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SYNTHESIS AND NMR STUDY OF 5-FURYLMETHYLENEHYDANTOINS AND 5-THIENYLMETHYLENEHYDANTOINS

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Two series of 5-furylmethylenehydantoins and 5-thienylmethylenehydantoins were prepared and their ^1H and ^{13}C NMR spectra studied in comparison with those of compounds in the analogous 5-aryl- and 5-pyridyl- series. Differences in the effects of the aromatic, six- or five-membered heteroaromatic rings are discussed. Spectral analysis enables *Z*/*E* configurations to be assigned with confidence and conformational preferences to be qualitatively deduced. Some interesting solvent effects were also observed.

INTRODUCTION

Various physicochemical properties of the two series of 5-arylmethylenehydantoins and 5-pyridylmethylenehydantoins have been investigated and the differences resulting from replacement of the benzene ring by the pyridine ring in the unsaturated side-chain of hydantoin have been discussed.[1–7] A survey of the literature revealed little work on the corresponding compounds with a furan or thiophene ring in place of benzene or pyridine. Although the preparations of 5-(2-furyl)-methylenehydantoin and 5-(2-thienyl)methylene-hydantoin have been described,[8–11] their properties remain largely unexplored and there appear to be no reports on the 3-furyl and 3-thienyl analogues. This prompted us to prepare the two series of 5-furyl-methylenehydantoins and 5-thienylmethylenehydantoins with the purpose of studying and comparing the effects of the two five-membered heterocycles on their properties. We report here a study of their ^1H and ^{13}C NMR spectra.

RESULTS AND DISCUSSION

Synthesis

Compounds **1–12** were prepared by condensation of hydantoin, 1-methylhydantoin or 3-methylhydantoin with 2-/3-furancarboxaldehyde or 2-/3-thiophenecarboxaldehyde in a buffered aqueous medium containing alanine and sodium carbonate.[12] This method gave much better yields than the previously reported methods for the preparation of 5-(2-furyl)methylene-hydantoin and 5-(2-thienyl)methylenehydantoin. In particular, excellent yields were obtained for the thienyl compounds. From the preparation of each of the *N*-unsubstituted and the 3-methyl-substituted compounds, only one of the two possible geometric isomers was isolated, but for each of the 1-methyl substituted compounds, both isomers were obtained. The melting points and analytical data are given in Table 1.

^1H NMR spectra

^1H NMR spectra were recorded in $(CD_3)_2SO$ and, with the exception of the sparingly soluble *N*-unsubstituted compounds **1–4**, also in $CDCl_3$ (Table 2).

Configurational assignments

As found from previous studies of the aryl and the pyridyl series,[1,5] the configurations of a given pair of geometric isomers can be distinguished readily by comparison of the chemical shifts of their H-6 signals. Only in the *Z*-configuration is this proton located close to and therefore deshielded by the anisotropic C-4 carbonyl group. Hence the *Z*-isomers may be expected to show lower field H-6 signals than the *E*-isomers. This order holds for the isolated pairs of isomers of the 1-methyl-substituted compounds **9**, **10** and **12** in their

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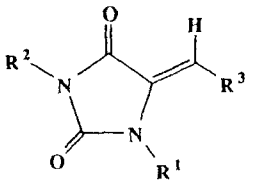
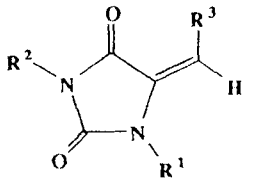


Z-isomer



E-isomer

Compound	R^1	R^2	R^3
1	H	H	
2	H	H	
3	H	H	
4	H	H	
5	H	Me	
6	H	Me	
7	H	Me	
8	H	Me	
9	Me	H	
10	Me	H	
11	Me	H	
12	Me	H	

spectra recorded in both solvents (Table 3). Interestingly, the H-6 signals of the two isomers of **11** follow the expected order in $CDCl_3$ but the reverse order in $(CD_3)_2SO$. This uncertainty, as far as configuration assignment of **11** is concerned, is resolved by reference to another part of the spectra. Only in the *E*-configuration would proton H-11 come under the deshielding influence of the C-4 carbonyl group when the thiophene ring adopts the *s-trans* conformation. This signal is indeed found to show the expected large difference in the spectra of the two isomers. Hence, that isomer of **11** which shows the more deshielded H-6 in $CDCl_3$ and less deshielded H-11 in either solvent is assigned the *Z*-configuration. The other isomer is therefore assigned the *E*-configuration. The reason for the unusually low-field resonance of H-6 of (*E*)-**11** in $(CD_3)_2SO$ is unclear.

The only isolated isomer of each of the 3-methyl-substituted compounds **5–8** is assigned the *Z*-configuration by comparison of its H-6 shifts in $CDCl_3$ with that of the *Z*-isomer of the corresponding 1-methyl-substituted analogues. As **1–4** are not sufficiently soluble in $CDCl_3$, their configurational assignments have been deduced from ^{13}C NMR spectra in $(CD_3)_2SO$. The assignments of configuration of all the other compounds **5–12** based on ^1H spectra are

Table 1. Melting points and analytical data for compounds **1**–**12**

Compound	Melting point (°C)	Calculated (%)				Found (%)			
		C	H	N	S	C	H	N	S
(*Z*)-**1**	235–327	53·9	3·4	15·7		53·6	3·5	15·6	
(*Z*)-**2**	252–254	53·9	3·4	15·7		53·5	3·1	15·6	
(*Z*)-**3**	262–264	49·5	3·1	14·4	16·5	49·7	2·9	14·6	16·9
(*Z*)-**4**	269·5–271	49·5	3·1	14·4	16·5	49·4	2·9	14·4	16·6
(*Z*)-**5**	217–219	56·2	4·2	14·6		56·2	4·0	14·5	
(*Z*)-**6**	243–246	56·2	4·2	14·6		56·2	4·0	14·4	
(*Z*)-**7**	267–269	51·9	3·8	13·6	15·4	51·9	3·7	13·3	15·8
(*Z*)-**8**	239–241	51·9	3·8	13·6	15·4	51·9	3·7	13·3	15·3
(*Z*)-**9**	194–196	56·2	4·2	14·6		56·0	4·1	14·4	
(*E*)-**9**	186–188	56·2	4·2	14·6		56·1	4·1	14·5	
(*Z*)-**10**	146–147	56·2	4·2	14·6		55·9	4·2	14·5	
(*E*)-**10**	210–212	56·2	4·2	14·6		56·0	4·1	14·8	
(*Z*)-**11**	137–138·5	51·9	3·8	13·5	15·4	51·7	3·6	13·2	15·6
(*E*)-**11**	218–220	51·9	3·8	13·5	15·4	52·1	3·7	13·5	15·9
(*Z*)-**12**	163–164	51·9	3·8	13·5	15·4	51·6	3·7	13·2	15·4
(*E*)-**12**	214·5–217	51·9	3·8	13·5	15·4	52·0	3·8	13·3	15·4

further supported by their ^{13}C spectra, as will be discussed later. X-ray crystallographic analysis of some of these compounds is in progress and configurations assigned to at least two of them have been confirmed so far. These crystallographic results will be reported later.

NH protons

In all the compounds studied, these protons give low-field signals in the ranges δ 10·2–10·5 and 11·1–11·5 in the spectra obtained in $(CD_3)_2SO$. Assignments of these signals to the protons at N-1 and N-3, respectively, for the *N*-unsubstituted compounds are confirmed by comparison with those given by the 3-methyl- or 1-methyl-substituted derivatives, each of which has only one NH proton. The N-3 proton is more deshielded by two adjacent carbonyl groups than the N-1 proton with only one neighbouring carbonyl group. These NH shift ranges appear at slightly higher field than those of similar protons in the series of 5-pyridylmethylenehydantoins,[5] consistent with the lower electron-withdrawing character of the furan/thiophene relative to the pyridine ring.

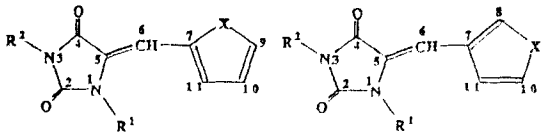
N-Me protons

The chemical shifts of the N(3)-Me protons measured in $(CD_3)_2SO$ are almost the same for all four 3-methyl-substituted compounds and are also very close to the values for similar protons in the 3-methyl-substituted compounds in the aryl and pyridyl series previously studied. This is not surprising since the N(3)-Me protons are far from and not conjugated with the unsaturated side-chain. By contrast, the chemical shifts of the N(1)-Me protons show more interesting variations according to structure, configuration and conformation

It has been reported earlier that in the *Z*-isomers of the 1-methyl-substituted compounds of the aryl and pyridyl series, the bulk of the methyl group causes the benzene/pyridine ring to twist out of the plane of the hydantoin ring. With the sole exception of (*Z*)-1-methyl-5-(2-pyridyl)methylenehydantoin, the 1-methyl protons in all the other compounds of these two series are within the shielding zone of the aromatic ring and therefore are upfield by 0·2–0·3 ppm relative to the corresponding protons in the *E*-isomers. This effect is less pronounced or not observed among the 1-methyl-substituted compounds of the furyl and thienyl series, probably because of less steric crowding between the smaller five-membered heterocycles and the N(1)-Me group in the *Z*-configuration. Only in the 3-thienyl compound **12** are the N(1)-Me protons slightly more shielded in the *Z*-isomer than in the *E*-isomer, but in the 2-thienyl compound **11** the corresponding protons are marginally more deshielded in the *Z*- than in the *E*-isomer.

With the even smaller furan ring in the *Z*-isomers of **9** and **10**, deviation of the molecules from planarity may not be sufficient to place the N(1)-Me protons in the aromatic shielding zone. The N(1)-Me signals of both *Z*- and *E*-isomers of the 3-furyl compound **10** are virtually the same. By contrast, a substantial downfield shift is observed for the N(1)-Me protons in the *Z*-isomer relative to the *E*-isomer of the 2-furyl compound **9**, suggesting a possible influence by the O atom of the furan ring in the *s-cis* conformation. This is reminiscent of the exceptional deshielding effect experienced by the corresponding protons of (*Z*)-1-methyl-5-(2-pyridyl)-

Table 2. ^{1}H shifts (ppm) of compounds **1–12** in $(CD_3)_2SO$ and $CDCl_3$



R^1 and R^2 = H or CH_3
X = O or S

Compound	N(1)-H	N(3)-H	N(1)-CH_3	N(3)-CH_3	H-6	H-8	H-9	H-10	H-11
(*Z*)-**1**	10·30[a]	11·21[a]			6·33[a]		7·75[a]	6·62[a]	6·93[a]
(*Z*)-**2**	10·17[a]	11·14[a]			6·34[a]	8·16[a]		7·74[a]	7·01[a]
(*Z*)-**3**	10·38[a]	11·17[a]			6·59[a]		7·70[a]	7·18[a]	7·61[a]
(*Z*)-**4**	10·36[a]	11·19[a]			6·50[a]	7·94[a]		7·61[a]	7·48[a]
(*Z*)-**5**	10·53[a]			2·96[a]	6·34[a]		7·78[a]	6·63[a]	6·96[a]
	8·19[b]			3·13[b]	6·55[b]		7·56[b]	6·51[b]	6·60[b]
(*Z*)-**6**	10·24[a]			2·95[a]	6·47[a]	8·19[a]		7·75[a]	7·04[a]
	7·62[b]			3·14[b]	6·64[b]	7·72[b]		7·53[b]	6·56[b]
(*Z*)-**7**	10·54[a]			2·95[a]	6·69[a]		7·71[a]	7·17[a]	7·61[a]
	7·35[b]			3·14[b]	6·94[b]		7·48[b]	7·12[b]	7·30[b]
(*Z*)-**8**	10·57[a]			2·96[a]	6·62[a]	7·99[a]		7·63[a]	7·51[a]
	7·99[b]			3·15[b]	6·78[b]	7·50[b]		7·44[b]	7·22[b]
(*Z*)-**9**		11·34[a]	3·35[a]		6·39[a]		7·82[a]	6·63[a]	6·87[a]
		8·50[b]	3·52[b]		6·57[b]		7·51[b]	6·50[b]	6·63[b]
(*E*)-**9**		11·28[a]	3·07[a]		6·30[a]		7·76[a]	6·62[a]	7·63[a]
		8·43[b]	3·19[b]		6·21[b]		7·49[b]	6·54[b]	7·78[b]
(*Z*)-**10**		—[c]	3·08[a]		6·39[a]	7·97[a]		7·73[a]	6·69[a]
		8·53[b]	3·19[b]		6·63[b]	7·55[b]		7·47[b]	6·46[b]
(*E*)-**10**		11·29[a]	3·05[a]		6·28[a]	8·31[a]		7·68[a]	7·16[a]
		7·84[b]	3·18[b]		6·05[b]	8·24[b]		7·44[b]	7·03[b]
(*Z*)-**11**		11·47[a]	3·10[a]		6·65[a]		7·68[a]	7·12[a]	7·29[a]
		7·78[b]	3·26[b]		6·90[b]		7·43[b]	7·06[b]	7·11[b]
(*E*)-**11**		11·33[a]	3·08[a]		6·74[a]		7·61[a]	7·10[a]	7·64[a]
		7·89[b]	3·20[b]		6·42[b]		7·44[b]	7·10[b]	7·65[b]
(*Z*)-**12**		11·38[a]	2·95[a]		6·56[a]	7·56[a]		7·65[a]	7·24[a]
		8·50[b]	3·07[b]		6·82[b]	7·29[b]		7·37[b]	7·08[b]
(*E*)-**12**		11·33[a]	3·07[a]		6·48[a]	8·82[a]		7·53[a]	7·78[a]
		8·05[b]	3·20[b]		6·26[b]	8·27[b]		7·32[b]	7·64[b]

[a] In $(CD_3)_2SO$.
[b] In $CDCl_3$.
[c] signal note detected.

Table 3. Difference in ^{1}H shifts (ppm) between *Z*- and *E*-isomers of compounds **9–12** in $(CD_3)_2SO$ and $CDCl_3$

	$\delta_Z - \delta_E$					
Compound	H-6	N(1)CH_3	H-8	H-9	H-10	H-11
9	0·09[a]	0·28[a]		0·06[a]	0·01[a]	−0·76[a]
	0·36[b]	0·33[b]		0·02[b]	−0·03[b]	−1·15[b]
10	0·11[a]	0·03[a]	−0·34[a]		0·05[a]	−0·47[a]
	0·58[b]	0·01[b]	−0·69[b]		0·03[b]	−0·57[b]
11	−0·09[a]	0·02[a]		0·07[a]	0·02[a]	−0·35[a]
	0·48[b]	0·06[b]		−0·01[b]	−0·04[b]	−0·54[b]
12	0·08[a]	−0·12[a]	−0·72[a]		0·12[a]	−0·54[a]
	0·56[b]	−0·13[b]	−0·98[b]		0·05[b]	−0·56[b]

[a] In $(CD_3)_2SO$.
[b] in $CDCl_3$.

methylenehydantoin, which has previously been attributed to intramolecular N-CH_3—N interaction.[5] The 2-thienyl compound (*Z*)-**11** does not show this strong effect owing to the lower electronegativity of the S atom. Changing the solvent from $(CD_3)_2SO$ to $CDCl_3$ does not alter the relative order of the N-Me shifts while the difference in the chemical shifts of N(1)-Me protons in the *Z* and *E* pair of **9** is further magnified in $CDCl_3$.

Vinyl proton H-6

In addition to the effects of configuration mentioned earlier, the H-6 resonances show another trend. The H-6 shift of a thienyl compound appears consistently at a lower field than that of the corresponding furyl compound. Assuming that the molecules are planar, or nearly so, this proton should lie in the deshielding region of the five-membered heteroaromatic ring so that the lower field H-6 signal in the thienyl compound could be a reflection of the stronger ring current effect of thiophene than furan.

Ring protons

The NMR spectra of furans and thiophenes have been the subject of a number of investigations.[13,14] The main differences between these two heterocycles can be rationalized on the basis of inductive and resonance effects. The α-ring protons are more deshielded in furan than in thiophene owing to the stronger electron-withdrawing effect of O than S. The reverse order holds for the β-ring protons, which are more deshielded in thiophene owing to its higher aromatic character. Hence, the ring proton signals in furan are generally more widely separated than those in thiophene. The coupling constants are also different, reflecting differences in bond orders and bond angles in these two ring systems. *Meta* coupling, especially across the heteroatom, is much stronger than in benzene. The splitting patterns of the ring protons are generally easily recognizable and facilitate signal assignments.

2-Furyl and 2-thienyl compounds

While configuration assignment can be made from comparison of the H-6 shifts, conformational information may be deduced from consideration of the ring proton shifts. In both $(CD_3)_2SO$ and $CDCl_3$, the chemical shifts of the ring protons follow the order H-9 > H-11 > H-10. The only α-proton H-9 is deshielded by the adjacent heteroatom, especially by the more electronegative O. Of the two β-protons, H-11 is more deshielded owing to the adjacent methylenehydantoin group. Both H-10 and H-11 in the 2-thienyl compounds generally resonate more downfield than those in the 2-furyl analogues because of the stronger diamagnetic ring current in the S-heterocycle.

Exceptions to the above order of ring proton shifts are shown by (*E*)-**9** in $CDCl_3$ and (*E*)-**11** in both $(CD_3)_2SO$ and $CDCl_3$. In these spectra, the order is H-11 > H-9 > H-10. Again, it is the upset of a general trend that generates additional interest. In this case, the effect that causes the β-proton H-11 to move further downfield than the α-proton H-9 could be conformational. In the *E*-configuration, H-11 will come closest to and be deshielded by the anisotropic C-4 carbonyl group if the ring adopts the *s-trans* conformation. In the *Z*-configuration, all ring protons are too far away from the influence of this carbonyl group so that comparison of the changes in the chemical shifts of the three ring protons accompanying the *Z* to *E* configurational change should provide useful information about conformations. From Table 3, it is clear that H-11 is the most affected, with the largest $\delta_Z - \delta_E$ value observed for **9** particularly when recorded in $CDCl_3$. This suggests that the predominant conformation in (*E*) – **9** is *s-trans*, the *s-cis* conformation being destablized by repulsion between the lone pairs of the carbonyl oxygen and the furan oxygen atoms. On the other hand, the interaction between the C-4 carbonyl oxygen and the thiophene sulphur atom in the *s-cis* conformation of (*E*)-**11** may be more complex. While the larger size of the sulphur atom may be a sterically destablizing factor, some S·····O non-bonded attraction of the donor–acceptor type[15] due to the vacant d-orbitals of sulphur may exist when S and O atoms come into close contact in this *s-cis* conformation. Without x-ray data, this remains a hypothetical possibility.

Since conformational changes are fast on the NMR scale, the observed signals of these ring protons are weighted averages of those in all possible conformations. If only the coplanar conformations are considered, as an approximation, then the larger $\delta_Z - \delta_E$ value observed for **9** than **11** indicates that the *s-trans* conformation is more strongly preferred in (*E*)-**9**, but significant populations of *s-trans* and *s-cis* conformers may coexist in (*E*)-**11**.

3-Furyl and 3-thienyl compounds

The two α-protons H-8 and H-10 are both deshielded by the adjacent heteroatom. H-8 is further deshielded by the adjacent unsaturated methylenehydantoin group. Hence, the general order of chemical shifts of the ring protons is H-8 > H-10 > H-11. Again two exceptions are noted. First, in the spectrum of the 3-thienyl compound (*Z*)-**12**, H-10 > H-8. A possible explanation is that the 3-thienyl and hydantoin rings in this compound are not coplanar owing to steric interference by the N(1)-methyl group so that the electron-withdrawing effect of the methylenehydantoin group cannot be efficiently transmitted to H-8. This is in contrast to the other 3-thienyl compounds (*Z*)-**4** and (*Z*)-**8**, which do not have a methyl group at N-1 and are there-

fore more likely to have coplanar rings. Further evidence for this steric inhibition of the conjugation effect can be adduced from the observation that both H-8 and H-10 are less deshielded in (*Z*)-**12** than in (*Z*)-**4**/**8**.

The usual order H-8 > H-10 holds for the 3-furyl compounds, not only (*Z*)-**2** and (*Z*)-**6** but also (*Z*)-**10**. In (*Z*)-**10**, the less severe steric interference between the N(1)-methyl group and the small furan ring could result in only a minor deviation from molecular planarity, the consequence of which may be reflected by the reduced difference between the chemical shifts of H-8 and H-10 for this compound relative to those for (*Z*)-**2** and (*Z*)-**6**. Second, in the spectrum of (*E*)-**12**, H-11 is more deshielded than H-10, suggesting that in this isomer H-11 comes within the deshielding one of the C-4 carbonyl group in the *s-trans* conformation. However, an examination of the $\delta_Z - \delta_E$ values shows that for this compound, H-8 experiences an even larger downfield shift than H-11, which may be interpreted as the result of deshielding by the carbonyl group in the *s-cis* conformation of the *E*-isomer. Therefore, it is likely that both conformers of (*E*)-**12** coexist with perhaps a slight preference for the *s-cis* form. For **10**, the $\delta_Z - \delta_E$ values for both H-8 and H-11 are comparable, showing that its *E*-isomer has no strong preference for either conformation.

^{13}C NMR spectra

Studies of the ^{13}C NMR spectra complement those of the ^{1}H NMR spectra. Assignments of the ^{13}C shifts of **1**–**12** (Table 4) are based on a comparison with those of compounds in the phenyl and pyridyl series [1,5] and with data on several monosubstituted furans and thiophenes.[16,17]

The chemical shifts of the two carbonyl signals C-2 and C-4 show little difference from those of their phenyl and pyridyl analogues, with the C-4 signal similarly at lower field than the C-2 signal. These carbons are far away from and therefore little influenced by the nature of the aromatic ring in the side-chain. As expected, more significant effects are observed at C-5 and C-6. Both C-5 and C-6 signals in **1**–**12** are found at higher fields than the corresponding signals in the phenyl and pyridyl compounds, in agreement with lower electron-withdrawing character of furan and thiophene rings relative to benzene and pyridine rings.

Regular trends are observed for the ^{13}C resonances in pairs of geometric isomers of **9**–**12** and therefore are useful for configuration assignments. Both carbonyl signals C-2 and C-4 are more deshielded in the *Z*- than the *E*-isomers. Following the tendency for an olefinic carbon in an *E*-isomer to resonate at lower field than in a *Z*-isomer,[18] the C-6 signals in all the *E*-isomers of the studied compounds, including (*E*)-**11**, are more deshielded than those in the corresponding *Z*-isomers. Hence, comparison of the C-2, C-4 and C-6 shifts of the *N*-unsubstituted compounds **1**–**4** and 3-methyl-substituted compounds **5**–**8** with those of **9**–**12** further supports the assignment of the *Z*-configuration to the only isolated isomers of those compounds. The 1-methyl carbons of **9**–**12** show a downfield shift in the *Z*-isomers relative to those in the *E*-isomers, following the trend observed among the 1-methyl-substituted compounds of the phenyl and pyridyl series. The 3-methyl carbons in **5**–**8** have identical chemical shifts which are also virtually the same as those previously observed for the 3-methyl-substituted compounds of the phenyl and pyridyl series.

In furan, the α-carbons resonate at substantially lower field than the β-carbons, whereas in thiophene the chemical shifts of the α- and β-carbons follow the reverse order but with much smaller differences. The

Table 4. ^{13}C shifts (ppm) of compounds **1**–**12** in $(CD_3)_2SO$

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	1-CH_3	3-CH_3
(*Z*)-**1**	154·9	164·9	126·0	96·5	149·1		144·3	112·8/112·5	112·5/112		
(*Z*)-**2**	155·2	165·1	126·9	99·6	119·0	144·3		144·2	109·9		
(*Z*)-**3**	155·3	165·1	126·2	101·5	135·9		128·3	128·9/128·7	128·7/128		
(*Z*)-**4**	155·3	165·5	128·4	102·9	134·2	126·7		126·7	128·4		
(*Z*)-**5**	154·6	163·7	124·7	97·41	149·0		144·5	112·6/113·3	113·3/112		24·2
(*Z*)-**6**	154·8	163·8	125·6	100·6	118·9	144·4		144·4	109·8		24·1
(*Z*)-**7**	154·9	163·8	125·0	102·4	135·8		128·6	128·6/129·2	129·2/128		24·2
(*Z*)-**8**	154·9	164·2	125·3	103·9	134·0	127·0		126·7	128·3		24·1
(*Z*)-**9**	155·0	164·4	126·8	97·1	147·8		145·1	115·8/112·5	112·5/115	29·4	
(*E*)-**9**	153·2	162·4	128·0	102·4	149·2		143·7	112·9/112·5	112·5/112	25·7	
(*Z*)-**10**	155·2	164·1	129·9	100·3	117·3	144·9		143·7	111·9	29·0	
(*E*)-**10**	153·2	162·7	129·0	104·7	119·3	144·7		142·9	111·7	25·4	
(*Z*)-**11**	155·2	164·1	127·7	102·2	134·1		128·6	129·5/130·7	130·7/129	29·4	
(*E*)-**11**	153·2	162·7	127·1	108·4	136·0		129·5	133·0/132·9	132·9/133	25·7	
(*Z*)-**12**	155·4	164·3	130·2	104·4	132·8	126·2		126·2	129·3	29·2	
(*E*)-**12**	153·2	162·9	129·0	109·2	134·4	127·8		125·4	130·1	25·7	

Table 5. Solvent effects on ^1H shifts (ppm)

	$\Delta\delta = \delta_{(CD_3)_2SO} - \delta_{(CDCl_3)}$				
Compound	N(1)-H	N(3)-H	N(1)-CH_3	N(3)-CH_3	H-6
(*Z*)-**5**	2.34			−0.17	−0.21
(*Z*)-**6**	2.62			−0.19	−0.17
(*Z*)-**7**	3.19			−0.19	−0.25
(*Z*)-**8**	2.58			−0.19	−0.16
(*Z*)-**9**		2.84	−0.17		−0.18
(*E*)-**9**		2.85	−0.12		0.09
(*Z*)-**10**			−0.11		−0.24
(*E*)-**10**		3.45	−0.13		0.23
(*Z*)-**11**		3.69	−0.16		−0.25
(*E*)-**11**		3.44	−0.12		0.32
(*Z*)-**12**		2.88	−0.12		−0.26
(*E*)-**12**		3.28	−0.13		0.22

methylenehydantoin group also deshields the ring carbon attached to it. Parallel to the trend observed for the ring protons, the signals of the α- and β-ring carbons are also better separated in the furyl than in the thienyl compounds.

Solvent effects

The ^1H spectra show an interesting and informative solvent dependence. Differences in chemical shifts observed in $(CD_3)_2SO$ and $CDCl_3$ for **5–12** are given in Table 5. Satisfactory spectra for **1–4** could not be obtained in $CDCl_3$. The low solubilities of all the compounds preclude studies in non-polar solvents such as CCl_4 or hydrocarbons. The most pronounced solvent effect is shown by the NH shifts. The dramatic upfield shifts that accompany a change of solvent from $(CD_3)_2SO$ to $CDCl_3$ appear to be related to the acidity of these protons. Solvation by hydrogen bonding with the basic dimethyl sulphoxide molecules results in a deshielding effect which is more pronounced in the case of the more acidic N-3 than the N-1 proton, as shown by the larger $\Delta\delta$ value for a 1-methyl-substituted compound such as (*Z*)-**12** than that for its 3-methyl-substituted analogue such as (*Z*)-**8**. The chloroform molecules have relatively little interaction with these protons.

The N-Me resonances follow an opposite trend of solvent dependence to that noted for the NH resonances. All N-Me signals shift downfield with change of solvent from $(CD_3)_2SO$ to $CDCl_3$. These divergent effects clearly indicate different modes of interaction. While the acidic NH protons interact directly with the basic dimethyl sulphoxide molecules, the N-Me protons are probably influenced indirectly. The dipolar dimethyl sulphoxide molecules would probably orientate themselves above or below the hydantoin ring, with their negative ends attracted to the partially positively charged nitrogen atoms. This interaction could cause an electron drift towards and thereby shield the neighbouring methyl protons. Understandably, such an indirect effect is of a much smaller magnitude, as reflected by the small but consistently negative $\Delta\delta$ values.

Interestingly, the $\Delta\delta$ value of the H-6 signal is found to be either positive or negative depending on the configuration of the compounds. For all the *Z*-isomers the H-6 signals shift upfield in $(CD_3)_2SO$ relative to $CDCl_3$, but for all the *E*-isomers the shift is downfield. H-6, being the β-proton of an α,β-unsaturated carbonyl system, may have same acidity and may possibly interact directly but weakly with the basic dimethyl sulphoxide solvent molecules in a manner similar to, although to a much smaller extent than, the interaction of the more acidic NH proton. This effect is observed only for the *E*-isomers, where H-6 is sterically more accessible to the solvent molecules, but not for the *Z*-isomers, where H-6 is close to and under the influence of the C-4 carbonyl oxygen.

Solvent effects on the chemical shifts of the heteroaromatic ring protons are more difficult to interpret and could be complicated by conformational changes in different solvents. The effects of the possible *s-cis* or *s-trans* conformations on the furan/thiophene ring proton signals have been discussed above. Thus, the experimentally observed solvent dependence of the ring proton signals may be related to variations in the relative populations of the conformers in the two solvents used.

EXPERIMENTAL

Compounds **1–12** were prepared by condensation of hydantoin, 1-methylhydantoin or 3-methylhydantoin (0·05 mol) with 2-/3-furancarboxaldehyde or 2-/3-thiophenecarboxaldehyde (0·05 mol) in an aqueous sol-

ution (8 ml) of DL-alanine (0·05 mol) and sodium carbonate (0·025 mol). The mixture was refluxed with magnetic stirring for 3 h at 120–140 °C. When furancarboxaldehyde was used, a slow stream of nitrogen was passed through the mixture during the reaction. A solid precipitate started to form within 20–30 min, depending on the preparation. At the end of the refluxing, the first crop of crude product was collected after cooling and diluting the mixture with an approximately equal volume of water. Acidifying the filtrate to pH 5–6 yielded a second crop of solid. For **1–8** both crops were mainly *Z*-isomers. For **9–12**, the first crop consisted of the *E*-isomers, which are the chief products. The *Z*-isomers were obtained in various lower yields from the second crop. All compounds were recrystallizable from ethanol or methanol, except (*Z*)-**9**, which was recrystallized from ispropanol.

^{1}H NMR and ^{13}C NMR spectra were recorded using a JELO FX90Q or a Bruker AC-F 300 HMz NMR spectrometer.

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