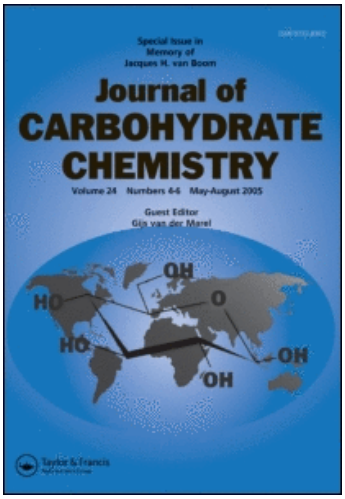

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El Sayed H. El Ashry[a]; Yeldez El Kilany[a]; Ahmed Mousaad[a]
[a] Chemistry Department, Faculty of Science Alexandria University, Alexandria, Egypt

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ISOPROPYLIDENATION OF 1-ARYL-(L-THREO-GLYCEROL-1-YL)-6,7-DIMETHYL-PYRAZOLO[3,4-b]QUINOXALINES*

El Sayed H. El Ashry,* Yeldez El Kilany, and Ahmed Mousaad

Chemistry Department
Faculty of Science
Alexandria University
Alexandria, Egypt

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ABSTRACT

The isopropylidenation of 1-aryl-(L-threo-glycerol-1-yl)-6,7-dimethyl-pyrazolo[3,4-b]quinoxaline gave regioselectively the corresponding α-threo-dioxolanes. The role of configuration of the glycerolyl residue in directing the location of the isopropylidene ring is discussed. Although the pyrazolo-quinoxaline ring was shown not to affect the regioselectivity, it has a considerable effect on the chemical shift of the methyl groups of the isopropylidene ring.

INTRODUCTION

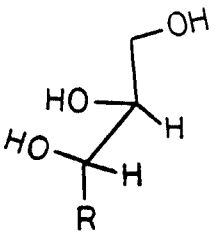
One of the major factors that governs the regioselectivity of the acetalization of polyols is the configuration of their hydroxyl groups.[2-6] We are interested in such reactions on acyclic C-nucleoside analogs.[7,8] Thus the L-threo-glycerolyls of the pyrazolinediones afforded, upon isopropylidenation under thermodynamically controlled conditions, the corresponding α-threo-1,3-dioxolanes as the major products, whereas, under kinetically controlled conditions, the α-terminal-1,3-dioxolanes prevailed, with lesser amounts of the β-terminal-1,3-dioxane being observed.[7] Although the formation of the latter ring is unfavorable, its possible formation has been reported.[9]

*To whom inquiries should be addressed.

The isopropylidenation of the D-erythro-glycerolyl moiety of the pyrazolo[3,4-b]quinoxaline has been reported,[10] and the shift rule of El Ashry[8] was shown to furnish good criteria for assigning the location of the isopropylidene ring in the products. In the present work, such a study was extended to the L-threo analogs.

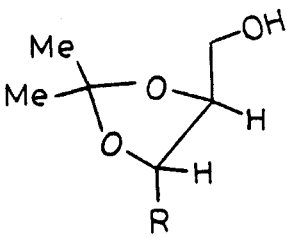
RESULTS AND DISCUSSION

Isopropylidenation of (L-threo-glycerol-1-yl)-6,7-dimethyl-1-phenyl-pyrazolo[3,4-b]quinoxaline (**1**, Scheme 1) and its p-chlorophenyl analog **2** with acetone in the presence of concentrated sulfuric acid afforded the 1,2-O-isopropylidene derivatives **3** and **4**, respectively. The position of the isopropylidene group in these compounds was established by comparing their ^{1}H NMR spectra with those of their acylated derivatives. Thus the acetylation of **3** and **4** with acetic anhydride in pyridine gave the corresponding monoacetates **5** and **6**, respectively. The ^{1}H NMR spectra (Table 1) of **3** and **5** showed no significant shift of the H-1 resonance (δ 5.63 to 5.55) due to acetylation, whereas a downfield shift of the resonances of H-2 (δ 5.19 to 5.40), H-3 (δ 4.03 to 4.53), and H-3' (δ 3.87 to 4.30) were observed. A similar pattern for the chemical shifts of the glycerolyl protons of **6** was also observed. Benzoylation of **3** and **4** with benzoyl chloride in pyridine gave the monobenzoates **7** and **8**, respectively. The ^{1}H NMR spectrum of **7** showed an even more pronounced downfield shift (δ 0.68) of the resonances of H-3 and H-3' of **3** upon benzoylation, whereas H-2 was shown to be less affected, and H-1 was almost unaffected. These results led to the conclusion that both the acetylation and benzoylation of either **3** or **4** resulted in a deshielding effect on the H-3 and H-3' resonances, which unequivocally proved the location of acyl groups on the C-3 hydroxyl groups. Thus the location of the isopropylidene group in the parent compounds **3** and **4** is established on the C-1 and C-2 oxygen atoms. On the other hand, the attempted deduction of the location of



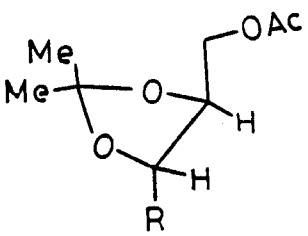
1 R = a

2 R = b



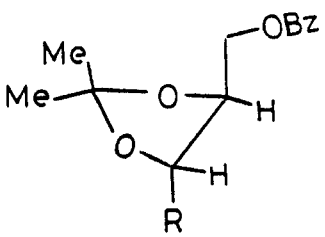
3 R = a

4 R = b



5 R = a

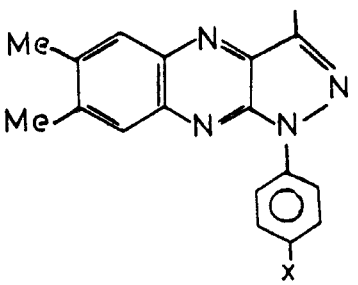
6 R = b



7 R = a

8 R = b

R =



a, X = H

b, X = Cl

SCHEME 1

Table 1. ^{1}H NMR Spectral Data for Compounds 3 - 7[a]

Compound No.	R	H-1 ($J_{1,2}$Hz)	H-2	H-3 ($J_{2,3}$Hz)	($J_{3,3'}$Hz)	H-3' ($J_{2,3'}$Hz)	OH	OAc	CMe_2	Aromatic
3	H	5.63d	5.19m	4.03q		3.87q	1.9bs		1.70s	7.44m
		(7.5)		(3)	(12)	(5)			1.80s	7.97d
										8.43d
4	Cl	5.60d	5.05m	———	4.0m	———			1.62s	7.45d
		(7.5)							1.70s	7.95d
										8.45d
5	H	5.55d	5.40m	4.53q		4.30q		2.03s	1.63s	7.45m
		(7.5)		(3)	(12)	(6)			1.77s	7.97d
										8.5d
6	Cl	5.45d	5.30m	4.48q		4.25q		2.03s	1.63s	7.50d
		(7.5)		(3)	(12)	(6)			1.72s	7.98d
										8.43d
7	H	5.62d	5.50m	———	4.63d	———			1.67s	7.40m
		(7.5)							1.79s	7.90m
										8.4d

[a] Chemical shifts are in δ units, and spin-spin couplings (J-values) are in Hz. Multiplicities are d, doublet; m, multiplet, q, quartet; s, singlet, and b, broad.

the isopropylidene ring from the shift rule[8] could not be accomplished since the value $\Delta\delta(\delta_1-\delta_2)$ of the resonances of the two methyl groups was found to be higher than the required value (0.05) for such a ring. This result may be attributed to the much higher influence of the anisotropic effect of the pyrazolo-quinoxaline ring on one of the two methyl groups of the isopropylidene ring.

Although mechanistically the isopropylidene ring may be formed in the first stage of the reaction at the terminal position, its rearrangement readily takes place under acid-catalyzed condensation to give the thermodynamically controlled product possessing the α-threo-dioxolane ring. Such rearrangement was shown to be enhanced by the transition from a situation having a dioxolane ring with unsymmetrical substituents to a more symmetrical one with trans substituents. This

type of rearrangement could not occur in the case of the erythro analogs[10] since the substituents would be in a cis position in the more symmetrical compounds.

In conclusion, the isopropylidenation of 1 and 2 afforded the α-threo-dioxolanes in a manner similar to that reported for the L-threo-glycerols possessing pyrazoledione rings.[7] These results indicated that the isopropylidenation of the L-threo glycerolyls occurred regioselectively, and the heterocyclic ring did affect the resonances of the methyl groups of the isopropylidene ring.

EXPERIMENTAL

General Procedures. Melting points were determined using a "Meltemp" apparatus and are uncorrected. IR spectra were recorded with a Unicam SP 1025 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian EM-390 spectrometer (for solutions in chloroform-d). Chemical shifts refer to an internal standard of tetramethylsilane (δ0.00). Signal multiplicities are given as d, doublet; m, multiplet; q, quartet; s, singlet. Elemental analyses were performed at the Microanalytical Laboratory, Cairo University.

3-(1,2-O-Isopropylidene-L-threo-glycerol-1-yl)-6,7-dimethyl-1-phenyl-pyrazolo[3,4-b]quinoxaline (3). Compound 1[1] (1 g, 2.74 mmol) was added to a mixture of dry acetone (40 mL) and 96% sulfuric acid (0.4 mL). The mixture was stirred for 2 h at room temperature and then kept overnight. It was then neutralized with solid, anhydrous sodium carbonate, filtered, and the filtrate was evaporated in vacuo to give the product (0.90 g, 81%), that was crystallized from ethanol to give yellow needles: mp 157-158 °C. IR (KBr) 3440 (OH) and 1600 cm^{-1} (C-N). Anal. Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.0; H, 5.7; N, 13.9.

1-(p-Chlorophenyl)-3-(1,2-O-isopropylidene-L-threo-glycerol-1-yl)-6,7-dimethyl-pyrazolo[3,4-b]quinoxaline (4). Compound 4 was prepared from 2[1] (1 g, 2.51 mmol) as above to give the product (0.79 g, 72%),

that crystallized from ethanol to give yellow needles: mp 154-155 °C. IR (KBr) 3450 (OH) and 1600 cm^{-1} (C=N). Anal. Calcd for $C_{23}H_{23}ClN_4O_3$: C, 62.94; H, 5.28; N, 12.76. Found: C, 62.7; H, 5.7; N, 12.5.

3-(3-O-Acetyl-1,2-O-isopropylidene-L-threo-glycerol-1-yl)-6,7-dimethyl-1-phenyl-pyrazolo[3,4-b]quinoxaline (5). A cold solution of **3** (0.5 g, 1.236 mmol) in dry pyridine (5 mL) was treated with acetic anhydride (5 mL). The mixture was kept overnight at room temperature, poured onto crushed ice, and the product was collected by filtration, washed with water, dried (0.48 g, 87%), and crystallized from ethanol to give **5** as yellow crystals: mp 87-89 °C. IR (KBr) 1750 (OAc) and 1605 cm^{-1} (C=N). Anal. Calcd for $C_{25}H_{26}N_4O_4$: C, 67.25; H, 5.87; N, 12.55. Found: C, 67.1; H, 6.3; N, 12.6.

3-(3-O-Acetyl-1,2-O-isopropylidene-L-threo-glycerol-1-yl)-1-(p-chlorophenyl)-6,7-dimethyl-pyrazolo[3,4-b]quinoxaline (6). Compound **6** was prepared from **4** (0.5 g, 1.14 mmol) as above to give the product (0.455 g, 83%) that crystallized from ethanol to give yellow crystals: mp 155-157 °C. IR (KBr) 1750 (OAc) and 1605 cm^{-1} (C=N). Anal. Calcd for $C_{25}H_{25}ClN_4O_4$: C, 62.43; H, 5.24; N, 11.65. Found: C, 62.7; H, 5.5; N, 11.8.

3-(3-O-Benzoyl-1,2-O-isopropylidene-L-threo-glycerol-1-yl)-6,7-dimethyl-1-phenyl-pyrazolo[3,4-b]quinoxaline (7). A cold solution of **3** (0.4 g, 0.989 mmol) in dry pyridine (5 mL) was treated with benzoyl chloride (1 mL). The mixture was kept overnight at room temperature, then poured onto crushed ice. The product was collected by filtration, sequentially washed with water and ethanol, dried, (0.407 g, 81%) and crystallized from ethanol to give **7** as yellow crystals: mp 101-102 °C. IR (KBr) 1725 (OBz) and 1605 cm^{-1} (C=N). Anal. Calcd for $C_{30}H_{28}N_4O_4$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.4; H, 5.7; N, 10.9.

3-(3-O-Benzoyl-1,2-O-isopropylidene-L-threo-glycerol-1-yl)-1-(p-chlorophenyl)-6,7-dimethyl-pyrazolo[3,4-b]quinoxaline (8). Compound **8** was prepared from **4** (0.4 g, 0.911 mmol) as above to give the product

(0.36 g, 73%) that crystallized from ethanol to give yellow crystals: mp 99-100 °C. IR (KBr) 1700 (OBz) and 1605 cm^{-1} (C=N). Anal. Calcd for $C_{30}H_{27}ClN_4O_4$: C, 66.36; H, 5.01; N, 10.32. Found: C, 66.1; H, 4.8; N, 10.0.

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., Adv. 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, and 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).

6. M. Miljkovic and P. Hagel, Carbohydr. Res., **111**, 319 (1983).

7. E. S. H. El Ashry, Y. El Kilany, and F. Singab, Carbohydr. Res., **118**, C10 (1983); ibid, **152**, 339 (1986); J. Chem. Soc., Perkin Trans. I, submitted.

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

9. G. Aslani-Shotorbani, J. G. Buchanan, A. R. Edgar, and P. K. Shahidi, Carbohydr. Res., **136**, 37 (1985).

10. E. S. H. El Ashry, Y. El Kilany, S. Kandil, and N. El Shimy, J. Carbohydr. Chem., preceding paper.