Communications to the Editor

Chem. Pharm. Bull. 30(3)1117—1120(1982)

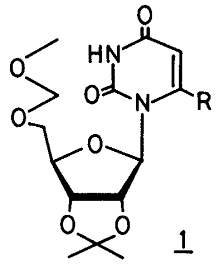
FIRST EXCEPTIONS TO THE "IMBACH RULE" FOR β-D-RIBOFURANOSYL NUCLEOSIDES

Hiromichi Tanaka, Hiroyuki Hayakawa, and Tadashi Miyasaka*
School of Pharmaceutical Sciences, Showa University,
Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan

Introduction of an anisotropic substituent to the C-6 position of 2',3'-O-isopropylideneuridine altered the differences in the chemical shift between the methyl signals (Δδ Me) of the isopropylidene group. Thus, exceptions to Imbach's criterion for β-D-ribofuranosyl nucleosides have now been observed for the first time.

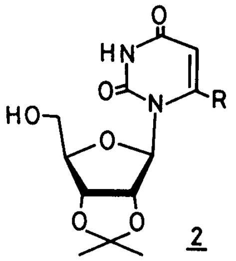
KEYWORDS——nucleoside; uridine; 6-substituted uridines; Imbach Rule; PMR; magnetic anisotropy; anomeric configuration

Among the methods for determining the anomeric configuration of ribofuranosyl nucleosides,1) the "Imbach Rule" seems to be the most widely used.2) That is, the endo methyl signal of the isopropylidene group resonates upfield due to the anisotropic effect of the aglycon in α-D-ribofuranosyl nucleosides, hence the Δδ Me value is smaller (<0.15 ppm) than that of the corresponding β-anomers (>0.15 ppm).2) Though a recent communication3) indicated the failure of this criterion in relation to some α-D-ribofuranosyl nucleosides, no exceptions have been reported for the β-series.



1

We have been concerned with the general method for converting uridine into 6-substituted analogs4,5) which have, so far, been known to be difficult to synthesize. During the course of our studies, we noticed that the Δδ Me values are rather small in some 2',3'-O-isopropylidene-5'-O-methoxymethyl derivatives (1) of 6-substituted uridines (Table I).5) This observation prompted a more precise PMR investigation of the corresponding 2',3'-O-isopropylidene derivatives (2), because Imbach's criterion is limited to ribofuranosyl nucleosides in which the 5'-hydroxyl groups are not substituted.



2

Isopropylidenation of free nucleosides was conducted in a conventional way (acetone/70% $HClO_4$, room temperature) to afford 2, whose PMR spectra were measured (100 MHz, in $CDCl_3$, digital resolution: 0.1220 Hz).6,7,8)

Table I. Isopropylidene Me Chemical Shifts and $\Delta\delta$ Me Values of Compounds 1 in $CDCl_3$

	δ ppm of isop. Me	$\Delta\delta$ Me (ppm)
1a	1.59, 1.36	0.23
1b	1.56, 1.35	0.21
1c	1.52, 1.37	0.15
1d	1.53, 1.36	0.17
1e	1.42, 1.31	0.11
1f	1.54, 1.37	0.17
1g	1.20, 1.09	0.11
1h	1.58, 1.35	0.23
1i	1.56, 1.36	0.20

C-6 substituent (R)

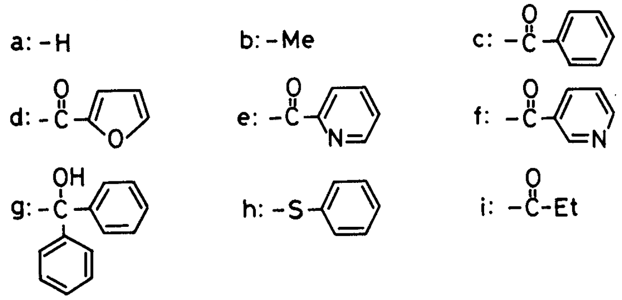
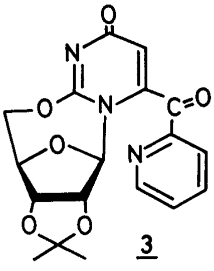


Table II. Isopropylidene Me Chemical Shifts and $\Delta\delta$ Me Values of Compounds 2 in $CDCl_3$

	δ ppm of isop. Me	$\Delta\delta$ Me (ppm)*
2a	1.5797, 1.3616	0.2181
2b	1.5613, 1.3567	0.2046
2c	1.3567, 1.3150	0.0417
2d	1.4511, 1.3334	0.1177
2e	1.3052, 1.2880	0.0172
2f	1.3922, 1.3211	0.0711
2g	1.1777, 1.0710	0.1067
2h	1.5932, 1.3677	0.2255
2i	1.5380, 1.3567	0.1813

* accuracy: ±0.0024 ppm

Since compounds 1 and 2 were originally synthesized from uridine,[4,5] a naturally occurring nucleoside, it is reasonable to conclude that all of them have the β-configuration. To further confirm the anomeric assignment we prepared the O^2,5'-cyclo derivative (3)[9] of 6-picolinyluridine by tosylation (p-TsCl/pyridine and 4-dimethylaminopyridine, room temperature) of 2e followed by cyclization (Et$_3$N/CHCl$_3$, reflux). The PMR spectrum of 3 is fully consistent with the O^2,5'-cyclo structure on the basis of the following observations. H-1' is located at δ 5.45 as a sharp singlet. The two 5'-protons appear as well-separated double-doublets centered at δ 4.27 and δ 4.52 (geminal coupling constant: J=12.8 Hz).


3

As summarized in Table II, removal of the methoxymethyl group of 6-aroyl derivatives (c, d, e, and f) reduced the Δδ Me values to an appreciable extent, and the values of 2c∿g do not meet Imbach's criterion for β-D-ribofuranosyl nucleosides. The available data indicates that the origin of these chemical shift changes is undoubtedly due to the magnetic anisotropy of the aryl group in the C-6 substituent, and a "C^6-C-Ar" structure seems to be necessary.

Thus, when determining anomeric configurations, one should keep in mind that pyrimidine β-D-ribofuranosyl nucleosides bearing an anisotropic substituent at their C-6 position – and presumably the C-8 position of purine counterparts as well – do not always obey the "Imbach Rule".

ACKNOWLEDGEMENT The authors thank Professor J-L. Imbach and Dr. A. Pompon for their cooperation through private communication concerning the current status of the "Imbach Rule".

REFERENCES AND NOTES

1) T. Nishimura and B. Shimizu, Chem. Pharm. Bull., 13, 803 (1965); F. E. Hruska, A. A. Grey, and I. C. P. Smith, J. Am. Chem. Soc., 92, 4008 (1970); R. J. Cushley, K. A. Watanabe, and J. J. Fox, Chem. Commun., 1968, 1611.

2) B. Rayner, C. Tapiero, and J-L. Imbach, Carbohydr. Res., 47, 195 (1976), and references cited therein.

3) A. Pompon and J-L. Imbach, private communication.

4) H. Tanaka, I. Nasu, and T. Miyasaka, Tetrahedron Lett., 1979, 4755; H. Tanaka, I. Nasu, H. Hayakawa, and T. Miyasaka, Nucleic Acids Symposium Series, 8, 33 (1980); H. Tanaka, H. Hayakawa, and T. Miyasaka, ibid., 10, 1 (1981).

5) H. Tanaka, H. Hayakawa, and T. Miyasaka, Chem. Pharm. Bull., 29, 3565 (1981).

6) PMR data (CDCl$_3$, δ ppm, after addition of D$_2$O) of compounds 2c∿i are as follows (supplementary to Table II).
   2c: 3.43∿3.80 (2H, m, CH$_2$-5'), 3.97∿4.13 (1H, m, H-4'), 4.83 (1H, dd, H-3'), 5.27 (1H, dd, H-2'), 5.56 (1H, d, J=3.2 Hz, H-1'), 5.72 (1H, s, H-5), 7.46∿7.83 (3H, m, phenyl), 7.91∿8.06 (2H, m, phenyl).
   2d: 3.53∿3.91 (2H, m, CH$_2$-5'), 3.99∿4.19 (1H, m, H-4'), 4.88 (1H, dd, H-3'), 5.25 (1H, dd, H-2'), 5.63 (1H, d, J=2.9 Hz, H-1'), 5.90 (1H, s, H-5), 6.69 (1H, dd, furan H-4), 7.43 (1H, d, furan H-5), 7.82 (1H, d, furan H-3).

2e: 3.64∿4.00 (2H, m, CH_2-5'), 4.03∿4.12 (1H, m, H-4'), 4.87 (1H, dd, H-3'), 5.24 (1H, dd, H-2'), 5.39 (1H, d, J=2.9 Hz, H-1'), 5.75 (1H, s, H-5), 7.52∿7.67 (1H, m, pyridine H-5), 7.88∿8.05 (1H, m, pyridine H-4), 8.13∿8.24 (1H, m, pyridine H-3), 8.71∿8.78 (1H, m, pyridine H-6).

2f: 3.41∿3.77 (2H, m, CH_2-5'), 3.97∿4.13 (1H, m, H-4'), 4.81 (1H, dd, H-3'), 5.26 (1H, dd, H-2'), 5.58 (1H, d, J=3.1 Hz, H-1'), 5.76 (1H, s, H-5), 7.46∿7.62 (1H, m, pyridine H-5), 8.21∿8.35 (1H, m, pyridine H-4), 8.85∿8.97 (1H, br, pyridine H-6), 9.13∿9.22 (1H, br, pyridine H-2).

2g: 3.75∿3.92 (2H, m, CH_2-5'), 3.94∿4.19 (1H, m, H-4'), 4.63∿4.81 (2H, m, H-2' and H-3'), 5.04 (1H, s, H-5), 6.46 (1H, d, J=1.5 Hz, H-1'), 7.09∿7.48 (10H, m, phenyl).

2h: 3.69∿4.01 (2H, m, CH_2-5'), 4.22∿4.34 (1H, m, H-4'), 4.98 (1H, s, H-5), 5.04 (1H, dd, H-3'), 5.30 (1H, dd, H-2'), 6.10 (1H, d, J=2.4 Hz, H-1'), 7.41∿7.62 (5H, m, phenyl).

2i: 1.22 (3H, t, $COCH_2CH_3$), 2.85 (2H, q, $COCH_2CH_3$), 3.67∿3.98 (2H, m, CH_2-5'), 4.12∿4.27 (1H, m, H-4'), 4.94 (1H, dd, H-3'), 5.22 (1H, dd, H-2'), 5.47 (1H, d, J=2.8 Hz, H-1'), 5.83 (1H, s, H-5).

7) Ultraviolet absorption maxima of 2c∿i are as follows (in MeOH, nm).
2c: 257. 2d: 290. 2e: 247, 274 (sh). 2f: 243, 274 (sh). 2g: 264.
2h: 280. 2i: 273.

8) High resolution MS data of 2c∿i are as follows.
2c: m/z 388.1293 (M^+) calcd. for $C_{19}H_{20}N_2O_7$ 388.1271.
2d: m/z 378.1040 (M^+) calcd. for $C_{17}H_{18}N_2O_8$ 378.1060.
2e: m/z 389.1228 (M^+) calcd. for $C_{18}H_{19}N_3O_7$ 389.1223.
2f: m/z 389.1264 (M^+) calcd. for $C_{18}H_{19}N_3O_7$ 389.1223.
2g: m/z 467.1782 ($M+1$) calcd. for $C_{25}H_{27}N_2O_7$ 467.1815.
2h: m/z 392.1006 (M^+) calcd. for $C_{18}H_{20}N_2O_6S$ 392.1041.
2i: m/z 340.1280 (M^+) calcd. for $C_{15}H_{20}N_2O_7$ 340.1270.

9) Spectral data of compound 3 are as follows.
PMR ($CDCl_3$, δ ppm): 1.32 (3H, s, isop. Me), 1.39 (3H, s, isop. Me), 4.27 (1H, dd, H-5'), 4.52 (1H, dd, H-5'), 4.68 (1H, br, H-4'), 4.97 (1H, d, H-3'), 5.04 (1H, d, H-2'), 5.45 (1H, s, H-1'), 6.34 (1H, s, H-5), 7.53∿7.69 (1H, m, pyridine H-5), 7.87∿8.07 (1H, m, pyridine H-4), 8.11∿8.29 (1H, m, pyridine H-3), 8.69∿8.80 (1H, m, pyridine H-6).
Ultraviolet absorption maximum (in MeOH, nm): 243, 278 (sh).
High resolution MS: m/z 371.1095 (M^+) calcd. for $C_{18}H_{17}N_3O_6$ 371.1115.

(Received February 22, 1982)