Aust. J. Chem., 1983, **36**, 633–8

The Preparation and ^{1}H N.M.R. Spectra of Some *N*-Methylpurines and Related Compounds

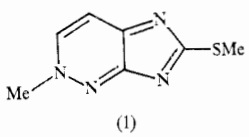
Gordon B. Barlin and M. David Fenn

Medical Chemistry Group, John Curtin School of Medical Research,
Australian National University, P.O. Box 334, Canberra City, A.C.T. 2601.

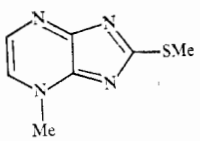
Abstract

A ^{1}H n.m.r. study of some methoxy-, methylthio- and chloro-*N*-methyl-purines and imidazo[4,5-*c*]-pyridines revealed that the signal due to the *N*-methyl group when present in the six-membered ring occurred at lower field than when present in the imidazole ring. The methylation of 2-, 6- and 8-methoxypurines with diazomethane, and metatheses of chloro-*N*-methylpurines each to methoxy-*N*-methylpurines are described.

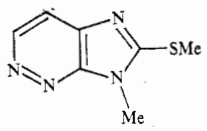
In earlier work[1,2] it was found than an *N*-methyl group when present in the six-membered ring of 6-methylthioimidazo[4,5-*c*]pyridazine[1] or 2-methylthioimidazo-[4,5-*b*]pyrazine[2] [for example compounds (1) and (2) respectively], gave a ^{1}H n.m.r. signal due to the *N*-methyl group at lower field than the corresponding compounds with the *N*-methyl group in the imidazole ring [e.g. (3) and (4)]. Published data for the *N*-methyl-2-methylthiopurines[3] are also consistent with these observations. We



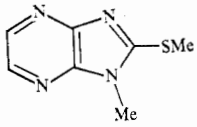
(1)



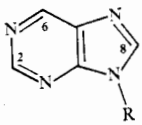
(2)



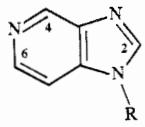
(3)



(4)



(5)



(6)

[1] Barlin, G. B., *Aust. J. Chem.*, 1981, **34**, 1361.
[2] Barlin, G. B., *Aust. J. Chem.*, 1982, **35**, 2299.
[3] Lister, J. H., *Aust. J. Chem.*, 1979, **32**, 2771.

0004-9425/83/030633$02.00

Table 1. ^{1}H n.m.r. spectra of purines (δ)

In the absence of couplings between *N*-methyl groups and aromatic protons, some aromatic proton signals could not be unambiguously assigned

Compound	Solvent	SMe	OMe	NMe	H2	H6	H8	*J* (Hz)
2-SMe-1-Me	$CDCl_3$[A]	2·78		4·08		9·22	8·55	
	Me_2SO	2·73		4·00		9·06	8·40	
2-SMe-7-Me	$CDCl_3$[A]	2·68		3·93		8·73	8·07	
	Me_2SO[A]	2·55		3·92		9·07	8·58	
2-SMe-9-Me	$CDCl_3$[A]	2·63		3·81		8·91	7·88	
	Me_2SO[A]	2·56		3·75		8·98	8·41	
6-SMe-3-Me	$CDCl_3$	2·81		4·20 d	8·28 d		8·30	$J_{2,3}$ 0·5
	D_2O	2·76		4·17	8·64		8·23	
	D_2O/DCl	2·89		4·31	9·05		8·77	
6-SMe-7-Me	$CDCl_3$	2·75		4·14	8·85		7·98	
	D_2O	2·64		4·02	8·51		8·22	
	D_2O/DCl	2·87		4·34 d	8·95		9·11 d	$J_{7,8}$ 0·5
6-SMe-9-Me	$CDCl_3$	2·74		3·89	8·75		7·94	
	D_2O	2·59		3·77	8·35		8·11	
	D_2O/DCl	2·95		4·07	9·11		8·99	
8-SMe-1-Me	$CDCl_3$	2·77		4·11	8·35 d	8·02 d		$J_{2,6}$ 2
	D_2O	2·68		4·19	8·68	8·49		
	D_2O/DCl	2·67		4·37	9·12	9·12		
8-SMe-3-Me	$CDCl_3$	2·78		4·17	8·34	8·64		
	D_2O	2·69		4·14	8·63	8·63		
	D_2O/DCl	2·92		4·35	9·09	9·09		
8-SMe-7-Me	$CDCl_3$	2·89		3·75	9·01	8·66		
	D_2O	2·78		3·71	8·76	8·71		
	D_2O/DCl	2·92		3·91	9·17	9·17		
8-SMe-9-Me	$CDCl_3$	2·83		3·73	8·92	8·85		
	D_2O	2·73		3·61	8·69	8·69		
	D_2O/DCl	2·87		3·87	9·19 d	9·09 d		$J_{2,6}$ 1
2-OMe-1-Me[B]	$CDCl_3$[B]		4·33	4·00		8·58	8·25	
2-OMe-7-Me	$CDCl_3$		4·09	3·95 d		8·71	8·06 d	$J_{7,8}$ 0·5
2-OMe-9-Me	$CDCl_3$		4·08	3·83		8·87	7·90	
6-OMe-3-Me[C]	$CDCl_3$		4·32	4·21 d	8·21 d		8·26	$J_{2,3}$ 0·5
	D_2O		4·22	4·11	8·55		8·13	
	D_2O/DCl		4·31	4·24 d	8·94 d		8·65	$J_{2,3}$ 0·5
	Me_2SO		4·21	4·10	8·74		8·05	
6-OMe-7-Me	$CDCl_3$		4·16	4·04 d	8·63		7·96 d	$J_{7,8}$ 0·5
	D_2O		4·05	3·91	8·33		8·14	
	D_2O/DCl		4·25	4·15	8·99		8·76	
	Me_2SO		4·09	3·98	8·52		8·41	
6-OMe-9-Me	$CDCl_3$[D]		4·20	3·89	8·56		7·91	
	D_2O		4·07	3·76	8·31		8·09	
	D_2O/DCl		4·22	4·04 d	8·74		9·32 d	$J_{8,9}$ 0·5
	Me_2SO		4·09	3·81	8·54		8·33	
8-OMe-7-Me	$CDCl_3$[B]		4·27	3·60	9·02	8·60		
8-OMe-9-Me	$CDCl_3$[D]		4·26	3·64	8·80	8·76		
8-Cl-3-Me	$CDCl_3$[C]			4·26	8·91	8·50		
8-Cl-7-Me	Me_2SO[E]			3·77	8·86	9·06		
8-Cl-9-Me	$CDCl_3$			3·87	9·02	8·97		
	D_2O			3·84	8·96	8·89		
	D_2O/DCl			4·01	9·41	9·37		

[A] Ref. 3. [B] Badger, R. J., and Barlin, G. B., *J. Chem. Soc., Perkin Trans. 2*, 1976, 1176. [C] Badger, R. J., and Barlin, G. B., *J. Chem. Soc., Perkins Trans. 1*, 1976, 151. [D] Reference cited in footnote[B] reports slightly different values. [E] Badger, R. J., and Barlin, G. B., *J. Chem. Soc., Perkin Trans. 2*, 1974, 1854.

have now extended these studies in various solvents to a significant number of purines (5) and imidazo[4,5-*c*]pyridines (6).

^{1}H N.M.R. Spectra

The ^{1}H n.m.r. spectra of the *N*-methylpurines and related compounds in chloroform (and other solvents where the availability of compound and literature data permitted comparisons) are recorded in Tables 1 and 2. For the compounds examined in (D)chloroform, the signal due to the *S*-methyl group appeared in the range δ 2·63–2·89 and *O*-methyl in the range 4·08–4·33.

Table 2. ^{1}H n.m.r. spectra of imidazo[4,5-*c*]pyridines (δ)

See subtitle to Table 1

Compound	Solvent	SMe	OMe	NMe	H2	H4	H6	H7	*J* (Hz)
2-SMe-1-Me	$CDCl_3$	2·83		3·67		8·94	8·36 d	7·18 d	$J_{6,7}$ 5
	D_2O	2·64		3·38		8·44	8·08 d	7·09 d	$J_{6,7}$ 5·5
	D_2O/DCl	2·89		3·89		9·02	8·55 d	8·04 d	$J_{6,7}$ 6·5
2-SMe-3-Me	$CDCl_3$	2·83		3·75		8·64	8·39 d	7·55 d	$J_{6,7}$ 5·5
	D_2O	2·76		3·75		8·66	8·29 d	7·57 d	$J_{6,7}$ 4
	D_2O/DCl	3·00		3·99		9·28	8·61 d	8·14 d	$J_{6,7}$ 6·5
2-SMe-5-Me	$CDCl_3$	2·77		4·14		8·16	7·50	7·50	
	D_2O	2·67		4·17		8·35	7·85 d	7·42 d	$J_{6,7}$ 7
	D_2O/DCl	2·91		4·45		9·13	8·56 d	8·03 d	$J_{6,7}$ 7
2-OMe-1-Me	$CDCl_3$		4·24	3·58		8·80	8·35 d	7·11 d	$J_{6,7}$ 5·5
	D_2O		4·17	3·52		8·51	8·21 d	7·31 d	$J_{6,7}$ 5·5
2-OMe-3-Me	$CDCl_3$		4·25	3·63		8·52	8·37 d	7·44 d	$J_{6,7}$ 5·5
	D_2O		4·19	3·60		8·51	8·25 d	7·45 d	$J_{6,7}$ 5·5
	D_2O/DCl		4·38	3·78		8·92	8·48 d	7·93 d	$J_{6,7}$ 6·5
6-Cl-1-Me	$CDCl_3$			3·84	7·90	7·38 d		8·85 d	$J_{4,7}$ 1
	D_2O			3·81	8·19	7·50		8·53	
	D_2O/DCl			4·12	8·17	9·06		9·29	
6-Cl-3-Me	$CDCl_3$			3·94	7·98	7·71 d		8·59 d	$J_{4,7}$ 1
	D_2O			3·90	8·27	7·33		8·49	
	D_2O/DCl			4·26	9·50	8·09		9·14	
6-Cl-5-Me	$CDCl_3$			4·24	8·55	7·88		8·59	
	D_2O			4·29	8·46	7·99 d		8·94 d	$J_{4,7}$ 1
	D_2O/DCl			4·50	8·48	9·12 d		9·57 d	$J_{4,7}$ 0·5

The ^{1}H n.m.r. spectra of the *N*-methyl derivatives of the methylthio-, methoxy- or chloro-purines or imidazo[4,5-*c*]pyridines confirmed the pattern for the *N*-methyl group observed previously. The *N*-methyl group when present in the pyrimidine ring of purines or the pyridine ring of imidazo[4,5-*c*]pyridines gave a signal in the range δ 4·00–4·26 but when present in the imidazole ring the signal appeared in the region 3·58–3·94 except for 7-methyl-6-methylthio- and 6-methoxy-7-methyl-purines which gave values of 4·14 and 4·04 respectively (models show steric hindrance between the 7-methyl group and the 6-methylthio or methoxy substituent). For each series, where a direct comparison of the *N*-methyl derivatives was possible, the observed signal due to the *N*-methyl group in the six-membered ring was always downfield of that when present in the imidazole ring.

A similar correlation was observed for solutions in deuterium oxide.

In deuterium oxide/deuterium chloride solutions the situation was more complicated. For example, the signal due to the *N*-methyl group in 7-methyl-6-methylthiopurine was observed at lower field than in 3-methyl-6-methylthiopurine. This apparent inconsistency is attributed to significant differences in the sites of protonation and cationic structures of these two compounds.[4]

Although it was not possible to assign unambiguously all ring protons recorded in Tables 1 and 2 the signal for H 6 of the 2-methylthioimidazo[4,5-*c*]pyridine in a given solvent was, as expected, upfield of that H 2 of the corresponding 8-methylthiopurine. A similar observation applied to the methoxy analogues.

Preparation of Compounds

Although the methylation of 2-, 6- and 8-methylthiopurines with diazomethane has been described,[3,5,6] similar methylations of 2-, 6- or 8-methoxypurines have not previously been examined. 2-Methoxypurine (prepared from its chloro-analogue[7]) with diazomethane gave mainly 2-methoxy-9-methylpurine together with *c.* 10% of the 7-methyl isomer. 6-Methoxypurine gave the 3-, 7- and 9-methyl derivatives in the ratio of 29 : 32 : 39; and 8-methoxypurine[8] gave the 9-methyl derivative as the only significant product. Unambiguous syntheses of 2-methoxy-7-(and 9)-methylpurine, 6-methoxy-7-(and 9)-methylpurine and 8-methoxy-9-methylpurine were effected from reaction of the known chloro analogues[9–13] with methoxide ions. The methylthio-*N*-methylpurines,[6,10,14] 8-chloro-3-methylpurine,[6] 8-chloro-9-methylpurine[12] and imidazo[4,5-*c*]pyridines[14–16] were prepared as described previously.

Experimental

Solids for analyses were dried at 100°, and melting points were taken in Pyrex capillaries. Analyses were performed by the Australian National University Analytical Services Unit. ^{1}H n.m.r. spectra were recorded at 90 MHz and 30° with a Jeol FX90Q Fourier transform spectrometer with tetramethylsilane as internal standard in chloroform and dimethyl sulfoxide solutions and sodium trimethylsilylpropane-1-sulfonate in aqueous solutions.

2-Methoxy-7-methylpurine

2-Chloro-7-methylpurine[9,10] (0·020 g) and sodium methoxide solution (0·6 ml; from 0·2 g sodium and 4·0 ml methanol) were mixed and allowed to stand at 20° for 4 days. The mixture was diluted with water, adjusted to pH 5·5, evaporated to dryness, the residue extracted with chloroform and the product crystallized from benzene to give *2-methoxy-7-methylpurine* (0·012 g), m.p. 191–192° (Found: C, 51·5; H, 4·8; N, 34·1. $C_7H_8N_4O$ requires C, 51·2; H, 4·9; N, 34·1%).

[4] Reichmann, U., Bergmann, F., Lichtenberg, D., and Neiman, Z., *J. Chem. Soc., Perkin Trans. 1*, 1973, 793.
[5] Brown, D. J., and Ford, P. W., *J. Chem. Soc. C*, 1969, 2620.
[6] Badger, R. J., and Barlin, G. B., *J. Chem. Soc., Perkin Trans. 1*, 1976, 151.
[7] Montgomery, J. A., *J. Am. Chem. Soc.*, 1956, **78**, 1928.
[8] Brown, D. J., and Mason, S. F., *J. Chem. Soc.*, 1956, 682.
[9] Fischer, E., *Ber. Dtsch. Chem. Ges.*, 1897, **30**, 2400.
[10] Badger, R. J., and Barlin, G. B., *J. Chem. Soc., Perkin Trans. 2*, 1974, 1854.
[11] Beaman, A. G., and Robins, R. K., *J. Org. Chem.*, 1963, **28**, 2310.
[12] Barlin, G. B., and Chapman, N. B., *J. Chem. Soc.*, 1965, 3017.
[13] Prasad, R. N., and Robins, R. K., *J. Am. Chem. Soc.*, 1957, **79**, 6401.
[14] Badger, R. J., and Barlin, G. B., *J. Chem. Soc., Perkin Trans. 2*, 1976, 1176.
[15] Barlin, G. B., *J. Chem. Soc., B*, 1966, 285.
[16] Barlin, G. B., and Fenn, M. D., *Aust. J. Chem.*, 1981, **34**, 1341.

2-Methoxy-9-methylpurine

This compound was prepared from 2-chloro-9-methylpurine[11,12] (0·020 g) with sodium methoxide similarly to the 7-methyl isomer above. The product was recrystallized from cyclohexane to give *2-methoxy-9-methylpurine* (0·014 g), m.p. 140–141° (Found: C, 51·1; H, 4·8; N, 34·2%).

2-Methoxypurine

2-Chloropurine[7] (0·811 g) and sodium methoxide solution (from 0·8 g sodium and 16 ml methanol) were heated in a sealed bomb at 150–155° for 3·5 h. The reaction mixture was diluted with water, adjusted to pH 5, evaporated to dryness, and the product recrystallized from water to give 2-methoxypurine (0·536 g), m.p. 217–219° (lit.[17] 205–206°) (Found: C, 47·7; H, 4·0; N, 36·8. Calc. for $C_6H_6N_4O$: C, 48·0; H, 4·0; N, 37·3%).

2-Methoxypurine with Diazomethane

2-Methoxypurine (0·450 g) was added to a solution of diazomethane in ether (from 3·0 g nitrosomethylurea) and the mixture allowed to stand at 20° for 4 days. The reaction mixture was evaporated to dryness, and ^{1}H n.m.r. spectroscopy (in $CDCl_3$) revealed the major product to be 2-methoxy-9-methylpurine together with *c.* 10% 2-methoxy-7-methylpurine as the only significant by-product. T.l.c. (alumina/chloroform) gave at higher R_F 2-methoxy-9-methylpurine (0·144 g; from cyclohexane), m.p. 137°, and the band at slightly lower R_F, after further t.l.c. (silica/ethyl acetate), gave 2-methoxy-7-methylpurine (0·006 g) (from benzene), m.p. 190·5–192°; both identical (^{1}H n.m.r.) with the products described above.

6-Methoxy-7-methylpurine

6-Chloro-7-methylpurine[13] (0·030 g) and sodium methoxide solution were allowed to stand at 20° for 30 min and the product isolated as described above. It was recrystallized from benzene to give *6-methoxy-7-methylpurine* (0·013 g), m.p. 182–184° (Found: C, 51·1; H, 4·9; N, 34·3%).

6-Methoxy-9-methylpurine

6-Chloro-9-methylpurine[12] (0·018 g) was allowed to react with sodium methoxide as described for the 7-methyl isomer. The product was recrystallized from cyclohexane to give *6-methoxy-9-methylpurine* (0·013 g), m.p. 150–151° (Found: C, 51·1; H, 5·3; N, 33·9%).

6-Methoxypurine with Diazomethane

6-Methoxypurine (0·5 g; Sigma) was added to a solution of diazomethane in ether (from 4·1 g nitrosomethylurea) and the mixture allowed to stand at 20° for 4·5 h, then evaporated to dryness. An examination of the ^{1}H n.m.r. spectrum in (D)chloroform of the crude product revealed the presence of the 3-, 7- and 9-methyl isomers in the ratio of 29 : 32 : 39. The crude product was boiled with cyclohexane, the insoluble solid (0·168 g) consisting of the 3-, and 7-methyl isomers was filtered off, and the filtrate on cooling gave a crystalline solid (0·313 g) consisting of a mixture of 3-, 7- and 9-methyl isomers.

The 6-methoxy-9-methylpurine was separated at higher R_F on t.l.c. (alumina/chloroform) and recrystallized from cyclohexane and the 7-methyl isomer was best separated at higher R_F on t.l.c. (silica/acetone) from the 3-methyl isomer and recrystallized from benzene.

8-Methoxy-9-methylpurine

8-Chloro-9-methylpurine[12] (0·020 g) and sodium methoxide were allowed to react at 20° for 1 h. This mixture was adjusted with methanolic hydrogen chloride until a test sample in water was pH 8, then it was worked up as for its isomers. The product recrystallized from cyclohexane gave 8-methoxy-9-methylpurine (0·010 g), m.p. 149–150° (lit.[14] 149–151°) (Found: C, 51·3; H, 5·0; N, 34·1%).

[17] Albert, A., and Brown, D. J., *J. Chem. Soc.*, 1954, 2060.

8-Methoxypurine was prepared from 8-methylthiopurine (EGA), through 8-methylsulfonylpurine,[14] followed by reaction with methoxide ion.[8]

8-Methoxypurine with Diazomethane

8-Methoxypurine was treated with ethereal diazomethane similarly to the way described above for its isomers. The crude product was subjected to t.l.c. (alumina/chloroform) and gave 8-methoxy-9-methylpurine, m.p. 148° (from cyclohexane), as the only significant product.

Acknowledgment

We thank Dr D. J. Brown for helpful discussion.

Manuscript received 20 December 1982

Corrigendum

Volume 35, Number 9

Page 1919, Scheme 5. *For* the central formula which is numbered (18a,i) or (22b,i) *read* (18a,i) or (18b,i).

Page 1923, heading in (*k*). *For* name of compound (18) *read* 7-ethenyl-8ξ-methyl-1,4-dioxaspiro-[4,5]decan-7-ol.