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INTERMOLECULAR AND INTRAMOLECULAR HYDROGEN BONDING IN 5-PYRIDYLMETHYLENEHYDANTOINS: IR AND NMR STUDY

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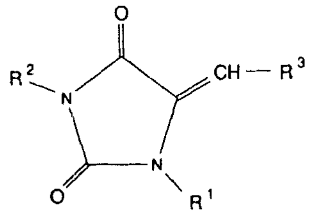
The patterns of the NH stretching vibrations in the solid-state IR spectra of a series of 5-pyridylmethylenehydantoins revealed the presence of various modes of hydrogen bonding: intermolecular NH····OC and intermolecular or intramolecular NH····N(py). These variations are related to the orientation of the pyridyl nitrogen and to stereochemistry. A distinction between intramolecularly and intermolecularly hydrogen-bonded compounds was also provided by comparison of the ^{1}H NMR spectra in $(CD_3)_2SO$ and in $CDCl_3$.

INTRODUCTION

IR and NMR spectroscopic methods have been extensively applied to the study of hydrogen bonding in heterocyclic compounds containing NH and CO groups.[1–4] In a study of a series of 5-pyridylmethylenehydantoins, we observed a propensity for hydrogen-bond formation. In addition to the NH and CO groups in the hydantoin ring, the pyridyl nitrogen also acts as a good proton acceptor. Thus, various modes of hydrogen bonds are possible. The N(1)H or N(3)H not only can bond intermolecularly with the C(2)=O or C(4)=O group of a neighbouring molecule, but may also be capable of forming intermolecular or intramolecular hydrogen bonds with the pyridyl nitrogen, depending on the position of the nitrogen atom in the pyridine ring and on its configurational and conformational relationship with the hydantoin ring. We have probed the structural and stereochemical dependence of the hydrogen-bond modes in this series of compounds by comparison of their IR spectra in the solid state and in solution and of their ^{1}H HMR spectra in deuterated chloroform and dimethyl sulphoxide.

RESULTS AND DISCUSSION

NH stretching vibrations in solid-state IR spectra



	R¹	R²	R³
(1)	H	H	2-py
(2)	H	H	3-py
(3)	H	H	4-py
(4)	H	Me	2-py
(5)	H	Me	3-py
(6)	H	Me	4-py
(7)	Me	H	2-py
(8)	Me	H	3-py
(9)	Me	H	4-py

The preparations, stereochemical and acidity studies of 5-pyridylmethylenehydantoins **1–9** have been reported.[5,6] Their IR spectra, recorded in KBr discs (Table 1), may be compared with those of hydantoin, 3-methylhydantoin, 1-methylhydantoin and (*Z*)-5-phenylmethylenehydantoin. The NH stretching vibrations are particularly informative with respect to hydrogren-bonding modes.

The IR spectrum of hydantoin in the solid state shows an absorption band in the 3400–3000 cm^{-1} region with maxima of sub-bands distinguishable at 3270, 3150 and 3070 cm^{-1}. The spectrum of 1-methylhydantoin shows a band in the region 3300–3000 cm^{-1} with maxima at 3150 and 3060 cm^{-1}

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Table 1. Infrared frequencies (cm^{-1}) in the NH, C=0 and C=C stretching regions obtained in the solid state (KBr)[a]

Compound	N(1)H	N(3)H	C=O	C=C
(*Z*)-**1**	3270(sh)	3175(s)	1776(s)	1669(s)
		3060(s)	1722(s)	
(*Z*)-**2**	3180(m)	2940(m)	1752(s)	1666(s)
	3075(w)	2705(m, b)	1722(s)	
(*Z*)-**3**	3215(m)	2930(w)	1735(s)	1664(s)
	3040(w)	2615(m, b)		
(*Z*)-**4**	3340(m)		1770(s)	1663(s)
	3065(w)		1747(w)	
(*Z*)-**5**	3315(w)		1771(s)	1669(s)
	3085, 3045(w, b)		1715(s)	
(*Z*)-**6**	3245(m)		1777(m)	1658(s)
	3035(w)		1713(s)	
(*Z*)-**7**		3190(m)	1769(s)	1648(s)
		3065(m)	1740(s)	
(*E*)-**7**		2955(w)	1785(sh)	1647(s)
		2705(m, b)	1766(sh)	
			1747(s)	
(*Z*)-**8**		2920(w)	1762(s)	1660(s)
		2675(m, b)	1742(s)	
(*E*)-**8**		2925(w)	1740(s)	1647(s)
		2680(m, b)		
(*Z*)-**9**		2905(m)	1753(s)	1660(s)
		2695(s, b)		
(*E*)-**9**		2925(w)	1764(s)	1635(s)
		2680(m, b)	1733(s)	

[a] sh = Shoulder, s = strong, m = medium, w = weak, b = broad

but no maximum above 3200 cm^{-1}. On the other hand, the spectrum of 3-methylhydantoin shows a narrower and stronger absorption at 3300 cm^{-1}. Hence the highest frequency absorption in the hydantoin spectrum has been assigned to N(1)–H stretching and those at lower frequency to N(3)–H stretching,[7] possibly with superimposed combination band of C=O stretching and N—H bending vibrations.[8] Although both NH groups are capable of forming intermolecular hydrogen bonds with CO groups of neighbouring molecules, N(3)H is a better donor group because of its known higher acidity.[9,10] This is reflected by the observed broader and lower frequency NH band of 1-methylhydantoin compared with the sharper absorption of 3-methylhydantoin.

Attachment of a benzylidene side-chain to C(5) of hydantoin as in (*Z*)-5-phenylmethylenehydantoin does not have a large effect on the NH absorptions, which appear as a band in a similar region but with only two maxima distinguishable at 3210 and 3060 cm^{-1}. The two sub-bands of hydantoin at 3270 and 3150 cm^{-1} could have merged to give the stronger sub-band at 3210 cm^{-1} in the spectrum of the phenylmethylene derivative. The NH stretching mode of (*Z*)-5-(4-methoxyphenyl)methylenehydantoin resembles more closely that of hydantoin with sub-bands at 3250, 3170 and 3060 cm^{-1}. X-ray crystallographic examination of this compound[11] has revealed intermolecular hydrogen bonds of both N(1)H····OC(2) and N(3)H····OC(4) types.

Replacement of the benzene ring in 5-phenylmethylenehydantoin by a pyridine ring as in the 5-pyridylmethylenehydantoins studied here results in significant changes in the NH stretching absorptions. The patterns of the NH stretching in the IR spectra of these compounds may be correlated with the presence and types of hydrogen bonding which, in turn, vary with the structure and configuration of the compounds. These are grouped into three classes for discussion.

1-Methyl-substituted compounds **7–9**

Each of these compounds has been obtained in both *Z*- and *E*-forms. In the spectra of (*E*)-**7** and both *Z*- and *E*-isomers of **8** and **9**, the NH stretching vibrations shift substantially to lower frequencies relative to those observed for their phenyl analogues. Two groups of bands are observed, one centred around 2950–2900 cm^{-1} and another broader and stronger band around 2700–2650 cm^{-1} [Figures1(a)–(c) and 2(b) and (c)]. Such broadening and low-frequency shifts are indicative of strong intermolecular hydrogen

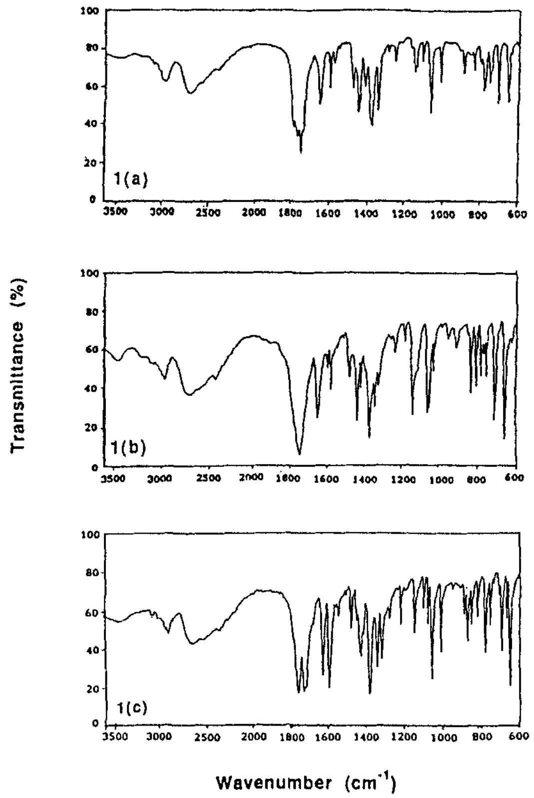

Figure 1. Infrared spectra of (a) (*E*)-**7**, (b) (*E*)-**8** and (c) (*E*)-**9** in the solid state

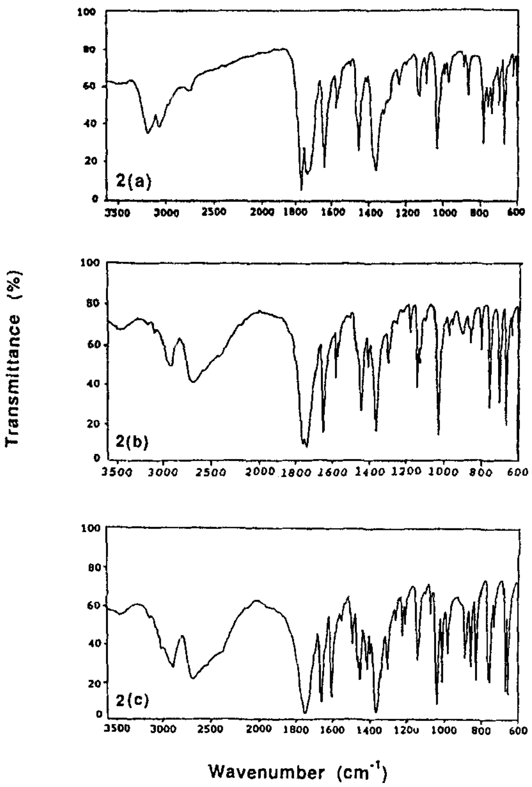

Figure 2. Infrared spectra of (a) (*Z*)-**7**, (b) (*Z*)-**8** and (c) (*Z*)-**9** in the solid state

bonding which is different from the NH····OC type present in 1-methylhydantoin. An intermolecular NH····N hydrogen bond is known to give rise to low-frequency NH absorptions in heterocycles such as imidazoles and pyrazoles.[12,13] In *N*-substituted granatanine-3-spiro-5′-hydantoin and nortropane-3-spiro-5′-hydantoin, a strong hydrogen bond exists between N(3)H and the basic piperidine nitrogen, resulting in broad, low-frequency NH absorptions in their IR spectra.[14] Similar intermolecular hydrogen bonds could be formed between N(3)H and the basic pyridyl nitrogen in *E*-isomers of **7**–**9** and *Z*-isomers of **8** and **9**.

Interestingly, the IR spectrum of (*Z*)-**7** differs strikingly from that of its *E*-isomer [Figure 2(a)]. The NH region now resembles more closely that of 1-methylhydantoin,[7] suggesting the absence of intermolecular N(3)H····N(py) hydrogen bond. Instead, the 2-pyridyl nitrogen may be engaged in intramolecular interaction with the N(1)-methyl protons when the 2-pyridyl group assumes the *s-cis* conformation with respect to the hydantoin ring, as previously deduced from NMR and p*K* measurements,[5,6] It may appear surprising that such a weak CH_3····N interaction could upset the possibility of the stronger NH····N hydrogen bond. However, in this compound, the favourable orientation coupled with the lower steric requirement of the 2-pyridyl nitrogen compared with an aryl CH group allow for close approach of the 1-methyl group so that the deviation from coplanarity of the pyridine and hydantoin rings may be relatively small. Consequently, there may be significant conjugative displacement of electrons from the N(1) position to the pyridine ring via the exocyclic double bond, leading to a simultaneously increased acidity of the 1-methyl protons and increased basicity of the 2-pyridyl nitrogen, which in turn enhance the intramolecular N(1)CH_3···N(py) interaction. Moreover, the methyl group also presents frontal steric hindrance to access the pyridyl nitrogen by the N(3)H group of another molecule to form an intermolecular hydrogen bond. Hence, the N(3)H group can now bond intermolecularly with a CO group as in 1-methylhydantoin.

This difference between the *Z*- and *E*-isomers of **7** is not observed for **8** and **9**. In (*Z*)-**8** and (*Z*)-**9**, steric hindrance between the 1-methyl group and the *ortho*-hydrogen of the pyridine ring causes the latter to twist out of the plane of the hydantoin ring. The 3- or 4-pyridyl nitrogen atom is also too distant from the 1-methyl group for any intramolecular interaction. Therefore, in both the *Z*- and *E*-isomers of **8** and **9**, the unencumbered pyridyl nitrogen is free to participate in intermolecular hydrogen bonding with the N(3)H of an adjacent molecule.

3-Methyl-substituted compounds **4–6**

Only the *Z*-isomers of the 3-methyl-5-pyridylmethylene hydantoins **4–6** are obtainable directly from the reported method of preparation. Differences observed in the NH stretching modes among the IR spectra of these three compounds and from those of **7–9** can be related to the different positions of the pyridyl nitrogen in **4–6** and the presence of a methyl substituent at N(3) instead of at N(1).

The NH stretching mode of the 3-pyridyl compound (*Z*)-**5** clearly differs from that of the 3-methylhydantoin.[7] It consists of a broad band of medium intensity around 3360–2600 cm^{-1} with maxima at 3315 and, less distinctly, at 3085 and 3043 cm^{-1} [Figure 3(b)]. This broadening and lowering of the frequency of the absorption band relative to that of 3-methylhydantoin again suggest the existence of an intermolecular NH····N(py) type of hydrogen bond. However, the downward shift of frequency of this band relative to that of 3-methylhydantoin is smaller than that noted above in the spectrum of (*Z*)-**8** relative to 1-methylhydantoin. Since one of the factors determining the strength of a hydrogen bond is the acidity of the donor and basicity of the acceptor group, the higher frequency of the NH bond in (*Z*)-**5** compared with that in (*Z*)-**8** could reflect a less strong hydrogen bond resulting from the lower acidity of the N(1)H than the N(3)H group. The spectrum of the 4-pyridyl compound (*Z*)-**6** also shows a broad band from about 3450 to 2700 cm^{-1} with superimposition of an intense absorption near 3245 cm^{-1} and a weaker peak at 3035 cm^{-1} [Figure 3(c)]. Hence both (*Z*)-**5** and (*Z*)-**6** are associated in the crystalline state.

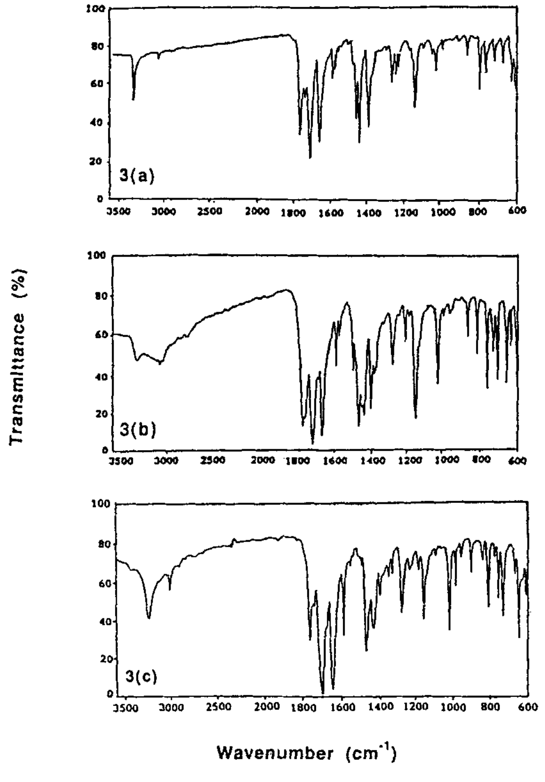

Figure 3. Infrared spectra of (a) (*Z*)-**4**, (b) (*Z*)-**5** and (c) (*Z*)-**6** in the solid state

By contrast, broad NH absorptions are absent in the spectrum of the 2-pyridyl compound (*Z*)-**4**, there being only a sharp peak of medium intensity at 3340 and a weak one at 3065 cm^{-1} [Figure 3(a)]. The existence of an intramolecular hydrogen bond between N(1)H and the nitrogen atom of the 2-pyridyl ring in its *s-cis* conformation has been postulated from previous NMR and p*K* studies in solution.[5,6] If this intramolecular interaction is also present in the solid state, then the N(1)H is not available for the formation of intermolecular hydrogen bonding.

N-*Unsubstituted compounds* **1–3**

The *N*-unsubstituted 5-pyridylmethylenehydantoins **1–3** are also obtained only in the *Z*-form directly from the usual method of preparation. From the above discussions of the 1- and 3-methyl-substituted compounds, one may expect the NH regions of the IR spectra of (*Z*)-**1** to (*Z*)-**3** to combine the features shown by the two groups of methyl derivatives. This appears to be the case for the 3-pyridyl compound (*Z*)-**2** and the 4-pyridyl compound (*Z*)-**3** as their spectra [Figures 4(b) and (c)] show broad bands centred around 2940–2930 and 2700–2600 cm^{-1}, which are similar to those shown by their 1-methyl analogues (*Z*)-**8** and (*Z*)-**9** and are assignable to intermolecular NH····N(Py) vibrations, in addition to another band around 3220–3180 cm^{-1} which may be attributed to NH····OC vibrations. The NH region of the spectrum of (*Z*)-**1**, however, closely resembles that of its 1-methyl analogue (*Z*)-**7** except for an additional shoulder at 3270 cm^{-1} [Figure 4(a)]. The molecules of (*Z*)-**1** are probably associated via N(3)H····OC bonds. the shoulder occurring at a frequency close to that of the sharp peak observed for its 3-methyl analogue (*Z*)-**4** may possibly arise from similarly intramolecularly hydrogen-bonded N(1)H stretching.

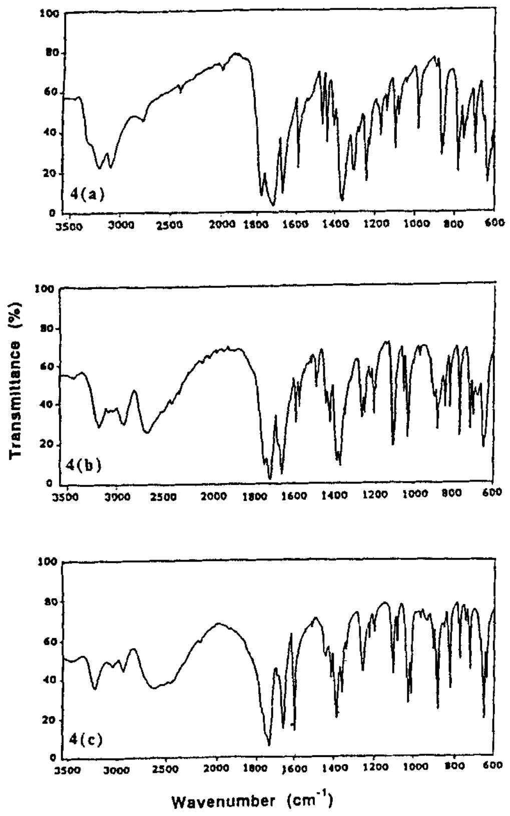

Figure 4. Infrared spectra of (a) (*Z*)-**1**, (b) (*Z*)-**2** and (c) (*Z*)-**3** in the solid state

NH stretching vibrations in IR spectra in $CHCl_3$

Without crystal structure determinations, the above deductions regarding hydrogen bonds in the solid state should be regarded as tentative. Attempts to study IR spectra in solution, especially to probe variations of absorption characteristics with concentration, are frustrated by the extremely low solubilities of these compounds in non-polar solvents. Using a 1-cm quartz cell which is transparent in the 4000–2800 cm^{-1} region and dilute solutions in the concentration range 0·5–1·8 mM in chloroform, the NH stretching absorptions of most compounds have been recorded (Table 2). However, some of the spectra are not very satisfactory owing to the poor solubility of the compounds and saturated solutions had to be used. Therefore, the intensities of these NH bands could not be determined accurately. Nevertheless, a few significant observations may be made.

Most noticeable is the disappearance of the broad and strong absorption bands which are so prominent in most of the solid-state spectra as discussed above. This indicates the absence of strong intermolecular hydrogen bonding in the dilute chloroform solutions used. Second, among the 3-methyl-substituted compounds, the NH stretching vibration of (*Z*)-**4** is shifted to significantly lower frequency relative to those of (*Z*)-**5** and (*Z*)-**6**, consistent with the possible presence of an intramolecular hydrogen bond in (*Z*)-**4**. This contrasts with the trend observed in the solid-state spectra of these three compounds, where intermolecular hydrogen bonds in (*Z*)-**5** and (*Z*)-**6** cause a considerable lowering of the NH stretching frequencies. Third, among the 1-methyl-substituted compounds **7**–**9**, the NH bands of the *Z*-isomers occur at slightly lower frequencies than those of the corresponding *E*-isomers. Finally, it is noteworthy that the order of frequencies of the N(1)H and N(3)H bands in chloroform solution appears to be reverse of that found in the solid-state spectra. Thus, the N(1)—H bonds in the 3-methyl-substituted compounds vibrate at lower frequencies than the N(3)—H bonds in the 1-methyl analogues. The reasons for these observed trends are not clear. Among the *N*-unsubstituted compounds, only (*Z*)-**1** is sufficiently soluble in chloroform to give a spectrum which shows two bands at 3390 and 3355 cm^{-1} due to the two N—H bonds.

Table 2. Infrared frequencies (cm^{-1}) in the NH stretching region obtained in $CHCl_3$ solutions

Compound[a]	N(1)H	N(3)H
Z)-**1**	3355(m)	3390(m)
(*Z*)-**4**	3315(m)	
(*Z*)-**5**	3375(m)	
(*Z*)-**6**	3350(w)	
(*Z*)-**7**		3405(m)
(*E*)-**7**		3430(m)
(*Z*)-**8**		3405(w)
(*E*)-**8**		3420(w)
(*Z*)-**9**		3400(w)
(*E*)-**9**		3440(m)

[a] (*Z*)-**2** and (*Z*)-**3** are hardly soluble in $CHCl_3$.

C=C and C=O stretching in solid-state IR spectra

The C=C stretching absorptions of these 5-pyridylmethylenehydantoins are comparable to those of the aryl analogues previously studied.[15] The *Z*-isomers of the 1-methyl-substituted compounds also show higher C=C stretching frequencies than their *E*-isomers.

No clear trend can be detected among the C=O stretching vibrations of **1**–**9**. The assignments of these bands to the two carbonyl groups at C(2) and C(4) have not been unequivocal.[16–18] In the solid state, these vibrations will also be affected by intermolecular hydrogen bonding and, without x-ray analytical data, it is uncertain which one or both carbonyl groups are involved.

^{1}H NMR spectra in $CDCl_3$

Owing to the low solubilities of **1**–**9** in most non-polar solvents, their NMR spectra have previously been studied in DMSO-d_6.[5] However, dimethyl sulphoxide is a good proton acceptor and is likely to interact with the NH groups in these compounds, thus disrupting intermolecular association. To probe further the existence of intermolecular and intramolecular hydrogen bonds among these compounds, attempts have been made to record their ^{1}H NMR spectra in $CDCl_3$ (Table 3) in which solvent–solute interactions should be much weaker. As expected, the most interesting differences are found in the NH signals. For (*Z*)-**1** in DMSO-d_6, the two signals at δ 10·35 and 11·31 were assigned to N(1)H nd N(3)H, respectively. In $CDCl_3$, the N(3)H signal shows a very large upfield shift to δ 7·95 whereas the N(1)H signal remains relatively little changed at δ 10·28. Assignments of these two resonances are based on comparison with the spectra of 1- and 3-methyl-substituted compounds which contain only one NH group in each case. Among the 1-methyl derivatives, only (*Z*)-**9** is sufficiently soluble in $CDCl_3$ to give a satisfactory spectrum which shows the N(3)H signal at δ 7·97. The 3-methyl derivatives are relatively more soluble and good spectra could be obtained for all three compounds. The 3-pyridyl compound (*Z*)-**5** and the 4-pyridyl compound (*Z*)-**6** each gives one N(1)H signal at δ 8·08 and 8·04, respectively, but the N(1)H signal of the 2-pyridyl compound (*Z*)-**4** is shifted dramatically downfield to δ 10·24. This very large deshielding effect strongly supports the postulation of an intramolecular hydrogen bond between N(1)H and the 2-pyridyl nitrogen in (*Z*)-**4**. If similar intramolecular chelation is present in the *N*-unsubstituted 2-pyridyl compound (*Z*)-**1**, then the signal at δ 10·28 must be assigned to the proton at N(1) and that at δ 7·95 to the proton at N(3). The similar chemical shifts of the N(1)H of (*Z*)-**1** and (*Z*)-**4** in both $CDCl_3$ and DMSO-d_6 indicate that for these 2-pyridyl compounds the N(1)H group is involved in intramolecular interactions and therefore virtually independent of the solvent. On the other hand, for the 3- and 4-pyridyl analogues (*Z*)-**5** and (*Z*)-**6**, the N(1)H signal is not intramolecularly chelated and its chemical shift in $CDCl_3$ is more than 2 ppm upfield from that in DMSO-d_6, owing to the strong intermolecular interaction of this proton with the latter but not the former solvent. Similar but even larger differences are noted in the chemical shifts of N(3)H protons measured in these two solvents, as shown in the spectra of (*Z*)-**1** and (*Z*)-**9**. This probably reflects the stronger interaction of the basic DMSO molecules with the more acidic N(3)H.

Table 3. ^{1}H shifts (from Me_4Si) for N(1)H and N(3)H in (a) $CDCl_3$ and (b) $(CD_3)_2SO$[a]

	N(1)H		N(3)H	
Compound	(a)	(b)	(a)	(b)
(*Z*)-**1**	10·28	10·35	7·95	11·31
(*Z*)-**4**	10·24	10·46		
(*Z*)-**5**	8·08	10·70		
(*Z*)-**6**	8·04	11·00		
(*Z*)-**9**			7·97	11·55

[a] From Ref. 5.

EXPERIMENTAL

Materials. 5-Pyridylmethylenehydantoins **1**–**9** were prepared according to published methods.[5]

Infrared spectra. Infrared spectra were recorded on a Philips PU 9706 infrared spectrophotometer. Polystyrene was used for instrument calibration. All compounds were compressed into KBr pellets. Saturated solutions of some of the compounds in chloroform were used to obtain the solution spectra.

^{1}H NMR spectra. ^{1}H NMR spectra were recorded in $CDCl_3$ solution with tetramethylsilane as internal reference using a JEOL FX90Q spectrometer.

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