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NMR SPECTROSCOPIC STUDY OF CONFIGURATIONS AND CONFORMATIONS OF 5-PYRIDYLMETHYLENEHYDANTOINS

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Nine 5-pyridylmethylenehydantoins were prepared. Each of the 1-methyl-substituted compounds was obtained in two stereoisomeric forms. Only one form of each of the 3-methyl-substituted and *N*-unsubstituted compounds was obtained directly from synthesis but could be partially converted into the other stereoisomer photochemically. The *Z*/*E* configurations and the conformational relationship between the pyridine and hydantoin rings were studied by ^{1}H and ^{13}C NMR spectroscopy, including variable-temperature ^{1}H NMR. The existence of N—H····N or C—H····N interactions and the possibility of tautomerism are suggested for some of the compounds. The *Z*-isomers of compounds with 2- or 3-pyridyl rings prefer an *s-cis* conformation whereas the *E*-isomers prefer an *s-trans* conformation.

INTRODUCTION

A systematic study of the *Z*–*E* isomerism of three series of 5-arylmethylenehydantoins, with or without substituents at the nitrogen atoms, has been reported.[1] NMR spectroscopy has been found to be particularly useful in configuration assignments. The configurations of a few of them have since been confirmed by x-ray crystallography.[2] The geometric isomers are interconvertible by thermal or photochemical methods and their relative stabilities have also been estimated.[3]

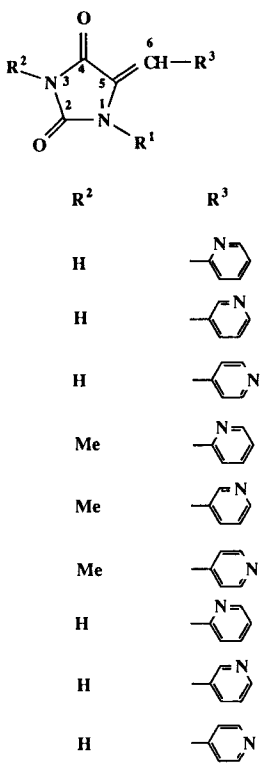
Very little is known about the pyridyl analogues of these compounds, although condensations of hydantoin with 2-pyridinecarboxaldehyde and of thiohydantoin with 3-pyridinecarboxaldehyde have been described, without a discussion of the stereochemistry.[4,5] This prompted us to extend our studies to these 5-pyridylmethylenehydantoins.

Compared with the 5-arylmethylenehydantoins, these pyridyl analogues provide additional structural and stereochemical features of interest. NMR spectroscopy not only allows unambiguous determination of the *Z*/*E* configuration but also a closer analysis of the spectral data, coupled with variable-temperature studies, has yielded further information on the effects of the orientation of the pyridyl nitrogen on conformational preferences of the pyridine ring relative to the hydantoin ring.

RESULTS AND DISCUSSION

Syntheses and geometric isomerism

The 5-pyridylmethylenehydantoins **1–9** (Scheme 1)



Scheme 1

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were synthesized by condensation of hydantoin, 3-methylhydantoin or 1-methylhydantoin with 2-, 3- or 4-pyridinecarboxaldehyde in an aqueous solution containing alanine and sodium carbonate.[6,7]

Attempted preparations of these compounds according to methods previously reported for 5-arylmethylenehydantoins, involving the use of acetic acid and sodium acetate[8] or piperidine[9] as condensing agents, gave either low yields or gummy products. The 1-methyl-substituted compounds **7–9** were each obtained directly in two stereoisomeric forms, whereas for the *N*-unsubstituted and the 3-methyl-substituted compounds **1–6**, only one isomer was isolated in each case. The melting points and analytical data are summarized in Table 1.

Configuration assignments by ^{1}H NMR spectra

The *Z*/*E* configurations of the two isolated stereoisomers of each of the 1-methyl-substituted compounds **7–9** could be readily distinguished by comparison of their ^{1}H NMR spectra. For each of compounds **1–6**, the configuration of the only isolated isomer could be deduced by comparison of its spectrum with those of the *Z*- and *E*-isomers of compounds **7–9**. This isomer was then partially converted photochemically into the other isomer and the NMR spectrum of the mixture was determined. The spectral data for the second isomer could then be obtained by subtracting the known signals of the first isomer (Table 2).

Table 1. Melting points and analytical data for compounds **1–9**

Compound	M.p.(°C)	Found (%)			Calculated (%)		
		C	H	N	C	H	N
(*Z*)-**1**	233·5–235·5	57·0	3·5	22·1	57·1	3·7	22·2
(*Z*)-**2**	292·5(dec·)	56·9	3·5	22·5	57·1	3·7	22·2
(*Z*)-**3**	>300	56·9	3·6	22·0	57·1	3·7	22·2
(*Z*)-**4**	224–225	59·0	4·3	20·8	59·1	4·4	20·7
(*Z*)-**5**	288–290	58·8	4·3	20·4	59·1	4·4	20·7
(*Z*)-**6**	247–248	58·8	4·4	20·8	59·1	4·4	20·7
(*Z*)-**7**	145–147	59·2	4·1	20·6	59·1	4·4	20·7
(*E*)-**7**	249·5–250·5	59·3	4·4	20·6	59·1	4·4	20·7
(*Z*)-**8**	227–229	58·9	4·4	20·7	59·1	4·4	20·7
(*E*)-**8**	244–246·5	59·3	4·4	21·0	59·1	4·4	20·7
(*Z*)-**9**	242–244	59·3	4·5	20·6	59·1	4·4	20·7
(*E*)-**9**	275·5–277·5	59·1	4·4	21·0	59·1	4·4	20·7

Table 2. ^{1}H NMR shifts (ppm) of compounds **1–9** [solvent, $(CD_3)_2$ SO]

Compound	N-1—H	N-3—H	H-6	H-8	H-9	H-10	H-11	H-12	1-CH_3	3-CH_3
(*Z*)-**1**	10·35	11·31	6·50	–	8·66	7·30	7·84	7·60	–	–
(*E*)-**1**	10·44	11·32	6·40	–	8·66	7·30	7·84	8·52	–	–
(*Z*)-**2**	10·69	11·34	6·43	8·77	–	8·49	7·41	8·04	–	–
(*E*)-**2**	10·45	11·22	6·31	8·82	–	8·49	7·42	8·39	–	–
(*Z*)-**3**	10·81	11·41	6·34	7·55	8·56	–	8·56	7·55	–	–
(*E*)-**3**	[a]	[a]	6·24	7·76	8·54	–	8·54	7·76	–	–
(*Z*)-**4**	10·46	–	6·59	–	8·66	7·29	7·84	7·60	–	2·98
(*E*)-**4**	10·56	–	6·46	–	8·66	7·29	7·84	8·40	–	2·94
(*Z*)-**5**	10·70	–	6·53	8·79	–	8·50	7·41	8·05	–	2·97
(*E*)-**5**	10·58	–	6·38	8·84	–	8·50	7·41	8·41	–	2·93
(*Z*)-**6**	11·00	–	6·46	7·58	8·57	–	8·57	7·58	–	2·97
(*E*)-**6**	10·89	–	6·31	7·78	8·55	–	8·55	7·78	–	2·94
(*Z*)-**7**	–	[a]	6·57	–	8·62	7·29	7·82	7·58	3·22	–
(*E*)-**7**	–	11·30	6·33	–	8·56	7·24	7·75	8·37	3·10	–
(*Z*)-**8**	–	11·47	6·63	8·62	–	8·53	7·42	7·83	2·81	–
(*E*)-**8**	–	11·36	6·39	8·87	–	8·45	7·37	8·35	3·10	–
(*Z*)-**9**	–	11·55	6·53	7·33	8·56	–	8·56	7·33	2·82	–
(*E*)-**9**	–	11·50	6·33	7·80	8·55	–	8·55	7·80	3·09	–

[a] Signal not detected.

For the purpose of distinguishing between *Z*- and *E*-configurations, the chemical shift of the vinyl proton at C-6 is most diagnostic. Without exception, a significant downfield shift was observed for proton H-6 of the *Z*-isomer, since only in the *Z*-configuration is H-6 close to and therefore deshielded by the anisotropic C-4 carbonyl group. A similar difference was previously observed for the *Z*- and *E*-isomers of 5-arylmethylenehydantoins, whose configuration assignments were supported by other spectroscopic considerations.[1] In addition to the effect of configuration, the chemical shift of this vinyl proton of the 5-pyridylmethylenehydantoins studied here also shows a dependence on the position of the pyridyl nitrogen relative to the hydantoin ring. Within each group of compounds **1**–**3** or **4**–**6**, this H-6 signal shifts upfield from 2- to 3- and 4-pyridyl compounds, probably as a result of its increasing distance from the electron-withdrawing and therefore deshielding effect of the pyridyl nitrogen.

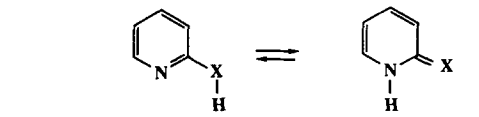
Correlation of other ^{1}H NMR data with configurations and conformations

NH protons

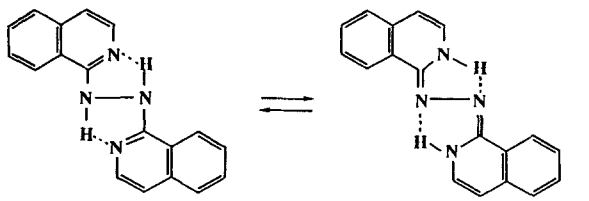
In general, the proton H-3, under the influence of two adjacent carbonyl groups, gives a lower field signal than H-1 with only one adjacent carbonyl group. Whereas H-6 is most deshielded in the 2-pyridyl and least in the 4-pyridyl compounds, the opposite trend is noted for H-1 among the *Z*-isomers of compounds of compounds **1**–**6**. To understand this, one needs to consider the geometry of these compounds. A previous x-ray crystallographic study showed that (*Z*)-5-benzylidenehydantoin has an almost planar structure with only a small dihedral angle between the phenyl and hydantoin rings.[2] Since the pyridine and benzene rings are similar in size and shape, one may speculate that approximate molecular planarity is also probable for the *Z*-isomers of **1**–**6** to allow maximum resonance interaction between the hydantoin and the aromatic moieties. In such coplanar, or nearly coplanar, conformations of these *Z*-isomers, H-1 would be in the deshielding zone of the aromatic ring and resonate more downfield than that in the corresponding *E*-isomers where it is not similarly affected. An analogous difference was previously observed between the H-1 resonances of the *Z*- and *E*-isomers of 5-benzylidenehydantoin. Molecular planarity also permits the transmission of the electron-withdrawing and therefore deshielding effect of the pyridine ring, particularly from the conjugated 2- and 4-positions, to the N-1 position. Although the H-1 signals of the *Z*-isomers of the 3- and 4-pyridyl compounds are, as expected, more deshielded than those of the corresponding *E*-isomers, with the downfield shift more pronounced for the 4- than the 3-pyridyl compounds, it is surprising to observe the reverse trend for the 2-pyridyl compounds. These unexpectedly upfield H-1 signals of the 2-pyridyl compounds (*Z*)-**1** and (*Z*)-**4** relative to those of (*E*)-**1** and (*E*)-**4** and also the 3-pyridyl compounds (*Z*)-**2** and (*Z*)-**5** and the 4-pyridyl compounds (*Z*)-**3** and (*Z*)-**6**, may possibly be rationalized by consideration of conformational effects and the possibility of prototropic tautomerism.

When the pyridine ring is unsymmetrical with respect to rotation about its bond to C-6, two limiting coplanar conformations are possible, with the pyridyl nitrogen orientated either *cis* (denoted by *s-cis*) or *trans* (denoted by *s-trans*) relative to the hydantoin ring. Only in the *s-cis* conformation of (*Z*)-**1** and (*Z*)-**4** does the close approach of H-1 and the pyridyl nitrogen allow a strong intramolecular interaction. Moreover, since N-1 is conjugated to the 2-pyridyl nitrogen through the exocyclic double bond, tautomeric transfer of a proton between these nitrogens could be facilitated by cyclic delocalization of electrons, resulting in theoretically possible tautomeric forms (T) and (T′). (Scheme 2).

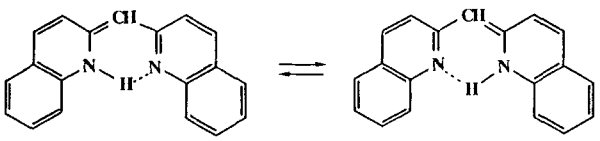
Prototropic tautomerism of numerous 2-substituted pyridines of general structure A has been well studied,[10] particularly where the geometry of the molecule makes such proton transfer facile. Compounds B[11] and C[12]



(A) X= O, NH or CH_2

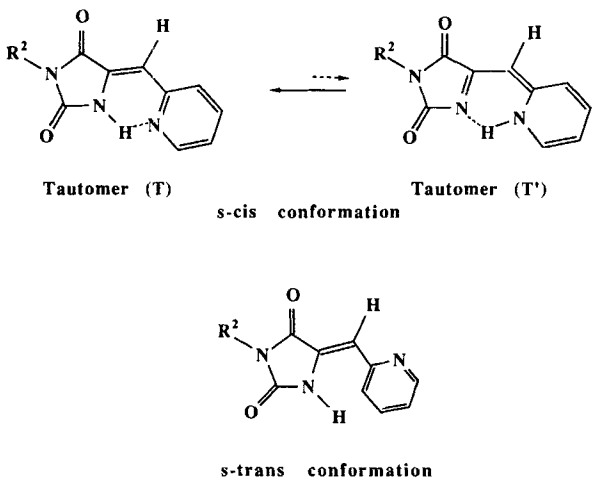


(B)



(C)

provide interesting examples. Given the favourable molecular geometry of (*Z*)-**1** and (*Z*)-**4**, proton transfer between (T) and (T′) is likely to be fast so that the chemical shift of H-1 could be observed as a weighted average of two types of NH protons. The amine type NH in form (T′) may be expected to be less deshielded



Scheme 2. Coplanar conformers of *Z*-isomers of **1** and **4**

than the amide-type NH in form (T). Hence the apparent small upfield shift of this signal for (*Z*)-**1** and (*Z*)-**4** relative to the corresponding signal for (*Z*)-**2** and (*Z*)-**5** suggests a possible small contribution from form (T'). Because only a very small adjustment of the position of the proton H-1 is required, the interconversion of the two forms may involve relatively little perturbation of the pyridine ring and its protons.

Methyl protons

Whereas the methyl protons at N-3 show minimal changes among the *Z*- and *E*-isomers of **4**–**6**, the methyl protons at N-1 in **7**–**9** show more interesting differences. As the 1-methyl group sterically hinders the coplanarity of the hydantoin and pyridine rings in the *Z*-isomers, its protons may now be in the shielding region of the aromatic ring and resonate at higher fields than the corresponding protons in the *E*-isomers. This is actually observed with **8** and **9**. Unexpectedly, the opposite difference is found for the *Z*-isomer of **7**. Again, this reversal is attributable to the special position of the 2-pyridyl nitrogen.

Examination of Leybold molecular models shows that since the pyridyl nitrogen does not carry a hydrogen, the steric crowding of the 1-methyl group with the 2-pyridyl ring is less severe than with the 3- or 4-pyridyl rings. Hence the deviation of the two rings from coplanarity is probably less in (*Z*)-**7** than in (*Z*)-**8** and (*Z*)-**9**. Moreover, if (*Z*)-**7** adopts the *s-cis* conformation, the interesting possibility of a hydrogen-bond-like interaction could exist between the 1-methyl protons and the 2-pyridyl nitrogen as a result of very close proximity. Similar C—H···N interactions have previously been postulated for other compounds with favourable molecular structures.[13]

Pyridyl protons

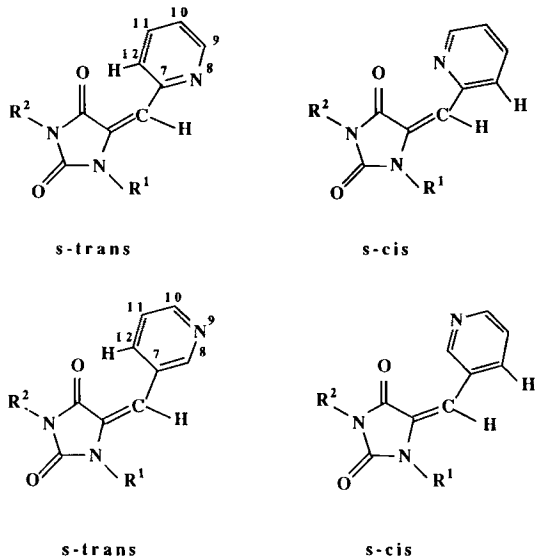
The ring protons of the 4-pyridyl compounds **3**, **6** and **9** give rise to twin doublets with finer 'inside lines' typical of 4-substituted pyridines.[14] Those of the 2-pyridyl compounds **1**, **4** and **7** and the 3-pyridyl compounds **2**, **5** and **8** give rise to more complex signals. Kowalewski and Kowalewski[15] made detailed analyses of the proton spectra of several 2- and 3-substituted pyridines. The patterns of the pyridyl protons of the 2- and 3-pyridyl compounds studied here agree particularly well with those of the published spectra of 2- and 3-acetylpyridines. Hence, assignments of the ring protons have been made based on the spin–spin coupling patterns and the expected strong electron-withdrawing effect of the pyridyl nitrogen.

Strking and interesting changes are observed in this portion of the spectra for all nine compounds **1**–**9** as the configuration changes from *Z* to *E*. These variations of the pyridyl proton shifts with configuration not only confirm the configuration assignments deduced earlier from study of the vinyl proton shifts, but also shed some light on the conformation of the pyridine ring. As expected, accompanying a *Z* to *E* change in configuration, the H-12 signal of the 2-pyridyl compounds and both H-8 and H-12 signals of the 3- and 4-pyridyl compounds move substantially downfield under the anisotropic influence of the C-4 carbonyl group (Table 3). Moreover, a more careful comparison of the magnitudes of these chemical shifts changes with configuration, $\Delta\delta$ ($\delta_E - \delta_Z$), reveals some subtle but nevertheless significant differences attributable to conformational effects.

Although the pyridine ring in each of these compounds may rotate about the C-6—C-7 bond, it is likely to prefer, wherever possible, a conformation coplanar with the hydantoin ring to achieve maximum resonance interaction (Scheme 3). By analogy with 5-benzylidenehydantoin and its 3- and 1-methyl

Table 3. Differences in chemical shifts of H-8 and H-12 in *Z*- and *E*-isomers

	$\Delta\delta$ ($\delta_E - \delta Z$) (ppm)	
Compound	H-8	H-12
1	–	0·93
2	0·00	0·35
3	0·21	0·21
4	–	0·80
5	0·05	0·36
6	0·21	0·21
7	–	0·79
8	0·26	0·52
9	0·47	0·47



Scheme 3. Coplanar conformers of *E*-isomers of **1**, **2**, **4**, **5**, **7** and **8**

derivatives,[2] it is reasonable to postulate that all the molecules of (*E*)-**1**–(*E*)-**9** and (*Z*)-**1**–(*Z*)-**6** could be planar or nearly so. However, unlike the symmetrical benzene ring, the 2- or 3-pyridyl ring may adopt either the *s-cis* or *s-trans* conformation with respect to the hydantoin moiety. In the *s-trans* conformation of the 2-pyridyl compounds (*E*)-**1**, (*E*)-**4** and (*E*)-**7**, the proton H-12 will experience the deshielding effect of the C-4 carbonyl very strongly but not in the *s-cis* conformation. The differences in the effect of the C-4 carbonyl group on the chemical shifts of the more remote protons H-9 and H-11 in the two conformers are expected to be smaller.

Hence, if the *s-trans* conformation is favoured for the *E*-isomers of **1**, **4** and **7**, the largest downfield shift accompanying configuration changes from *Z* to *E* will be shown by the H-12 signals. Based on a similar argument, for the 3-pyridyl compounds (*E*)-**2**, (*E*)-**5** and (*E*)-**8** the H-12 signal will experience a larger downfield shift than the H-8 signal if the *s-trans* is preferred to the *s-cis* conformation. On the other hand, in the 4-pyridyl compounds (*E*)-**3**, (*E*)-**6** and (*E*)-**9**, H-8 and H-12 are equivalent so that, on average, each proton experiences less of the deshielding effect of the C-4 carbonyl than that expected from a static model. Hence the $\Delta\delta$ ($\delta_E - \delta_Z$) values observed for H-8/H-12 provide a means of estimating the relative populations of the *s-cis* and *s-trans* conformations for each of the 2- and 3-pyridyl compounds. It is noted that the H-12 signals in the 2-pyridyl compounds (*E*)-**1**, (*E*)-**4** and (*E*)-**7** show the largest downfield shift ($\Delta\delta$) of 0·8–0·9 ppm. This suggests that the *s-trans* conformation is considerably preferred. Interestingly, the $\Delta\delta$ values for the H-8 and H-12 signals in the 3-pyridyl compounds (*E*)-**2**, (*E*)-**5** and (*E*)-**8** are not the same, being significantly larger for H-12 than for H-8. Since conformational changes are fast on the NMR time scale, the observed proton signals would be averages of those for all possible conformations. If, as an approximation, we consider only the two coplanar conformations and not the intermediate non-planar conformations, then the difference in $\Delta\delta$ for H-8 and H-12 may be interpreted in terms of the coexistence of both *s-trans* and *s-cis* conformations with the population of the former being higher than that of the latter so that, on average, H-12 experiences greater deshielding than H-8. That the $\Delta\delta$ values for the H-12 signal of the 3-pyridyl compounds are smaller than those for the H-12 signal of the corresponding 2-pyridyl compounds suggests a less strong preference for the *s-trans* conformation in the case of the 3-pyridyl compounds. For both groups of compounds the *s-cis* conformation is less favourable, probably because of repulsion between the lone pairs of electrons on the pyridyl nitrogen and on the C-4 carbonyl oxygen. Understandably, this effect is stronger when the two atoms concerned are closer together as in the 2-pyridyl compounds, as shown by examination of Leybold models.

Variable-temperature ^1H NMR studies

The temperature dependence of NMR spectra provides a valuable tool for conformation studies. This technique was applied to examine further the relative stabilities of the *s-trans* and *s-cis* conformations of the *E*-isomers of **1**–**9**. However, a low temperature study could not be carried out as deuterated dimethyl sulphoxide was used as the solvent. Low solubilities of these compounds in solvents such as deuterated acetone or acetonitrile make them also unsuitable for low-temperature study. Instead, spectra in deuterated dimethyl sulphoxide were obtained at various higher temperatures from 25 to 120 °C. For the *E*-isomers of the 2- and 3-pyridyl compounds, if the *s-trans* conformation is indeed more stable than the *s-cis* conformation as suggested above, then raising the temperature could make the latter more accessible and increase its population at the expense of the former conformation, although at elevated temperatures contributions from the non-planar conformations probably also increase. Such shifts in conformational equilibria should be reflected by the differences in the observed temperature effects on the chemical shifts of the various proton signals, particularly those of the pyridyl protons (Table 4). While a general slight upfield shift is observed in the pyridyl protons with increasing temperature, this is most pronounced for H-12. Although the magnitude of the temperature effect on

Table 4. Temperature dependence of the ^{1}H NMR shifts (ppm) of the pyridyl protons of (*E*)-**1**–(*E*)-**9**

Compound	Hydrogen	Temperature (°C) 25	65	90	120	$\delta_{120} - \delta_{25}$
(*E*)-**1**	H-9	8·65	8·65	8·65	8·65	0·00
	H-10	7·29	7·28	7·27	7·26	−0·03
	H-11	7·84	7·83	7·82	7·80	−0·04
	H-12	8·52	8·49	8·46	8·42	−0·10
(*E*)-**2**	H-8	8·82	8·82	8·81	8·80	−0·02
	H-10	8·43	8·42	8·41	8·41	−0·02
	H-11	7·37	7·35	7·32	7·30	−0·07
	H-12	8·39	8·35	8·31	8·28	−0·11
(*E*)-**3**	H-9, 11	8·54	8·53	8·53	8·54	0·00
	H-8, 12	7·79	7·76	7·73	7·72	−0·07
(*E*)-**4**	H-9	8·65	8·66	8·65	8·66	0·01
	H-10	7·30	7·29	7·28	7·27	−0·03
	H-11	7·83	7·83	7·82	7·81	−0·02
	H-12	8·56	8·52	8·49	8·45	−0·11
(*E*)-**5**	H-8	8·86	8·85	8·84	8·84	−0·02
	H-10	8·48	8·45	8·45	8·45	−0·03
	H-11	7·38	7·35	7·34	7·32	−0·06
	H-12	8·43	8·38	8·35	8·32	−0·11
(*E*)-**6**	H-9, 11	8·56	8·55	8·54	8·52	−0·04
	H-8, 12	7·82	7·78	7·76	7·73	−0·09
(*E*)-**7**	H-9	8·57	8·56	8·55	8·54	−0·03
	H-10	7·27	7·25	7·24	7·22	−0·05
	H-11	7·78	7·76	7·75	7·73	−0·05
	H-12	8·40	8·37	8·35	8·31	−0·09
(*E*)-**8**	H-8	8·87	8·87	8·86	8·86	−0·01
	H-10	8·45	8·44	8·41	8·43	−0·02
	H-11	7·38	7·36	7·33	7·33	−0·05
	H-12	8·38	8·35	8·31	8·29	−0·09
(*E*)-**9**	H-9, 11	8·55	8·53	8·52	8·52	−0·03
	H-8, 12	7·80	7·77	7·75	7·73	−0·07

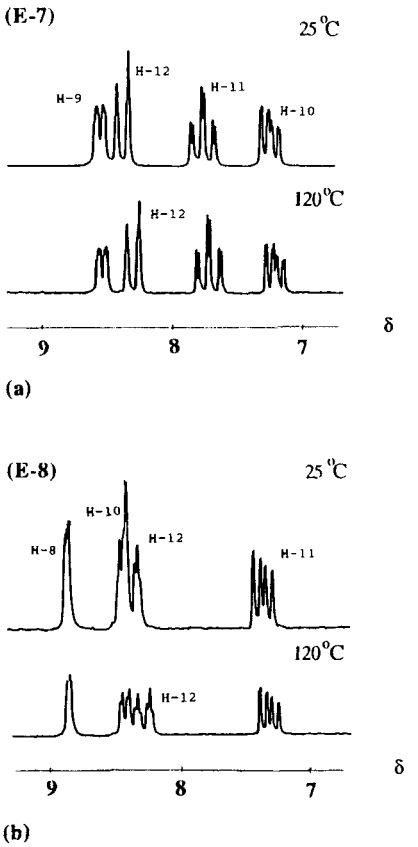


Figure 1. Temperature dependence of the chemical shifts of the pyridyl protons of (a) (*E*)-**7** and (b) (*E*)-**8**

chemical shift differences is understandably small, the much larger change in the position of the H-12 signal relative to the signals of the other pyridyl protons is unmistakably evident on comparison of the spectra at 25 and 120 °C, as illustrated in Figure 1. This pronounced relative upfield shift of H-12 with increase in temperature is consistent with a decrease of residence time in the *s-trans* conformation where this proton is particularly deshielded by the anisotropic C-4 carbonyl group. A similar but smaller upfield shift is observed for the signal of the more distant H-11 on the same side of the pyridine ring. The opposite changes are expected for the protons H-8 and H-9 on the other side of the pyridine ring. This is clearly demonstrated by the almost negligible change in the H-8 signals of (*E*)-**2**, (*E*)-**5** and (*E*)-**8** with temperature, which may be interpreted as the combined effects of a general upfield shift with temperature increase and an expected downfield shift due to an increased residence time in the *s-cis* conformation where H-8 approaches closely the C-4 carbonyl. In the case of (*E*)-**3**, (*E*)-**6** and (*E*)-**9**, symmetry of the 4-pyridyl ring does not distinguish *s-trans* and *s-cis* conformations. That the signals of H-8 and H-12 still show larger upfield shifts with increasing temperature than those of H-9 and H-11 may be due to increased contributions from the non-planar conformations in which the pyridyl protons, especially H-8 and H-12, move away from the deshielding influence of the C-4 carbonyl group.

^{13}C NMR spectra

Differences in the ^{13}C NMR spectra of the *Z*- and *E*-isomers of **1**–**9** (Table 5) show considerable regularity and provide further correlation with configuration.

Studies of pairs of geometric isomers of alkenes have revealed a tendency for the olefinic carbons in the *E*-isomers to resonate at lower field than those in the *Z*-isomers.[16] The C-6 signals, and to a much lesser extent the C-5 signals, of **1**–**9** conform to this trend. It is interesting that the direction of the change in C-6 shift with configuration is opposite to that of the

Table 5. ^{13}C NMR shifts (ppm) of compounds **1–9** [solvent, $(CD_3)_2$ SO]

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	1-CH_3	3-CH_3
(*Z*)-**1**	154·6	165·1	131·7	104·9	153·6	–	149·4	122·2	137·1	125·4	–	–
(*E*)-**1**	153·6[a]	163·4	132·0	115·3	152·1	–	149·1	122·2	135·9	124·0	–	–
(*Z*)-**2**	155·6	165·2	129·5	104·4	129·1	150·2	–	148·6	123·6	135·7	–	–
(*E*)-**2**	153·8	163·4	131·3	110·9	131·3	150·4	–	148·4	122·9	136·1	–	–
(*Z*)-**3**	155·5	165·0	131·2	104·4	140·1	123·0	149·8	–	149·8	123·0	–	–
(*E*)-**3**	154·1	163·5	133·3	111·2	140·5	123·5	149·4	–	149·4	123·5	–	–
(*Z*)-**4**	154·2	163·8	130·5	105·9	153·5	–	149·4	122·3	137·0	125·5	–	24·1
(*E*)-**4**	153·5[a]	161·9	130·7	116·1	152·1	–	149·1	122·3	135·9	124·1	–	24·1[b]
(*Z*)-**5**	155·3	163·9	128·9	105·3	128·4	150·2	–	148·7	123·6	135·7	–	24·2
(*E*)-**5**	153·4	162·0	130·0	111·8	128·3	150·6	–	148·5	122·9	136·1	–	24·0
(*Z*)-**6**	155·4	164·0	130·4	105·5	140·0	123·1	150·0	–	150·0	123·1	–	24·3
(*E*)-**6**	153·5	161·9	132·0	112·3	140·0	123·3	149·5	–	149·5	123·3	–	24·1
(*Z*)-**7**	155·6	164·6	131·9	108·1	151·9	–	149·0	122·4	136·5	126·1	30·6	–
(*E*)-**7**	153·4	162·7	132·6	114·6	152·1	–	149·0	122·4	135·8	124·3	25·7	–
(*Z*)-**8**	155·3	163·9	132·0	105·4	128·8	149·8	–	148·6	122·9	136·7	29·5	–
(*E*)-**8**	153·3	162·7	131·9	110·8	129·1	150·7	–	148·4	122·8	136·2	25·8	–
(*Z*)-**9**	155·4	163·9	132·6	105·8	140·6	124·1	149·1	–	149·1	124·1	29·6	–
(*E*)-**9**	153·5	162·7	133·5	111·3	140·5	123·8	149·4	–	149·4	123·8	25·9	–

[a] The C-2 signal of the *E*-isomer probably merged with the C-7 signal of the *Z*-isomer.
[b] The 3-CH_3 signal of the *E*-isomer probably merged with that of the *Z*-isomer.

change in H-6 shift. Similarly, it is observed that the 1-methyl carbons of **7–9** show a downfield shift in the *Z*-isomers relative to those in the *E*-isomers, although the 1-methyl protons of **8** and **9** show an opposite shift with configuration. This is not surprising as it is well known that an anisotropic neighbouring group has a large effect on proton shieldings but its effect on carbon shielding is small and often cannot be separated from or even masked by other contributions.[17] The C-2 and C-4 signals of all compounds **1–9** are consistently more deshielded in the *Z*-isomers than in the *E*-isomers. On the other hand, the 3-methyl carbon of **4–6**, being more distant from the olefinic bond, is less affected by configurational changes, as shown by the minimal differences in their chemical shifts in the two isomers.

EXPERIMENTAL

5-Pyridylmethylenehydantoins **1–9** were prepared by condensation of hydantoin, 3-methylhydantoin or 1-methylhydantoin (0·01 mol) with 2-, 3- or 4-pyridinecarboxaldehyde (0·01 mol) in an aqueous solution (10 ml) of alanine (0·01 mol) and sodium carbonate (0·005 mol). The mixture was refluxed for 2–3 h, cooled, diluted with water and acidified with hydrochloric acid. The *Z*- and *E*-isomers of **7–9** were separated by fractional recrystallization with methanol. All the other compounds were also recrystallized from methanol except **3**, which was purified using 5 M acetic acid as it was very sparingly soluble in most of the common solvents.

The *Z*-isomers of **1–6** were partially converted into the *E*-isomers by photoisomerization, using a Hanovia mercury-vapour lamp (654A-0360) and a solution filter made up of 0·27 g l^{-1} K_2CrO_4 and 1 g l^{-1} Na_2CO_3 and having a transmission maximum around 313 nm. Samples further enriched in *E*-isomers could be obtained by careful and selective recrystallization. ^1H and ^{13}C NMR spectra were recorded in $(CD_3)_2SO$ solution with tetramethylsilane as internal reference using a JEOL FX90Q spectrometer. In the variable-temperature experiments, the concentrations of the solutions were kept at 20 mg ml^{-1}.

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