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Note

Regioselective formation of terminal 1,3-dioxolanes from 1-*C*-substituted-D-*erythro*-glycerols*

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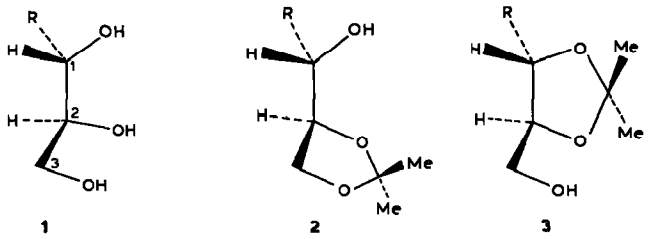
Investigations[2–4] of the regioselective acid-catalysed isopropylidenation of 1-*C*-substituted-L-*threo*-glycerols have shown that the products of reaction of L-*threo* vicinal diols (αT)[5,6] are thermodynamically more stable than those of terminal vicinal diols (α). Thus, **1** gives the 1,2-*O*-isopropylidene (αT) derivative **3**, but the 2,3-derivative (**2**, α) could be the kinetic product. 1,3-Dioxane-type isopropylidene derivatives can also be formed from polyhydric alcohols[7].



1 **2** **3**

R = 1-phenyl-4-(phenylhydrazono)-4,5-pyrazoledione-3-yl

We have reinvestigated the ketalation of the D-*erythro* analogue of **1** in relation to the formation of dioxolane or dioxane ring derivatives. The isopropylidenation of **4** has been reported by Ohle[8] to give **7** in which the position of the isopropylidene group was confirmed, since 5,6-*O*-isopropylidene-D-*erythro*-2,3-hexodiulosono-1,4-lactone 2,3-bis(phenylhydrazone) (**15**) could be rearranged to give **7**. The isopropylidene derivative **15** and the acetate **10** were described by Ohle[8] and by Ozawa and Nakamura[9], but the spectral data were not given.

The work of Ohle[8] has been repeated and extended to substituted analogues

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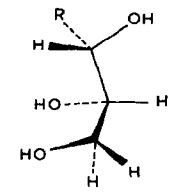
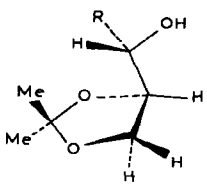
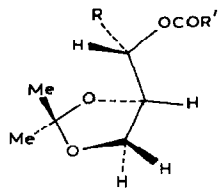


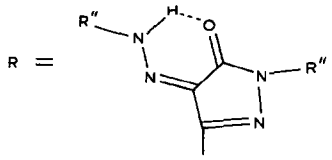
4 R″= Ph
5 R″= *p*-Br-C_6H_4
6 R″= *p*-Cl-C_6H_4

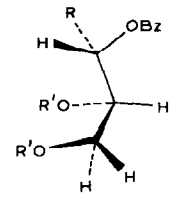


7 R″= Ph
8 R″= *p*-Br-C_6H_4
9 R″= *p*-Cl-C_6H_4

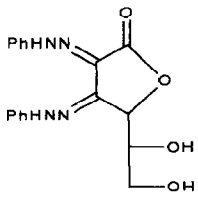


10 R′ = Me, R″= Ph
11 R′ = R″= Ph





12 R′ = H, R″ = Ph
13 R′ = Bz, R″ = Ph



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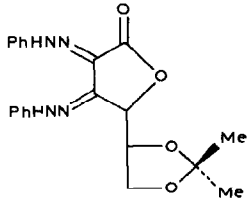

15

of **4**. Acid-catalysed isopropylidenation of **4–6** gave the respective crystalline products **7–9**, the position of the isopropylidene ring in which was confirmed by a combination of chemical and physical methods. Thus, benzoylation of **7** gave the benzoate **11**, treatment of which with acid cleaved the isopropylidene residue to give 3-(1-*O*-benzoyl-D-*erythro*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**12**), characterised as the tribenzoate **13**. Compound **15** had i.r. absorption for a lactone carbonyl at a wave number (1730 cm^{-1}) lower than anticipated for a 1,4-lactone, which could be attributed to hydrogen bonding with the NH of the C-2 hydrazone residue[2]. This inference was confirmed by the ^{1}H-n.m.r. spectrum, which contained signals for the NH protons with chemical shifts (δ 10.90 and 11.87) indicating their involvement in hydrogen bonding. Moreover, the downfield shift (δ 5.25) of the doublet for H-4 compared to those of H-5 (δ 4.6) and H-6,6′ (δ 4.1) confirmed the involvement of HO-4 in the lactone ring and consequently the 5,6-location of the isopropylidene ring (*i.e.*, positions 2 and 3 in **7**). In order to confirm that no isopropylidene migration had occurred during the

rearrangement **15**→**7**, the effect of acylation of **7** on the chemical shift of the signals of the protons of the glycerolyl residue was determined. There was a pronounced downfield shift of the signal for H-1 (δ 4.98 to 6.18 and 6.43, respectively) on acetylation and benzoylation, indicating that HO-1 in **10** and **11** was acetylated. The singlet at δ 2.9 due to the hydroxyl group of **7** did not appear in the ^{1}H-n.m.r. spectra of **10** and **11**. The chemical shifts of the signals of the other glycerolyl protons were not affected by acetylation.

The acetylated derivatives showed i.r. bands typical of ester carbonyl in addition to the band due to the OCN group.

Thus, isopropylidenation of 1-*C*-substituted-D-*erythro*-glycerols afforded the corresponding 2,3-acetals as the sole isolated products, indicating that the reaction proceeded regioselectively.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler-block or a "Meltemp" apparatus and are uncorrected. I.r. spectra were recorded with Unicam SP 200 and 1025 spectrophotometers. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian EM-390 spectrometer. Microanalyses were performed in the Chemistry Department, Cairo University.

*3-(2,3-*O*-Isopropylidene-*D*-*erythro*-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone)* (**7**). — Prepared as described by Ohle[8], **7** (92%) crystallised from ethanol as orange needles, m.p. 181–182° (lit.[8] m.p. 181–182°); ν_{max}^{KBr} 1660 (OCN), 3100 (NH), and 3360 cm^{-1} (OH). ^{1}H-N.m.r. data: δ 1.37 and 1.48 (2 s, 6 H, 2 Me), 2.9 (bs, 1 H, OH), 4.1 and 4.25 (2 q, 2 H, $J_{3,3'}$ 9.0, $J_{2,3'}$ 5.5, $J_{2,3}$ 4.5 Hz, H-3,3'), 4.6 (m, 1 H, H-2), 4.98 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1), 7.3 and 7.9 (m and q, 10 H, 2 Ph), and 13.7 (bs, 1 H, NH).

Anal. Calc. for $C_{21}H_{22}N_4O_4$: C, 64.0; H, 5.6; N, 14.2. Found: C, 64.1; H, 5.6; N, 14.6.

*1-(p-Bromophenyl)-3-(2,3-*O*-isopropylidene-*D*-erythro-glycerol-1-yl)-4,5-pyrazoledione 4-(p-bromophenylhydrazone)* (**8**). — Compound **5** (0.5 g) was stirred vigorously with dry acetone (20 mL) and aqueous 96% sulphuric acid (0.2 mL) for 2 h. The mixture was then stored at room temperature overnight, and the product (45%) was collected under dry conditions, washed with dry acetone, and dried. The filtrate was neutralised with solid anhydrous sodium carbonate and filtered, and the inorganic salts were washed with dry acetone. The combined filtrate and washings were concentrated to give more product (85% total yield) that was crystallised from ethanol as orange needles, m.p. 205–206°; ν_{max}^{KBr} 1665 (OCN) and 3400 cm^{-1} (OH). ^{1}H-N.m.r. data: δ 1.33 and 1.43 (2 s, 6 H, 2 Me), 2.8 (bs, 1 H, OH), 4.1 and 4.2 (m, 2 H, H-3,3'), 4.5 (m, 1 H, H-2), 4.90 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1), 7.4 and 7.8 (m and q, 8 H, aromatic protons), and 13.6 (bs, 1 H, NH).

Anal. Calc. for $C_{21}H_{20}Br_2N_4O_4$: C, 45.7; H, 3.7; N, 10.1. Found: C, 45.6; H, 4.1; N, 10.3.

*1-(p-Chlorophenyl)-3-(2,3-O-isopropylidene-*D*-erythro-glycerol-1-yl)-4,5-pyrazoledione 4-(p-chlorophenylhydrazone)* (**9**). — A mixture of **6** (0.2 g), acetone (15 mL), and aqueous sulphuric acid (0.1 mL) was processed as in the preparation of **8**, to give **9** (68%) that crystallised from ethanol as orange needles, m.p. 208–209°; ν_{max}^{KBr} 1660 (OCN), 3100 (NH), and 3340 cm^{-1} (OH). ^{1}H-N.m.r. data: δ 1.33 and 1.43 (2 s, 6 H, 2 Me), 2.7 (bs, 1 H, OH), 4.1 and 4.2 (m, 2 H, H-3,3′), 4.5 (m, 1 H, H-2), 4.92 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1), 7.3 and 7.9 (m and q, 8 H, aromatic protons), and 13.6 (bs, 1 H, NH).

Anal. Calc. for $C_{21}H_{20}Cl_2N_4O_4$: C, 54.4; H, 4.4; N, 12.1. Found: C, 54.1; H, 4.4; N, 12.2.

*5,6-O-Isopropylidene-*D*-erythro-2,3-hexodiulosono-1,4-lactone 2,3-bis-(phenylhydrazone)* (**15**). — Prepared by the isopropylidenation of **14**, **15** (89%) crystallised from ethanol as red needles, m.p. 224–225° (lit.[8] m.p. 224–225°; lit.[9] m.p. 220–221°); ν_{max}^{KBr} 1730 (COO) and 3300 cm^{-1} (NH). ^{1}H-N.m.r. data: δ 1.39 (s, 6 H, 2 Me), 4.1 (m, 2 H, H-6,6′), 4.6 (m, 1 H, H-5), 5.25 (d, 1 H, $J_{4,5}$ 3.0 Hz, H-4), 7.2 (m, 10 H, 2 Ph), 10.90 and 11.87 (2 s, 2 H, 2 NH).

Anal. Calc. for $C_{21}H_{22}N_4O_4$: C, 64.0; H, 5.6; N, 14.2. Found: C, 64.2; H, 5.5; N, 13.8.

*3-(1-O-Acetyl-2,3-O-isopropylidene-*D*-erythro-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone)* (**10**). — Acetylation of **7** gave **10** (92%), which crystallised from ethanol as orange needles, m.p. 154–155° (lit.[8] m.p. 152–153°); ν_{max}^{KBr} 1665 (OCN) and 1755 cm^{-1} (OAc). ^{1}H-N.m.r. data: δ 1.37 and 1.46 (2 s, 6 H, 2 Me), 2.17 (s, 3 H, COMe), 4.2 (m, 2 H, H-3,3′), 4.7 (m, 1 H, H-2), 6.18 (d, 1 H, $J_{1,2}$ 5.3 Hz, H-1), 7.3 and 7.9 (m and q, 10 H, 2 Ph), and 13.7 (bs, 1 H, NH).

Anal. Calc. for $C_{23}H_{24}N_4O_5$: C, 63.3; H, 5.5; N, 12.8. Found: C, 63.4; H, 5.5; N, 13.0.

*3-(1-O-Benzoyl-2,3-O-isopropylidene-*D*-erythro-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone)* (**11**). — Conventional treatment of **7** (1.0 g) with dry pyridine (5 mL) and benzoyl chloride (4 mL), with recrystallisation of the product (85%) from ethanol, gave **11** as orange needles, m.p. 189–190°; ν_{max}^{KBr} 1665 (OCN) and 1725 cm^{-1} (OBz). ^{1}H-N.m.r. data: δ 1.4 (s, 6 H, 2 Me), 4.3 (m, 2 H, H-3,3′), 4.9 (m, 1 H, H-2), 6.43 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 7.3 and 8.9 (2 m, 15 H, 3 Ph), and 13.7 (bs, 1 H, NH).

Anal. Calc. for $C_{28}H_{26}N_4O_5$: C, 67.5; H, 5.3; N, 11.2. Found: C, 67.8; H, 4.9; N, 11.4.

*3-(1-O-Benzoyl-*D*-erythro-glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone)* (**12**). — (*a*) A suspension of **11** (0.5 g) in water (15 mL) and acetic acid (40 mL) was boiled under reflux until dissolution was complete, and then kept for 24 h at room temperature. The mixture was diluted with cold water, and the product (70%) was collected and recrystallised from ethanol to give **12** as orange needles, m.p. 192–194°; ν_{max}^{KBr} 1590 (C=N), 1665 (OCN), 1725 (OBz), and 3360 cm^{-1} (OH). ^{1}H-N.m.r. data: δ 2.5 and 3.2 (2 bs, 2 H, 2 OH), 3.9 (m, 2 H, H-3,3′), 4.5 (m, 1 H, H-2), 6.33 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 7.4 and 8.0 (2 m, 15 H, 3 Ph), and 13.7 (bs, 1 H, NH).

Anal. Calc. for $C_{25}H_{22}N_4O_5$: C, 65.5; H, 4.8; N, 12.2. Found: C, 65.3; H, 5.2; N, 11.8.

(*b*) A solution of **11** (0.5 g) in aqueous 90% trifluoroacetic acid (10 mL) was kept for 15 min at room temperature, and then diluted with cold water. The product (92%) was collected and recrystallised from ethanol to give **12** as orange needles, m.p. 192–194° alone or in admixture with the product from (*a*).

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