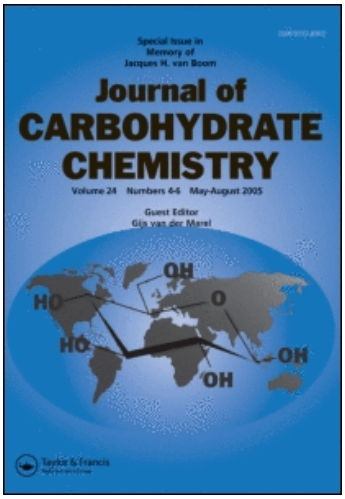

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Regioselective Protection of Hydroxyl Groups of Acyclic *C*-Nucleoside Analogs: 1-Aryl-3-(D-erythro-glycerol-1-yl)6,7-dimethylflavazoles[1]

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REGIOSELECTIVE PROTECTION OF HYDROXYL GROUPS OF ACYCLIC C-NUCLEOSIDE ANALOGS: 1-ARYL-3-(D-ERYTHRO-GLYCEROL-1-YL)-6,7-DIMETHYLFLAVAZOLES[1]

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ABSTRACT

Isopropylidenation of 1-aryl-3-(D-erythro-glycerol-1-yl)-6,7-dimethylflavazoles under thermodyanmically controlled conditions occurred regioselectively to give products having α-terminal isopropylidene rings. The role of the steric orientation of the hydroxyl groups on the regioselectivity was discussed. The location of the isopropylidene ring was confirmed by acylation and by studying the spectra of the products. The difference in the chemical shift (Δδ) between the proton resonances of the two methyl groups of the isopropylidene ring agreed with the shift rule of El Ashry.

INTRODUCTION

Acetalization of the hydroxyl groups of carbohydrate molecules is a well-known[2] means for their protection. The process can be followed by sequential modification of the rest of the hydroxyl groups, including even the masked ones. Formation of acetals is controlled by various factors,[2-9] one of them being the configuration of the hydroxyl groups in the carbohydrate moiety. Recently a shift rule was developed by El

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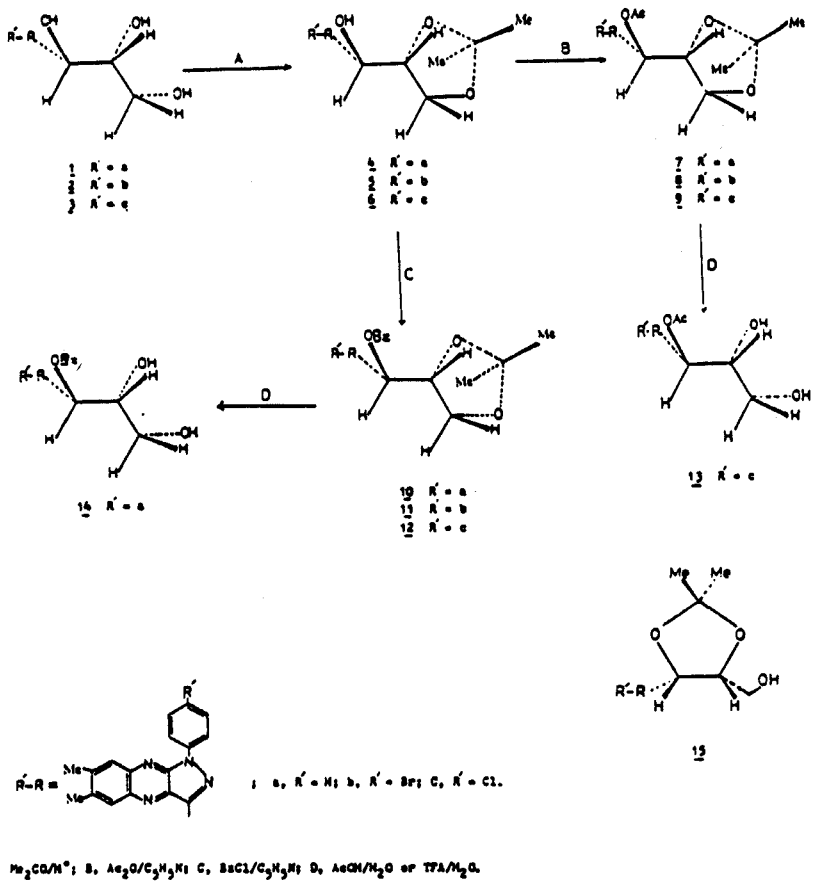
Ashry[8] for assigning the configuration of the isopropylidenated hydroxyl groups from the chemical shift differences ($\Delta\delta$) between the proton resonances of the two methyl groups observed in their ^{1}H NMR spectra. This chemical shift phenomenon was observed in the products of isopropylidenation of C-polyhydroxyalkyl pyrazolinediones, and a correlation between the configuration of their hydroxyl groups and the location of the isopropylidene ring was developed.[8,9] In the present work, the isopropylidenation of a class of acyclic C-nucleoside analogs, the 1-aryl-3-(D-erythro-glycerol-1-yl)-6,7-dimethylflavazoles, was investigated in order to extend the application of this shift rule. Moreover, such partially protected derivatives could be useful precursors, e.g., as an alternative synthesis of artificial antigens.[10]

RESULTS AND DISCUSSION

When 3-(D-erythro-glycerol-1-yl)-6,7-dimethyl-1-phenyl-flavazole (1, Scheme 1) was subjected to the action of acetone in the presence of an acid catalyst, a product was isolated in a crystalline form whose structure proved to be **4**, as it will be later shown. Similarly, the isopropylidenation of 2 and 3 afforded **5** and **6**, respectively. The formation of the α-terminal dioxolane ring from such a reaction, and not the α-erythro ring, agreed with the previous conclusions on the role of configuration of the hydroxyl groups.[2] The kinetic and the thermodynamic products obtained on acetalization of the L-threo isomer are different. Thus, rearrangement of the α-terminal-dioxolane occurred readily in the case of the L-threo isomer to give the α-threo-dioxolane, whereas the α-terminal ring in the case of the D-erythro isomer did not rearrange to the α-erythro-dioxolane ring.[9] The latter dioxolane was not favored, since, in spite of the more symmetrical substitution on the 4- and 5-positions, the substitutents will be unfavorably cis oriented. This leads to a difference in the relative free energy of such dioxolanes, which is of considerable significance in



SCHEME 1

determining the structure of the product. On the other hand, the rearrangement of the α-terminal ring of the L-threo isomer to the α-threo ring having a more symmetrical substitution could be promoted by the concomitant existence of the 4,5-substituents in a trans disposition.

The location of the isopropylidene ring on the glycerolyl residues was deduced by the application of the shift rule of El Ashry.[8] Thus the ^{1}H NMR spectra of 4-6 (Table 1) showed two singlets for the two methyl groups, designated as δ_1 and δ_2 at δ1.29-1.39 and δ1.17-1.27,

Table 1. ^{1}H NMR Spectral Data for Isopropylidine Derivatives (4 - 6)

Compound No.	H-1 ($J_{1,2}$)Hz	H-2	H-3,3'	OH	CMe_2	2 Me	Aromatic
	Chemical shifts (δ)						
4	5.13 (d, 7)	4.93 (q)	4.23 (d)	6.20 (d)	1.27, 1.39 (2s)	2.4 (s)	7.60-8.37 (m)
5	5.16 (d, 7.5)	4.93 (q)	4.21 (d)	6.10 (d)	1.20, 1.33 (2s)	2.5 (s)	7.76-8.40 (m)
6	5.13 (d, 7.5)	4.93 (q)	4.18 (d)	6.23 (d)	1.17, 1.29 (2s)	2.5 (s)	7.70-8.43 (m)

respectively. The value of $\Delta\delta$ (δ_1-δ_2) was then calculated in each case, and it was found to be ca. 0.12, i.e., within the upper range of that value required for a terminal ring. In order to confirm this conclusion, the structures of the products have been verified by combination of both chemical and physical methods. Thus the ^{1}H NMR spectrum of **4** showed two doublets at δ4.23 (H-3,3') and 5.13 (H-1), a quartet at δ 4.93 (H-2), in addition to a multiplet at δ 7.60-8.37 (aromatic protons), and a singlet at δ2.4 (6 and 7-methyls).

Although these data did confirm the presence of an isopropylidene group, they did not confirm its location on the glycerolyl residue. However, this was achieved by the comparison of this spectral data with that of the corresponding acylated derivative. Thus acetylation of **4** with acetic anhydride in pyridine aforded the monoacetyl derivative **7**. Its IR spectrum showed the presence of a band at 1760 cm^{-1} (OAc) instead of a band at 3425 cm^{-1} (OH) in **4**. The ^{1}H NMR spectrum of **7** (Table 2) showed two singlets at δ1.28 and 1.37, assigned for the isopropylidene

Table 2. ^{1}H NMR Spectral Data for Acylated Derivatives 7, 9, and 10-12.

Compound No.	H-1 ($J_{1,2}$)Hz	H-2	H-3,3' ($J_{2,3}$, $J_{2,3'}$, $J_{3,3'}$)Hz	CMe_2	Ac	2 Me	Aromatic
			Chemical shifts (δ)				
7	6.47 (d, 6)	5.0 (q)	4.28 (d)	1.28, 1.35 (2s)	2.19 (s)	2.43 (s)	7.4-8.36 (m)
9	6.53 (d, 6)	5.0 (s)	4.23 (d)	1.30, 1.37 (2s)	2.20 (s)	2.50 (s)	7.48-8.43 (m)
10	5.50 (d, 6)	4.93 (d)	4.46, 4.20 (2q, 4.5, 6.0, 10.5)	1.40, 1.47 (2s)		2.50 (s)	7.22-8.47 (m)
11	5.46 (q, 6)	4.90 (q)	4.40, 4.26 (2q, 4.5, 6.0, 10.5)	1.43, 1.50 (2s)		2.56 (s)	7.22-8.4 (m)
12	6.73 (d, 6)	5.06 (q)	4.38 (m)	1.33, 1.40 (2s)		2.53 (s)	7.48-8.47 (m)

group, followed by a singlet at δ 2.19 due to the acetyl group. The 6,7-dimethyl groups appeared as a singlet at δ2.43. The C-3 methylene protons appeared as a doublet at δ 4.28. The H-2 and H-1 appeared as a quartet and doublet at δ5.0 and 6.47, respectively.

The chemical shifts of the protons on the glycerolyl side chain of the isopropylidene and its acetate indicated that H-1 is the only proton highly affected by the acetylation, and consequently this is the position at which the hydroxyl group was acetylated. This fact led to the conclusion that the isopropylidene group was located on positions 2 and 3 of the glycerolyl side chain. The product was therefore formulated as 3-(1-O-acetyl-2,3-O-isopropylidene-D-erythro-glycerol-1-yl)-6,7-dimethyl-1-phenylflavazole (7).

Benzoylation of 4 with benzoyl chloride in pyridine afforded the monobenzoylated derivative **10**, whose IR spectrum showed the presence of the OBz group at 1730 cm^{-1}. The ^{1}H NMR spectrum of 4 showed two singlets at δ 1.40 and 1.47 assigned for the isopropylidene group, and a

singlet at δ2.50 for the 6,7-dimethyl groups. The difference in the chemical shifts of the protons on the glycerolyl side chain of the isopropylidene **4** and its benzoate **10** indicated that benzoylation had occurred on the C-1 hydroxyl group. The benzoate was thus formulated as 3-(1-O-benzoyl-2,3-O-isopropylidene-D-erythro-glycerol-1-yl)-6,7-dimethyl-1-phenylflavazole (**10**).

Deacetylation of **7** gave the acetal **4**, confirming that no migration had taken place during the step of acylation. Acid hydrolysis of **9** by the action of aqueous acetic acid afforded the corresponding monoacylated derivative, 3-(1-O-acetyl-D-erythro-glycerol-1-yl)-1-(p-chlorophenyl)-6,7-dimethylflavazole (**13**). Similarly, acid hydrolysis of **10** gave 3-(1-O-benzoyl-D-erythro-glycerol-1-yl)-6,7-dimethyl-1-phenylflavazole (**14**). Compounds **13** and **14** showed in their IR spectra bands at 1720 (OAc) and at 1715 cm^{-1} (OBz), respectively.

A similar sequence of reactions was conducted on the p-substituted phenyl analogues **2** and **3**, and the structures of the products were confirmed (see experimental and tables).

The starting materials **1-3** required for the above study were prepared from 3-(1-arylhydrazono-D-erythro-2,3,4-trihydroxybutyl)-6,7-dimethyl-dihydroquinoxalin-2-one, and their structures have been confirmed.[11]

In conclusion, the configuration of the hydroxyl groups of the D-erythro analogues **1 - 3** plays a role in directing the isopropylidenation regioselectively to form the α-terminal-1,3-dioxolanes. The α-erythro dioxolane **15** could not be detected. These data indicate that the presence of a bulky substituent on the glycerolyl residue does not affect the regioselectivity of the reaction. The difference (Δδ) of the two methyls of the isopropylidenes agreed with El Ashry's shift rule,[8] whereby the dioxolane ring could be deduced to be a terminal one. The higher value of Δδ could be attributed to the much higher influence on one of the methyl groups by the anisotropic effect of the bulky flavazole ring.

EXPERIMENTAL

General Procedures. Melting points were determined with a "Meltemp" apparatus using a 76-mm immersion thermometer, and are uncorrected. Infrared spectra were recorded with a Pye Unicam SP 1025 spectrometer. ^{1}H NMR spectra were determined with a Varian EM-390 spectrometer for solutions in $CDCl_3$ or in DMSO-d_6 with tetramethylsilane (Me_4Si) as internal or external reference, respectively. The spectra are reported as chemical shifts downfield from Me_4Si. TLC was performed on "Baker-Flex" silica gel B-F plates. Microanalyses were performed in the Faculty of Science at Cairo University.

1-Aryl-3-(2,3-O-isopropylidene-D-erythro-glycerol-1-yl)-6,7-dimethylflavazole (4 - 6). To a stirred solution of dry acetone (20 mL) and concentrated sulfuric acid (0.5 mL), the compound **1 - 3** (1 mmol) was added, and the reaction mixture was left overnight at room temperature. The resulting solution was neutralized with anhydrous sodium carbonate, and the product was filtered off and recrystallized from ethanol to give **4-6** as yellow needles. For physicochemical data, see Table 3.

3-(1-O-Acetyl-2,3-O-isopropylidene-D-erythro-glycerol-1-yl)-1-aryl-6,7-dimethylflavazole (7 - 9). A solution of compound **4 - 6** (1 mmol) in dry pyridine (10 mL) was cooled and then treated with acetic anhydride (5 mL). The reaction mixture was left overnight at room temperature and then poured onto crushed ice. The acetate derivative that separated out was filtered off, washed with water, and recrystallized from ethanol to give **7 - 9** as yellow needles. For physicochemical data, see Table 3.

3-(1-O-Acetyl-D-erythro-glycerol-1-yl)-1-p-chlorophenyl-6,7-dimethylflavazole (13). A suspension of **9** (481 mg, 1 mmol) in 80% aqueous trifluoroacetic acid (10 mL) was kept for 15 min at room temperature with occasional shaking, whereby the solid dissolved. The mixture was diluted with cold water, and the product that separated out was filtered, washed with water, and recrystallized from ethanol to give **13** as pale yellow needles (295 mg, 67%): mp 183 °C. IR (KBr) 1720 cm^{-1}

Table 3. Microanalytical and IR Spectral Data for 1-Aryl-3-(2,3-O-isopropylidene-D-Erythro-glycerol-1-yl)-6,7-Dimethylflavazoles (4 - 6) and their Acylated Derivatives (7 - 12).

Compound No.	R'	mp (°C)	Yield (%)	Molecular formula	Calculated (%) C	H	N	Found (%) C	H	N	IR (KBr) cm^{-1} C=N	OH
4	H	182	62	$C_{23}H_{24}N_4O_3$	68.30	5.98	13.85	68.0	6.0	13.9	1600	3425
5	Br	157	65	$C_{23}H_{23}BrN_4O_3$	57.15	4.80	11.59	56.8	4.8	11.3	1590	3400
6	Cl	152	67	$C_{23}H_{23}ClN_4O_3$	62.94	5.28	12.76	62.5	5.5	12.9	1600	3440
7	H	185	68	$C_{25}H_{26}N_4O_4$	67.25	5.87	12.55	67.6	5.5	12.5	1605	1760
8	Br	203	65	$C_{25}H_{25}BrN_4O_4$	57.15	4.80	10.66	56.9	4.8	10.4	1595	1745
9	Cl	150	70	$C_{25}H_{25}ClN_4O_4$	62.43	5.24	11.65	60.2	5.4	11.5	1605	1760
10	H	102	70	$C_{30}H_{28}N_4O_4$	70.85	5.55	11.02	70.6	5.1	10.9	1612	1730
11	Br	165	72	$C_{30}H_{27}BrN_4O_4$	61.34	4.63	9.54	61.3	4.4	9.8	1595	1735
12	Cl	106	78	$C_{30}H_{27}ClN_4O_4$	66.36	5.01	10.33	66.1	4.8	10.1	1601	1737

(OAc). Anal. Calcd for $C_{22}H_{21}ClN_4O_4$: C, 59.93; H, 4.80; N, 12.71. Found: C, 59.6; H, 5.3; N, 12.9.

1-(Aryl-3-(1-O-benzoyl-2,3-O-isopropylidene-D-erythro-glycerol-1-yl)-6,7-dimethylflavazole (10 - 12). A solution of compound **4 - 6** (1 mmol) in dry pyridine (10 mL) was cooled and treated with benzoyl chloride (5 mL). The reaction mixture was left overnight at room temperature and then poured onto crushed ice. The benzoate derivative that separated out was filtered off, washed with water, and recrystallized from ethanol to give 10 - 12 as yellow needles. For physicochemical data, see Table 3.

3-(1-O-Benzoyl-D-erythro-glycerol-1-yl)-6,7-dimethyl-1-phenylflavazole (14). A solution of **10** (509 mg, 1 mmol) in 80% aqueous trifluoroacetic acid (10 mL) was kept for 15 min at room temperature. The reaction mixture was diluted with cold water, and the product that separated out was filtered, washed with water, and recrystallized from ethanol to give **14** as pale yellow needles (328 mg, 70%): mp 165 °C. IR (KBr) 1595 (C=N), 1715 (OBz), 3340 cm^{-1} (OH); ^1H NMR (DMSO-d_6) δ 2.47 (s, 6H, $2CH_3$), 3.8 (q, 2H, H-3,3'), 4.45 (m, 3H, H-2 and 2OH), 5.1 (d, 1H, H-1), and 7.3-8.5 (m, 7H, aromatic). Anal. Calcd for $C_{27}H_{24}N_4O_4$: C, 69.22; H, 5.16; N, 11.96. Found: C, 68.8; H, 5.6; N, 12.0.

REFERENCES AND FOOTNOTES

1. A part in the series, Heterocycles from Carbohydrate Precursors.

2. J. Gelas, Adv. Carbohydr. Chem. Biochem., **39**, 71 (1981); D. M. Clode, Chem. Rev., **79**, 491 (1979); A. N. de Belder, Adv. Carbohydr. Chem. Biochem., **34**, 179 (1977); R. F. Brady, Jr., Carbohydr. Chem. Biochem., **26**, 197 (1971); B. Capon, Chem. Rev., **69**, 407 (1969); A. N. De Belder, Adv. Carbohydr. Chem., **20**, 219 (1965); J. A. Mills, Adv. Carbohydr. Chem., **10**, 1 (1955).

3. S. A. Barker and E. J. Bourne, J. Chem. Soc., 905 (1952); S. A. Barker and E. J. Bourne, Adv. Carbohydr. Chem., **7**, 137 (1952); S. A. Barker, E. J. Bourne, and D. H. Whiffen, J. Chem. Soc., 3865 (1952).

4. R. M. Hann and C. S. Hudson, J. Am. Chem. Soc., **66**, 1909 (1944); A. T. Ness, R. M. Hann, and C. S. Hudson, J. Am. Chem. Soc., **70**, 765 (1948).

5. A. B. Foster in "The Carbohydrates" Vol. IA, W. Pigman, and D. Horton, Eds., Academic Press, New York, NY, 1972, p. 391; K. W. Buck, A. B. Foster, R. H. Rees, J. M. Webber, J. Lehmann, Carbohydr. Res., **1**, 329 (1965); N. Baggett, K. W. Buck, A. B. Foster, R. Jeferis, B. H. Rees, and J. M. Webber, J. Chem. Soc., 3382 (1965); M. L. Wolfrom and G. C. Parekh, Carbohydr. Res., **11**, 547 (1969); M. L. Wolfrom, A. B. Diwadkar, J. Gelas, and D. Horton, Carbohydr. Res., **35**, 87 (1974); J. Gelas and D. Horton, Carbohydr. Res., **45**, 181 (1975); J. Gelas and D. Horton, Heterocycles, **16**, 1587 (1981).

6. J. G. Buchanan, S. J. Moorhouse, and R. H. Wightman, J. Chem. Soc. Perkin I, 2258 (1981); J. G. Buchanan, M. E. Chacon Fuertes, A. R. Edgar, S. J. Moorhouse, D. I. Rawson, and R. H. Wightman, Tetrahedron Lett., **21**, 1795 (1980); G. Aslani-Shotorbani, J. G. Buchanan, A. R. Edgar, and P. K. Shahidi, Carbohydr. Res., **136**, 37 (1985); J. G. Buchanan and R. M. Saunders, J. Chem. Soc., 1796 (1964).

7. S. J. Angyal and R. J. Beveridge, Carbohydr. Res., **65**, 229 (1978); S. J. Angyal, D. Greeves, and J. A. Mills, Aust. J. Chem., **27**, 1447 (1974); P. L. Durette and D. Horton, Adv. Carbohydr., Chem. Biochem., **26**, 49 (1971); T. Nakagawa, H. Tokuoka, K. Shinoto, J. Yoshimura, and T. Sato, Bull. Chem. Soc. Jpn., **40**, 2150 (1967); M. E. Evans and F. W. Parrish, Carbohydr. Res., **54**, 105 (1977); R. G. Ault, W. N. Haworth, and E. L. Hirst, J. Chem. Soc., 517 (1935).

8. E. S. H. El Ashry, J. Chem. Soc. Chem. Commun., 1024 (1986); 4th European Carbohydr. Symp., Darmstadt, FRG, C-35 (1987).

9. E. S. H. El Ashry, Y. El Kilany, and F. Singab, Carbohydr. Res., **118**, C10 (1983); ibid., **152**, 339 (1986).

10. E. S. H. El Ashry and C. Schuerch, Bull. Chem. Soc. Jpn., **59**, 1581 (1986); L. Awad, E. S. H. El Ashry, and C. Schuerch, ibid., **59**, 1587 (1986); ibid., Carbohydr. Res., **122**, 69 (1983), and references cited therein.

11. Y. El Kilany, A. Mousaad, N. El Shimy, and E. S. H. El Ashry, J. Carbohydr. Chem., in press.

12. E. S. H. El Ashry, Y. El Kilany, and A. Mousaad, J. Carbohydr. Chem., preceding paper.