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CHARACTERIZATION OF N7 AND N9 ALKYLATED PURINE ANALOGUES BY ^{1}H AND ^{13}C NMR

Jonas Kjellberg* and Nils Gunnar Johansson*
Department of Antiviral Chemotherapy, Research & Development Laboratories
Astra Alab AB, S-151 85 Södertälje, Sweden

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Abstract: The use of ^{1}H and ^{13}C NMR for differentiating N7 and N9 alkylated guanine derivatives is described.

Some acyclic guanosine analogues show potent antiviral activity: acyclovir (9-(2-hydroxyethoxymethyl)guanine)[1], buciclovir ((R)-9-(3,4-dihydroxybutyl)guanine)[2] and 9-(1,3-dihydroxy-2-propoxymethyl)guanine[3]. They are open-chain analogues to guanosine and they are phosphorylated by herpes virus thymidine kinase[4]. Recently it has been shown that some N9 alkylated derivatives of 2-aminopurine are substrates for xanthine oxidase[5].

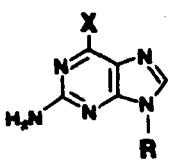
The synthesis of N9 substituted purines usually involves alkylation of the unsubstituted purines in the presence of a base. We have studied the alkylation of various guanine precursors, and have obtained mixtures of primarily N7 and N9 alkylated products[6]. The compounds are purified by flash chromatography in combination with recrystallization.

The regio-isomers, originally synthesized by unambiguous pathways, have been characterized by UV and NMR methods[7], but in many cases the ultraviolet spectra are not very distinct. However, the regio-isomeric N7 and N9 pairs of alkylated guanine and guanine precursors exhibit characteristic shift differences in their ^{1}H and ^{13}C NMR spectra, that can be used to distinguish the products in the mixtures.

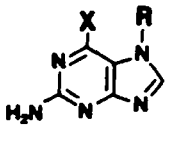
By summarizing the spectroscopic data of purine analogs, prepared by us, we are able to present general rules for ^{1}H and ^{13}C NMR shifts. The signals of H-8 for the N9-isomer shifted upfield relative to the corresponding H-8 signal for the N7-isomer. The corresponding NH_2 signals are shifted downfield for the N9-isomer relative to the corresponding NH_2 signals for the N7-isomer. The ^{13}C NMR signals of C8 and C1' of the N9-isomers are shifted upfield relative to the corresponding signals of the N7-isomers. On the contrary, the signals of C5 are deshielded relative to those of the N7-alkylated compounds. The difference in the shift is most pronounced for the C5 signal, but the shift differences are easily detected for the other signals as well.

Similar ^{13}C shift differences have been reported for adenine, hypoxanthine and 6-mercaptopurine regio-isomeric derivatives[7e] and we have recently reported the use of ^{15}N NMR for similar purposes[8]. The carbon shifts have been assigned by ^{13}C-^{1}H spin coupling and with deuterium induced ^{13}C shift[9].

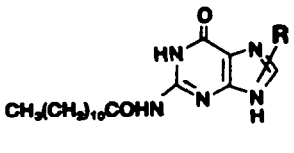
	Entry	X	R	H-8
N9	1a	OH	$CH_2CH_2CH_2CH_2OH$	7.72
N7	1b	OH	$CH_2CH_2CH_2CH_2OH$	7.87
N9	2a	$OCH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_2OAc$	7.87
N7	2b	$OCH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_2OAc$	8.08
N9	3a	$OCH_2CH_2OCH_3$	$CH_2(CH_2)_4CH_3$	7.87
N7	3b	$OCH_2CH_2OCH_3$	$CH_2(CH_2)_4CH_3$	8.08
N9	4a	$OCH_2CH_2OCH_3$	$CH_2CH_2CH_2CH_2OAc$	7.93
N7	4b	$OCH_2CH_2OCH_3$	$CH_2CH_2CH_2CH_2OAc$	8.08
N9	5a	$OCH_2CH_2OCH_3$	$CH_2C_6H_5$	7.98
N7	5b	$OCH_2CH_2OCH_3$	$CH_2C_6H_5$	8.32
N9	6a	Cl	$CH_2(CH_2)_4CH_3$	8.15
N7	6b	Cl	$CH_2(CH_2)_4CH_3$	8.40
N9	7a	Cl	$CH_2CH_2CHCH_2$ (O,O)	8.10
N7	7b	Cl	$CH_2CH_2CHCH_2$ (O,O)	8.36
N9	8a	Cl	$CH_2C_6H_5$ (O,O)	8.25
N7	8b	Cl	$CH_2C_6H_5$ (O,O)	8.51
N9	9a	H	$CH_2(CH_2)_4CH_3$	8.07
N7	9b	H	$CH_2(CH_2)_4CH_3$	8.27
N9	10a	H	$CH_2CH_2CHCH_2$ (O,O)	8.07
N7	10b	H	$CH_2CH_2CHCH_2$ (O,O)	8.27
N9	11a		$CH_2CH_2CH_2CH_2OAc$ (O,O)	7.65
N7	11b		$CH_2CH_2CH_2CH_2OAc$	7.7
N9	12a		$CH_2CH_2CH_2CH_2OAc$	7.67
N7	12b		$CH_2CH_2CH_2CH_2OAc$	7.90
N9	13a		$CH_2CH_2CH_2CH_2OAc$	7.68
N7	13b		$CH_2CH_2CH_2CH_2OAc$	7.80
N9	14a		$CH_2CH_2CH_2CH_2OAc$	7.91
N7	14b		$CH_2CH_2CH_2CH_2OAc$	8.08



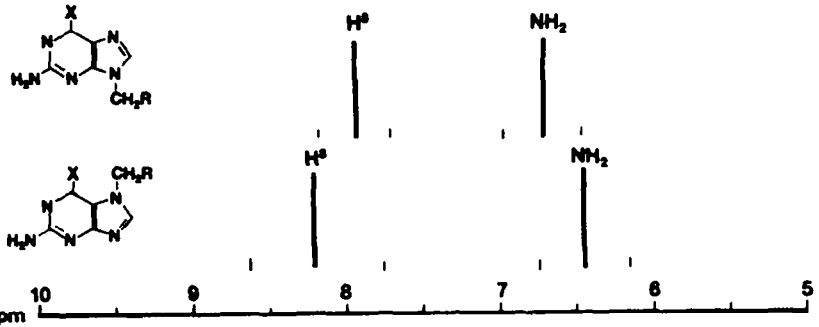
1a–10a



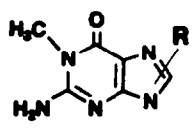
1b–10b



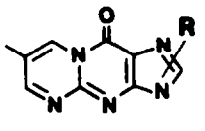
11a,11b



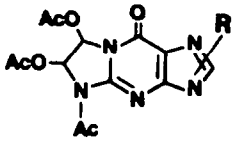
NH_2	C1'	C5	C8	Ref.
6.49	43.1	117.1	138.0	10
6.05	46.2	108.3	143.2	10
6.37	42.45	114.09	139.77	11
6.10	46.61	105.96	145.32	11
6.40	42.79	113.80	139.92	6
6.11	46.85	105.89	145.69	6
6.45	42.57	113.75	140.16	11
6.12	46.39	105.89	145.56	11
6.46	45.95	113.87	139.92	6
6.14	49.99	104.56	145.73	6
6.92	43.23	123.63	143.47	6
6.63	46.51	114.99	147.97	6
6.82	40.25	123.70	143.80	6
6.64	43.80	114.95	149.80	6
6.96	46.37	123.53	143.47	6
6.69	49.43	115.09	149.77	6
6.50				6
6.19				6
6.51	40.48	127.18	142.92	6
6.21	42.38	119.12	147.73	6
-	43.3	121.8	138.8	6
-	47.1	112.4	143.0	6
6.85	42.1	115.8	137.7	6
6.53	45.5	107.5	143.6	6
-	43.10	120.80	139.31	12
-	46.20	111.48	143.54	12
-	43.69	118.68	141.67	10
-	47.19	110.27	146.58	10



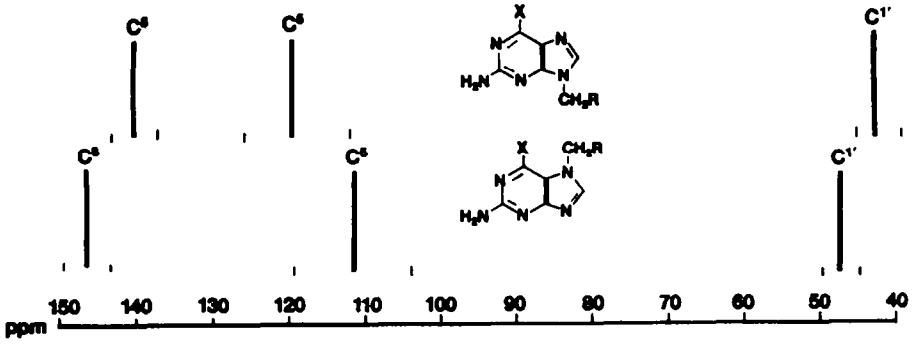
12a,12b



13a,13b



14a,14b



The table shows the δ values, relative to TMS, for some N9 and N7 substituted purine derivatives. Apart from the compounds 13a, 13b, 14a and 14b where $CDCl_3$ was used the solvent used in all cases was deuterated DMSO.

REFERENCES

1. H. J. Schaeffer, L. M. Beauchamp, P. de Miranda, G. B. Elion, D. J. Bauer, P. Collins, Nature (London), 272, 583 (1978).
2. A. Larsson, B. Öberg, S. Alenius, C.-E. Hagberg, N. G. Johansson, B. Lindborg, G. Stening, Antimicrob. Agents Chemother., 23, 664 (1983).
3. K. O. Smith, K. S. Galloway, W. S. Kennel, K. K. Ogilvie, B. K. Radatus, Antimicrob. Agents Chemother., 22, 55 (1982).
4. A. Larsson. Ph. D. Thesis. Biomedical Center, Uppsala University, 1985, and references therein.

5.a) T. A. Krenitsky, W. W. Hall, P. de Miranda, L. M. Beauchamp, H. J. Schaeffer, P. D. Whiteman, Proc. Natl. Acad. Sci. USA, 81, 3209 (1984).

b) J. C. Martin, G. A. Jeffrey, D. P. C. McGee, M. A. Tippie, D. F. Smee, T. R. Matthews, J. P. H. Verheyden, J. Med. Chem., 28, 358 (1985).

c) R. Datema, A.-C. Ericson, N. G. Johansson, J. Kjellberg, A. Larsson. Manuscript in preparation.

6. J. Kjellberg, N. G. Johansson. Manuscript submitted for publication to Nucleosides & Nucleotides and references therein.

7.a) B. Singer, Progress in Nucleic Acid Research and Molecular Biology, 15, Academic Press, 219 (1975).

b) J. Zemlicka, Nucleosides & Nucleotides, 3, 245 (1984).

c) K.K. Ogilvie, N. Nguyen-Ba, R. G. Hamilton, Can. J. Chem. 62, 1622 (1984).

d) H. C. Box, K. T. Lilja, J. L. Alderfer, J.B. French, J. Potienko, J. Carbohydrates Nucleosides Nucleotides, 6, 255 (1979).

e) M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, L. B. Townsend, J. Am. Chem. Soc., 97, 4636 (1975).

8. G. Remaud, J. Kjellberg, H. Bazin, N. G. Johansson, J. Chattopadhyaya. Manuscript accepted for publication in Tetrahedron.
9. C.-E. Hagberg. Manuscript presented at the 2nd Int. Conf. on Synthetic Oligonucleotides in Molecular Biology, August 18-24, 1985.
10. J. Kjellberg, C.-E. Hagberg, A. Malm, J. O. Norén, N. G. Johansson, Acta Chem Scand., B 40, 310 (1986).
11. J. Kjellberg, M. Liljenberg, N. G. Johansson, Tetrahedron Lett., 27, 877 (1986).
12. J. Kjellberg, N. G. Johansson, J. Heterocyclic Chem. 23, 625 (1986).