Carbohydrate Research, 33 (1974) 184–187

Note

The use of proton magnetic resonance spectra in the identification of 1′,2′-*cis*- and *trans*-furanosyl nucleosides*

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(Received september 28th, 1973; accepted in revised form, November 8th, 1973)

It is well established that the anomeric configuration of aldofuranosyl derivatives cannot be determined from the $J_{1',2'}$ coupling constants[1], although no exception has yet been found to the empirical rule that H-1′ resonates at lower field when the 1′,2′-substituents are *cis* than when they are *trans*[2–4]. Unfortunately, application of this rule requires that both α and β anomers be obtained in every case. Although the suggestion of Leonard[5] concerning the use of the $J_{1',2'}$ coupling constants of 2′,3′-*O*-isopropylidene derivatives of furanosyl nucleosides has been confirmed[6], most nucleosides are prepared from acylated sugars, so that to use this method it is necessary to remove the acyl groups and prepare the isopropylidene acetal before positive identification can be made.

Cushley *et al.*[7] have observed the anisotropic effect of the 5,6-double bond of the pyrimidine on the 2′-OAc signal of acetylated pyrimidine furanosyl nucleosides; in the case of two 1′,2′-*cis* nucleosides, this results in an upfield shift of the shielded methyl group. Hydrogenation of the 5,6-double bond of these compounds caused a downfield shift of 0.05 and 0.10 p.p.m. of these signals, placing them in the range of the signals of the 2′-OAc groups of 1′,2′-*trans* furanosyl nucleosides. We have observed the 2′-OAc signals of a number of pairs of 1′,2′-*cis*- and *trans*-furanosylpurines and have found in every case that the 2′-OAc signal of the *cis* nucleosides occurs between 0.11 and 0.34 p.p.m. upfield from the highest signal from the corresponding *trans* nucleoside, and there is no overlap of the ranges (see Table I). In addition to these anomeric pairs, the spectra of 10 other acetylated β-D-ribofuranosyl derivatives have been examined, and in all cases the OAc signals fell between δ 2.04 and 2.19. The assignment of the 2′-OAc signal of the 1′,2′-*cis* nucleosides is evident upon comparison of the three types of α,β pairs. The acetoxyl-group signals of the β-D-ribofuranosylpurines, which have neither a C-2′ nor C-3′-*cis*-acetoxyl group, all

*This work was supported by the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare, Contract No. NIH-NCI-C-73-3712.

occur downfield from 2.05 p.p.m. The signals from the α-D-arabinofuranosyl- and β-D-xylofuranosylpurines, which have their C-3′-acetoxyl function *cis* to the purine ring, also all occur downfield from 2.05 p.p.m. The β-D-arabinofuranosyl-, α-D-xylofuranosyl-, and α-D-ribofuranosylpurines, all of which have their 2′-OAc group *cis* to the purine ring, give one methyl signal upfield from 1.95 p.p.m. As noted by Fox[8],

TABLE I

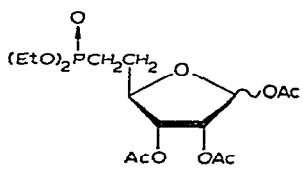
P.M.R. DATA

Nucleoside	*Anomer*	*Chemical shifts of Me of acetyl, p.p.m.*	*Ref.*[a]
Ethyl 2,3-di-*O*-acetyl-1,5,6-trideoxy-1-[2,6-dichloropurin-9-yl]-D-*arabino*-heptofuranuronate	α	2.08, 2.16	11
	β	1.95, 2.18	
9-(2,3,5-tri-*O*-acetyl-D-arabinofuranosyl)-2,6-dichloropurine[b]	α	2.10, 2.12, 2.16	12
	β	1.90, 2.12, 2.17	
9-(2,3,5,-tri-*O*-acetyl-D-arabinofuranosyl)-6-chloro-2-fluoropurine[b]	α	2.11, 2.13, 2.17	12
	β	1.90, 2.13, 2.17	
9-(2,3,5-tri-*O*-acetyl-D-arabinofuranosyl)-2,6-difluoropurine[b]	α	2.11, 2.13, 2.17	12
	β	1.90, 2.13, 2.17	
Ethyl 2,3-di-*O*-acetyl-1,5,6-trideoxy-1-[2,6-dichloropurin-9-yl]-D-*ribo*-heptofuranuronate	α	1.87, 2.07	11
	β	2.07, 2.14	
9-(2,3-di-*O*-acetyl-5-deoxy-D-ribofuranosyl)-2,6-dichloropurine[b]	α	1.87, 2.07	13
	β	2.06, 2.13	
9-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)-6-chloropurine[b,c]	α	1.80, 2.12, 2.17	
	β	2.08, 2 12, 2.17	
9-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)-6-methylpurine[b]	α	1.84, 2.10, 2.15	14
	β	2.07, 2.10, 2.15	
9-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)-2-fluoro-6-methylpurine	α	1.88, 2.11, 2.13	14
	β	2.07, 2.13, 2.15	
9-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)-6-ethylpurine[b]	α	1.85, 2.12, 2 17	14
	β	2.08, 2.12, 2.17	
9-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)-2,6-diaminopurine[b]	α	1.90, 2.10, 2.15(2)	15
	β	2.05, 2.08, 2.15(2)	
9-(2,3,5-tri-*O*-acetyl-D-xylofuranosyl)-6-methylpurine[b]	α	1.90, 2.11, 2.13	14
	β	2.08, 2.11, 2.13	
9-(2,3,5-tri-*O*-acetyl-D-xylofuranosyl)-2,6-dichloropurine[b]	α	1.85, 2.11, 2.15	12
	β	2.07, 2.11, 2.15	
9-(2,3,5-tri-*O*-acetyl-D-xylofuranosyl)-2,6-difluoropurine[b]	α	1.86, 2.12, 2.16	12
	β	2.09, 2.11, 2.13	
9-(2,3,5-tri-*O*-acetyl-D-xylofuranosyl)-2,6-diaminopurine[b]	α	1.90, 2.11, 2.13	12
	β	2 08, 2.11, 2.13	

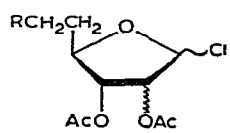
[a]Synthesis of compounds. [b]Assignments made from a spectrum of a mixture of the two anomers. The ratios of the integrals of the signals from the methyl groups were consistent with the integrals of the signals from the anomeric protons. Assignments for the *trans* isomer were later confirmed on the anomerically pure compound. [c]J. A. Montgomery and K. Hewson, unpublished data.

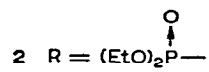
the double bonds of purine nucleosides are not so readily reduced as are those of the pyrimidine nucleosides. Our observations appear to preclude the necessity for such a reduction, as they are the basis for a reliable method of determining the anomeric configuration of acetylated purine nucleosides directly, which complements the method of Leonard[5] for *O*-isopropylidene derivatives. Further, identification is possible with only one anomer if (as is usually the case) one or more additional acetoxyl groups are present in the sugar moiety, by comparing the signal from the 2′-OAc group with the signals from the other acetoxyl groups, none of which is affected to such a degree by the anisotropic effect.

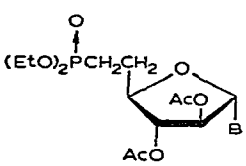
We have used this method to establish that the nucleoside obtained by reaction of the chloro sugar prepared from **1** and the chloromercury derivative of *N*-benzoyladenine is a 1′,2′-*trans* nucleoside rather than the α-D-*ribo*-nucleoside (**5**) as previously reported[9], as both methyl signals occur downfield from δ 2.05 p.p.m. Furthermore, the $J_{1',2'}$ and $J_{2',3'}$ coupling constants are about 2.7 Hz, showing that H-1′, H-2′, and H-3′ must have a *trans–trans* relationship[10]. A close comparison of the complete spectrum of this nucleoside with those of the α-D-*arabino*- and β-D-*xylo*-nucleosides listed in Table I shows that it resembles the α-D-*arabino*-nucleosides and not the β-D-*xylo*-nucleosides, as the signals from H-2′ and H-3′ of the β-D-*xylo*-nucleosides overlap and fall near δ 5.5, whereas the signals from the nucleoside in question and the α-D-*arabino*-nucleosides are clearly separated, occurring at 5.30–5.40 and 5.75–5.85. On the basis of all of these features in the p.m.r. spectrum of this nucleoside, we have now assigned to it the α-D-*arabino* structure (**4**).



1







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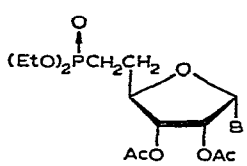

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B=*N*—Benzoyladenin-9-yl

Examination of the p.m.r. spectrum of the chloro sugar **2** indicates that this sample was actually a mixture of at least three compounds, the two major components being present in almost equal amounts. Also, the spectrum of the chloro

sugar **2** closely resembles that[11] of compound **3**. Although we cannot firmly identify from these data the second major component of this glycosyl halide mixture as the arabinofuranosyl chloride, it is now reasonable to assume that it is; this constitutes another example of a readily epimerized ribofuranose[11], rather than an exception to the *trans* rule[9], and leads to the proposition that substitution, at least by certain types of groups, at O-5′ of furanoses increases the instability of the *ribo* isomers. That the epimerization must have occurred during preparation of the chloro sugar is clear from the fact that the reaction of the sugar aldehyde[9,11] with tetraethylmethylene-bisphosphonate gave only a single sugar, the *trans* alkene, as shown by t.l.c. and p.m.r. Reduction of the alkenic sugar gave a single sugar (t.l.c. and p.m.r.), and acetolysis of that sugar gave **1** as a single anomeric pair (t.l.c. and p.m.r.).

ACKNOWLEGDMENTS

The author is indebted to Dr. W. C. Coburn, Jr., and Mrs. Martha Thorpe for the p.m.r. data presented here and for helpful discussions.

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