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Isobutylidenation of 1-*C*-substituted polyols. Attempted extension of the NMR shift rule via the chemical shift difference of their two methyl groups

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Abstract

The isobutylidenation of 1-*C*-substituted L-*threo*-, D-*erythro*-glycerols, and D-*arabino*-tetritol has been studied. The location of the acetal could be adjusted by selecting the conditions for acetalation as well as the configuration of the polyol. The structure of the products was deduced by a combination of physical and chemical methods. The shift rule for the isopropylidene group has been extended to include the chemical shift difference of the two methyl groups of the isobutylidene rings.

Keywords: Acetal; Synthesis; NMR shift rule; 2-Butylidene acetal

1. Introduction

The development of a method for the recognition of the configuration of a diol functionality in acyclic compounds was reported earlier [1,2] and was called the El Ashry shift rule. The method was based on the difference in the chemical shift ($\Delta\delta$) between the ^{1}H NMR signals for the two methyls of the isopropylidene group which was found to be a criterion for determining the configuration of the diol functionality masked by the ring. Thus, $\Delta\delta$ will be ≤ 0.05 for the *threo* configuration, whereas a comparatively higher value of ≥ 0.05 for the terminal and a much more higher value > 0.10 for the *erythro* configuration were found. Although a deviation from this rule

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was found in some cases [3], it was valid for various types of compounds [4]. In the formation of an isopropylidene ring, acetone, a symmetrical ketone, was used [1–10]. When an unsymmetrical ketone or an aldehyde is used as the acetalating agent, a mixture of diastereomers would be expected [11–17]. This feature was used in the present investigation to extend the method of recognition of diols via the reaction with ethyl methyl ketone, which would form a diastereomeric mixture in which the two methyl groups will exist in two different environments. Consequently, this will create different chemical shift values for the two methyl groups of the diastereomer, which might be parallel with that of the respective isopropylidene function. To confirm such an assumption and to investigate it as a possible extension to the shift rule, the synthesis, structural, and spectral investigation of the isobutylidene derivatives of acyclic *C*-nucleoside analogues with varying configurations of the polyol residues is the objective of this paper.

2. Results and discussion

Isobutylidenation of the terminal diol of **1** was achieved by its reaction with 2-butanone (**2**) in the presence of *p*-toluenesulfonic acid (PTSA) as catalyst to give the 5,6-*O*-isobutylidene derivative **3**. The location of the acetal group in **3** was deduced from the fact that the conditions of acetalation do not affect the preexisting five-membered lactone ring [10], which was confirmed spectroscopically. Thus the infrared (IR) spectrum of **3** showed in the carbonyl frequency region a band at 1740 cm^{-1} due to the lactone carbonyl group, the low value of which could be attributed to its involvement in hydrogen bonding. This was confirmed by the presence of the two resonances of the two NHs in its ^1H NMR spectrum at lower magnetic field at δ 10.83 and 11.83. Moreover, the deshielding effect of the doublet of H-4 (δ 5.07) confirmed that C-4 is a part of the lactone ring.

The lactone ring in **3** could be considered as a temporary protection for O-4, which is easily amenable for opening by alkali, that upon neutralization a cyclization of the generated carboxyl group took place to give the pyrazolinone derivative **6**, without rearrangement of the isobutylidene ring. On the other hand, when the isobutylidenation of **4** was carried out, it was found that the pattern of the reaction products was dependent on the acid catalyst. Thus, the use of the pyridinium *p*-toluenesulfonate as a catalyst led to the formation of **6** as a major product and **7** as a minor product after one day's reaction. A reverse pattern was found for the products from the use of sulfuric acid as a catalyst, where **7** was found as the major product. Monitoring the reaction by TLC indicated that the two products were formed immediately, where the proportion of **7** is increased with time until equilibrium was attained. When the concentration of the sulfuric acid catalyst was decreased, a third product appeared, and the ratio of the products was found to be initially in the order **6** > **7** > third product. With time the proportion of **6** increased and the third product disappeared. The ratio of **6**:**7** was then independent of the concentration of the acid. Similarly, the reaction of **5** with **2** gave **8** as a major product. Since each pathway of the reaction, under such experimental conditions, is expected to be reversible and a true equilibrium is established, the

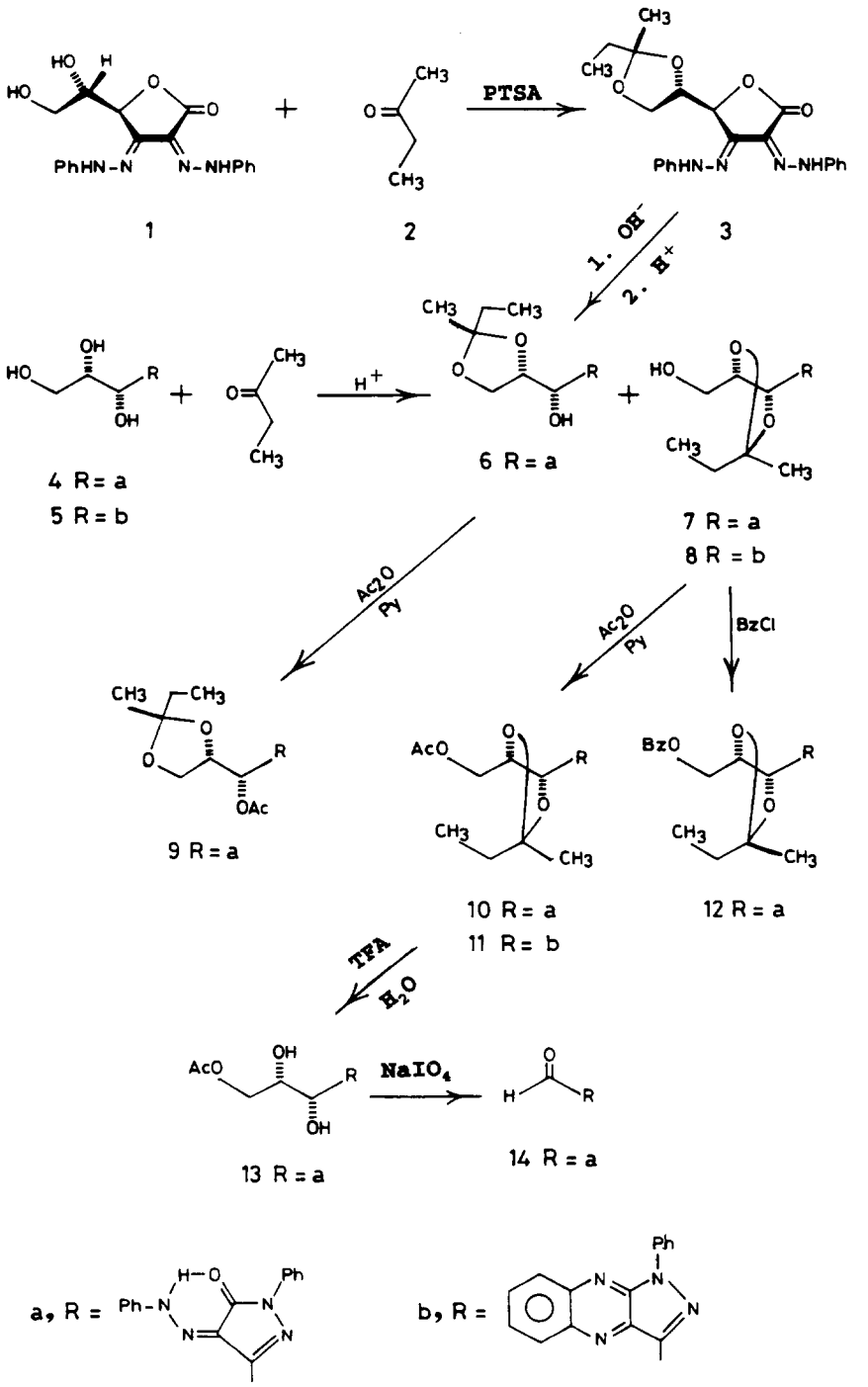
composition of the products is quite independent of the mechanism of the reaction and is determined solely by the relative thermodynamic stabilities of the products. According to the accepted mechanism [11], the formation of a terminal dioxolane as in **6** or a dioxane, which could not be isolated (it is most probably the third product), is anticipated to take place initially, the rearrangements of which will give **8**. This was attributed to the unsymmetrical substitution around the dioxolane ring in **6** which is relieved upon rearrangement to **8** that carries the 4- and 5-substituents in a *trans* orientation. The location of the isobutylidene ring in the reaction product of **4** with **2** as **6** was deduced from its identity with the product resulting from the rearrangement of **3**. Moreover, acetylation of **6** gave compound **9**, the ^{1}H NMR spectrum of which showed a downfield shift of the doublet due to H-1 (δ 6.10) of the glycerolyl side chain upon acylation. This indicated that acylation occurred at O-1. Since, the C-2 methine proton (δ 4.89) and the C-3 methylene protons (δ 3.89 and 4.13) were virtually unchanged, the acetal ring would occupy O-2 and O-3.

The locations of the isobutylidene groups in **7** was also deduced by studying the deshielding effect experienced by the protons of the glycerolyl residues upon acetylation and benzoylation, where compound **7** afforded the corresponding mono-*O*-acylated derivatives **10** and **12**, respectively. The ^{1}H NMR spectra of the mono-*O*-acylated derivatives showed that the chemical shifts of the signals for H-3, 3′ (δ 3.90) of **7** were markedly affected by the acylation and shifted to a downfield region for **10** (δ 4.17 and 4.48) and **12** (δ 4.64). In contrast, the signals of the two methine protons H-1 and H-2 of the glycerolyl side chain of **7** suffered no appreciable change. Moreover, comparison of the chemical shifts with that of the tri-*O*-acyl derivative confirmed the assignment. This indicated that the acetal ring occupied the two secondary hydroxyl groups, which was confirmed by the deisobutylidenation of **10** with aqueous acetic acid or trifluoroacetic acid to give **13**, the periodate oxidation of which gave **14**.

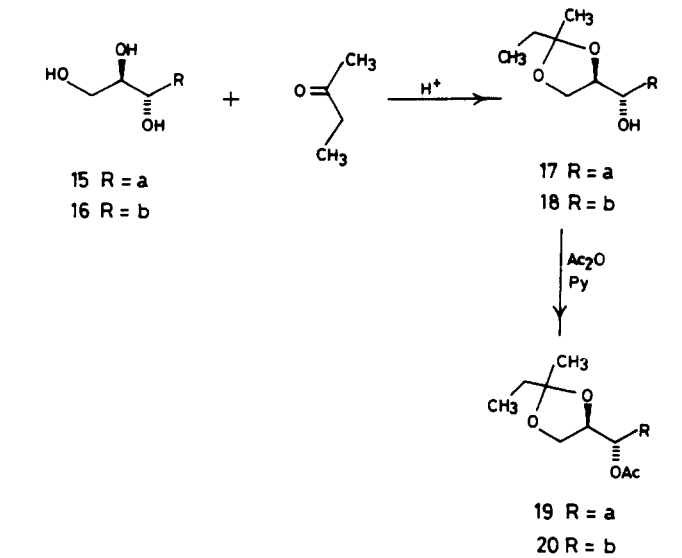
Acid-catalyzed isobutylidenation of **15** gave **17**, the acetylation of which afforded **19**. The pronounced downfield shift of the signal for H-1 (δ 4.94 and 4.98 to 6.18 and 6.22) on acetylation of **17** indicated that this was the position that was acetylated. The singlet at δ 2.90, due to the hydroxyl group of **17**, did not appear in the spectrum of **19**. The chemical shifts of the signals of the other glycerolyl protons were not affected by the acetylation. Similarly, the reaction of **16** gave **18**, the acetylation of which gave **20**. The rearrangement of the isobutylidene ring in **19** or **20** was prohibited due to the generation of *cis* substituents at the 4 and 5 positions.

When the isobutylidenation was carried out on the tetritolyl derivative **21**, various chances for the reaction should be considered to take place. However, it was possible to isolate two products, the structures of which were deduced to be **22** and **23**. The structures were based on their acetylation whereby **24** was obtained from **22** but **23** could not be acetylated. Interpreting their ^{1}H NMR spectra led to the conclusion that **22** has an α-terminal ring.

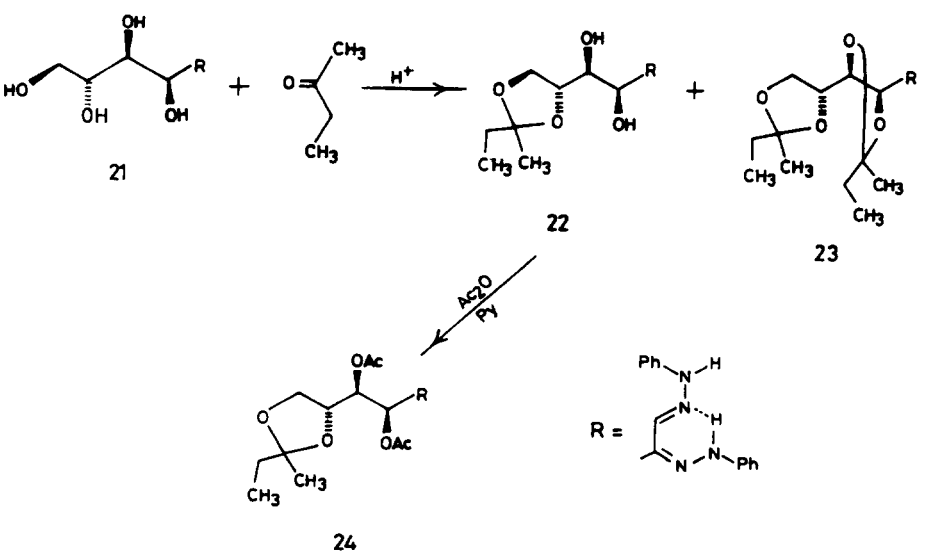
The isobutylidenation of a diol functionality led to the formation of a mixture of diastereomers. This is clear in the ^{1}H NMR spectra where two singlets appear in all the spectra for the methyl group, in addition to the quartet and triplet, each of which appeared in the form of two resonances. Inspection of the resonances of the two methyl groups indicated that the values of $\Delta\delta$ for the terminal ring is in the range 0.07–0.10,


PTSA
1
2
3
1. OH⁻
2. H⁺
4 R = a
5 R = b
6 R = a
7 R = a
8 R = b
Ac2O
Py
BzCl
9 R = a
10 R = a
11 R = b
12 R = a
TFA
H2O
NaIO4
13 R = a
14 R = a
a, R =
b, R =

Scheme 1.



Scheme 2.



Scheme 3.

and the *threo* ring is 0.05. This agrees with the shift rule for the isopropylidene rings. On the other hand, the acyl groups have an influence on the chemical shift of the methyl groups and consequently affected the $\Delta\delta$ values. This effect is probably due to an anisotropic effect of the carbonyl ester groups.

3. Experimental

General methods.—Melting points were determined with a Mel-Temp apparatus and are uncorrected. IR spectra were recorded for compounds in KBr with a Unicam SP 200 spectrophotometer. ^{1}H NMR spectra were measured with a Varian EM-390 spectrometer for solutions in $CDCl_3$ using Me_4Si as internal standard. Chemical shifts are given in the δ scale. TLC was performed on Baker-Flex Silica Gel 1B-F precoated plates. Elemental analyses were carried out by the microanalytical laboratory at Cairo University.

*5,6-O-Isobutylidene-*L-threo*-2,3-hexodiulosono-1,4-lactone 2,3-bis(phenylhydrazone)* (**3**).—A suspension of dry **1** (3.5 g; 10.0 mmol) in a mixture of dry 2-butanone (90 mL) and *p*-toluenesulfonic acid (0.05 g, 0.26 mmol) was stirred vigorously for 1 h. The mixture was kept overnight at room temperature and then neutralized by the addition of solid anhyd sodium carbonate. The mixture was filtered, and the inorganic salts were washed with dry 2-butanone, and the combined filtrate and washings were evaporated in vacuo. Petroleum ether was added to the resulting viscous syrup, and the product that separated out was filtered off, washed with EtOH, and dried (3.7 g, 92%). The product was crystallized from EtOH as red crystals; mp 136–139°C; ν_{max} 1610 (C=N), 1740 cm^{-1} (OCO); ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3 H, CH_3-CH_2), 1.23, 1.36 (2 s, 3 H, CH_3), 1.67 (q, 2 H, CH_3-CH_2), 4.27 (m, 3 H, H-5,6,6′), 5.07 (d, 1 H, $J_{4,5}$ 4.5 Hz, H-4), 7.15 (m, 10 H, Ar Hs), 10.83 and 11.83 (2 s, 2 H, 2 NH). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.7; H, 5.9, N, 13.7. Found: C, 64.9; H, 5.7; N, 13.9.

*3-[2,3-O-Isobutylidene-*L-threo*-glycerol-1-yl]-1-phenyl-2-pyrazoline-4,5-dione 4-(phenylhydrazone)* (**6**).—(*a*) A solution of **3** (1.0 g, 2.4 mmol) in 2 M KOH (100 mL) was stirred at 60–80°C for 1 h, and the solution was then cooled and neutralized with acetic acid. The product was filtered off, washed with EtOH and dried. The product was crystallized from EtOH as yellow-orange needles (0.7 g, 70%): mp 110–113°C; ν_{max} 1600 (C=N), 1660 (OCN), and 3500 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$): δ 1.33 (t, 3 H, CH_3-CH_2), 1.40 and 1.45 (2 s, 3 H, CH_3), 1.69 (q, 2 H, CH_2CH_3), 3.06 (bs, 1 H, OH), 4.03 (m, 2 H, H-3,3′), 4.66 (m, 1 H, H-2), 4.79 (d, 1 H, H-1), 7.36 (m, 8 H, Ar Hs), 7.83 (d, 2 H, *J* 7.5 Hz, *o*-Ar Hs), and 13.60 (s, 1 H, NH). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.7; H, 5.9, N, 13.7. Found: C, 65.0; H, 6.1; N, 13.6.

(*b*) A mixture of **4** (3.5 g; 10.0 mmol) in dry *N*,*N*-dimethylformamide (5 mL), dry 2-butanone (90 mL), and pyridinium *p*-toluenesulfonate (0.1 g) was stirred vigorously for 1.5 h at 90–110°C. The mixture was kept overnight at room temperature, and was then processed as before, and the product was subjected to preparative TLC (2:5 ethyl acetate–hexane) to give **6**; mp 110–113°C (identical with the product from *a*).

*3-[1,2-O-Isobutylidene-*L-threo*-glycerol-1-yl]-1-phenyl-2-pyrazoline-4,5-dione 4-(phenylhydrazone)* (**7**).—A mixture of **4** (3.5 g, 10.0 mmol) in dry *N*,*N*-dimethylfor-

mamide (5 mL), dry 2-butanone (90 mL), and 96% sulfuric acid (0.5 mL) was stirred overnight and then processed as before. The major product (2.9 g, 72%) was crystallized from EtOH as orange needles; mp 134–137°C; ν_{max} 1600 (C=N), 1655 (OCN), and 3500 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 1.00 (t, 3 H, CH_3CH_2), 1.48 and 1.53 (2 s, 3 H, CH_3), 1.83 (q, 2 H, CH_3CH_2), 2.10 (bs, 1 H, OH), 3.90 (m, 2 H, H-3,3′), 4.73 (m, 1 H, H-2), 5.02 and 5.12 (2 d, 1 H, H-1), 7.40 (m, 8 H, Ar Hs), 7.91 (d, 2 H, *J* 9.0 Hz, *o*-Ar Hs), and 13.83 (bs, 1 H, NH). The signal at δ 13.83 disappeared upon deuteration. Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.7; H, 5.9, N, 13.7. Found: C, 64.7; H, 5.6; N, 13.8.

*3-[1,2-*O*-Isobutylidene-*L*-threo-glycerol-1-yl]-1-phenylflavazole* (**8**).—A mixture of **5** (3.36 g, 10.0 mmol) in dry 2-butanone (90 mL) and 96% sulfuric acid (0.5 mL) was stirred vigorously for 1 h and then kept overnight at room temperature. The mixture was processed as before, and the product (2.7 g, 69%) was crystallized from EtOH as yellow needles; mp 122–126°C; ν_{max} 1595 (C=N), 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 1.10 (t, 3 H, CH_3-CH_2), 1.63 and 1.68 (2 s, 3 H, CH_3), 1.93 (q, 2 H, CH_2CH_3), 2.40 (bs, 1 H, OH), 3.99 (m, 2 H, H-3,3′), 5.09 (m, 1 H, H-2), 5.56 and 5.65 (2 d, 1 H, H-1), 7.53 and 8.26 (2 m, 9 H, Ar Hs). The signal at δ 2.40 was exchangeable with deuterium oxide. Anal. Calcd for $C_{22}H_{22}N_4O_3$: C, 67.7; H, 5.7, N, 14.4. Found: C, 68.0; H, 5.2; N, 14.0.

*3-[1-*O*-Acetyl-2,3-*O*-isobutylidene-*L*-threo-glycerol-1-yl]-1-phenyl-2-pyrazoline-4,5-dione 4-(phenylhydrazone)* (**9**).—A cold solution of **6** (0.4 g, 1.0 mmol) in dry pyridine (2 mL) was treated with Ac_2O (1 mL), and the mixture was kept overnight at room temperature. The mixture was poured onto crushed ice, and the product (0.3 g, 68%) was crystallized from EtOH as orange needles; mp 98–101°C; ν_{max} 1595 (C=N), 1660 (OCN), and 1750 cm^{-1} (OAc); ^1H NMR ($CDCl_3$): δ 0.96 (t, 3 H, CH_3CH_2), 1.36 and 1.43 (2 s, 3 H, CH_3), 1.63 (q, 2 H, CH_2CH_3), 2.20 (s, 3 H, $COCH_3$), 3.89 and 4.13 (2q, 2 H, H-3,3′), 4.89 (m, 1 H, H-2), 6.10 (d, 1 H, H-1), 7.33 (m, 8 H, Ar Hs), 7.90 (d, 2 H, *J* 7.5 Hz, *o*-Ar Hs) and 13.60 (bs, 1 H, NH). The signal at δ 13.60 disappeared upon deuteration. Anal. Calcd for $C_{24}H_{26}N_4O_5$: C, 64.0; H, 5.8; N, 12.4. Found: C, 63.6; H, 5.3; N, 12.1.

*3-[3-*O*-Acetyl-1,2-*O*-isobutylidene-*L*-threo-glycerol-1-yl]-1-phenyl-2-pyrazoline-4,5-dione 4-(phenylhydrazone)* (**10**).—A cold solution of **7** (0.4 g; 1.0 mmol) in dry pyridine (2 mL) was acetylated as before. The product (0.4 g, 90%) was crystallized from EtOH as orange needles; mp 150–153°C; ν_{max} 1590 (C=N), 1660 (OCN); and 1730 cm^{-1} (OAc); ^1H NMR ($CDCl_3$): δ 1.07 (t, 3 H, CH_3CH_2), 1.53 and 1.63 (2 s, 3 H, CH_3), 1.86 (q, 2 H, CH_2CH_3), 2.15 (s, 3 H, $COCH_3$), 4.17 (dd, 1 H, $J_{2,3'}$ 6.0, $J_{3,3'}$ 12.0 Hz, H-3′), 4.48 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-3), 4.90 (m, 2 H, H-1, 2), 7.37 (m, 8 H, Ar Hs), 7.93 (d, 2 H, *J* 7.5 Hz, Ar Hs) and 13.87 (bs, 1 H, NH). The signal at 13.87 disappeared with addition of deuterium oxide. Anal. Calcd for $C_{24}H_{26}N_4O_5$: C, 64.0; H, 5.8; N, 12.4. Found: C, 64.0; H, 5.8; N, 12.7.

*3-[3-*O*-Acetyl-1,2-*O*-isobutylidene-*L*-threo-glycerol-1-yl]-1-phenylflavazole* (**11**).—Conventional acetylation of **8** gave **11** (93%) that was crystallized from EtOH as yellow crystals; mp 113–116°C; ν_{max} 1610 (C=N) and 1750 cm^{-1} (OAc); ^1H NMR ($CDCl_3$): δ 1.13 and 1.17 (2 t, 3 H, CH_3CH_2), 1.53 and 1.73 (2 s, 3 H, CH_3), 1.98 (q, 2 H, CH_3CH_2), 2.00 (s, 3 H, $COCH_3$), 4.24 (dd, 1 H, $J_{2,3'}$ 6.0, $J_{3,3'}$ 12.0 Hz, H-3′), 4.53 (dd, 1 H, $J_{2,3}$ 3.5 Hz, H-3), 5.27 (m, 1 H, H-2), 5.49 and 5.57 (2 d, 1 H, H-1), 7.55, and

8.30 (2 m, 9 H, Ar Hs). Anal. Calcd for $C_{24}H_{24}N_4O_4$: C, 66.7; H, 5.6; N, 13.0. Found: C, 66.7; H, 5.8; N, 12.9.

*3-[3-O-Benzoyl-1,2-O-isobutylidene-*L-threo-*glycerol-1-yl]-1-phenyl-2-pyrazoline-4,5-dione 4-(phenylhydrazone)* (**12**).—A cold solution of **7** (0.4 g, 1.0 mmol) in dry pyridine (2 mL) was treated with benzoyl chloride (0.5 mL), and kept overnight at room temperature. The mixture was poured onto crushed ice, and **12** (0.3 g, 60%) was crystallized from EtOH as orange-yellow crystals; mp 140–143°C; ν_{max} 1600 (C=N), 1655 (OCN); and 1725 cm^{-1} (OBz); ^1H NMR ($CDCl_3$): δ 1.00 and 1.10 (2 t, 3 H, CH_3CH_2), 1.43 and 1.53 (2 s, 3 H, CH_3), 1.86 (q, 2 H, CH_2CH_3), 4.64 (d, 2 H, H-3,3′), 5.07 (m, 2 H, H-1,2), 7.36 and 8.04 (2 m, 15 H, Ar Hs), and 13.80 (bs, 1 H, NH). The signal at δ 13.80 disappeared upon deuteration. Anal. Calcd for $C_{29}H_{28}N_4O_5$: C, 68.0; H, 5.5; N, 10.9. Found: C, 68.0; H, 5.4; N, 10.6.

*Preparation of 3-[3-O-acetyl-*L-threo-*glycerol-1-yl]-1-phenyl-2-pyrazoline-4,5-dione 4-(phenylhydrazone)* (**13**).—A suspension of **10** (0.45 g; 1.0 mmol) in 80% aq CF_3CO_2H (10 mL) was kept for 15 min at room temperature. The mixture was diluted with cold water, and the product that separated out was filtered off, washed with water, and dried. It was crystallized from EtOH as orange needles (0.35 g, 88%); mp 160–162°C (lit. [6] mp 160–161°C).

Preparation of 3-carbaldehyde-1-phenyl-2-pyrazoline-4,5-dione 4-(phenylhydrazone) (**14**).—A suspension of **13** (0.39 g, 1.0 mmol) in distilled water (10 mL) was treated with a solution of sodium metaperiodate (0.2 g, 1.0 mmol) in distilled water (10 mL). The mixture was stirred at room temperature for 4 h and then left overnight in the dark. The product was filtered off, washed with water, dried, and crystallized from EtOH as orange needles (0.25 g, 87%); mp 135–137°C (lit. [18] mp 139–141°C).

*3-[2,3-O-Isobutylidene-*D-erythro-*glycerol-1-yl]-1-phenyl-2-pyrazoline-4,5-dione 4-(phenylhydrazone)* (**17**).—Compound **15** (3.5 g, 10.0 mmol), dry 2-butanone (90 mL), and *p*-toluenesulfonic acid (0.05 g, 0.26 mmol) was stirred vigorously for 1 h and then kept overnight at room temperature. The mixture was processed as before, and the product (3.0 g, 78%) was crystallized from EtOH as orange crystals; mp 143–146°C; ν_{max} 1600 (C=N), 1660 cm^{-1} (OCN). ^1H NMR ($CDCl_3$): δ 0.92 and 0.96 (2 t, 3 H, CH_3CH_2), 1.27 and 1.38 (2 s, 3 H, CH_3), 1.63 (q, 2 H, CH_2CH_3), 2.90 (bs, 1 H, OH), 4.15 (m, 2 H, H-3, 3′), 4.51 (m, 1 H, H-2), 4.94 and 4.98 (2 d, 1 H, *J* 4.5 Hz, H-1), 7.28 (m, 8 H, Ar Hs), 7.88 (d, 2 H, *J* 7.2 Hz, *o*-Ar Hs) and 13.70 (s, 1 H, NH). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.7; H, 5.9; N, 13.7. Found: C, 64.3; H, 5.8; N, 13.5.

*3[2,3-O-Isobutylidene-*D-erythro-*glycerol-1-yl]-1-phenylflavazole* (18).—A mixture of **16** (3.36 g, 10.0 mmol) in dry 2-butanone (90 mL) and *p*-toluenesulfonic acid (0.05 g, 0.26 mmol) was stirred vigorously for 1 h and then kept overnight at room temperature. The mixture was processed as before, and the product (2.5 g, 64%) was crystallized from EtOH as yellow needles; mp 97–100°C; ν_{max} 1600 (C=N), and 3490 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 0.89 and 1.03 (2 t, 3 H, CH_3CH_2), 1.33 and 1.40 (2 s, 3 H, CH_3), 1.66 (m, 2 H, CH_3CH_2), 3.40 (d, 1 H, OH), 4.33 (m, 2 H, H-3, 3′), 4.91 (m, 1 H, H-2), 5.57 (d, 1 H, H-1), 7.62 and 8.31 (2 m, 9 H, Ar Hs). The signal at δ 3.40 was exchangeable with deuterium. Anal. Calcd. for $C_{22}H_{22}N_4O_3$: C, 67.7; H, 5.7; N, 14.4. Found: C, 67.3; H, 5.9; N, 14.2

*3-[1-O-Acetyl-2,3-O-isobutylidene-*D-erythro-*glycerol-1-yl]-1-phenyl-2-pyrazoline-*

4,5-dione 4-(phenylhydrazone) (**19**).—Conventional acetylation of **16** as before gave the acetyl derivative **19** (91%) that was crystallized from EtOH as orange needles; mp 118–121°C; ν_{max} 1590 (C=N), 1660 (OCN) and 1740 cm^{-1} (OAc); ^1H NMR ($CDCl_3$): δ 0.89 (t, 3 H, CH_3CH_2), 1.24 and 1.33 (2 s, 3 H, CH_3), 1.63 (q, 2 H, CH_2CH_3), 2.07 (s, 3 H, $COCH_3$), 4.12 (d, 2 H, H-3, 3'), 4.68 (m, 1 H, H-2) 6.18 and 6.22 (2 d, 1 H, H-1), 7.33 (m, 8 H, Ar Hs), 7.88 (d, 2 H, *J*, 7.5 Hz, *o*-Ar Hs) and 13.60 (bs, 1 H, NH). Anal. Calcd for $C_{24}H_{26}N_4O_5$: C, 64.0; H, 5.8; N, 12.4. Found: C, 64.4; H, 6.3; N, 12.2.

*3-[1-*O*-Acetyl-2,3-*O*-isobutylidene-*D*-erythro-glycerol-1-yl]-1-phenylflavazole* (**20**).—Acetylation of **18** as before gave a product (46%) that was crystallized from EtOH as yellow crystals; mp 70–72°C; ν_{max} 1600 (C=N), and 1750 cm^{-1} (OAc); ^1H NMR ($CDCl_3$): δ 0.83 (t, 3 H, CH_3CH_2), 1.26 and 1.30 (2 s, 3 H, CH_3), 1.63 (q, 2 H, CH_2CH_3), 2.20 (s, 3 H, $COCH_3$), 4.16 (d, 2 H, H-3,3'), 5.00 (m, 1 H, H-2), 6.56 and 6.62 (2 d, 1 H, H-1), 7.47 and 8.23 (2 m, 9 H, Ar Hs). Anal. Calcd for $C_{24}H_{24}N_4O_4$: C, 66.7; H, 5.6; N, 13.0. Found: C, 66.5; H, 5.3; N, 12.8.

*5,6-*O*-Isobutylidene-*D*-arabino-hexosulose bis(phenylhydrazone)* (**22**).—A suspension of **21** (3.6 g, 10 mmol) in dry *N,N*-dimethylformamide (5 mL), dry 2-butanone (45 mL), and *p*-toluenesulfonic acid (0.05 g; 0.26 mmol) was stirred vigorously for 1.5 h. The product was subjected to silica gel column chromatography using (1:1 ethylacetate–hexane) as eluent to give **22** (2.5 g, 60%); mp 128–130°C; ν_{max} 1580 and 1615 (C=N), 3280 (NH) and 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 0.86 and 1.33 (2 t, 3 H, CH_3CH_2), 1.60 and 1.46 (2 s, 3 H, CH_3), 1.76 (q, 2 H, CH_2CH_3), 3.21 (s, 2 H, 2 OH), 4.06 (m, 4 H, H-4,5,6,6'), 4.50 (bs, 1 H, H-3), 7.06 (m, 10 H, Ar Hs), 7.72 (s, 1 H, H-1), 9.97 and 12.16 (2 s, 2 H, 2 NH). Anal. Calcd for $C_{22}H_{28}N_4O_4$: C, 64.1; H, 6.8; N, 13.6. Found: C, 64.5; H, 6.6; N, 13.7.

*3,4-5,6-Di-*O*-isobutylidene-*D*-arabino-hexosulose bis(phenylhydrazone)* (**23**).—The same as above, but the reaction was allowed to proceed for 24 h whereby **23** could be separated by column chromatography. The minor product **23** (2.0, g, 47%); R_f 0.8 (1:1 ethyl acetate–hexane); mp 191–194°C; ν_{max} 1570, 1610 (C=N) and 3300 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 0.94 (m, 6 H, 2 CH_3CH_2), 1.23 and 1.45 (2 s, 6 H, 2 CH_3), 1.72 (m, 4 H, 2 CH_2CH_3), 3.59 and 4.14 (2 m, 3 H, H-5,6,6'), 4.73 (m, 2 H, H-3,4), 7.17 (m, 10 H, Ar Hs), 7.60 (s, 1 H, H-1), 7.57 and 12.32 (2 s, 2 H, 2NH). Anal. Calcd for $C_{26}H_{34}N_4O_4$: C, 66.9; H, 7.3; N, 12.0. Found: C, 66.7; H, 7.1; N, 12.3.

*3,4-Di-*O*-Acetyl-5,6-*O*-isobutylidene-*D*-arabino-hexose phenylosazone* (**24**).—Conventional acetylation of **22** gave the product (0.36 g; 60%) that was crystallized from EtOH as yellow crystals; mp 157–160°C; ν_{max} 1580 and 1620 (C=N), 1750 and 1770 (OAc) and 3345 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 0.88 (m, 3 H, CH_3CH_2), 1.27 and 1.30 (2 s, 3 H, CH_3), 1.60 (m, 2 H, CH_3CH_2), 2.06 (s, 6 H, 2 $COCH_3$), 4.03 (m, 3 H, H-5,6,6'), 5.60 (d, 2 H, H-3,4), 7.27 (m, 10 H, Ar Hs), 7.80 (s, 1 H, H-1), 7.51 and 12.30 (2 s, 2 H, 2 NH). Anal. Calcd for $C_{26}H_{32}N_4O_6$: C, 62.9; H, 6.5; N, 11.3. Found: C, 62.8; H, 6.4; N, 11.2.

References

[1] E.S.H. El Ashry, *J. Chem. Soc., Chem. Commun.*, (1986) 1024–1026.
[2] E.S.H. El Ashry, *European Carbohydr. Symp.*, Darmstadt, FRG, 1987, p C-35.

[3] E.S.H. El Ashry, Y. El Kilany, and A. Mousaad, *J. Carbohydr. Chem.*, 8 (1989) 507–513.
[4] E.S.H. El Ashry, Y. El Kilany, S. Kandil, and N. El Shimy, *J. Carbohydr. Chem.*, 8 (1989) 497–506.
[5] E.S.H. El Ashry, Y. El Kilany, and F. Singab, *J. Chem. Soc., Perkin Trans. 1* (1988) 133–137.
[6] E.S.H. El Ashry, Y. El Kilany, and F. Singab, *Carbohydr. Res.*, 154 (1986) 265–269.
[7] E.S.H. El Ashry, Y. El Kilany, and A. Mousaad, *Carbohydr. Res.*, 163 (1987) 262–264.
[8] Y. El Kilany, L. Awad, F. Singab and E.S.H. El Ashry, *Alex. J. Pharm. Sci.*, 11 (1988) 142–143.
[9] N. Rashed, H. Abdel Hamid, and E.S.H. El Ashry, *Carbohydr. Res.*, 243 (1993) 399–405.
[10] E.S.H. El Ashry, A. Mousaad, and N. Rashed, *Adv. Heterocycl. Chem.*, 53 (1992) 233–312.
[11] D.M. Clode, *Chem. Rev.*, 79 (1979) 491–513; B. Capon, *Chem. Rev.*, 69 (1969) 407–498.
[12] S.A. Barker and E.J. Bourne, *J. Chem. Soc.*, (1952) 905–909; S.A. Barker, E.J. Bourne, and D.H. Whiffen, *ibid.*, (1952) 3865–3870.
[13] R.M. Hann and C.S. Hudson, *J. Am. Chem. Soc.*, 66 (1944) 1909–1912; A.T. Ness, R.M. Hann, and C.S. Hudson, *ibid.*, 70 (1948) 765–770.
[14] N. Baggett, K.W. Buck, A.B. Foster, R. Jeferis, B.H. Rees, and J.M. Webber, *J. Chem. Soc.*, (1965) 3382–3388.
[15] J.G. Buchanan, S.J. Moorhouse, and R.H. Wightman, *J. Chem. Soc., Perkin 1*, (1981) 2258–2266; J.G. Buchanan, M.E. Chacon Fuertes, A.R. Edgar, S.J. Moorhouse, D.I. Rawson, and R.H. Wightman, *Tetrahedron Lett.*, 21 (1980) 1793–1796.
[16] J.G. Buchanan and R.M. Saunders, *J. Chem. Soc.*, (1964) 1796–1803.
[17] R.G. Ault, W.N. Haworth, and E.L. Hirst, *J. Chem. Soc.*, (1935) 517–518.
[18] H. Ohle, *Chem. Ber.*, 67 (1934) 1750–1762.