Recognition of the *threo* and *erythro* Isomers of 1-C-Substituted Glycerols†

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A method for the differentiation of the *threo* and *erythro* isomers of 1-C-substituted glycerols has been developed, based on the difference in the chemical shift ($\Delta\delta$) between the proton resonances of the two methyl groups of the corresponding isopropylidenes as a criterion of the location of the isopropylidene group on a polyol residue, as well as the regioselective formation of the isopropylidenes.

A method has been developed to recognise the configuration of hydroxy groups, whether *threo* or *erythro*, in 1-C-substituted glycerols which may form a part of acyclic sugar derivatives or acyclic nucleosides. The method was based on (i) the difference in the chemical shift ($\Delta\delta$) between the ^{1}H n.m.r. signals for two methyl groups of an isopropylidene group, which has been found to be a criterion for its location on a polyol residue, and (ii) the regioselectivity of the isopropylidenation[1—5] under thermodynamic control of various 1-C-substituted glycerols.

† For part 1 in the series 'Acetals,' see ref. 1.

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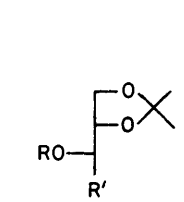
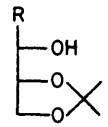


(1) R = R′ = H
(2) R = H, R′ = CH_2OH
(3) R = Bn R′ = CH_2OH



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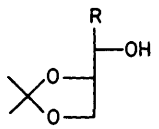

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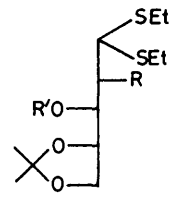
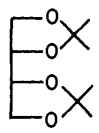


(6) R = OH, R′ = H
(7) R = OAc, R′ = Ac
(8) R = NHAc, R = H



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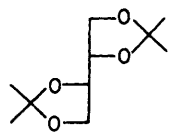

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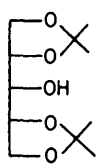

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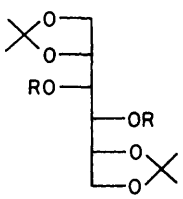
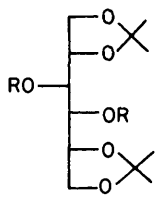
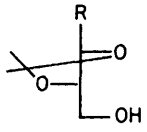


(12) R = Ac
(13) R = CSSMe



(14) R = Ac
(15) R = Ts



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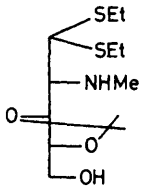

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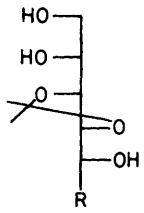
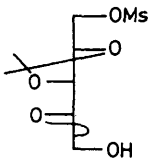


(18) R = CH_2OH
(19) R = Me



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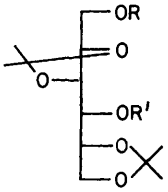
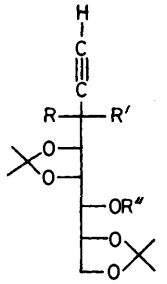
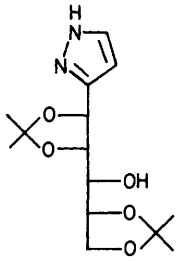


(21) R = R′ = Ms
(22) R = R′ = Ts



(23) R = OH, R′ = R″ = H
(24) R = R″ = H, R″ = OH



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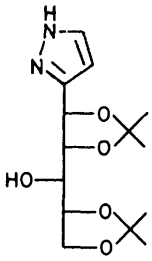

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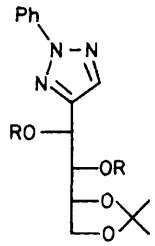

(27) R = H
(28) R = Ac

Bn = benzyl
Ts = tosyl
Ms = mesyl

It has been found that, if the ^1H n.m.r. signals for the two methyl groups of the isopropylidene derivatives (**1**)—(**28**) are designated as δ_1 and δ_2 for those appearing at low and high magnetic field, respectively, the difference in the chemical shift, $\Delta\delta$, is ≥ 0.05 for the α-terminal[6] isopropylidene derivatives, whereas $\Delta\delta$ is ≤ 0.05 for the α-*threo* isopropylidene derivatives (Table 1). These data indicated that the isopropylidene group could be recognised as an α-*threo* or α-terminal ring from $\Delta\delta$ values.

The difference in $\Delta\delta$ values is due to an invariable effect resulting from the deshielding nature of the 1,3 methyl substituent interaction, whereby only one methyl group on an α-terminal ring suffers from such an effect, compared with both of the methyl groups on an α-*threo* ring. This causes a larger difference between δ_1 and δ_2 values in the former, whereas in the latter case these values become closer depending on the difference in the extent of the effect; a similar interaction leads to equal δ values *i.e.* $\Delta\delta = 0$. This explanation is supported by an earlier investigation,[7] which classed the methyl groups into three types (α, β, and γ, where the former is the least deshielded). Accordingly the literature values[8] of δ for the methyl groups of some isopropylidenes such as (**21**)—(**26**) may be assigned to an α-terminal, -*threo*, or -*erythro* ring. The above described shift rule for $\Delta\delta$ may thus be used to recognise the configuration of the hydroxy groups in 1-C-substituted glycerols as follows. Since this configuration governs the regioselectivity of the isopropylidenation, as shown from the accumulated data,[1,5] whereby the *threo* configuration gives the corresponding α-*threo* ring whereas the *erythro* configuration gives an α-terminal ring, the value of $\Delta\delta$ will indicate the location of the acetal and thus the configuration of the hydroxy groups in the substituted glycerol. This shift rule for $\Delta\delta$ values is valid for various types of compounds. However, deviation from this rule was found for some terminal isopropylidenes. This may be explained by various effects encountered on the methyl groups such as the remote effect of the anisotropy of substituents or the conformation of the side chain which may result in the proximity of a remote substituent and consequently affect indirectly the chemical shift of the methyl groups. Moreover, there is the effect of solvent on the type of hydrogen bonding which may change the extent of the effect of substituents on the methyl groups. These factors also explain the low value of $\Delta\delta$ for the α-*erythro* ring in some compounds, contrary to the

Table 1. ^{1}H N.m.r. data for the methyl groups of the isopropylidene derivatives.[4,7,11]

	δ_1(Me)	δ_2(Me)	Δδ		δ_1(Me)	δ_2(Me)	Δδ
α-terminal							
(**1**)	1.21	1.16	0.05	(**22**)	1.30	1.20	0.10
(**2**)	1.44	1.36	0.08	(**23**)	1.41	1.36	0.05
(**3**)	1.42	1.34	0.08	(**24**)	1.41	1.35	0.06
(**4a**)[a]	1.48	1.37	0.11	(**25**)	1.46	1.32	0.14
(**4b**)[a]	1.43	1.33	0.10	(**26**)	1.48	1.38	0.10
(**4c**)[a]	1.43	1.33	0.10	(**27**)	1.37	1.30	0.07
(**4d**)[a]	1.29	1.17	0.12	(**28**)	1.40	1.32	0.08
(**5a**)[a]	1.50	1.40	0.10	α-*threo*			
(**6**)	1.44	1.30	0.14	(**16a**)[a]	1.62	1.57	0.05
(**7**)	1.38	1.24	0.14	(**16b**)[a]	1.60	1.57	0.03
(**8**)	1.46	1.36	0.10	(**17**)	1.43	1.42	0.01
(**9**)	1.22	1.15	0.07	(**18**)	1.17	1.17	0.00
(**10**)	1.19	1.14	0.05	(**19**)	1.19	1.19	0.00
(**11**)	1.24	1.16	0.08	(**20**)	1.40	1.40	0.00
(**12**)	1.35[b]	1.30	0.05	α-*erythro*			
(**13**)	1.34	1.26	0.08	(**23**)	1.53	1.36	0.19
(**14**)	1.40	1.35	0.05	(**24**)	1.54	1.35	0.19
(**15**)	1.30	1.25	0.05	(**25**)	1.61	1.32	0.29
(**21**)	1.45	1.35	0.10	(**26**)	1.64	1.38	0.26

[a] **a**, R = 5-oxo-1-phenyl-4-(phenylhydrazono)-2-pyrazolin-3-yl; **b**, R = 1-(*p*-bromophenyl)-4-(*p*-bromophenylhydrazono)-5-oxo-2-pyrazolin-3-yl; **c**, R = 1-(*p*-chlorophenyl)-4-(*p*-chlorophenylhydrazono)-5-oxo-2-pyrazolin-3-yl; **d**, R = 1-(*p*-chlorophenyl)-6,7-dimethyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-3-yl. [b] In our hands this appeared at δ 1.36, thus giving Δδ = 0.06.

expected higher values for the α-*erythro* ring as shown in Table 1.[8]

A similar correlation was reported by Imbach *et al.*[9–11] for determining the anomeric configuration of ribofuranosyl nucleosides, which was attributed to the anisotropic influence of the aglycone group.

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