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PARTIAL PROTECTION AND SUBSTITUTION OF L-*threo*-GLYCEROL-1-YLPYRAZOLEDIONE*

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ABSTRACT

Partial protection of the glycerolyl side-chain in 3-(L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**2**) was achieved *via* its acetonation; *p*-toluenesulfonylation then gave 3-(2,3-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone). Benzoylation of the 2,3-isopropylidene acetal of **2** gave 3-(1-*O*-benzoyl-2,3-*O*-isopropylidene-L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) that, upon deacetalation, gave 3-(1-*O*-benzoyl-L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone), benzoylated to 1-phenyl-3-(1,2,3-tri-*O*-benzoyl-L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(phenylhydrazone). Debenzoylation followed by periodate oxidation gave the same aldehyde, 3-formyl-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone), as was obtained on similar treatment of **2**. Bromination of **2** afforded 1-(*p*-bromophenyl)-3-(L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(*p*-bromophenyl)-hydrazone, and that gave a monoisopropylidene acetal. The structures of these compounds were confirmed by i.r. spectroscopy.

INTRODUCTION

During our investigations on the synthesis of *C*-(polyhydroxyalkyl) nitrogen-heterocyclic compounds[2–5], we have been interested, as previously reported from our laboratory[6–15], in the synthesis of those having a pyrazoledione residue as the nitrogen-heterocyclic ring. The synthesis of such compounds has thus far been limited to the rearrangement of the bis(arylhydrazones) of L-*threo*-2,3-hexodiulosono-1,4-lactone (and its analogs) to 1-aryl-(L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(arylhydrazones) (and their analogs). During such a rearrangement, three possible substituents on the heterocyclic ring could be changed; these are on N-1, C-3, and C-4. Thus, the aryl groups on N-1 and on the 4-hydrazone residue can be either

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similar or different, depending on the type of bis(hydrazone) precursor, where the hydrazone residues are either similar or different; the first type was prepared from the reaction of L-*threo*-2,3-hexodiulosono-1,4-lactone (**1**) (or its analogs) with an excess of the requisite arylhydrazine. On the other hand, the second type was prepared[8-10,13,14] by the condensation of L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(arylhydrazone) (or its analogs) with a molar proportion of an arylhydrazine having the required aryl group on N-1 of the heterocyclic ring.

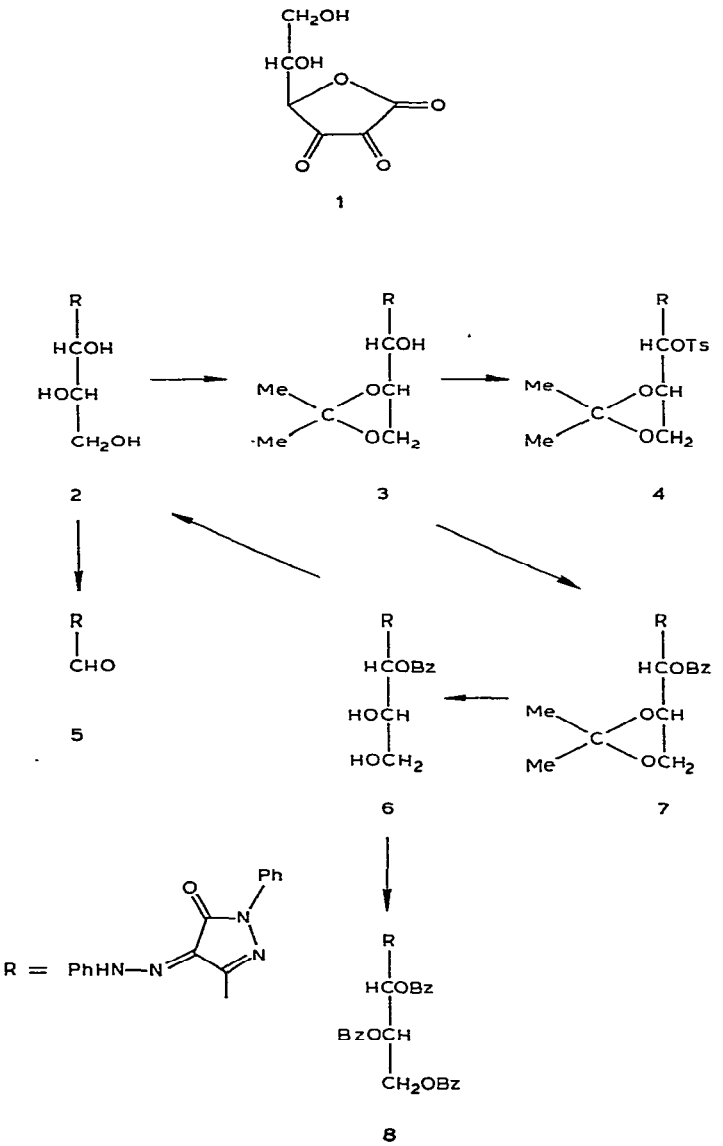
The third variation possible was achieved on C-3; pyrazolediones having glycerol-1-yl side-chains of the D-*erythro*, D-*threo*, and L-*threo* configurations, as well as those having tetritol-1-yl side-chains of the D-*arabino* and L-*xylo* configurations, were prepared from the corresponding derivatives of L-ascorbic acid and its analogs, of which the only ones commercially available are L-ascorbic acid and its D-*erythro* analog, the others having to be prepared from the corresponding glycosuloses. Continuing our efforts towards the synthesis and modification of these [(polyhydroxy)alkyl]pyrazolediones, we now report the partial protection of the side chain, as well as bromination of their phenyl rings.

RESULTS AND DISCUSSIONS

The starting material used in this investigation was the readily available[16] 3-(L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**2**), which, on protection with acetone in the presence of sulfuric acid, afforded 3-(2,3-*O*-isopropylidene-L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**3**). Treatment of **3** with *p*-toluenesulfonyl chloride in pyridine afforded 3-(2,3-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**4**). Benzoylation of **3** gave 3-(1-*O*-benzoyl-2,3-*O*-isopropylidene-L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**7**).

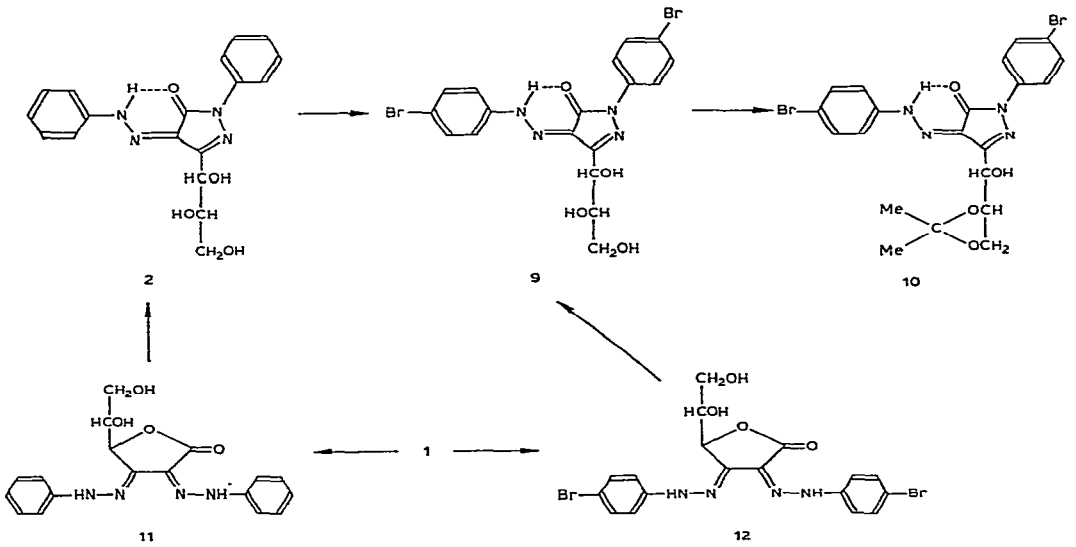
Deacetalation of compound **7** with aqueous acetic acid afforded the monobenzoyl derivative, 3-(1-*O*-benzoyl-L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**6**), that, on benzoylation, gave the per-*O*-benzoyl derivative, 1-phenyl-(1,2,3-tri-*O*-benzoyl-L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(phenylhydrazone) (**8**). Both **6** and **7** showed, in their i.r. spectra, an absorption band at 1720 cm^{-1} due to the *O*-benzoyl group, in addition to a band at 1660 cm^{-1} for the OCN group. Debenzoylation of **6** and **8** with sodium hydroxide gave 3-(L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**2**), whose i.r. spectrum did not show a band for the *O*-benzoyl group (that appeared in the spectra of their precursors), and its periodate oxidation afforded 3-formyl-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**5**), identical with that obtained by similar treatment of **2**. The partially protected derivatives just described are suitable precursors for the synthesis of other analogs of these pyrazolediones.

Bromination of sugar osazones has been studied extensively by El Khadem *et al.*[17], and it constitutes an efficient method for the preparation of the corresponding *p*-bromo-osotriazoles. When the bis(phenylhydrazone) **11** of dehydro-L-ascorbic



acid was subjected to bromination, bromination of the phenyl groups occurred with the loss of two hydrogen atoms, affording 3,6-anhydro-3-(*p*-bromophenylazo)-L-*xylo*(*lyxo*)-2-hexulosono-1,4-lactone 2-(*p*-bromophenylhydrazone)[18].

We have found that bromination of **2** afforded a product whose elemental analysis agreed with that calculated for $C_{18}H_{16}Br_2N_4O_4$, indicating substitution by two bromine atoms. Moreover, the product was identical with 1-(*p*-bromophenyl)-3-(L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(*p*-bromophenyl)hydrazone (**9**), obtained by the rearrangement of the bis(*p*-bromophenyl)hydrazone **12**. This indicates



that the two bromine atoms are in the *para* positions of the phenyl rings. Acetonation of **9** afforded 1-(*p*-bromophenyl)-3-(2,3-*O*-isopropylidene-L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(*p*-bromophenyl)hydrazone (**10**). Both **9** and **10** showed in their i.r. spectra the expected OCN band.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler-block apparatus. I.r. spectra were recorded with a Unicam SP-200 spectrophotometer. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

*3-(2,3-*O*-Isopropylidene-*L*-threo-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone)* (**3**). — A suspension of compound **2** (6 g) in dry acetone (50 mL) containing concentrated sulfuric acid (3 mL) was stirred for 2 h at room temperature and then kept overnight. The resulting mixture was made neutral by addition of solid anhydrous sodium carbonate, filtered, the solid washed with dry acetone, and the combined filtrate evaporated *in vacuo*. The resulting, viscous syrup crystallized from ethanol in orange needles (yield 79%); m.p. 174–176° (lit.[16] m.p. 170–171°); ν_{max}^{Nujol} 1660 cm^{-1} (OCN).

*3-(2,3-*O*-Isopropylidene-1-*O*-p-tolylsulfonyl-*L*-threo-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone)* (**4**). — A solution of compound **3** (4 g) in dry pyridine (30 mL) was treated with tosyl chloride (4 g) and kept for 2 days at room temperature. The mixture was then poured onto crushed ice, and the solid product was filtered off, repeatedly washed successively with water and ethanol, and dried

(yield 80%). It was recrystallized from ethanol, to give orange needles; m.p. 167–169°; ν_{max}^{Nujol} 1660 cm^{-1} (OCN).

Anal. Calc. for $C_{28}H_{28}N_4O_6S$: C, 61.3; H, 5.1. Found: C, 61.7; H, 5.3.

*3-(1-O-Benzoyl-2,3-O-isopropylidene-*L*-threo-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone)* (**7**). — A solution of compound **3** (0.5 g) in dry pyridine (5 mL) was treated with benzoyl chloride (2 mL) and kept overnight at room temperature. The mixture was processed as usual and the product (yield 79%) was recrystallized from ethanol–benzene, to give orange needles; m.p. 155–157°; $[\alpha]_D^{20}$ −13° (*c* 0.6, pyridine); ν_{max}^{Nujol} 1720 (OBz), 1660 (OCN), and 1600 cm^{-1} (C=N).

Anal. Calc. for $C_{28}H_{26}N_4O_5$: C, 67.5; H, 5.3; N, 11.2. Found: C, 67.3; H, 5.0; N, 11.5.

*3-(1-O-Benzoyl-*L*-threo-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione (4-phenylhydrazone)* (**6**). — Compound **7** (0.1 g) was dissolved at 50° in 75% aqueous acetic acid (2 mL); the solution was kept overnight at room temperature, diluted with water, and the product (yield 75%) recrystallized from ethanol, to give orange needles; m.p. 164–166°; ν_{max}^{Nujol} 1720 (OBz) and 1660 cm^{-1} (OCN).

Anal. Calc. for $C_{25}H_{22}N_4O_5$: C, 65.5; H, 4.8; N, 12.2. Found: C, 65.4; H, 5.1; N, 12.3.

*1-Phenyl-3-(1,2,3-tri-O-benzoyl-*L*-threo-glycerol-1-yl)-4,5-pyrazoledione 4-(phenylhydrazone)* (**8**). — A solution of compound **6** (0.1 g) in dry pyridine (5 mL) was treated with benzoyl chloride (0.5 mL) and kept overnight at room temperature. The mixture was poured onto crushed ice, and the solid product was washed repeatedly with water, and dried (yield 75%). It was recrystallized from ethanol, to give orange needles; m.p. 154–156° (lit.[6] m.p. 153–155°); it was identical in all respects with the product obtained by per-*O*-benzoylation of **2**.

*3-(*L*-threo-Glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone)* (**2**). — A suspension of compound **6** (0.1 g) in water (5 mL) was heated with 2M sodium hydroxide solution (3 mL) until dissolution occurred. The base was neutralized with glacial acetic acid, and the product that separated was filtered off, washed several times with water, and dried. It was recrystallized from ethanol–water, to give orange needles identical with an authentic sample of **2**.

Periodate oxidation of **2**. — When a suspension of **2** in water was subjected to periodate oxidation, a product was formed that was identified as 3-formyl-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**5**).

*1-(*p*-Bromophenyl)-3-(*L*-threo-glycerol-1-yl)-4,5-pyrazoledione 4-(*p*-bromophenyl)hydrazone* (**9**). — A suspension of **2** (2 g) in water (20 mL) was treated dropwise with bromine (2 mL), with occasional shaking. The mixture was kept overnight at room temperature and the product was filtered off, washed repeatedly with water and ethanol (yield 83%), and recrystallized from ethanol, giving orange needles; m.p. 228–230° (lit.[6] m.p. 229–231°); ν_{max}^{Nujol} 3450 (OH) and 1660 cm^{-1} (OCN).

Anal. Calc. for $C_{18}H_{16}Br_2N_4O_4$: C, 42.2; H, 3.2; N, 10.9. Found: C, 42.3; H, 3.5; N, 11.3.

*1-(*p*-Bromophenyl)-3-(2,3-O-isopropylidene-*L*-threo-glycerol-1-yl)-4,5-pyrazole-*

dione 4-(p-bromophenyl)hydrazone (**10**). — A suspension of compound **9** (0.5 g) in dry acetone (20 mL) and concentrated sulfuric acid (0.5 mL) was stirred for 2 h at room temperature and then kept overnight. The resulting mixture was made neutral by the addition of solid anhydrous sodium carbonate, and filtered, and the inorganic salts were washed with acetone. The filtrate was evaporated *in vacuo*, and the resulting syrup crystallized from ethanol as orange needles; m.p. 188–190°; ν_{max}^{Nujol} 1660 cm^{-1} (OCN).

Anal. Calc. for $C_{21}H_{20}Br_2N_4O_4$: C, 45.7; H, 3.7; N, 10.1. Found: C, 45.7; H, 3.3; N, 10.5.

REFERENCES

1 E. S. H. El Ashry, M. M. A. Abdel Rahman, and N. Rashed, *Carbohydr. Res.*, 82 (1980) 15–23.
2 E. S. H. El Ashry, I. E. El Kholy, and Y. El Kilany, *Carbohydr. Res.*, 60 (1978) 303–314, 396–399; 64 (1978) 81–88; 67 (1978) 495–499.
3 E. S. H. El Ashry, M. M. A. Abdel Rahman, M. Nassr, and A. Amer, *Carbohydr. Res.*, 67 (1978) 403–414.
4 E. S. H. El Ashry, M. M. A. Abdel Rahman, N. Rashed, and A. Amer, *Carbohydr. Res.*, 67 (1978) 423–432.
5 H. El Khadem, R. Sindric, and E. S. H. El Ashry, *Carbohydr. Res.*, 30 (1973) 165–174.
6 H. El Khadem and E. S. H. El Ashry, *J. Chem. Soc.*, (1968) 2248–2250.
7 H. El Khadem, M. H. Meshreki, E. S. H. El Ashry, and M. El Sekily, *Carbohydr. Res.*, 21 (1972) 430–439.
8 E. S. H. El Ashry and Y. El Ashry, *Chem. Ind. (London)*, (1976) 372–373.
9 E. S. H. El Ashry, *Carbohydr. Res.*, 52 (1976) 69–77.
10 E. S. H. El Ashry, Y. El Kilany, and F. Singab, *Carbohydr. Res.*, 56 (1977) 93–104.
11 M. El Sekily, S. Mancy, I. El Kholy, E. S. H. El Ashry, H. S. El Khadem, and D. L. Swartz, *Carbohydr. Res.*, 59 (1977) 141–149.
12 E. S. H. El Ashry, I. E. El Kholy, and Y. El Kilany, *Carbohydr. Res.*, 59 (1977) 417–426.
13 R. Soliman, E. S. H. El Ashry, I. E. El Kholy, and Y. El Kilany, *Carbohydr. Res.*, 67 (1978) 179–188.
14 E. S. H. El Ashry, I. E. El Kholy, and Y. El Kilany, *Carbohydr. Res.*, 67 (1978) 415–422.
15 E. S. H. El Ashry, Y. El Kilany, and F. Singab, *Carbohydr. Res.*, 79 (1980) 151–154.
16 H. Ohle, *Ber.*, 67 (1934) 1750–1762.
17 H. El Khadem, *Adv. Carbohydr. Chem.*, 18 (1963) 99–121.
18 E. S. H. El Ashry, Y. El Kilany, and F. Singab, unpublished results.