

**A NATURAL ABUNDANCE  $^{17}\text{O}$  NMR INVESTIGATION OF SUBSTITUTED 1-METHYL  
AND 1-PHENYL-2-THIOHYDANTOINS**

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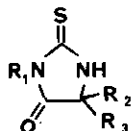
**Abstract** - Natural abundance  $^{17}\text{O}$  nmr spectroscopic data for seventeen 1-methyl- and 1-phenyl-2-thiohydantoin obtained in acetonitrile are reported; the relationship of  $^{17}\text{O}$  chemical shift to structure is discussed.

The chemistry of thiohydantoin constitutes an important area of heterocyclic chemistry.<sup>1,2</sup> The Edmans approach, a useful method for identification of N-terminal amino acids in peptides and proteins, involves characterization of 1-methyl and 1-phenyl-2-thiohydantoin.<sup>3,4</sup> A number of spectroscopic studies on thiohydantoin have been reported;<sup>2,5,6</sup> however, no study of the  $^{17}\text{O}$  nmr spectroscopic properties of these compounds has appeared. The rapidly expanding field of  $^{17}\text{O}$  nmr spectroscopy of organic systems is an increasingly important method for addressing a wide variety of structural questions.<sup>7</sup>  $^{17}\text{O}$  nmr spectroscopy has been successfully used to estimate electronic characteristics of a number of functional groups and changes in the environment near oxygen-containing functional groups resulting from both electronic<sup>8</sup> and steric factors.<sup>9</sup> Recent reports have shown that  $^{17}\text{O}$  chemical shifts correlate well with torsion angles for a wide range of functional groups attached to aromatic rings.<sup>10,11,12</sup> In rigid systems in which conformational flexibility is restricted, it has been demonstrated that the large *t*-butyl group causes in-plane distortions of molecular structure.<sup>13</sup> The influence of structure variation on the  $^{17}\text{O}$  nmr chemical shifts of thiohydantoin is of interest not only because of their importance in the protein field but also because they provide a framework to systematically assess the influence of structure variation on cyclic amide chemical shifts. This report describes the  $^{17}\text{O}$  chemical shifts and their relationship to structure for twelve 1-methyl and five 1-phenyl thiohydantoin.

The  $^{17}\text{O}$  nmr data for the thiohydantoin (1-17), determined from 0.5 M solutions at natural abundance in dry acetonitrile at 75°C, are listed in Table 1. The  $^{17}\text{O}$  chemical shifts of the thiohydantoin appear in the range of 340 to 360 ppm which is consistent with values reported for simple N,N-dialkylamides<sup>14</sup> and cyclic dipeptides.<sup>15</sup> Comparison of the two parent molecules 1-methyl (1) and 1-phenyl thiohydantoin (13) shows a chemical shift difference of 4 ppm, the shift

of 1 being downfield of 13. This result is consistent with the electronic properties of the two groups assuming that for 13 the phenyl group is not coplanar with the thiohydantoin ring. This

Table 1.  $^{17}\text{O}$  nmr Chemical Shift Data for 1-Methyl and 1-Phenyl-2-Thiohydantoins in  $\text{CH}_3\text{CN}$  at  $75^\circ\text{C}$ .<sup>a</sup>



Comp. No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	$\delta$ (ppm)
1	CH <sub>3</sub>	H	H	348.0
2	CH <sub>3</sub>	CH <sub>3</sub>	H	343.0
3	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	341.0
4	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	H	346.5
5	CH <sub>3</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	H	352.0
6	CH <sub>3</sub>	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H	346.5
7	CH <sub>3</sub>	-C(CH <sub>3</sub> ) <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	H	351.0
8	CH <sub>3</sub>	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H	346.0
9	CH <sub>3</sub>	-CH <sub>2</sub> PH	H	347.7
10	CH <sub>3</sub>	b	H	349.2
11	CH <sub>3</sub>	c	H	349.8
12	CH <sub>3</sub>	CH <sub>2</sub> SCH <sub>3</sub>	H	346.4
13	Ph	H	H	352
14	Ph	CH <sub>3</sub>	H	349.4
15	Ph	C <sub>2</sub> H <sub>5</sub>	H	351.7
16	Ph	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H	350.7
17	Ph	CH(CH <sub>3</sub> ) <sub>2</sub>	H	356

a) Reported in ppm; taken at  $75^\circ\text{C}$  as 0.5 M solutions in dry acetonitrile, with 2-butanone as an internal control. b) The thiohydantoin resulting from  $\text{CH}_3\text{NCS}$  and proline. c) The thiohydantoin resulting from  $\text{CH}_3\text{NCS}$  and hydroxyproline; the OH signal appears at 27.7 ppm.

difference of approximately 4 ppm is consistent throughout the comparable 1-methyl and 1-phenyl thiohydantoins (1, 2, 4, 5, 8 and 13-17). These results suggest very similar solution phase geometry for the thiohydantoins.

In the series of 4-alkyl-substituted 1-methylthiohydantoins 2-8 the  $^{17}\text{O}$  chemical shifts are affected by the various alkyl groups in a fashion analogous to the influence of alkyl groups on  $^{17}\text{O}$  chemical shifts reported for simple aliphatic aldehydes and ketones;<sup>16</sup>  $\gamma$  substituents cause shielding and  $\delta$  substituents cause deshielding. The chemical shift of the 4-methyl compound 2 is upfield (343 ppm) of the parent 1 (348 ppm); introduction of a second methyl group at position-4, 3, produces a further upfield shift (341 ppm). These upfield shifts are consistent with the  $\gamma$  shielding effect described for aldehydes and ketones.<sup>16</sup> Introduction of substituents in the  $\delta$  position as in 4, 6 and 8 results in deshielding (346 ppm) which was expected based upon the earlier carbonyl results.<sup>16</sup> As anticipated, introduction of a second  $\delta$  substituent as in 5 and 7 results in greater downfield shifts (352 and 351 ppm). The signal for benzyl derivative 9, for which there is not a published precedent in the aldehyde-ketone work, is only slightly deshielded as a consequence of the "branched"  $\delta$  effect of the phenyl group. Introduction of a fused ring derived from proline (10) and hydroxyproline (11) causes a slight increase in deshielding (3 ppm) over that noted from a single  $\delta$  substituent (compare to 4 and 8). This result may reflect a modest change in the thiohydantoin ring conformation.

In the more limited series of 1-phenylthiohydantoins (13-17) similar, though less pronounced, trends are noted for  $\gamma$  and  $\delta$  substituents. In the cyclic amides (thiohydantoins) studied here, it is apparent that the  $^{17}\text{O}$  chemical shift of the amide carbonyl is affected by alkyl substituents in a manner analogous to that reported earlier for acyclic aliphatic aldehydes and ketones.<sup>16</sup>

#### EXPERIMENTAL

The  $^{17}\text{O}$  spectra were recorded on a Varian VXR-400 spectrometer equipped with a 10 mm broad-band probe operated at 54.22 MHz. All spectra were acquired at natural abundance at 75°C in dry acetonitrile (Aldrich) containing 1% of 2-butanone. The concentration of the thiohydantoins (Sigma) employed in these experiments was 0.5 M. The signals were referenced to external deionized water at 75°C. The 2-butanone resonance (558±1 ppm) was used as an internal check on the chemical shift measurements for these compounds. The instrumental settings were: spectral width 35 kHz, 2 K data points, 90° pulse angle (40  $\mu\text{s}$  pulse width), 300  $\mu\text{s}$  acquisition delay, 29 ms acquisition time and ca. 30,000 scans. The spectra were recorded with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 25 Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to ±0.1 ppm by zero filling to 8 K data points. The reproducibility of the chemical shift data is estimated to be ±1.0.

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