Reference Data

^{13}C NMR Spectral Assignments of Some Cyclopentyluracils and 5-Halouracils

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The ^{13}C NMR spectra of several 1-(2-hydroxymethylcyclopentyl)- and 1-(2-hydroxymethylcyclopentylmethyl)uracils and 5-halouracils (X = Cl, Br or I) were fully assigned with the aid of one- (^{13}C, ^{1}H–^{1}H NOE, DEPT) and two-dimensional (HMQC) NMR experiments.

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INTRODUCTION

Carbocyclic analogues of nucleosides form an interesting class of biologically active compounds, several of which are potent antitumour and/or antiviral agents.[1,2] For some years, we have been investigating a group of such analogues, 1,2-disubstituted carbocyclic nucleosides, in which the hydroxymethyl group and heterocyclic base are attached to contiguous carbons of the carbocycle.[3] In continuance of our work on the elucidation of the structures of these analogues,[4] we now report the fully assigned ^{13}C NMR spectra of a series of pharmacologically interesting uracils bearing a 2-hydroxymethylcyclopentyl moiety (Fig. 1). This work supplements the ^{13}C NMR spectra data available for uracil, uridine[5] and various uridine analogues.[6] Additionally, one- and two-dimensional NMR spectroscopic techniques were used to examine the effects on the carbocycle of a halogen (Cl, Br or I) substituent at position 5 of the uracil ring, of a methyl group between the base and the pseudo-glycosidic bond and of a *cis* or *trans* relationship between the base and the 2-hydroxymethyl group.

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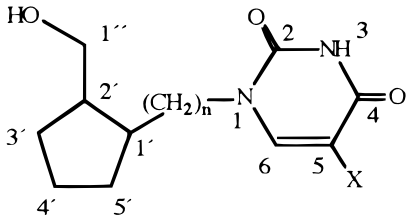
RESULTS AND DISCUSSION

Table 1 lists the ^{13}C chemical shift data for compounds **1–12**.

The signals due to the cyclopentyl ring carbons were fully assigned by comparison of the ^{13}C NMR spectra of compounds **1–12** with the corresponding heteronuclear multiple-quantum correlation (HMQC) spectra of 2-hydroxymethylcyclopentyls bearing a guanine or 2,6-diaminopurine base.[7] As would be expected, C-1′ was heavily



Compound	n	Isomer	X
1	0	*cis*	H
2	0	*trans*	H
3	1	*cis*	H
4	1	*trans*	H
5	0	*cis*	Cl
6	0	*cis*	Br
7	0	*cis*	I
8	0	*trans*	I
9	1	*cis*	Cl
10	1	*cis*	Br
11	1	*cis*	I
12	1	*trans*	I

Figure 1. Compounds **1–12**.

Table 1. ^{13}C NMR chemical shifts (δ, ppm) of compounds 1–12

Compounds	C-1′	C-2′	C-3′	C-4′	C-5′	C-1″	$(CH_2)_n$–N	C-2	C-4	C-5	C-6
1	58.1	42.6	27.5	22.5	29.2	61.0	—	151.9	163.6	100.4	143.8
2	59.0	45.8	27.5	22.5	30.9	62.8	—	151.3	163.4	101.4	143.3
3	40.8	43.3	27.6	22.3	28.2	61.1	47.9	151.1	163.7	100.7	145.9
4	41.6	45.2	29.1	24.2	30.2	64.6	51.8	151.5	164.0	100.9	146.3
5	59.2	41.7	27.2	22.5	28.8	61.0	—	151.0	159.5	105.8	141.1
6	59.2	41.7	27.3	22.5	28.9	61.1	—	151.2	159.7	94.3	143.5
7	59.1	41.9	27.3	22.5	29.0	61.1	—	151.6	161.0	67.7	148.0
8	60.1	45.2	27.1	22.1	30.6	62.8	—	150.8	160.6	68.7	147.6
9	41.1	43.7	28.0	22.7	28.5	61.4	48.7	151.0	160.2	106.4	143.2
10	41.1	43.7	28.0	22.7	28.5	61.4	48.7	150.9	159.9	94.8	145.8
11	40.8	43.4	27.6	22.3	28.1	61.1	48.2	150.9	161.0	67.8	150.1
12	43.4	45.3	29.2	24.8	31.5	66.6	53.9	151.5	161.0	67.9	149.8

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deshielded by the heterocycle: in the 2-hydroxycyclopentyl compounds (**1**, **2** and **5–8**) the C-1′ signal appeared at 59.1 ± 1 ppm and in the 2-hydroxycyclopentylmethyl compounds (**3**, **4** and **9–12**) it was shifted to higher frequencies, appearing at 42.1 ± 1.3 ppm, so that C-2′ (43.5 ± 1.8 ppm) became the most deshield cyclopentyl ring carbon. The remaining cyclopentyl ring carbons were only slightly affected by changes in the stereochemistry and/or substituent at position 5 of the uracil ring: the C-5′ signal appeared at 29.8 ± 1.7 ppm, very close to the C-3′ signal at 28.1 ± 1 ppm, and the C-4′ signal appeared at 23.5 ± 1.4 ppm.

The signals due to the uracil ring carbons were mainly assigned by comparison of their chemical shifts with these data for uridine;[5] nonetheless, to distinguish between the closely lying signals due to the C-2 quaternary and the C-2 methine groups of the 5-halouracils (**5–12**), DEPT experiments were also carried out. The effects of the halogen substituents are evident from the ^{13}C chemical shift data: deshielding at C-5 increases in the order I < Br < Cl, whereas at C-6 it increases in the order Cl < Br < I. Deshielding by the 5-halo substituent was also evident in the ^{1}H NMR spectra, in which the NH (3) and C-6 signals of compounds **5–12** had chemical shifts approximately 0.5 ppm higher than in the corresponding uracil compounds (**1–4**). For the latter uracil compounds and the 5-ioduracil compounds (**7**, **8**, **11** and **12**), there were only minor differences between the chemical shifts for the uracil ring carbons of *cis* and *trans* isomers.

EXPERIMENTAL

Compounds **1–4** were synthesized by constructing the uracil base about an appropriate preformed amino alcohol.[7] The amino alcohol was first reacted with 3-ethoxy-2-propenoyl isocyanate in DMF at −20 °C and then the resulting urea was cyclized in sulphuric acid[8,9] (compounds **1** and **2** were separated by flash chromatography on silica gel, with $CHCl_3$ as eluent). The 5-halouracil compounds (**5–12**) were obtained by treatment of compounds **1–4** with iodine and HNO_3 in dioxane,[10] or with *N*-chloro- or *N*-bromosuccinimide in acetic acid.[11] All compounds were fully characterized, both physically and spectroscopically, and their stereochemistry was determined by means of ^{1}H–^{1}H nuclear Overhauser effect (NOE) experiments by irradiation of CH (1′).[3,4,7]

^{13}C and ^{1}H NMR spectra of samples as approximately 10% solutions in DMSO-d_6 were recorded at room temperature in 5 mm o.d. tubes. The chemical shifts were internally referenced to TMS (0 ppm).

One-dimensional ^{13}C NMR spectra were recorded on a Bruker AMX 300 NMR spectrometer operating at 75.47 MHz, typically with a 30° pulse flip angle, a pulse repetition time of 1.8 s and a spectral width of 17 857 Hz with 32K data points. For the DEPT sequence, the width of the 90° pulse for ^{13}C was 4 μs and that of the 90° pulse for ^{1}H was 9.5 μs; the delay $2J_{C-H}^{-1}$ was set at 3.45 ms.

^{1}H NMR and homonuclear NOE[12] experiments were performed on a Bruker WM-250 Fourier transform spectrometer operating at 250.13 MHz, typically with a 30° pulse flip angle, a pulse repetition time of 2 s and a spectral width of 2726 Hz with 16K data points.

^{1}H-detected, one-bond HMQC spectra were recorded on a Bruker AMX 500 spectrometer using a pulse sequence (the INV4GS micro program of the Bruker software) that allowed gradient selection. Spectra were collected in the t_1 domain in 256 experiments with 2K data points, and spectral widths of 5050 and 27 669 Hz in the F_2 (^{1}H) and F_1 (^{13}C) dimensions, respectively. The relaxation delay, D_1, was set to 2 s and D_2 was empirically optimized to 3.5 ms. Data were processed using sine-bell weighting functions in both dimensions.

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