Anomeric Configuration of Pyrimidine Nucleosides by N.m.r.

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SINCE 1958[1] the ability to establish configuration at C-1–C-2 of pyranosides based on the $J_{\text{H-1-H-2}}$ coupling constant has found wide application. Unfortunately, with furanose compounds the flexible nature of the ring can lead to $J_{\text{H-1-H-2}}$ values of 3·5—8 c./sec. for *cis*-hydrogens at C-1–C-2 and 0—8 c./sec. for *trans*-hydrogens.[2] Actually only values of $J \leqslant 1$ c./sec. (*trans*-H-1–H-2) give unequivocal assignments to anomeric configurations.[2] Recently Nishimura and Shimizu[3] have suggested that anomeric configurational assignments in pentofuranosyl nucleosides can be made by comparing the chemical shifts of anomeric protons of *both* anomers.

We have found a new method for assignment of anomeric configuration of pentofuranosyl pyrimidine nucleosides based on the removal of the anisotropic effect of the 5,6-double bond. This method requires only one anomer.

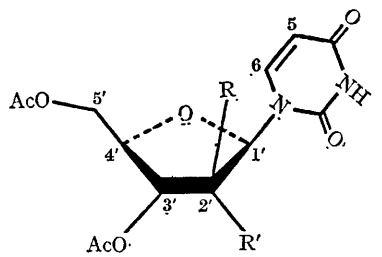
Recent o.r.d. studies on pentofuranosyls of uracil, thymine, and cytosine[4] have suggested that there is a preferred conformation in which the aglycone is not only nearly perpendicular to the plane of the 5-membered ring[5] but also that its 5,6-double bond sits "over" the 5-membered ring (see Figure). Inspection of models shows that a large diamagnetic effect due to the 5,6-double bond should be found on a *cis*-*O*-acetyl

TABLE. *N.m.r. data for acetylated derivatives of 1-β-D-aldopentofuranosyl nucleosides in perdeutero-DMSO*

Compound	Sugar moiety	Aglycone	Acetyl resonance (τ)[a]	C-2′-Acetyl resonance (τ)[a]	Δτ (p.p.m.)	C-1′–C-2′ configuration
(I)	2′-Deoxy-*ribo*	Uracil	7·94 (2)[b]	—		
(II)	2′-Deoxy-*ribo*[c]	5,6-Dihydrouracil	7·93 (2)	—		
(III)	*arabino*	Uracil	7·90, 7·93, 8·00	8·00	−0·05	*cis*
(IV)	*arabino*[c]	5,6-Dihydrouracil	7·92 (2), 7·95	7·95		
(V)	*lyxo*	Uracil	7·89, 7·93, 8·07	8·07	−0·10	*cis*
(VI)	*lyxo*[c]	5,6-Dihydrouracil	7·89, 7·95, 7·97	7·97		
(VII)	*ribo*	Uracil	7·91, 7·93 (2)	7·92[d]	+0·02	*trans*
(VIII)	*ribo*[c]	5,6-Dihydrouracil	7·92, 7·95 (2)	7·94[d]		
(IX)	*xylo*	Uracil	7·89, 7·92, 7·95	7·92[d]	+0·01	*trans*
(X)	*xylo*[c]	5,6-Dihydrouracil	7·91 (2), 7·97	7·93[d]		
(XI)	*xylo*	Thymine	7·88 (2), 7·93	7·90[d]	+0·02	*trans*
(XII)	*xylo*[e]	5,6-Dihydrothymine	7·90 (2), 7·95	7·92[d]		
(XIII)	*ribo*	Thymine	7·90, 7·92 (2)	7·91[d]	+0·01	*trans*
(XIV)	*ribo*[c]	5,6-Dihydrothymine	7·89, 7·93 (2)	7·92[d]		

[a] τ-Values are accurate to ±0·01 p.p.m. [b] Numbers in parentheses refer to number of acetyl groups with a particular resonance signal. [c] These new compounds gave satisfactory analyses. [d] Numbers are average of values in column 4. [e] Mixture containing 20% of (XI).

methyl group at the 2′-position [*e.g.*, (III) in Figure]. Alternatively if the *O*-acetate at position 2′ is *trans*, a much smaller diamagnetic (or perhaps paramagnetic) shift should be observed [*e.g.*, (VII) in Figure].



(III), *arabino*, R = OAc, R′ = H

(VII), *ribo*, R = H, R′ = OAc

FIGURE

Hydrogenation (room temperature, atmospheric pressure) of the acetylated *arabino-*, *lyxo-*, *ribo-*, and *xylo*-isomers of 1-β-D-aldofuranosyluracils and the *xylo-* and *ribo*-isomers of 1-β-D-aldofuranosylthymines was carried out in ethanol solution with 50% (w/w) rhodium (5%) on alumina catalyst.[6] The reaction was complete when the theoretical amount of H_2 was consumed and selective absorption at 260 mμ disappeared. As shown in the Table for the 2′-deoxy-*ribo*-nucleosides (I and II), saturation of the 5,6-double bond produces, as expected, little, if any, effect on the C-3′ and C-5′ acetyl signals. In the case of the two *cis*-pairs (III—IV) and (V—VI), a large paramagnetic (downfield) shift in the C-2′-acetoxy-resonance is observed upon removal of the anisotropy of the 5,6-double bond. With the four *trans*-pairs, (VII—VIII), (IX—X), (XI—XII), and (XIII—XIV), the C-2′-acetoxy-resonance is in the region of the C-3′ and C-5′ acetates [*cf.* (I and II)] hence it is not subject to significant shielding. Upon removal of the anisotropy of the 5,6-double bond, no dramatic shift is observed but it is seen that all of the peaks tend to shift slightly upfield. If one therefore takes the average of the three acetyl signals one finds a small but significant diamagnetic (upfield) shift in the C-2′-acetoxy-resonance signal of the *trans*-isomers upon removal of the anisotropy of the 5,6-double bond. Thus, with acetylated pentofuranosyl nucleosides, a *cis*-C-1′–C-2′ relationship causes a paramagnetic shift in the C-2′-acetoxy-resonance upon saturation of the double bond; whereas by similar treatment the *trans*-nucleosides will exhibit a small diamagnetic shift.

This method should have wide application for the assignment of anomeric configuration in the nucleoside area.

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