A Carbon-13 and Proton Nuclear Magnetic Resonance Study of 5,6-Dihydro-2-methyl-1,4-oxathiin Derivatives

By **Michael J. McGlinchey** * and **Brian G. Sayer**, McMaster University, Department of Chemistry, Hamilton, Ontario L9G 1R4, Canada
Francis I. Onuska * and **Michael E. Comba**, Canada Centre for Inland Waters, Analytical Methods Research Section, Burlington, Ontario L7R 4A6, Canada

Proton and carbon-13 n.m.r. spectral data for a series of 5,6-dihydro-2-methyl-1,4-oxathiins and the corresponding 4-oxide and 4,4-dioxide derivatives are reported. Results show that while the oxathiins and the 4,4-dioxide derivatives are conformationally mobile, the 4-oxide derivatives preferentially adopt the conformer which possesses an axial oxide.

THE major thrust of environmental programmes has been directed toward studies related to undesirable chlorinated and polynuclear aromatic hydrocarbon contaminants. The recent introduction of sulphur-containing compounds as substitutes for environmentally unfavourable compounds necessitates a greater awareness of their chemical, physical, and biological properties. Analytical data on sulphur-containing compounds, in particular 1,4-oxathiins, is virtually non-existent, and as part of our continuing studies, mass spectrometry[1,2] and liquid and thin layer chromatography[3,4] have been employed. Proton and carbon-13 n.m.r. data are now presented for a series of 5,6-dihydro-1,4-oxathiin metabolites or possible photoalteration products. It is hoped that elucidation of their structural conformation will prove invaluable in assessing their toxicological and metabolic activities.

EXPERIMENTAL

Carbon-13 n.m.r. spectra were obtained on a Bruker WH 90 spectrometer operating at 22.62 MHz at 32 °C. Concentrations of 0.3—0.4M were used in [$^2H_6$]dimethyl sulphoxide as the solvent; tetramethylsilane was used as an internal standard. Field-frequency stabilization was achieved by ' locking ' to the deuterium signal of the solvent.

Typically 3 000 (15°) pulses were required for proton noise decoupled spectra and transforms involving 8 K (real) data points were employed.

Proton spectra were obtained with a Varian HA 100 spectrometer operating at 100 MHz at 35 °C and a homonuclear lock was employed to achieve field-frequency stabilisation.

Spectral simulation was performed with a Nicolet 1080 computer using NIC-17-30712 iterative n.m.r. program.

Preparations.—5,6-Dihydro-2-methyl-1,4-oxathiin derivatives (I)—(XIII) were prepared by standard synthetic

---

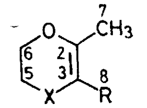
[1] F. I. Onuska, A. G. Harrison, and M. E. Comba, *Biomedicin. Mass Spectrometry*, 1976, **3**, 248.

[2] F. I. Onuska and A. G. Harrison, *Org. Mass Spectrometry*, 1978, **13**, 35.

[3] A. W. Wolkoff, F. I. Onuska, M. E. Comba, and R. H. Larose, *Analyt. Chem.*, 1975, **47**, 754.

[4] F. I. Onuska and M. E. Comba, *J. Chromatog.*, 1975, **100**, 247.

procedures,[5-8] 5,6-dihydro-2-methyl-1,4-oxathiin 4-oxide derivatives (sulphoxides) were prepared according to Leonard and Johnson,[7] and the subsequent 5,6-dihydro-2-methyl-1,4-oxathiin 4,4-dioxides (sulphones) according to the procedure outlined by Kulka *et al.*[5]



(I)	R = H,	X = S
(II)	R = CO_2H,	X = S
(III)	R = CO_2H,	X = SO
(IV)	R = CO_2H,	X = SO_2
(V)	R = CONHPh,	X = S
(VI)	R = CONHPh,	X = SO
(VII)	R = CONHPh,	X = SO_2
(VIII)	R = $CON(CH_3)Ph$,	X = S
(IX)	R = $CON(CH_3)Ph$,	X = SO
(X)	R = $CON(CH_3)Ph$,	X = SO_2
(XI)	R = CONH-*p*-$C_6H_4CH_3$,	X = S
(XII)	R = CONH-*p*-$C_6H_4CH_3$,	X = SO
(XIII)	R = CONH-*p*-$C_6H_4CH_3$,	X = SO_2

RESULTS AND DISCUSSION

Recent studies on sulphur-containing heterocycles have focused on the changes in chemical shifts and coupling constants brought about by oxidation at sulphur.[9-11] In particular, the role of the sulphoxide group, the anisotropy of which has been likened to the acetylenic functionality,[12] has been studied with a view to probing molecular conformations.[13,14] Thus, in the thian 1-oxide system, the conformational equilibrium slightly favours the axial conformer;[15] however, the sulphoxide oxygen can be locked in either the axial or equatorial position by use of a bulky substituent at the 4-position and these configurations are readily differentiated by ^{13}C n.m.r. spectroscopy.[11,14]

TABLE 1

Proton chemical shifts * of 5,6-dihydro-2-methyl-1,4-oxathiins and their corresponding 4-oxides and 4,4-dioxides

Compound	Solvent	5eq-H	5ax-H	6eq-H	6ax-H	3-H	CH_3	Aryl	NCH_3	$ArCH_3$
(I)	$CDCl_3$	2.86	2.86	4.24	4.24	4.75	1.78			
(II)	DMSO	2.94	2.94	4.26	4.26		2.22			
(III)	DMSO	3.01	2.77	4.66	4.24		2.35			
(IV)	DMSO	3.52	3.52	4.68	4.68		2.24			
(V)	DMSO	3.24	3.24	4.28	4.28		2.01	*ca.* 7.3		
(VI)	DMSO	3.13	2.82	4.67	4.19		2.14	*ca.* 7.3		
(VII)	DMSO	3.59	3.59	4.74	4.74		2.02	*ca.* 7.3		
(VIII)	DMSO	2.77	2.77	4.01	4.01		1.65	7.32	3.24	
	$CDCl_3$	2.73	2.73	4.08	4.08		1.84	7.36	3.44	
(IX)	DMSO	2.99	2.54	4.46	3.88		1.67	7.26	3.35	
	$CDCl_3$	2.86	2.47	4.35	4.17		1.71	7.32	3.34	
(X)	DMSO	3.50	3.50	4.56	4.56		1.72	7.37	3.32	
	$CDCl_3$	3.18	3.18	4.59	4.59		1.83	7.35	3.43	
(XI)	DMSO	3.02	3.02	4.16	4.16		1.98	*ca.* 7.3		2.23
(XII)	DMSO	3.09	2.79	4.64	4.17		2.10	*ca.* 7.3		2.24
(XIII)	DMSO	3.50	3.50	4.71	4.71		2.00	*ca.* 7.3		2.26

* Chemical shifts in are relative to Me_4Si and considered to be within ± 0.03 p.p.m.

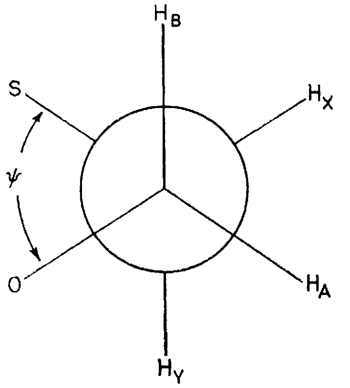


FIGURE 1 Newman projection along the C-5–C-6 axis of 5,6-dihydro-1,4-oxathiin

In a close analogue to our system, Kitchin and Stoodley[10] have found that 2,3-dihydro-6-methoxycarbonyl-1,4-thiazine 1-oxides prefer to form the conformer which possesses an axial oxide. They also found that axial protons at the 2-position resonated upfield of the equatorial protons, but that the 3-proton was deshielded when it could adopt a *syn*-axial position relative to the sulphoxide moiety. In the 5,6-dihydro-2-methyl-1,4-oxathiin 4-oxides studied, the axial protons at both C-5 and -6 are upfield of their equatorial partners (see Table 1).

Interestingly, in heteroanalogues of cyclohexane, axial protons are generally observed at lower field than the equatorial protons. Thus, in 1,4-oxathian 4-oxide, where the sulphoxide oxygen adopts an axial position,[9]

---

[5] M. Kulka, D. S. Thiara, and W. A. Harrison, U.S.P. 3,393,202/1968.

[6] B. Von Schmeling, M. Kulka, D. S. Thiara, and W. A. Harrison, U.S.P. 3,249,499/1966.

[7] N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, 1962, **27**, 272.

[8] M. A. Corbiel, M. Curcumelli, R. J. Fanning, B. A. Graham, M. Kulka, and J. B. Pierce, *Canad. J. Chem.*, 1973, **51**, 2650.

[9] W. A. Szarek, D. M. Vyas, A-M. Sepulchre, S. D. Gero, and G. Lukacs, *Canad. J. Chem.*, 1974, **52**, 2041.

[10] J. Kitchin and R. J. Stoodley, *Tetrahedron*, 1973, **29**, 3023.

[11] G. Barbarella, P. Dembech, A. Garbesi, and A. Fava, *Org. Magnetic Resonance*, 1976, **8**, 108.

[12] D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, 1971, **36**, 1314 and references therein.

[13] R. Lett and A. Marquet, *Tetrahedron*, 1974, **30**, 3365.

[14] G. W. Buchanan and T. Durst, *Tetrahedron Letters*, 1975, 1683.

[15] J. B. Lambert and R. G. Keske, *J. Org. Chem.*, 1966, **31**, 3429.

the *syn*-axial protons at C-3 and -5 are deshielded relative to the corresponding equatorial protons. However, caution is advised since so-called ' reversed shifts ' have been observed in dithians.[16]

It has been shown [10] that dihydro-1,4-thiazines with an axial oxygen atom at sulphur, and an equatorial substituent at C-3 may be characterised by the following coupling constants (substitute N for O in Figure 1), $J_{B,Y}$ 12.6—13.6, $J_{B,X}$ 1.7—3.0 Hz. In the present study, the 5,6-dihydro-2-methyl-1,4-oxathiin 4-oxides exhibit coupling constants in the ranges 12.9—13.2 for $J_{B,Y}$ and 1.3—1.7 Hz for $J_{B,X}$; hence it seems not unreasonable to assume that the sulphoxide oxygen adopts the axial position preferentially, and perhaps exclusively.

Since the coupling constants from these ABXY systems were readily obtained (and verified by computer simulation), it seemed worthwhile to calculate approximate bond angles by assuming that a Karplus-type equation [17] could be applied to the four vicinal couplings in the same molecule. Over the past decade, the *R* value method [18,19] has been widely adopted and its utility has been demonstrated for larger systems [20] than the six-membered cyclic molecules to which it was originally applied. In the present instance, for sulphoxides (III), (VI), (IX), and (XII), the values of $(J_{B,Y} + J_{A,X})/(J_{A,Y} + J_{B,X})$ leads to dihedral angles, ψ, varying from 63.8 to 64.3°. The mean internal dihedral angle of *ca.* 64° indicates the oxathiin 4-oxide ring system to be rather highly puckered.

It has been suggested [21] that the closely analogous 1,4-thiazine 1-oxide systems have an almost planar arrangement of atoms 1 and 3—6 with the methylene group at C-2 above the plane in a ' sofa ' conformation. If such an arrangement was extant in the oxathiin 4-oxide series, then, assuming normal values for the bond lengths, the C–O–C angles would be *ca.* 127°.[22] This rather large angle to be expected at oxygen presumably militates against an almost planar conformation in the oxathiin series.

In contrast to the 5,6-dihydro-2-methyl-1,4-oxathiin 4-oxide series (sulphoxides) in which the molecule was assigned a dominant conformation, the corresponding 5,6-dihydro-2-methyl-1,4-oxathiins (sulphides) and 5,6-dihydro-2-methyl-1,4-oxathiin 4,4-dioxides (sulphones) were conformationally mobile, analogous to the behaviour of the corresponding oxathian derivatives,[9] and gave rise to AA'XX' proton spectra (see Figure 2). Unambiguous assignment of such spectra is particularly difficult and, in the case of the sulphide [compound (VIII)], analysis was facilitated by measuring coupling constants for compound (I) in which the 3-position was unsubstituted. In this case, a spectrum was obtained from the neat liquid and then at greater magnitude (× 100) in order to observe the weaker outer transitions. Differentiation of these weak transitions from impurity signals was achieved by removing the long range coupling from the proton at C-3. Computer simulation was then achieved by matching the low intensity signals as well as those of normal intensity. Small changes in chemical shifts were observed upon cooling sulphide (VIII), sulphoxide (IX), and sulphone (X); however coupling constants remained essentially unchanged. In the case of sulphone (X), chemical shifts became sufficiently different at —30 °C to benefit computer analysis.

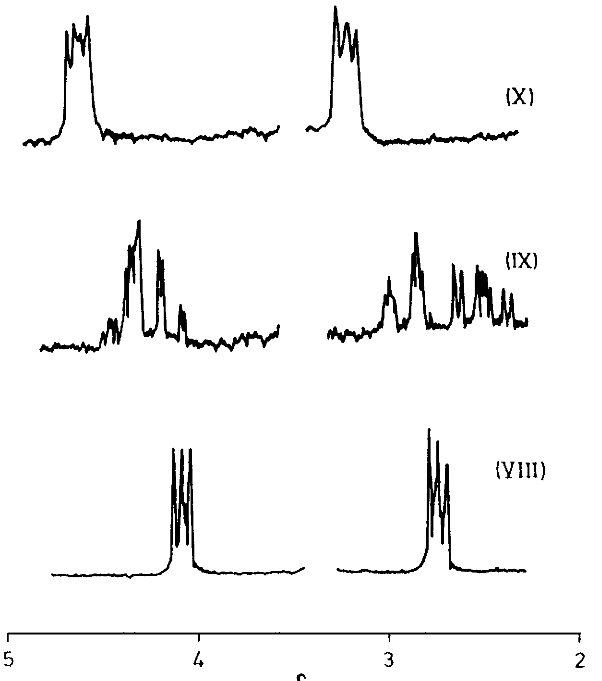


FIGURE 2 ^{1}H N.m.r. spectra (5- and 6-H) of 5,6-dihydro-2-methyl-1,4-oxathiin-3-*N*-methylcarbanilide (VIII), its 4-oxide (IX), and 4,4-dioxide (X) in $CDCl_3$

Some data listed in Table 2 have sizeable error limits and hence supposed differences in J_{AX} and $J_{A'X'}$ are not considered meaningful as such systems would be expected

TABLE 2

Coupling constants (Hz) of the protons at C-5 and -6 in 5,6-dihydro-2-methyl-1,4-oxathiins

Compound	$J_{A,B}$	$J_{A,X}$	$J_{A,Y}$	$J_{B,X}$	$J_{B,Y}$	$J_{X,Y}$	Error (Hz)
(I)	−12.5	6.0	2.5	2.0	8.0	−14.5	±2.0
(III)	−11.9	2.9	3.1	1.7	13.2	−14.5	±0.2
(VI)	−11.9	2.9	3.2	1.5	13.0	−14.8	±0.2
(VIII)	−13.0	7.0	3.0	2.0	7.0	−14.0	±2.0
(IX)	−11.5	2.8	3.3	1.3	13.2	−14.5	±0.2
(X)	−14.5	9.0	3.0	3.5	7.5	−15.0	±2.0
(XII)	−12.3	2.8	3.2	1.5	12.9	−14.7	±0.2

---

[16] E. L. Eliel, V. S. Rao, and F. G. Riddell, *J. Amer. Chem. Soc.*, 1976, **98**, 3583.

[17] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11; *J. Amer. Chem. Soc.*, 1963, **85**, 2870.

[18] H. R. Buys, *Rec. Trav. chim.*, 1969, **88**, 1003.

[19] J. B. Lambert, *Accounts Chem. Res.*, 1971, **4**, 87.

[20] C. Krieger, E. Langer, and H. Lehner, *Monatsh.*, 1976, **107**, 19.

[21] A. R. Dunn, I. McMillan, and R. J. Stoodley, *Tetrahedron*, 1968, **24**, 2895.

[22] Local version of COORD, P. E. Stevenson and J. E. Merrill, Atomic Cartesian Coordinates for Molecules, Program 186, Quantum Chemistry Program Exchange, Indiana University, 1971.

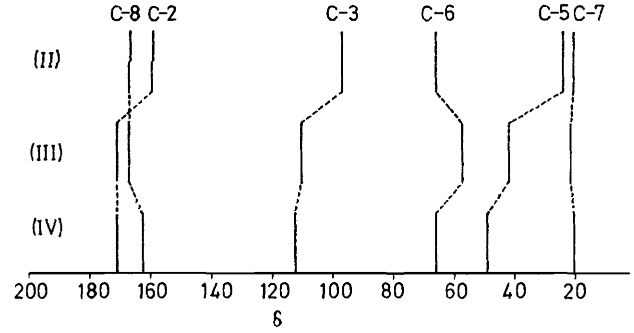


FIGURE 3 Carbon-13 chemical shift correlations for 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid (II), its 4-oxide (III), and 4,4-dioxide (IV)

to exhibit only two vicinal coupling constants under conditions of rapid interconversion. The signs of the geminal coupling constants were not determined and were assumed to be negative. The averaged coupling constants observed for the sulphide and sulphone are not unreasonable in the light of the *J* values obtained for the conformationally fixed sulphoxide and attempts to stop the conformational interconversion for the sulphide and sulphone were unsuccessful even at —70 °C.

TABLE 3

Carbon-13 chemical shifts * of 5,6-dihydro-2-methyl-1,4-oxathiins and their corresponding 4-oxides and 4,4-dioxides

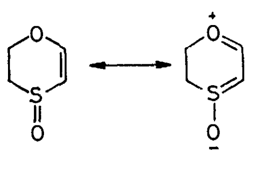
	1,4-Oxathiin ring						Aromatic ring					
Compound	C-2	C-3	C-5	C-6	C-7	C=O	C-1	C-2, -6	C-3, -5	C-4	NCH_3	$ArCH_3$
(I)	147.4	86.7	24.2	65.9	21.6							
(II)	159.3	97.0	24.1	66.4	21.1	166.7						
(III)	170.9	110.3	42.1	57.4	21.6	166.3						
(IV)	170.8	112.4	49.1	66.0	20.7	162.5						
(V)	149.6	98.7	24.1	65.5	19.9	164.1	138.5	119.3	128.1	123.0		
(VI)	161.7	115.3	42.9	56.9	20.3	163.9	139.0	119.5	128.8	123.7		
(VII)	161.3	114.8	48.4	65.6	19.4	157.4	138.0	119.2	128.3	123.6		
(VIII)	145.7	98.3	24.0	65.3	19.3	166.1	143.1	125.2	128.1	126.1	36.9	
(IX)	158.6	112.6	43.2	56.7	19.8	166.1	143.6	126.5	128.6	126.5	37.4	
(X)	159.4	113.0	47.9	65.8	19.5	160.1	143.0	125.8	128.9	126.9	37.6	
(XI)	149.4	99.7	24.2	65.5	19.9	163.9	136.0	119.4	128.4	131.9		20.3
(XII)	161.5	115.3	42.9	56.9	20.4	163.7	136.5	119.5	129.1	132.7		20.3
(XIII)	161.7	115.2	48.4	65.8	19.5	157.7	136.0	119.6	129.2	133.1		20.4

* Chemical shifts (δ) are relative to Me_4Si and considered to be within ±0.1 p.p.m.

^{13}C N.m.r. data (Table 3) allow a comparison of the effects on neighbouring saturated and unsaturated carbon atoms brought about by functionalisation at sulphur. Assignment of carbon-13 chemical shifts was essentially straightforward and any ambiguities were resolved by gated decoupling techniques. A carbon-13 chemical shift correlation diagram for the series 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid is given in Figure 3 and is typical of the trends observed with all the compounds studied.

The behaviour of the saturated portion (C-5 and -6) of the molecule, where the geometry is more cyclohexane-like, closely parallels that reported for the thian,[11] 1,4-oxathian,[9] and thiochroman-4-one systems.[23] The C-5 resonances in the 5,6-dihydro-2-methyl-1,4-oxathiin 4-oxide series showed downfield shifts (relative to the parent sulphide) of *ca.* 19 p.p.m. attributable to the β effect of the sulphoxide oxygen. This unusually large β effect associated with the sulphoxide oxygen has also been observed in acyclic molecules.[11] The upfield shift (*ca.* 8.7 p.p.m.) at C-6 upon conversion into the sulphoxide is very similar to that found in the corresponding oxathian (9.5 p.p.m.),[9] where the oxygen atom is known to adopt an axial configuration. Interestingly, the γ effect of the oxygen of the sulphoxide group in *cis*- and *trans*-4-t-butylthian 1-oxide (14) shows the shift at C-3 and -5 for the isomer with the axial oxide to be 7.5 p.p.m. to higher field than in its equatorial counterpart. Hence, the observed shift in the 5,6-dihydro-1,4-oxathiin 4-oxide system is almost certainly too large to be attributed to a γ-oxygen disposed equatorially. Conversion into the sulphone results in a downfield shift at both C-5 and -6 as is to be expected from studies on the oxathian system.[9]

In comparison, the olefinic carbons in 5,6-dihydro-2-methyl-1,4-oxathiins display the expected deshielding at C-3 for the sulphoxide relative to the sulphide, but the 12 p.p.m. downfield shift at C-2 deserves comment in view of the fact that it does not occur in the thiochroman-4-one series.[23] The extent of the deshielding implies the presence of a neighbouring atom of relatively high electronegativity; if one were to postulate (see below) a sizeable contribution from a structure such as (XIV), then the deshielding at C-2 would not be unreasonable. Such a contribution would not, of course, be expected in the thiochroman-4-one analogue.



(XIV)

The conversion of the sulphoxides to sulphones has a smaller effect at C-2 and -3 than is observed for C-5 and -6; this emphasises the somewhat unpredictable behaviour of the sulphone functionality. Finally, the increase in shielding of C-8 (the carbonyl carbon at C-3)

---

[23] M. S. Chauhan and I. W. J. Still, *Canad. J. Chem.*, 1975, **53**, 2880.

upon converting the sulphoxide into the sulphone is mildly surprising, but may be due to an S=O : C=O interaction somewhat analogous to the *gauche* O,O effect discussed by Perlin *et al.* for a number of carbohydrates.[24]

Conclusions.—Qualitative similarities in conformational behaviour have been observed between cyclohexene and its heteroanalogues,[25] and the data presented here for 5,6-dihydro-2-methyl-1,4-oxathiins support this view. Hence, both proton and carbon-13 n.m.r. spectra show that the 4-oxide derivatives exist predominantly, if not entirely, with the S=O bond in an axial configuration. The sulphide and sulphone derivatives of the 5,6-dihydro-2-methyl-1,4-oxathiins are, however, conformationally mobile analogous to 1,4-oxathians.[9]

Use of the *R* value method to obtain conformational data from vicinal coupling constants predicts that the ring is puckered with a mean internal torsional angle of *ca.* 64°.

We thank Dr. F. G. Riddell, University of Stirling, for helpful advice on the early stages of this work.

[7/1357 *Received*, 26*th July*, 1977]

---

[24] A. S. Perlin, B. Casu, and H. J. Koch, *Canad. J. Chem.*, 1970, **48**, 2596.

[25] H. Labaziewiecz, F. G. Riddell, and B. G. Sayer, *J.C.S. Perkin II*, 1977, 619.