Reference Data

Assignment of the ^{13}C NMR Spectra of some Adenine, Hypoxanthine and Guanine Carbonucleosides

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The ^{13}C NMR spectra of various 9-(2-hydroxymethylcyclopentyl)-purines and 9-(2-hydroxymethylcyclopentylmethyl)purines (purine = adenine, hypoxanthine or guanine) were fully assigned with the aid of one- (^1H, ^1H–^1H NOE, DEPT) and two-dimensional (HMQC) NMR experiments. © 1997 John Wiley & Sons, Ltd

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INTRODUCTION

The utility of analogues of purine nucleosides as drugs is well documented.[1,2] For some years, we have been working on the synthesis and structural and biological evaluation of carbonucleosides incorporating a cyclopentane ring with a hydroxymethyl group and a heterocyclic base on adjacent carbons.[3,4] As part of our work on the effects of these modifications on the analogue structure,[5,6] we report here fully assigned ^{13}C NMR spectra for a new series of analogues.[7] These compounds comprise a guanine, hypoxanthine or adenine base attached through position 9 to a 2-hydroxymethylcyclopentane or a 2-hydroxymethylcyclopentylmethyl carbocyle, *cis* or *trans* to the hydroxymethyl group (compounds **1**–**12**, Fig. 1). Spectral assignments were made by reference to the ^{13}C NMR spectra of adenosine,[8] inosine[8] and guanosine,[9] and with the aid of one- (^1H, ^1H–^1H NOE, DEPT) and two-dimensional (HMQC) NMR experiments.

RESULTS AND DISCUSSION

Table 1 lists the ^1H chemical shift data for the heterocyclic bases of compounds **1**–**12** and Table 2 the ^{13}C chemical shift data for these compounds.

The *cis* or *trans* stereochemistry of compounds **1**–**12** was assigned on the basis of nuclear Overhauser effect (NOE) experiments performed on their synthetic precursors. These were the corresponding 6-chloropurines in the case of the compounds with a 1-hydroxymethylcyclopentyl carbocycle (**1**, **2**, **5**, **6**, **9** and **10**) and the

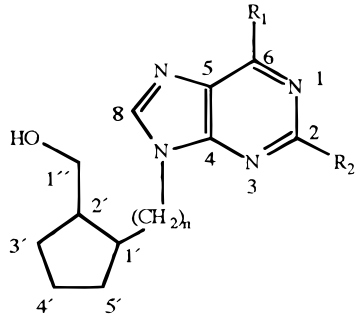

Figure 1. Compounds studied.

Table 1 ^1H NMR chemical shifts (δ, ppm) of the purine base of compounds 1–12.

Compound	H-2	H-8	6-OH	2-NH_2
1	8.07	8.11	—	7.18
2	8.11	8.17	—	7.14
3	8.11	8.13	—	7.13
4	8.11	8.13	—	7.17
5	8.01	8.05	12.19	—
6	8.01	8.15	12.26	—
7	8.01	8.10	12.25	—
8	8.02	8.09	11.82	—
9	—	7.63	10.58	6.44
10	—	7.74	10.52	6.46
11	—	7.68	10.53	6.44
12	—	7.84	10.42	7.67

Table 2 ^{13}C NMR chemical shifts (δ, ppm) of compounds 1–12

Compound	C-1	C-2	C-3	C-4	C-5	C-1″	CH_2-N	C-2	C-4	C-5	C-6	C-8
1	56.5	45.7	27.5	22.6	30.7	60.8	—	152.5	150.3	118.9	156.3	140.5
2	57.9	47.1	27.7	23.0	32.5	62.6	—	152.4	149.8	119.6	156.3	140.3
3	41.8	43.7	28.0	22.6	29.1	61.4	44.0	152.6	150.0	119.0	156.3	141.3
4	42.5	45.5	29.2	24.1	30.4	64.5	47.5	152.7	150.0	118.9	156.3	141.1
5	56.5	45.0	27.3	22.3	30.6	60.5	—	145.2	148.8	123.7	156.8	139.6
6	58.1	47.5	27.7	23.0	32.9	62.5	—	145.5	148.6	124.7	157.1	139.6
7	41.5	43.1	27.4	22.1	28.5	60.9	43.9	145.2	148.3	123.7	156.5	140.3
8	42.7	45.5	29.2	24.1	30.4	64.5	47.9	145.7	148.9	124.1	157.1	140.8
9	56.0	45.6	27.3	22.4	30.7	60.8	—	153.7	151.8	116.5	157.2	136.7
10	57.0	47.1	27.6	22.9	32.8	62.5	—	153.6	151.4	117.2	157.2	136.5
11	41.7	43.5	28.1	22.7	29.1	61.3	43.8	153.7	151.6	116.8	157.2	138.0
12	42.3	45.5	29.2	24.1	30.3	64.5	47.3	153.7	151.7	116.6	157.3	138.2

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starting aminomethyl alcohols in the case of the compounds with a 1-hydroxymethylcyclopentylmethyl carbocycle (**3**, **4**, **7**, **8**, **11** and **12**).[7]

Regarding the ^{1}H NMR spectra, the close-lying signals ($0.02 \leqslant \Delta\delta \leqslant 0.14$ ppm; Table 1) due to the protons at positions 2 and 8 of the adenine and hypoxanthine bases of compounds **1**–**8** were assigned with the aid of one-bond heteronuclear multiple-quantum correlation (HMQC) spectra of compounds **3** and **6**.

With regard to the ^{13}C NMR spectra, assignment of the signals due to the purine ring carbons of compounds **1**–**12** was partly based on the assignments made for adenosine,[8] inosine[8] and guanosine.[9] In addition, it was necessary to carry out DEPT experiments on **4** and **6** in order to distinguish between the signals for carbons 2 and 4 ($\Delta\delta \approx 2.5$ ppm) of these compounds and, by extension, those of the other adenines and hypoxanthines. Also, an HMQC spectrum of guanine **9** was obtained in order to distinguish between the signals for carbons 2 and 4 of this compound ($\Delta\delta \approx 2$ ppm) and, by extension, those of the other guanine compounds.

The signals due to the cyclopentane rings of **6** and **9** were assigned with the aid of HMQC spectra. By extension, the signals due to the cyclopentane carbons of the rest of the compounds could also be assigned.[6]

EXPERIMENTAL

Adenines **1**–**4** and hypoxanthines **5**–**8** were synthesized by condensation of the appropriate starting amino alcohol with 5-amino-4,6-dichloropyrimidine, followed by conversion of the amine product to the corresponding 6-chloropurine by treatment with triethyl orthoformate in acidic medium.[7] Nucleophilic substitution of the chlorine by heating the 6-chloropurine in methanolic ammonia[10] or sodium hydroxide[11] afforded the desired adenines or hypoxanthines, respectively.

Guanines **9**–**12** were obtained by an analogous procedure that included an intermediate step to introduce the amino group that would occupy position 7 in the target compounds. This step involved coupling the amine formed by condensation of the aminomethyl alcohol with 2-amino-4,6-dichloropyrimidine with *p*-chlorobenzenediazonium chloride, followed by reduction.[4] Formation of the imidazole ring of the base and introduction of the ring substituents were carried as described for compounds **1**–**8**.

All compounds were fully characterized, both physically and spectroscopically.

^{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 were recorded with 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 with a spectral width of 17857 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 2 $J_{C\text{-}H}^{-1}$ was set at 3.45 ms.

^{1}H NMR and homonuclear NOE[12] experiments were performed with 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 with 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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References

1. J. B. Hobbs, in *Comprehensive Medicinal Chemistry* edited by C. Hansch, Vol. 2, pp. 299–332. Pergamon Press, Oxford (1990).
2. E. De Clercq, *Med. Res. Rev.* **16**, 125 (1996).
3. L. Santana, M. Teijeira, E. Uriarte, E. De Clercq, J. Balzarini, *Nucleosides Nucleotides* **14**, 521 (1995).
4. L. Santana, M. Teijeira, E. Uriarte, C. Terán, G. Andrei, R. Snoeck and E. De Clercq, *Nucleosides Nucleotides* in press.
5. (a) L. Santana, M. Teijeira, C. Terán, E. Uriarte, V. Casselato and R. Graziani, *Nucleosides Nucleotides*, **15**, 1179 (1996); (b) L. Santana, M. Teijeira, E. Uriarte, A. Fadda, G. Podda, S. Catinella and P. Traldi, *Rapid Commun. Mass Spectrom.* 1316 (1996).
6. M. Teijeira and E. Uriarte, *Magn. Reson. Chem.* **35**, 348 (1997).
7. M. Teijeira, Doctoral Thesis, University of Santiago de Compostela (1996).
8. M. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica and L. B. Townsend, *J. Am. Chem. Soc* **97**, 4627 (1975).
9. L. G. Marcilli, B. de Castro and C. Solorzano, *J. Am. Chem. Soc.* **104**, 461 (1982).
10. N. Katagiri, M. Nomura, H. Sato, C. Kaneko, K. Yusa and T. Tsuruo, *J. Med. Chem* **35**, 1882 (1992).
11. R. Vince and M. Hua, *J. Med. Chem.* **33**, 17 (1990).
12. M. Kinns and J. K. M. Sanders, *J. Magn. Reson.* **56**, 518 (1984).