HETEROCYCLES FROM CARBOHYDRATE PRECURSORS: CYCLOHEXYLIDENATION OF 1-*p*-BROMOPHENYL-3-(L-*Threo*-GLYCEROL-1-YL)-4-PYRAZOLINE-4, 5-DIONE-4-(*p*-BROMOPHENYLHYDRAZONE)

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INTRODUCTION

Partial protection of the hydroxyl groups of a polyol molecule is of great interest in organic synthesis. One of the ways to achieve such protection is by acetalization of the corresponding polyol [1–8]. If the polyol is a glycerolyl derivative, protection of two out of the three of its hydroxyl groups by acetalization is anticipated. As a continuation of our investigations in this field, we have studied the mode of isopropylidenation [1, 2], cyclohexylidenation [4], and benzylidenation [5] of some C-glycerolyl heterocycles. The present work reports the cyclohexylidenation of the title compound and the structure of the product formed.

RESULTS AND DISCUSSION

Inspection of the possible structures of the cyclohexylidenes that could be obtained from the cyclohexylidenation of a 1-C-substituted glycerol indicated [5–8] the possible formation of three products. When 1-(*p*-bromophenyl)-3-(L-*threo*-glycerol-1-yl)-4-pyrazoline-4,5-dione-4-(*p*-bromophenylhydrazone) (**1**) was allowed to react with cyclohexanone in the presence of catalytic amount of sulfuric acid, under conditions of thermodynamic control, a product could be isolated whose structure was found to be **2**. The product **2** gave, upon acetylation with acetic anhydride in pyridine, 3-(3-*O*-acetyl-1, 2-*O*-cyclohexylidene-L-*threo*-glycerol-1-yl)-1-(*p*-bromophenyl)-4-pyrazoline-4,5-dione-4-(*p*-bromophenylhydrazone) (**3**). Acid hydrolysis of **3** caused its decyclohexylidenation to give 3-(3-*O*-acetyl-L-*threo*-glycerol-1-yl)-1-(*p*-bromophenyl)-4-pyrazoline-4,5-dione-4-(*p*-bromophenylhydrazone) (**4**). The latter upon periodate oxidation afforded the aldehyde, 1-(*p*-bromophenyl)-3-formyl-4-pyrazoline-4,5-dione-4-(*p*-bromophenylhydrazone) (**5**) which was identified as its oxime (**6**) and its *p*-nitrobenzoylhydrazone **7**.

The isolation of the aldehyde **5**, from the reaction of **4** with periodate, indicated the presence of a vicinal diol system and an acetyl group on O-3. Consequently, the acetal ring should be on O-1 and O-2.

The whole series of compounds showed a band at 1655 cm^{-1} due to the OCN group, in addition to a band at 1740 cm^{-1} in compound **3** due to the OAc group and a band at 1700 cm^{-1} in compound **5** due to the aldehydic group.

The n.m.r. spectrum of **2** showed a multiplet at δ 1.7 assigned to the cyclohexylidene group. This was followed by two quartets at δ 3.9 and 4.1 assigned to the C-3 methylene protons, each split by a large geminal coupling, $J_{3,3'} = 12$ Hz and a smaller coupling ($J_{2,3'} = 3$ Hz, $J_{2,3} = 3.5$ Hz respectively), a multiplet at δ 4.7 assigned to H-2 and a doublet at δ 5.1 assigned to H-1, which is split, by H-2

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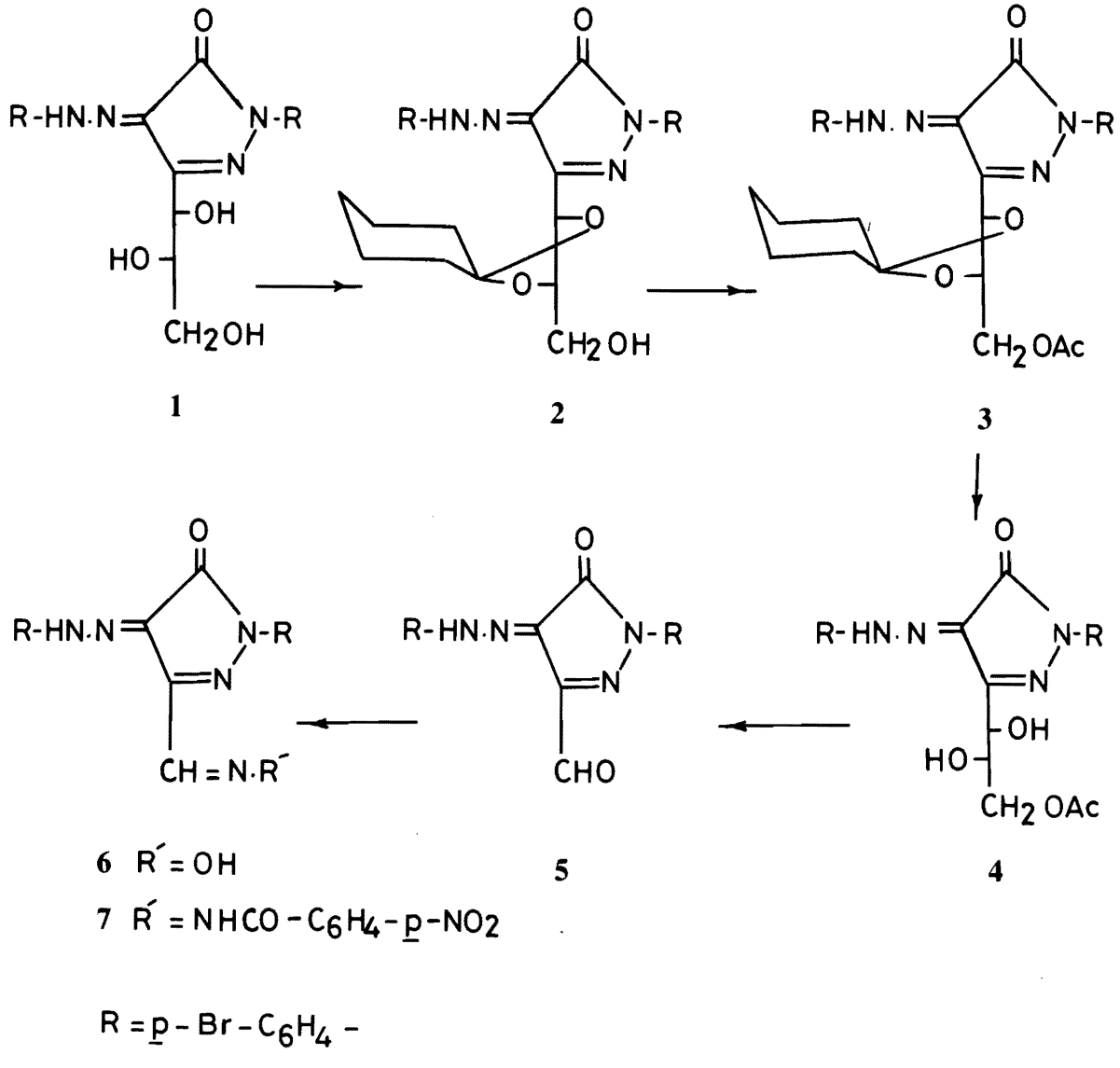
($J_{1,2}$ = 7.5 Hz). The aromatic protons appeared at δ 7.4 and the NH appeared as a broad singlet at δ 13.8. The downfield position of the NH proton indicated its involvement in hydrogen bonding with the C-5 carbonyl of the heterocyclic ring. The ^{1}H-n.m.r. spectrum of the acetate **3** showed the presence of one acetyl group as a singlet at δ 2.2. The H-3,3′ signals appeared as two quartets at δ 4.2 and 4.4. Their chemical shifts were downfield compared to that of the respective protons of **2**. The H-2 and H-1 appeared as a multiplet and a doublet at δ 4.7 and 5.1, respectively. Since the difference in the chemical shifts of the protons on the glycerolyl side chain of the cyclohexylidene and its acetate indicated that the H-3 and H-3′ are the only protons affected by the acetylation, this is the position of the acetylated hydroxyl group. This led to the conclusion that the cyclohexylidene group was located on positions 1 and 2 of the glycerolyl side chain and consequently the product of cyclohexylidenation is formulated as 1-(*p*-bromophenyl)-3-(1, 2-*O*-cyclohexylidene-L-*threo*-glycerol-1-yl)-4-pyrazoline-4,5-dione-4-(*p*-bromophenylhydrazone) (**2**).



Scheme 1

EXPERIMENTAL

General methods. Melting points were determined with a "Meltemp" apparatus with 76 mm immersion thermometer, and are uncorrected. Infrared spectra were recorded with a Unicam SP 1025 spectrometer. ^{1}H-n.m.r. spectra were determined with a varian EM-390 spectrometer for solution in chloroform-*d* with tetramethylsilane (Me_4Si) as internal reference. The spectra are reported with chemical shifts (δ) downfield from Me_4Si. Microanalyses were performed by the Unit of Microanalysis, Faculty of Science, Cairo University.

1-(*p*-Bromophenyl)-3-(1,2-*O*-cyclohexylidene-L-*threo*-glycerol-1-yl)-4-pyrazoline-4,5-dione-4-(*p*-bromophenylhydrazone) (2)

A suspension of compound **1** (1.0 g) was stirred vigorously with dry cyclohexanone (30 ml) and 96% sulfuric acid (0.5 ml) for 1 h, and then kept overnight at room temperature. The reaction mixture was neutralized by the addition of solid anhydrous sodium carbonate and filtered. The inorganic salts were well washed with dry cyclohexanone. The combined filtrate and washing were evaporated *in vacuo* at 40°C. Petroleum ether was added to the resulting viscous syrup and the product that separated out was filtered and washed with ethanol. It was recrystallized from ethanol as orange needles.

Yield: 90%; m.p.: 161–163°C; IR (KBr): 1670, 3400; ^{1}H-n.m.r. ($CDCl_3$): δ 1.7 (m, 10 H, cyclohexylidene protons), 3.9 (q, 1 H, $J_{2,3'}$ 3.5 Hz, $J_{3,3'}$ 12 Hz, H-3′), 4.1 (q, 1 H, $J_{2,3}$ 3 Hz, H-3), 4.7 (m, 1 H, H-2), 5.10 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 7.9 (m, 8 H, aromatic protons), and 13.8 (bs, 1 H, NH); the NH is exchangeable with deuterium.

Analysis: *Calc.* for $C_{24}H_{24}Br_2N_4O_4$ C: 48.6%; H: 4.1; Br: 27.0; N: 9.5. *Found:* C: 48.4; H: 4.0; Br: 26.9; N:9.6.

3-(3-*O*-Acetyl-1,2-*O*-cyclohexylidene-L-*threo*-glycerol-1-yl)-1-(*p*-bromophenyl)-4-pyrazoline-4,5-dione-4-(*p*-bromophenylhydrazone) (3)

A cold solution of compound **2** (0.1 g) in dry pyridine (2 ml) was treated with acetic anhydride (1 ml) and kept overnight at room temperature. The reaction mixture was poured onto crushed ice and the product that separated was filtered, washed repeatedly with water and dried. It was recrystallized from ethanol as yellow orange needles.

Yield: 95%; m.p.: 110–112°C; IR (KBr): 1660, 1740; ^{1}H-n.m.r. ($CDCl_3$): δ 1.7 (m, 10 H, cyclohexylidene protons), 2.2 (s, 3 H, $COCH_3$), 4.2 (q, 1 H, $J_{2,3'}$ 3.5 Hz, $J_{3,3'}$ 12 Hz, H-3′), 4.4 (q, 1 H, $J_{2,3}$ 3 Hz, H-3), 4.7 (m, 1 H, H-2), 5.1 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 7.9 (m, 8 H, aromatic protons), and 13.8 (bs, 1 H, NH); the NH is exchangeable with deuterium.

Analysis: *Calc.* for $C_{26}H_{26}Br_2N_4O_5$ C: 49.2%; H: 4.1; Br: 25.2; N: 8.8; *Found:* C: 48.9; H: 4.0; Br: 24.9; N:8.5.

3-(3-*O*-Acetyl-L-*threo*-glycerol-1-yl)-1-(*p*-bromophenyl)-4-pyrazoline-4,5-dione-4-(*p*-bromophenylhydrazone) (4)

A suspension of compound **3** (0.5 g) in 80% aqueous trifluoroacetic acid (10 ml) was kept for 15 minutes at room temperature. The reaction mixture was diluted with cold water and the product that separated out was filtered, washed repeatedly with water, and dried. It was recrystallized from ethanol as orange needles.

Yield: 75%; m.p.: 153–155°C; IR (KBr): 1660, 1740, 3400; Analysis: *Calc.* for $C_{20}H_{18}Br_2N_4O_5$ C: 43.4%; H: 3.2; N: 10.1; *Found:* C: 43.4; H: 3.1; N:10.0.

Periodate Oxidation of Compound 4

A suspension of compound **4** (0.5 g) in distilled water (50 ml) was treated with a solution of sodium metaperiodate (0.5 g) in distilled water (5 ml). The reaction mixture was stirred at room temperature for 4 h and then left overnight in a dark place. It was filtered off, washed with water and dried. The product was crystallized from ethanol to give **5** as orange needles. Yield: 75%; m.p.: 200–202°C (lit. [9] m.p.: 198–201°C). A solution of compound **5** (0.45 g) in ethanol (10 ml) was treated with a solution of hydroxylamine hydrochloride (0.14 g) and sodium acetate (1.6 g) in ethanol (10 ml) and few drops of dimethylformamide and the reaction mixture was heated under reflux for 10 min. The oxime that separated out on cooling was filtered, washed with ethanol and ether and dried. It was crystallized from ethanol as red needles.

Yield: 86%; m.p.: 250–253°C; IR (KBr): 1665; Analysis: *Calc.* for $C_{16}H_{10}Br_2N_5O_2$ C: 41.2%; H: 2.3; N: 15.0; *Found:* C: 41.2; H: 2.4; N:15.0.

p - Nitrobenzoylhydrazone of 1 - (p - bromophenyl) - 3 - formyl - 4 - pyrazoline - 4, 5 - dione - 3 - yl - 4 - (p-bromophenylhydrazone) (7)

A solution of compound **5** (0.3 g) in ethanol (20 ml) was treated with a solution of *p*-nitrobenzoylhydrazone (0.25 g) in ethanol (10 ml). The reaction mixture was heated under reflux for 10 min. On cooling, the product that separated was filtered, washed with ethanol, ether, and dried. It was crystallized from ethanol as red–orange needles. Yield: 95%; m.p.: 150–153°C; IR (KBr): 1600, 1660, 3400; Analysis: *Calc.* for $C_{23}H_{15}Br_2N_7O_4$ C: 45.1%; H: 2.4; N: 15.9; *Found:* C: 45.1; H: 2.5; N:16.1.

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