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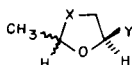
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Received February 12, 1986

Carbon-13 nmr spectra of several 1,3-oxathiolane, 1,3-oxathiolane-3-oxide and 1,3-oxathiolane-3,3-dioxide derivatives are reported. Relationships between some stereochemical features and chemical shift are discussed.

*J. Heterocyclic Chem.*, **23**, 1487 (1986).

During our research on the molecular requirements of the recognition site of the cholinergic receptor [1,2], we synthesized and studied several compounds carrying a 1,3-oxathiolane, 1,3-oxathiolane-3-oxide, and 1,3-oxathiolane-3,3-dioxide nucleus. Their synthesis and their stereoisomerism, which was assigned on the basis of <sup>1</sup>H nmr spectra, have been reported previously [3,4,5]; several of them were also obtained as chiral compounds [5,6].



X = S, SO, SO<sub>2</sub>

Y = -CH<sub>2</sub>Cl, -COOMe, -CON(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>N<sup>+</sup>(CH<sub>3</sub>)<sub>3</sub><sup>-</sup>

Since these products (**1-24**) represent a homogeneous and fairly complete set of compounds, we thought it of some interest to report and briefly comment on their <sup>13</sup>C spectra (Tables I-III).

As a matter of fact, although 1,3-oxathiolanes have been studied intensively by mean of <sup>1</sup>H nmr spectroscopy [7-10], to our knowledge no <sup>13</sup>C data are available in the literature, and only a few data concerning some methyl derivatives can be found in the Bruker <sup>13</sup>C data bank. Moreover, as regards the 1,3-oxathiolane 3-oxides and 1,3-oxathiolane 3,3-dioxides, these two systems are quite new [3,4], and have not so far been studied from this point of view.

## Results and Discussion.

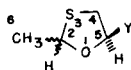
Carbon-13 chemical shifts for the oxathiolanes were assigned starting from the two isomeric esters **1** and **2**. In this case the determination of the signals of the carbon of carbonyl (C<sub>7</sub>), methoxyl (C<sub>8</sub>) and 2-methyl (C<sub>6</sub>) was straightforward on the basis of established chemical shift considerations [11].

The determination of the 4-methylene carbon had the same basis, an assignment which proved very useful for resolving the ambiguity in those members of the series where another methylene group is present in position 5 (**5-8**).

All these assignments were confirmed by the multiplicity

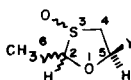
of the signals in off-resonance experiments. In these cases carbon 2 and carbon 5 of compounds **1** and **2** appeared as a doublet, but the assignment to carbon 2 of the downfield signals ( $\delta$  82.74 and 82.27 respectively), although reasonable in terms of chemical shift considerations, required further evidence. To this end, a <sup>1</sup>H-coupled <sup>13</sup>C-spectrum experiment showed that carbon 2 has higher multiplicity than carbon 5, which is consistent with the presence of an adjacent methyl group whose protons are coupled to carbon 2 by a <sup>1</sup>J<sub>C<sub>2</sub>-H<sub>6</sub> of 5.5 Hz in both isomers **1** and **2**. When the 2-methyl protons were decoupled, the C<sub>2</sub> signals of both isomers collapsed to a doublet of doublets because of the partial collapsing of <sup>3</sup>J<sub>C<sub>2</sub>-H<sub>4</sub> while the coupling with proton at C<sub>5</sub> was still present. From the same experiment the values for <sup>1</sup>J coupling of carbon 2 with its hydrogen (<sup>1</sup>J<sub>C<sub>2</sub>-H<sub>2</sub> = 163.3 and 165.2 respectively) and <sup>3</sup>J with hydrogen in 4 or 5 were evaluated (<sup>3</sup>J<sub>C<sub>2</sub>-C<sub>4</sub> = 3.3 Hz for **1** and 3.7 Hz for **2**; <sup>3</sup>J<sub>C<sub>2</sub>-H<sub>5</sub> = 2.4 Hz for both **1** and **2**).</sub></sub></sub></sub></sub>

Once assigned for the two esters **1** and **2**, the signals were easily determined for the other compounds studied. In fact, the chemical shifts of the corresponding carbons of the three series shown in Tables I-III are similar and actual variations can be accounted for by the different functionalities at position 3 and at carbon 7 and by the following discussion which considers the influence of stereoisomerism on chemical shift. The geometry of *cis* and *trans*-substituted compounds must be different as the *cis* isomers have 1,3-diaxial like interactions between the substituents which should distort the ring relative to the *trans* isomers and influence the chemical shifts of the two series in different ways. However the results of such interactions appear, at least in this case, difficult to predict. For instance, while in **5**, **7**, **21**, **23**, the steric compression between the two *cis* substituents slightly shields, as expected, the signals of the 2-methyl groups with respect to those of the corresponding *trans* compounds **6**, **8**, **22**, and **24**, the 5-methylene groups of the same *cis* compounds are actually deshielded with respect to those of their *trans* counterparts. In the 1,3-oxathiolane 3-oxide series this effect cannot be evaluated as it is overwhelmed by the adjacent sulfonoxide function.

Table I  
<sup>13</sup>C Chemical Shifts [a] [b]


No.	Y	Stereochemistry	C <sub>2</sub>	C <sub>4</sub>	C <sub>5</sub>	C <sub>6</sub>	C <sub>7</sub>	C <sub>8</sub>	C <sub>9</sub>	Solvent
1	<sup>17</sup> COO <sup>8</sup> CH <sub>3</sub>	<i>cis</i>	82.74	35.54	80.16	21.45	169.44	52.24	—	Deuteriochloroform
2		<i>trans</i>	82.27	35.01	79.33	22.01	170.74	52.04	—	Deuteriochloroform
3	<sup>17</sup> CO-N( <sup>8</sup> CH <sub>3</sub> ) <sub>2</sub>	<i>cis</i>	82.32	34.17	80.12	21.41	166.89	35.54	36.68	Deuteriochloroform
4		<i>trans</i>	81.99	34.27	77.70	21.19	168.47	35.48	36.68	Deuteriochloroform
5	<sup>17</sup> CH <sub>2</sub> -N( <sup>8</sup> CH <sub>3</sub> ) <sub>2</sub>	<i>cis</i>	82.86	36.50	81.33	21.38	62.01	45.70	—	Deuteriochloroform
6		<i>trans</i>	79.22	34.76	77.67	21.67	59.88	44.16	—	Deuteriochloroform
7	<sup>17</sup> CH <sub>2</sub> -N( <sup>8</sup> CH <sub>3</sub> ) <sub>3</sub> I <sup>-</sup>	<i>cis</i>	82.10	35.55	76.22	21.35	66.64	53.21	—	DMSO-d <sub>6</sub>
8		<i>trans</i>	80.99	35.68	75.00	22.69	66.02	53.24	—	DMSO-d <sub>6</sub>

[a] Tetramethylsilane as reference. [b] (+) and (-) enantiomers were also studied, in all cases the <sup>13</sup>C nmr spectrum, in the same solvent, was identical to that of the racemate.

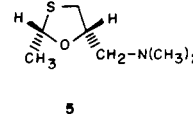
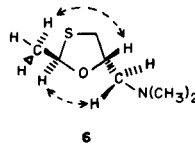
 Table II  
<sup>13</sup>C Chemical Shifts [a] [b]


No.	Y	Stereochemistry [c]	C <sub>2</sub>	C <sub>4</sub>	C <sub>5</sub>	C <sub>6</sub>	C <sub>7</sub>	C <sub>8</sub>	Solvent
9	<sup>17</sup> CH <sub>2</sub> Cl	2c, 3t, 5r	104.28	54.11	79.28	15.79	43.36	—	Deuteriochloroform
10		2t, 3c, 5r	100.17	53.33	80.43	15.22	44.08	—	Deuteriochloroform
11		2t, 3t, 5r	93.50	54.15	78.14	12.08	44.82	—	Deuteriochloroform
12		2c, 3c, 5r	94.17	56.96	79.41	11.68	44.30	—	Deuteriochloroform
13	<sup>17</sup> CH <sub>2</sub> N( <sup>8</sup> CH <sub>3</sub> ) <sub>2</sub>	2c, 3t, 5r	105.52	55.93	78.80	15.91	61.12	45.70	Deuteriochloroform
14		2t, 3c, 5r	100.12	55.19	78.63	15.25	61.76	45.51	Deuteriochloroform
15		2t, 3t, 5r	93.14	56.14	77.45	12.52	61.64	45.89	Deuteriochloroform
16		2c, 3c, 5r	94.47	58.92	78.21	11.81	62.27	45.54	Deuteriochloroform
17	<sup>17</sup> CH <sub>2</sub> N( <sup>8</sup> CH <sub>3</sub> ) <sub>3</sub> I <sup>-</sup>	2c, 3t, 5r	104.66	54.53	74.75	16.20	66.64	53.41	DMSO-d <sub>6</sub>
18		2t, 3c, 5r	100.14	54.82	74.75	15.36	67.24	53.17	DMSO-d <sub>6</sub>
19		2t, 3t, 5r	92.82	55.07	73.54	12.25	66.69	53.29	DMSO-d <sub>6</sub>
20		2c, 3c, 5r	94.22	58.14	73.53	11.91	67.39	53.28	DMSO-d <sub>6</sub>

[a], [b] See the corresponding footnotes of Table I. [c] Stereochemistry is assigned relative to the C-5 substituent; the symbols mean c = *cis*; t = *trans* with respect to the reference (r).

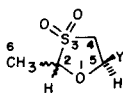
In the 1,3-oxathiolane series, both carbons 2 and 5 (which are the ones supporting the side chains) of the *trans* isomers **2**, **4**, **6**, and **8** were shielded with respect to the corresponding atoms of the *cis* counterparts **1**, **3**, **5**, and **7**.

This effect, although small, was generalized throughout the series and was maximal for the 5-dimethylaminomethyl derivatives **5** and **6**. It can be attributed to a  $\gamma$ -gauche like situation [12] which is present in the *trans* but not in the *cis* isomers. The situation is shown in the Figure for compounds **5** and **6**. When there were no protons in the 5-side chain, the effect on carbon **2** was much smaller **1**, **2**, **3**, and **4**.



The same situation was present in the 1,3-oxathiolane 3,3-dioxide derivatives, where again the *trans* isomers showed the carbons in 2 and in 5 shielded with respect to the *cis* isomers. On the other hand, although this effect is probably present in the 1,3-oxathiolane 3-oxide series, it did not give a clear-cut pattern, perhaps because of the modifications induced by the sulfoxide function.

Table III  
<sup>13</sup>C Chemical Shifts [a] [b]



No.	Y	Stereochemistry	C <sub>2</sub>	C <sub>4</sub>	C <sub>5</sub>	C <sub>6</sub>	C <sub>7</sub>	C <sub>8</sub>	Solvent
<b>21</b>	<sup>13</sup> CH <sub>2</sub> -N( <sup>13</sup> CH <sub>3</sub> ) <sub>2</sub>	<i>cis</i>	88.76	51.66	74.36	12.11	61.28	45.69	Deuteriochloroform
<b>22</b>		<i>trans</i>	85.20	50.60	72.70	12.90	60.90	45.70	Deuteriochloroform
<b>23</b>	<sup>13</sup> CH <sub>2</sub> -N <sup>+</sup> ( <sup>13</sup> CH <sub>3</sub> ) <sub>3</sub> I <sup>-</sup>	<i>cis</i>	88.10	50.26	70.44	11.95	65.97	53.57	DMSO-d <sub>6</sub>
<b>24</b>		<i>trans</i>	83.96	48.87	69.13	12.15	65.69	53.57	DMSO-d <sub>6</sub>
<b>25</b>	HS- <sup>13</sup> CH <sub>2</sub> - <sup>13</sup> CH(OH)- <sup>13</sup> COO <sup>13</sup> CH <sub>3</sub>		—	28.63	70.73	—	173.00	52.67	Deuteriochloroform

[a], [b] See corresponding footnotes of Table I.

As a matter of fact the sulfoxide group has a strong influence on the chemical shift of the neighboring carbons and on the 2-methyl, in terms both of electronic and of steric effects.

In particular the anisotropy of the sulfoxide function as well as its Van der Waal's effects with the *cis* 2-methyl **11**, **12**, **15**, **16**, **19**, and **20** afforded a greater shielding than in the case where the two groups are *trans* to each other **9**, **10**, **13**, **14**, **17**, and **18**. This effect of course is always present in the 3,3-dioxide series where the 2-methyl is in any case always facing an oxygen atom; accordingly the 2-methyl of **21-24** has a chemical shift which is close to that of **11**, **12**, **15**, **16**, **19**, and **20**.

It is interesting to compare the chemical shift of carbon 4 and 5 in the cyclic esters **1** and **2** with the corresponding carbons of the methyl ester of 3-mercapto-2-hydroxypropionic acid **25**. The rigidity imposed by the cycle results in a very strong deshielding of the two nuclei.

To conclude, it should be mentioned that when chiral compounds (that is the enantiomers of **1-8**, **13**, **16**, **17**, **20**, **21** and **23**) were studied in the same solvent, their <sup>13</sup>C spectra were always identical to the racemic ones.

The identification of the chemical shift of all carbon atoms and their correlation with some stereochemical features has a number of useful consequences: 1) It provides a rapid and reliable way of determining the stereochemistry to either *cis* or *trans* 1,3-oxathiolanes whatever the side chain in position 2 and 5 [4,7]. 2) It gives sound and reliable information on the relationships of the 2-methyl group with the sulfoxide functions, avoiding the more troublesome use of shift reagents [3]. 3) It makes possible a rapid and precise quantification of the stereoisomers in reaction mixtures, *e.g.* in cases where there are more than two isomers present and the proton signals of the <sup>1</sup>H nmr

are too crowded to give any indication; the <sup>13</sup>C signals of the 2-methyl group are particularly useful for this purpose.

As far as possible relationships with pharmacological activity are concerned, no apparent correlation was found between cholinergic potency [2] and <sup>13</sup>C chemical shift. Perhaps the only interesting feature is that all active compounds **7**, **8**, **17-20**, **23**, and **24** show a very close chemical shift for the trimethylammonium carbons.

This lack of relationships is not unexpected if one considers that the cholinergic potency of such compounds is probably due, to the stereoisomerism of the molecule, the lipophilic bond of the 2-methyl group, and the strength of the dipole in position 3 [13].

## EXPERIMENTAL

The natural abundance <sup>13</sup>C nmr spectra were run on a Varian FT-80A spectrometer at 20 MHz in the Fourier transform mode. All samples were recorded in 10 mm o.d. tubes at the probe temperature (38°) with concentrations of approximately 10% w/v in deuteriodimethyl sulfoxide or deuteriochloroform, which provided the deuterium signal for the field frequency lock. Chemical shifts were measured relative to the central peak of the solvent (deuteriodimethyl sulfoxide = 39.6 ppm; deuteriochloroform = 76.9 ppm) and corrected to internal tetramethylsilane. Typical acquisition parameters included: a spectral width of 5000 Hz, a flip angle of 42° and an interpulse delay between acquisitions of 510 μ seconds. Chemical shift values were reproducible to better than ±0.05 ppm. The decoupled spectra were obtained without pulse delay and with a digitization of 2 points per Hz. The coupled spectra with nuclear Overhauser effect (NOE) were obtained by putting the decoupler on during a pulse delay of 1.6 seconds and off during an acquisition time of 0.8 seconds. The digitization of the coupled spectra was 1.6 points per Hz.

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