4,5-PYRAZOLINEDIONE 4-(PHENYLHYDRAZONE)S (**22**, **23**)

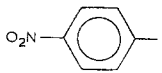
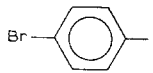
| *Compound* | *R* | *M.p.* (*degrees*) | *Yield* (%) | *Formula* | | *Analysis* | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | *C* | *H* | *N* |
| **22** |  | 230–231 | 60 | $C_{18}H_{17}N_5O_6$ | Calc. | 54.13 | 4.29 | 17.54 |
| | | | | | Found | 54.28 | 4.21 | 17.64 |
| **23** |  | 156–158 | 62 | $C_{18}H_{17}BrN_4O_4$ | Calc. | 49.90 | 3.95 | 12.93 |
| | | | | | Found | 49.86 | 3.72 | 12.76 |

TABLE IV

U.V.- AND I.R.-SPECTRAL DATA FOR SOME OF THE COMPOUNDS PREPARED

| *Compound* | *λ (nm)* | | *log ε* | *ν ($cm^{-1}$) for CO* |
|---|---|---|---|---|
| **7** | max | 228, 268, 342, 410 (sh), 500 (sh) | 4.28, 4.28, 4.48, 4.22, 3.52 | 1720 |
| | min | 243, 293 | 4.24, 3.52 | |
| **8** | max | 247, 352, 460 | 4.09, 4.34, 4.35 | 1730 |
| | min | 293, 395 | 3.71, 3.94 | |
| **9** | max | 205, 263 (sh), 280, 350, 445 | 4.03, 4.19, 4.27, 3.90, 4.22 | 1720 |
| | min | 220, 320, 385 | 3.78, 3.81, 3.78, | |
| **10** | max | 207, 248, 278, 412 | 3.96, 4.14, 4.10, 4.27 | 1680, 1740 |
| | min | 213, 265, 340 | 4.00, 2.95 | |
| **11** | max | 213, 252, 293 (sh), 418 | 3.93, 4.31, 3.83, 4.25 | 1680, 1720 |
| | min | 222, 320 | 3.91, 3.52 | |
| **12** | max | 218, 240 (sh), 280, 417 | 4.02, 4.17, 4.11, 4.29 | 1670, 1720 |
| | min | 220, 255, 342 | 3.70, 4.10, 3.19 | |
| **13** | max | 232, 262, 397 | 4.68, 4.23, 4.31 | 1680, 1740 |
| | min | 250, 295 | 4.01, 4.18 | |
| **14** | max | 238, 252, 398 | 4.11, 3.98, 4.22 | 1660, 1740 |
| | min | 246, 276 | 3.81, 3.76 | |
| **15** | max | 225, 253, 322, 475 | 4.44, 4.46, 4.55, 3.78 | 1730 |
| | min | 235, 280, 440 | 4.39, 4.12, 3.72 | |
| **16** | max | 253, 352, 440 | 5.60, 6.02, 5.02 | 1730 |
| | min | 295, 396 | 5.28, 5.38 | |
| **17** | max | 203, 262, 280, 355, 446 | 4.12, 4.26, 4.28, 3.95, 4.26 | 1735 |
| | min | 222, 270, 325, 390 | 3.87, 4.21, 3.74, 3.92 | |
| **18** | max | 210, 253, 287, 4.20 | 3.96, 4.17, 4.11, 4.29 | 1735 |
| | min | 268, 343 | 4.06, 3.32 | |
| **19** | max | 238, 253 (sh), 270, 403 | 4.45, 4.13, 3.96, 4.49 | 1740 |
| | min | 317 | 3.19 | |
| **20** | max | 213, 245, 307, 422 | 3.81, 4.02, 3.95, 3.89 | 1740 |
| | min | 272, 345 | 3.71, 3.46 | |
| **21** | max | 240, 275 (sh), 400 | 4.24, 3.96, 4.59 | 1725, 1770 |
| | min | 317 | 3.76 | |
| **22** | max | 227, 400 | 4.04, 4.32 | 1660 |
| | min | 268 | 3.65 | |
| **23** | max | 216, 255, 403 | 4.21, 4.23, 4.56 | 1660 |
| | min | 223, 302 | 4.12, 4.00 | |

## EXPERIMENTAL

*General methods.* — Melting points were determined on a Kofler block, and are uncorrected. Microanalyses were made in the Department of Chemistry and Chemical Engineering, Michigan Technological University, and the Chemistry Department of the University of Paris. I.r. and u.v. spectra were recorded with Unicam Sp-200 and Unicam Sp-800 instruments. N.m.r. spectra were recorded with a Varian HA 100 instrument, and mass spectra with a Varian M 60 spectrometer.

L-threo-*2,3-Hexodiulosono-1,4-lactone 3-oxime 2-phenylhydrazone* (**2**). — A solution of L-*threo*-2,3-hexodiulosono-1,4-lactone 2-phenylhydrazone[6,7] (**1**) (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. It was concentrated, water (10 ml) was added, and the solid that separated was filtered off, washed successively with water, ethanol, and ether, and dried (yield 0.8 g). Compound **2** was recrystallized from ethanol, giving yellow needles, m.p. 224–226°; $\nu_{max}^{KBr}$ 3200 (OH), 1735 (COO), and 1630 $cm^{-1}$ (C=N); $\lambda_{max}^{EtOH}$ 228,286, and 383 nm (log ε 4.24, 3.62, and 4.41); $\lambda_{max}^{EtOH}$ 265 and 308 nm (log ε 3.54 and 3.38). It is soluble in acetone, chloroform, or benzene, sparingly soluble in methanol or ethanol, and insoluble in water.

*Anal.* Calc. for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.74; H, 4.75; N, 15.21.

4-[L-threo-*2,3-Diacetoxy-(1-hydroxypropyl)*]-*2-phenyl-1,2,3-triazole-5-carboxylic acid lactone* (**3**). — A suspension of compound **2** (0.5 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 was filtered off, washed with water, and dried (yield 0.4 g). Compound **3** was recrystallized from ethanol, giving colorless needles, m.p. 94–95°; $\nu_{max}^{KBr}$ 1800 (OAc+COO), 1720, and 1600 $cm^{-1}$(C=N).

*Anal.* Calc. for $C_{16}H_{15}N_3O_6$: C, 55.65; H, 4.38; N, 12.17. Found: C, 55.43; H, 4.33; N, 12.24.

*2-Phenyl-4-*(L-threo-*1,2,3-trihydroxypropyl)-1,2,3-triazole-5-carboxamide* (**4**). — A solution of the triazole **3** (0.5 g) in methanol (30 ml) was treated with liquid ammonia (10 ml), kept overnight at room temperature, and concentrated under diminished pressure to a small volume; the solid that separated was filtered off, successively washed with water and ethanol, and dried (yield 0.4 g). It was recrystallized from ethanol, giving colorless needles, m.p. 184–185°; $\nu_{max}^{KBr}$ 3300, 1660, and 1600 $cm^{-1}$. It is soluble in benzene, chloroform, or acetone, sparingly soluble in methanol or ethanol, and insoluble in water.

*Anal.* Calc. for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.83; H, 5.19; N, 20.27.

*2-Phenyl-4-*(L-threo-*1,2,3-triacetoxypropyl-1,2,3-triazole-5-carboxamide* (**5**). — A suspension of compound **4** (0.1 g) in acetic anhydride (10 g) was boiled under reflux for 30 min, and poured onto crushed ice; the product was filtered off, washed with water, and dried. It was recrystallized from benzene, giving colorless needles, m.p. 125–126°.

*Anal.* Calc. for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99; N, 13.85. Found: C, 53.85; H, 5.04; N, 13.99.

*4-(Hydroxymethyl)-2-phenyl-1,2,3-triazole-5-carboxamide* (**6**). — A suspension of compound **4** (0.2 g) in water (25 ml) was treated with a solution of sodium metaperiodate (1 g) in water (20 ml), and the mixture was shaken for 1 h. The solid that separated was filtered off, washed with water, and dried. It was dissolved in ethanol (20 ml), and treated with a solution of sodium borohydride (0.2 g) in water (10 ml), added in small portions with occasional shaking. The solution was acidified with

acetic acid, and the solid that separated was filtered off and dried (yield 50 mg). It was recrystallized from benzene, giving pale-yellow needles, m.p. 145–146°.

*Anal.* Calc. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.67. Found: C, 55.04; H, 4.62; N, 26.05.

L-threo-*2,3-Hexodiulosono-1,4-lactone 2,3-bis(hydrazone)s* (**7–14**). — A solution of L-*threo*-2,3-hexodiulosono-1,4-lactone 2-phenylhydrazone (**1**) (0.01 mole) and the substituted aryl- or aroyl-hydrazine (15 mmoles) in 1:1 ethanol–water containing a few drops of acetic acid was boiled for 1 h on a steam bath. The solid that separated on cooling was filtered off, successively washed with water, ethanol, and ether, and dried. The 2,3-bis(hydrazone)s were recrystallized from ethanol–chloroform, giving needles. Melting points, yields, formulas, and analyses are listed in Table I, and the u.v. and i.r. data in Table IV.

*5,6-Di-*O*-acetyl-*L*-threo-2,3-hexodiulosono-1,4-lactone 2,3-bis(hydrazone)s* (**15–21**). — To a solution of an L-*threo*-2,3-hexodiulosono-1,4-lactone 2,3-bis(hydrazone) (**7–14**) (1 mmole) in dry pyridine (10 ml) was added acetic anhydride (5 ml), 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 with water, and dried. The diacetates were recrystallized from ethanol. Melting points, yields, formulas, and analyses are listed in Table II, and the u.v. and i.r. data in Table IV.

*1-Aryl-3-*(L-threo-*glycerol-1-yl*)*-4,5-pyrazolinedione 4-(phenylhydrazone)s* (**22, 23**). — (*a*). A solution of an L-*threo*-2,3-hexodiulosono-1,4-lactone bis(arylhydrazone) (**8, 9**) (1 mmole) in ethanol (20 ml) was treated with hydrazine hydrate (2 ml) and a few drops of acetic acid, and boiled under reflux for 20 min, concentrated, and allowed to cool to room temperature. The solid that separated out was filtered off, washed successively with water, ethanol, and ether, and dried (yield 95%). The products were recrystallized from ethanol–chloroform, giving orange needles.

(*b*). A suspension of an L-*threo*-2,3-hexodiulosono-1,4-lactone bis(arylhydrazone) (**8, 9**) (1 g) in water (50 ml) was treated with 1.5M sodium hydroxide solution (20 ml) for 10 min at 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, successively washed with water, ethanol, and ether, and dried. The 4-(phenylhydrazone)s were recrystallized from ethanol–chloroform, giving orange needles. Melting points, yields, formulas, and analyses are listed in Table III, and the u.v. and i.r. data in Table IV.

## REFERENCES

1 H. El Khadem and S. H. El Ashry, *J. Chem. Soc., C*, (1968) 2251–2258.
2 H. El Khadem, M. H. Meshreki, S. H. El Ashry, and M. El Sekeili, *Carbohydr. Res.*, 21 (1972) 430–439.
3 H. El Khadem, *Adv. Carbohydr. Chem.*, 18 (1963) 99–121.
4 H. El Khadem, *Adv. Carbohydr. Chem.*, 20 (1965) 139–181.
5 L. Mester and H. El Khadem, in W. Pigman and D. Horton (Eds.), *The Carbohydrates*, Vol. IB, Academic Press, New York, in press.
6 F. Micheel and K. Hesse, *Ber.*, 69 (1936) 879–881.
7 H. El Khadem and S. H. El Ashry, *Carbohydr. Res.*, 13 (1970) 57–61.
8 H. El Khadem and S. H. El Ashry, *J. Chem. Soc., C*, (1968) 2248–2250.
9 E. H. El Ashry, *Carbohydr. Res.*, 52 (1976) 69–77.