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Novel types of acyclic *C*-nucleoside analogues *via* the reaction of hydrogen bromide in acetic acid with L-*threo*-(glycerol-l-yl)pyrazolinediones

Hamida Abdel Hamid, Nagwa Rashed, Yeldez El Kilany, and El Sayed H. El Ashry
Chemistry Department, Faculty of Science, Alexandria University, Alexandria (Egypt)

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ABSTRACT

The reaction of hydrogen bromide in acetic acid with a number of L-*threo*-glycerolylpyrazolinediones and their partially acetalated, acetylated, benzoylated, and *p*-toluenesulfonylated derivatives has been investigated. The presence of an *O*-isopropylidene ring at the C-1 and C-2 positions and/or an acetyl group at position C-3 does not affect the mode of the reaction. The products are 1,3-dibromo-1,3-dideoxy-2-*O*-acetyl-L-*erythro*-glycerolyl derivatives, which are identical with those obtained from the corresponding triol precursor. The conditions of the reaction promote ester migration *via* the apparent formation of a dioxolanylium ion. However, ester migration was not observed in the corresponding 3-benzoate and 3-(*p*-toluenesulfonate), whereby 1-bromo-1-deoxy derivatives having the L-*erythro* configuration were obtained. The reaction of 6-bromo-6-deoxy-dehydro-L-ascorbic acid with phenylhydrazine gave a mixture of the corresponding bis(phenylhydrazone) and the 3-bromo-3-deoxy glycerolyl derivative of the pyrazolinedione.

INTRODUCTION

Alditols, such as mitolactol, having bromine atoms on their terminal positions are considered as bifunctional alkylating agents having significant cytostatic activity. Their metabolic pathways have been investigated[1–7]. This, in addition to the well-known biological properties of *C*-nucleosides[8], led us to construct deoxyhalogeno *C*-nucleoside analogues having a structural feature combining these aspects. Three types were thus prepared. The former possesses a 1,3-dibromo-1,3-dideoxyglycerolyl residue, where one terminus is a heterocyclic ring geminal to the bromine atom. The other types have one bromine atom at either C-1 or C-3.

RESULTS AND DISCUSSION

It has been reported[9], that the reaction between vicinal diols and hydrogen bromide in acetic acid requires as a key step a hydroxy group and a proximally situated protonated acetoxy group to form 1,3-dioxolan-2-ylium ion, which is not otherwise impeded by conformational demands within this species. The reaction has been successfully applied in the carbohydrate field[10–15]. In the present study the scope of this reaction on a series of acyclic *C*-nucleoside analogues has been investigated. The type of

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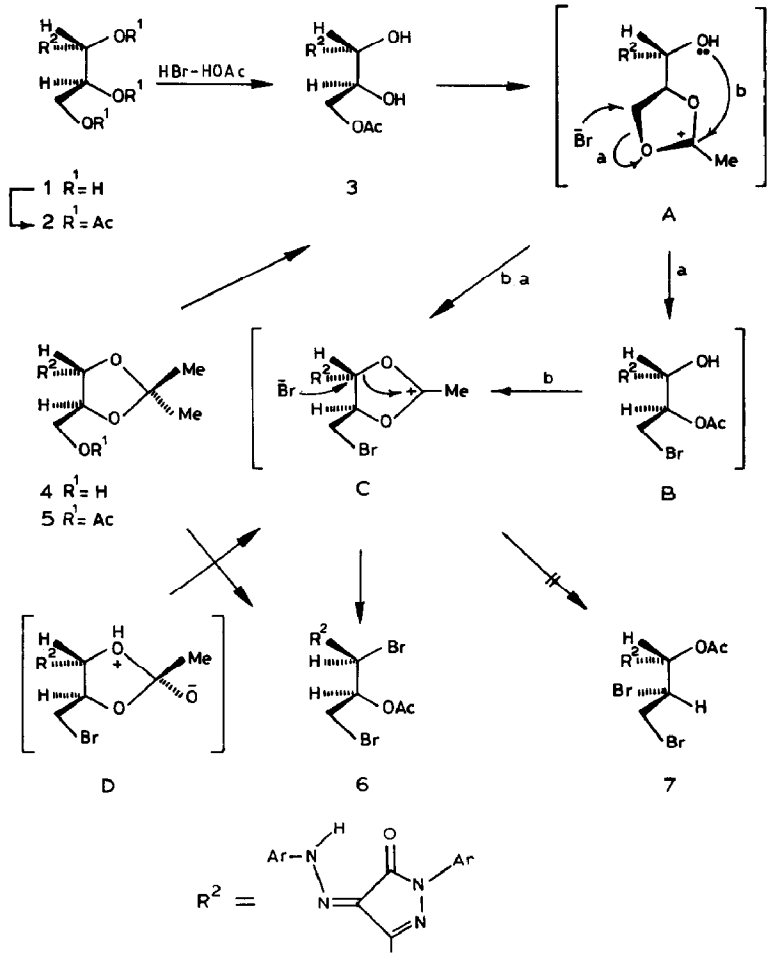
substituents on the alditolyl residue played a major role on the type of product, whereby the corresponding dibromodideoxy or monobromodeoxy derivatives were obtained. Thus, the reaction of HBr–HOAc with **1a–1c** gave the 1,3-dibromo-1,3-dideoxy derivatives **6a–6c**. Similarly, **6a** was obtained from the 1,3-dioxolane derivative **4a**, as well as from the acetates **3a** or **5a**. Combustion analysis of **6** indicated the presence of two bromine atoms, and the products from **3a**, **4a**, and **5a** showed identical infrared (i.r.) and ^{1}H-n.m.r. spectra with that resulting from **1a**, as well as a band in the carbonyl frequency region (1740 cm^{-1}), in addition to the OCN band (1670 cm^{-1}) of the heterocyclic ring. The ^{1}H-n.m.r. spectrum indicated[16] the presence of only one acetoxy group (δ 2.04) on C-2, as shown by the downfield shift of H-2 (δ 5.90) as compared with that value of H-2 (δ 5.85) for **2**. The doublet of H-1 (δ 5.42) appeared at comparatively higher field than

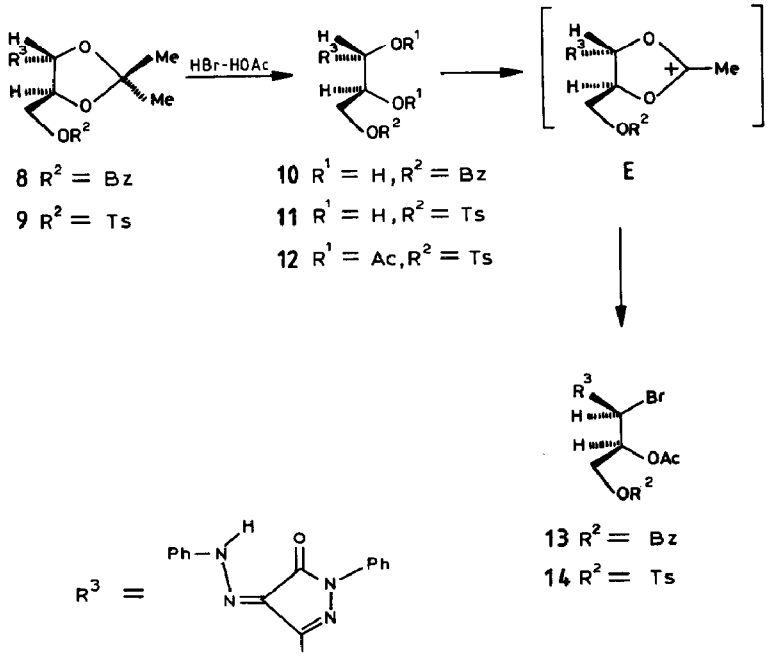


Scheme 1

that of the corresponding carbon bearing acetoxyl groups in **2**. Moreover, H-1 is more shielded than H-2 in **6a–6c**, in contrast to the shifts in compound **2**, where H-1 is more deshielded than H-2. Similarly, H-3 and H-3′ are more shielded than the corresponding protons of **2**, but they appeared approximately at the same chemical shift of the corresponding 3-bromodeoxy analogues. This fact led to the conclusion that the two bromine atoms in **6** are attached to C-1 and C-3. The location of the bromine atoms as well as the inversion of configuration of C-1 in **6a** have been firmly established by X-ray crystallography[16].

When the hydroxy group on C-3 of **1** or **4** was replaced by a benzoyloxy group, such as in **8** and **10**, and then subjected to reaction with HBr–HOAc, these compounds afforded the same product **13**. Similarly, the *p*-toluenesulfonyloxy derivatives **9** and **11** afforded **14**. The structures of **13** and **14** were deduced from their ^{1}H-n.m.r. spectra. The chemical shift of H-1 (~ δ 5.4) indicated its attachment to the carbon bearing the bromine atom. H-2 appeared at a chemical shift (δ 6.12 and 5.86 respectively for **13** and **14**) indicating its attachment to a carbon bearing an acetoxy group. That of **13** is more deshielded as a consequence of the anisotropic effect of the C-3 benzoyloxy group. The C-3 is attached to the benzoyloxy and *p*-toluenesulfonyloxy groups, respectively, as indicated from the comparison of the chemical shifts of H-3 and H-3′ with those of their precursors.

The introduction of bromine atoms in vicinal diols using HBr–HOAc apparently occurred *via* a 1,3-dioxolan-2-ylium ion intermediate to give a bromoacetate, a product with an exclusive *trans* stereochemistry. Thus the bromine atom in **6** may be introduced



Scheme 2

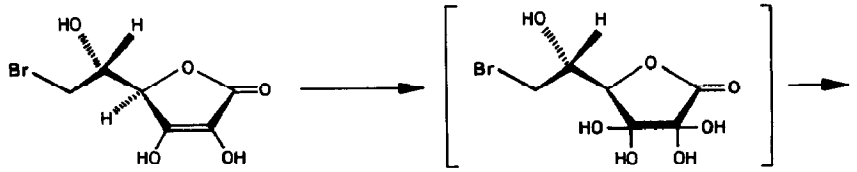
via the formation of a monoacetate **3**, which forms the dioxolanylium ion intermediate **A**, whose stereospecific attack at C-3 with a bromide ion may give the bromoacetate **B**, which again forms a dioxolanylium ion **C**. Alternatively, the attack of bromide would afford **D**. Further, nucleophilic attack by a bromide ion would then occur with inversion of configuration at C-1 to give the L-*erythro* isomer **6**. The preference attack on C-1 to give **6** rather than on C-2 to give **7** may due to the increase of the positive charge on C-1 due to the effect of the heterocyclic ring. Moreover, this effect may be enhanced by the formation of an intermediate such as **D**, which rapidly undergoes ring opening. The similar formation of **6** from the *O*-isopropylidene derivative **4** or its acetate **5** indicated the facile acid hydrolysis of the acetal ring and the formation of a monoacetyl derivatives from **4** at the first stage of the reaction that followed by the formation of a dioxolanylium ion. Also, the formation of **13** from the benzoate **8** may confirm the facile acid hydrolysis of the acetal. On the other hand, the above data indicate that the benzoyl and *p*-toluenesulfonyl groups in **8** and **9** do not migrate, which leads to the formation of the monobromo derivatives **13** and **14**. As the migration of the acetyl group should be through its transformation to a dioxolanylium ion, the benzoyl and *p*-toluenesulfonyl groups do not readily form such ions under the present reaction conditions. The acetylation of **10** and **11** may have taken place on O-1 or O-2, and that was followed by the formation of a dioxolanylium ion **E** and subsequent ring opening with inversion of configuration of C-1 to give **13** and **14**, respectively.

The monobromodeoxy derivative **17** was prepared by the oxidation of 6-bromo-6-deoxy-L-ascorbic acid (**15**) (ref. 10) to give the corresponding dehydro derivative **F**, which was subsequently reacted, without isolation, with excess phenylhydrazine to give **17**, in addition to the anticipated bishydrazone **16**. Rearrangement of **16** to **17** had taken place under the conditions of the reaction. Acetylation of **16** and **17** gave the acetates **18** and **19**, respectively. The ^{1}H-n.m.r. spectrum of **19** showed a downfield shift for H-1 (δ 6.41) compared to the corresponding proton of **6**. On the other hand, resonances for H-2 (δ 5.78) and H-3 (δ 3.70) and H-3′ (δ 3.58) appeared at almost the same chemical shifts as the corresponding protons of **6**.

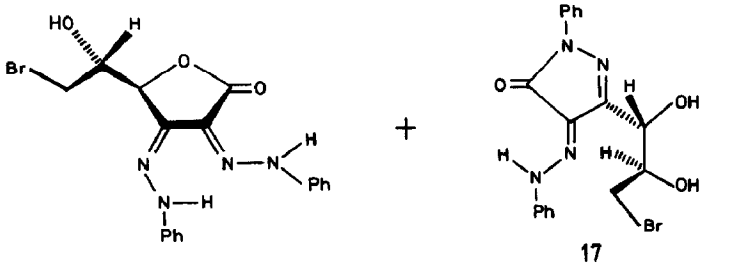
In conclusion, it is possible in a glycerolyl residue to substitute one or two of its hydroxy groups by selecting the substituent on the hydroxy group and subjecting it to the reaction with HBr–HOAc.

EXPERIMENTAL

General methods. — Melting points were determined with a Mel-Temp apparatus and are uncorrected. I.r. spectra were recorded for compounds in a matrix of KBr with a Unicam SP 1025 spectrophotometer. ^{1}H-N.m.r. spectra were determined with a Varian XL-100 and EM-390 spectrometers for solutions in $CDCl_3$ using Me_4Si as the internal standard. Chemical shifts are given on the δ scale. T.l.c. was performed on Baker-Flex Silica Gel 1B-F precoated plates. The spots were detected by their characteristic colors. Elemental analyses were carried out by the microanalytical laboratories at either Technische Hochschule Darmstadt and or at Cairo University.



15 F



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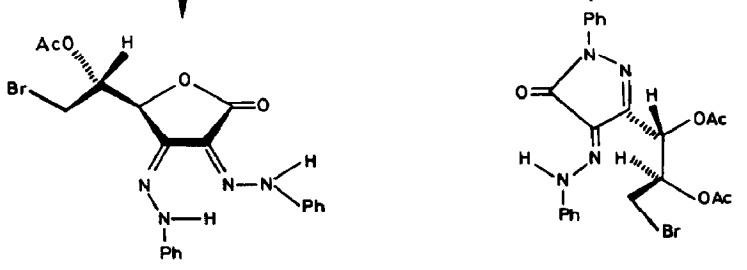

18 19

Scheme 3

*3-(2-*O*-Acetyl-1,3-dibromo-1,3-dideoxy-*L*-*erythro*-glycerol-1-yl)-1-phenylpyrazoline-4,5-dione 4-(phenylhydrazone)* (**6a**). — A suspension of compounds **3a** (0.4 g, 1.0 mmol), **4a** (1.0 mmol), or **5a** (0.91 mmol) in satd. HBr–HOAc (2.0 mL) was stirred until dissolution was complete. The solution was then kept overnight at room temperature, at the end of which time the mixture was diluted with ice-cold water, and the product was filtered, washed repeatedly with water, and dried to yield 0.34–0.42 g (70–80%) of crude **6a**. The crude product was recrystallized from ethanol to give orange needles: m.p. 197–200°; ν_{max} 1740 (OAc), 1670 (OCN), and 1600 cm^{-1} (C = N); ^{1}H-n.m.r. ($CDCl_3$): δ 2.04 (s, 3 H, OAc), 4.08 (d, 2 H, H-3,3'), 5.42 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.90 (m, 1 H, $J_{2,3}$ 4.0 Hz, $J_{2,3'}$ 7.5 Hz, H-2), 7.43 and 7.95 (2 m, 10 H, Ar), and 13.76 (bs, 1 H, NH) (The latter singlet disappeared upon deuteration). The i.r. and ^{1}H-n.m.r. spectra of the product from each compound were identical with those of the product obtained from a similar reaction on **1a** (ref. 16).

*3-(2-O-Acetyl-1,3-dibromo-1,3-dideoxy-*L-erythro-*glycerol-1-yl)-1-(p-bromophenyl)pyrazoline-4,5-dione 4-(p-bromophenylhydrazone)* (**6b**). — A solution of compound **1b** (1.0 g, 1.95 mmol) in satd. HBr–HOAc (4.0 mL) was processed as in the preceding paragraph, and the product (1.19 g, 90%) was recrystallized from ethanol to give **6b** as orange needles: m.p. 186–190°; ν_{max} 1740 (OAc) and 1660 cm^{-1} (OCN); ^{1}H-n.m.r. ($CDCl_3$): δ 2.03 (s, 3 H, OAc), 4.05 (m, 2 H, H-3,3'), 5.38 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.90 (m, 1 H, $J_{2,3}$ 4.0 Hz, $J_{2,3'}$ 7.0 Hz, H-2), 7.47 and 7.86 (2 m, 8 H, Ar), and 13.70 (bs, 1 H, NH) (The latter singlet disappeared upon deuteration).

Anal. Calc. for $C_{20}H_{16}Br_4N_4O_3$: C, 35.3; H, 2.4; N, 8.2. Found: C, 35.1; H, 2.4; N, 8.3.

*3-(2-O-Acetyl-1,3-dibromo-1,3-dideoxy-*L-erythro-*glycerol-1-yl)-1-(p-fluorophenyl)pyrazoline-4,5-dione 4-(p-fluorophenylhydrazone)* (**6c**). — A solution of compound **1c** (0.40 g, 1.02 mmol) was dissolved in satd. HBr–HOAc (2.0 mL). The reaction was processed as in the foregoing, and the product was recrystallized from ethanol to give 0.40 g (70%) of **6c** as orange needles: m.p. 175–176°; ν_{max} 1745 (OAc) and 1665 cm^{-1} (OCN); ^{1}H-n.m.r. ($CDCl_3$): δ 2.03 (s, 3 H, OAc), 4.02 (d, 2 H, H-3,3'), 5.35 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.84 (m, 1 H, H-2), 7.24 and 7.85 (2 m, 8 H, Ar), and 13.57 (bs, 1 H, NH).

Anal. Calc. for $C_{20}H_{16}Br_2F_2N_4O_3$: C, 43.0; H, 2.9; N, 10.0. Found: C, 43.0; H, 2.9; N, 10.0.

*3-(2-O-Acetyl-3-O-benzoyl-1-bromo-1-deoxy-*L-erythro-*glycerol-1-yl)-1-phenylpyrazoline-4,5-dione 4-(phenylhydrazone)* (**13**). — Compound **13** was prepared from **8** using satd. HBr–HOAc as above. The product (0.34 g, 75%) was recrystallized from ethanol to give orange needles: m.p. 158–160°; ν_{max} 1740 (OAc), 1725 (OBz), and 1660 cm^{-1} (OCN); ^{1}H-n.m.r. ($CDCl_3$): δ 2.00 (s, 3 H, OAc), 4.84 (q, 1 H, $J_{2,3'}$ 4.9 Hz, $J_{3,3'}$ 12.0 Hz, H-3'), 5.10 (q, 1 H, $J_{2,3}$ 3.0 Hz, H-3), 5.40 (d, 1 H, $J_{1,2}$ 9.0 Hz, H-1), 6.12 (m, 1 H, H-2), 7.43 and 8.03 (2 m, 15 H, Ar).

Anal. Calc. for $C_{27}H_{23}BrN_4O_5$: C, 57.6; H, 4.1; N, 9.9. Found: C, 57.3; H, 3.9; N, 10.0.

*3-(2-O-Acetyl-1-bromo-1-deoxy-3-O-(p-toluenesulfonyl)-*L-erythro-*glycerol-1-yl)-1-phenylpyrazoline-4,5-dione 4-(phenylhydrazone)* (**14**). — Compound **14** was prepared from **9** using satd. HBr–HOAc. The product (0.40 g, 88%) was recrystallized from ethanol to give orange needles: m.p. 161–162°; ν_{max} 1740 (OAc) and 1660 cm^{-1} (OCN); ^{1}H-n.m.r. ($CDCl_3$): δ 1.95 (s, 3 H, OAc), 2.44 (s, 3 H, Me), 4.66 (d, 2 H, H-3,3'), 5.36 (d, 1 H, $J_{1,2}$ 9.0 Hz, H-1), 5.86 (m, 1 H, $J_{2,3}$ 3.2 Hz, $J_{2,3'}$ 6.0 Hz, H-2) 7.38 and 7.91 (2 m, 14 H, Ar).

Anal. Calc. for $C_{27}H_{25}BrN_4O_6S$: C, 52.9; H, 4.1; N, 9.1. Found: C, 52.6; H, 4.1; N, 9.3.

*3-(1,2-Di-O-acetyl-3-O-(p-toluenesulfonyl)-*L-threo-*glycerol-1-yl)-1-phenyl-pyrazoline-4,5-dione 4-(phenylhydrazone)* (**12**). — A solution of compound **11** (0.1 g, 0.20 mmol) in pyridine (2.0 mL) was cooled and treated with acetic anhydride (2.0 mL). The mixture was processed as usual, and the product was recrystallized from ethanol to give 0.10 g, (90%) of **12** as yellow orange needles: m.p. 152–154°; ν_{max} 1740 (sh), 1730 (OAc) and 1665 cm^{-1} (OCN); ^{1}H-n.m.r. ($CDCl_3$): δ 2.02 and 2.10 (2 s, 6 H, 2 OAc), 2.34

(s, 3 H, Me), 4.29 (q, 1 H, $J_{2,3'}$ 5.5 Hz, $J_{3,3'}$ 12.0 Hz, H-3'), 4.43 (q, 1 H, $J_{2,3}$ 4.0 Hz, H-3), 5.76 (m, 1 H, H-2), 6.31 (d, 1 H, $J_{1,2}$ 6.4 Hz, H-1), 7.40 and 7.80 (2 m, 14 H, Ar).

Anal. Calc. for $C_{29}H_{28}N_4O_8S$: C, 58.8; H, 4.8; N, 9.5. Found: C, 58.5; H, 4.5; N, 9.3.

*Reaction of 6-bromo-6-deoxy-*L*-ascorbic acid with phenylhydrazine.* — A suspension of L-ascorbic acid (1.0 g, 5.70 mmol) in satd. HBr–HOAc (10.0 mL) was stirred until dissolution was achieved, and then the solution was left overnight at room temperature. At the end of this time, the mixture was diluted with water (100 mL), stirred for 5 h, and left standing overnight. The solution was then concentrated under reduced pressure. Iodine was added until its color persisted, and then a solution of phenylhydrazine (3.0 mL) in ethanol (100 mL) was added. The mixture was heated on a water-bath for 10 min, and the product was fractionally crystallized from ethanol to give **16** and **17**, which were purified as described in the following paragraphs.

*6-Bromo-6-deoxy-*L-threo*-2,3-hexodiulosono-1,4-lactone 2,3-bis(phenylhydrazone)* (**16**). — Crude **16** was recrystallized from ethanol to give 0.36 g (15%) of pure product: m.p. 193–195°; ν_{max} 3500 (OH), 1740, and 1725 cm^{-1} (OCO).

Anal. Calc. for $C_{18}H_{17}BrN_4O_3$: C, 51.9; H, 4.1; N, 13.4. Found: C, 51.9; H, 4.0; N, 13.5.

*3-(3-Bromo-3-deoxy-*L-threo*-glycerol-1-yl)-1-phenylpyrazoline-4,5-dione 4-(phenylhydrazone)* (**17**). — Compound **17** was recrystallized from ethanol to give 0.83 g (35%) of pure product as orange needles: m.p. 183–185°; ν_{max} 1660 cm^{-1} (OCN).

Anal. Calc. for $C_{18}H_{17}BrN_4O_3$: C, 51.9; H, 4.1; N, 13.4. Found: C, 51.7; H, 3.8; N, 13.7.

*5-O-Acetyl-6-bromo-6-deoxy-*L-threo*-2,3-hexodiulosono-1,4-lactone 2,3-bis(phenylhydrazone)* (**18**). — Acetylation of **16** as for **12** (foregoing section) with acetic anhydride in pyridine and crystallization of the product from ethanol gave 0.08 g (75%) of pure **18** as red crystals: m.p. 181–184°; ν_{max} 1750 (OAc) and 1735 cm^{-1} (OCO).

Anal. Calc. for $C_{20}H_{19}BrN_4O_4$: C, 52.3; H, 4.2; N, 12.2. Found: C, 52.2; H, 4.1; N, 12.3.

*3-(1,2-Di-O-acetyl-3-bromo-3-deoxy-*L-threo*-glycerol-1-yl)-1-phenylpyrazoline-4,5-dione 4-(phenylhydrazone)* (**19**). — Acetylation of **17** as for **12** in the foregoing section gave 0.11 g (90%) of the title compound, which was recrystallized from ethanol as orange crystals: m.p. 131–132°; ν_{max} 1745 (OAc) and 1665 cm^{-1} (OCN); ^{1}H-n.m.r. ($CDCl_3$): δ 2.08 and 2.18 (2 s, 6 H, 2 OAc), 3.58 (q, 1 H, $J_{2,3'}$ 6.0 Hz, $J_{3,3'}$ 11.0 Hz, H-3'), 3.70 (q, 1 H, $J_{2,3}$ 5.0 Hz, H-3), 5.78 (m, 1 H, H-2), 6.41 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1), 7.34 and 7.95 (2 m, 10 H, Ar), 13.72 (s, 1 H, NH).

Anal. Calc. for $C_{22}H_{21}BrN_4O_5$: C, 52.7; H, 4.2; N, 11.2. Found: C, 52.9; H, 4.0; N, 11.4.

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