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IONIZATION CONSTANTS OF 5-FURYLMETHYLENEHYDANTOINS AND 5-THIENYLMETHYLENEHYDANTOINS IN 80% (w/w) DIMETHYL SULPHOXIDE–WATER AT 25 °C

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The ionization constants of sixteen 5-furylmethylenehydantoins and 5-thienylmethylenehydantoins were measured in 80% (w/w) dimethyl sulphoxide–water solvent at 25 °C. The effects of the 2-/3-furyl and 2-/3-thienyl rings and the effects of configuration and conformation on acidity are discussed. The very low acidity of (*Z*)-5-(2-furyl)methylene-3-methylhydantoin suggests the possibility of some weak intramolecular interaction between the proton at N-1 and the 2-furyl oxygen in the *s-cis* conformation.

INTRODUCTION

The acidic ionization constants of hydantoin and its 1-methyl, 3-methyl and 5,5-dimethyl derivatives and those of a series of 5-arylmethylenehydantoins and a series of 5-pyridylmethylenehydantoins in 80% (w/w) dimethyl sulphoxide–water at 25 °C have been reported.[1,2] Compounds in the pyridyl series are also basic by virtue of the pyridyl nitrogen. The nature of substituents in the phenyl ring, the position of the nitrogen atom in the pyridyl ring and the *Z*/*E* configuration about the exocyclic double bond and the conformational relationship between the hydantoin and aromatic rings have been found to influence significantly the acid–base behaviour. As an extension to this study, we have now determined the ionization constants of two related series of compounds, namely the 5-furylmethylenehydantoins and 5-thienylmethylene-hydantoins,[3] with the view of assessing the effects of the five-membered heteroaromatic furan or thiophene ring in the side-chain on acidity.

RESULTS AND DISCUSSION

Electronic spectra

As spectrophotometric methods were used for the determinations of the ionization constants of compounds **1**–**12**, their UV absorption characteristics were first examined (Table 1). In 80% (w/w) dimethyl sulphoxide–water, all the compounds show one main intense band in the region of 310–360 nm, arising from conjugation of the heteroaromatic ring with both N-1 and C-4=O groups of the hydantoin ring via the intervening double bond. In the spectra of the 2-furyl compounds (*Z*)-**1** and (*Z*)-**5**, this band consists of two closely spaced maxima of nearly equal intensity. The spectra of the 2-thienyl compounds (*Z*)-**3** and (*Z*)-**7**, show one intense band with a shoulder on the longer wavelength side. In the spectra of the remaining compounds, the shoulders are not clearly distinguishable.

It is noted that the 2-furyl and 2-thienyl compounds absorb at longer wavelength than the corresponding 3-furyl and 3-thienyl compounds. Also, among the 1-methyl-substituted compounds, the *E*-isomers absorb at longer wavelengths than their *Z*-isomers.

Virtually no change occurs in the spectra on changing from neutral to strongly acidic solutions. This shows that, unlike their pyridyl counterparts, these furyl and thienyl compounds have negligible basicity.

On the other hand, more pronounced changes occur in strongly alkaline solutions due to deprotonation. The spectral changes vary depending on whether the compounds are 1-methyl-substituted, 3-methyl-substituted or *N*-unsubstituted. The 1-methyl-substituted compounds (*Z*/*E*)-**9**–(*Z*/*E*)-**12** deprotonate to form N-3 anions. In each case, the alkaline spectrum shows only a small shift in wavelength with a lowering of the molar absorptivity of the main absorption band. Another

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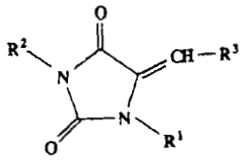
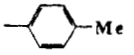
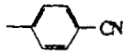
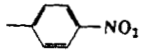


Compd	R^1	R^2	R^3
1	H	H	
2	H	H	
3	H	H	
4	H	H	
5	H	Me	
6	H	Me	
7	H	Me	
8	H	Me	
9	Me	H	
10	Me	H	
11	Me	H	
12	Me	H	

Compd	R^1	R^2	R^3
A1	H	H	
A2	H	H	
A3	H	H	
A4	H	H	
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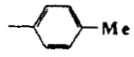
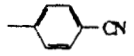
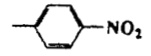
A6	H	Me	
A7	H	Me	
A8	H	Me	
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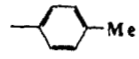
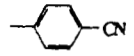
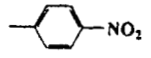
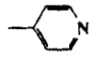
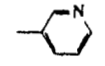
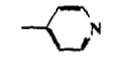
A10	Me	H	
A11	Me	H	
A12	Me	H	
B1	H	H	
B2	H	H	
B3	H	H	
B4	H	Me	
B5	H	Me	
B6	H	Me	
B7	Me	H	
B8	Me	H	
B9	Me	H	

Table 1. UV absorptions in 80% (w/w) dimethyl sulphoxide–water

Compound	λ_{max}(nm)(log ε)[a] Neutral	Acidic	Alkaline
(*Z*)-**1**	338 (4·11)	338	338
	353 (4·08)	353	353 sh
			395 br
(*Z*)-**2**	312 (4·01)	312	313
			365 br
(*Z*)-**3**	340 (4·11)	340	342
	355 sh	355 sh	357
			395 br
(*Z*)-**4**	320 (4·08)	320	325
			375 br
(*Z*)-**5**	340 (3·98)	340	255
	353 (3·95)	353	380
(*Z*)-**6**	313 (4·16)	313	255
			352
(*Z*)-**7**	340 (4·11)	340	268
	355 sh	355 sh	386
(*Z*)-**8**	322 (4·08)	322	250
			366
(*Z*)-**9**	344 (4·10)	344	295
	360 sh	360 sh	346
(*E*)-**9**	358 (4·00)	358	295
			356
(*Z*)-**10**	315 (3·85)	315	284
			319
(*E*)-**10**	330 (3·89)	330	263
			332
(*Z*)-**11**	344 (3·87)	344	274
			345
(*E*)-**11**	357 (4·01)	357	274
			356
(*Z*)-**12**	320 (4·08)	320	270
			325
(*E*)-**12**	340 (3·98)	340	279
			345

[a] sh = Shoulder; br = broad band of lower intensity.

band at a shorter wavelength, which is very weak under neutral or acidic conditions, becomes a distinct band of moderate intensity. By contrast, the main absorption band of each of the 3-methyl-substituted compounds (*Z*)-**5**–(*Z*)-**8** undergoes a substantial bathochromic shift in alkaline solution on formation of the N-1 anion. Spectra recorded at different pH values pass through distinct isosbestic points, consistent with conversion to a single anionic species in each case.

The spectral changes shown by the *N*-unsubstituted compounds (*Z*)-**1**–(*Z*)-**4** from neutral to alkaline solutions resemble more closely the changes noted above for their 1-methyl derivatives rather than their 3-methyl derivatives. This confirms that, although each *N*-unsubstituted compound possesses two ionizable protons, first deprotonation gives chiefly the N-3 anion. This is not surprising as it is known that in hydantoin, the N-3

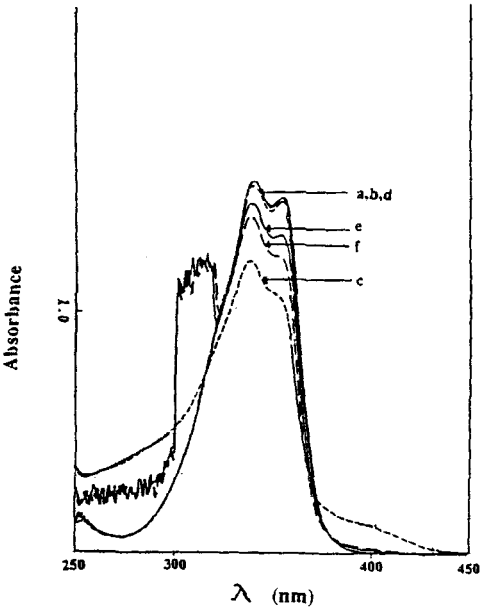


Figure 1. Electronic spectra of $9{\cdot}4 \times 10^{-5}$ M (*Z*)-**1** in 80% (w/w) dimethyl sulphoxide–water: (a) neutral; (b) with 1×10^{-2} M HCl; (c) with 1×10^{-2} M NaOH; (d) with acetic acid buffer of pH 8·07; (e) and (f) with *p*-cyanophenol buffers of pH 9·79 and 10·16, respectively

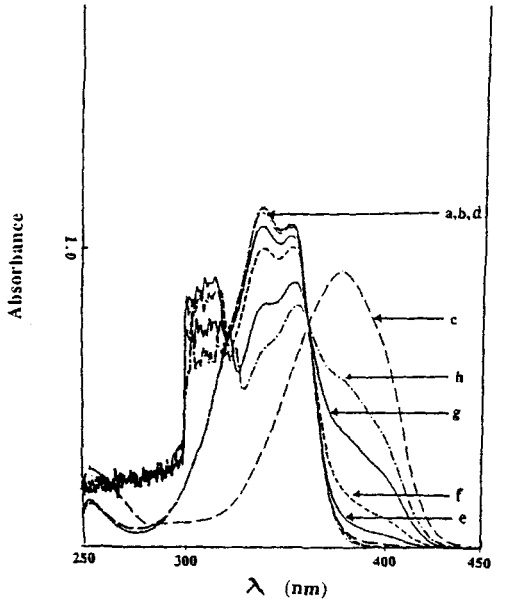


Figure 2. Electronic spectra of $1{\cdot}2 \times 10^{-4}$ M (*Z*)-**5** in 80% (w/w) dimethyl sulphoxide–water: (a) neutral; (b) with 1×10^{-2} M HCl; (c) with 1×10^{-2} M NaOH; (d) with acetic acid buffer of pH 8·07; (e), (f), (g) and (h) with *p*-cyanophenol buffers of pH 9·79, 10·16, 10·62 and 11·06, respectively

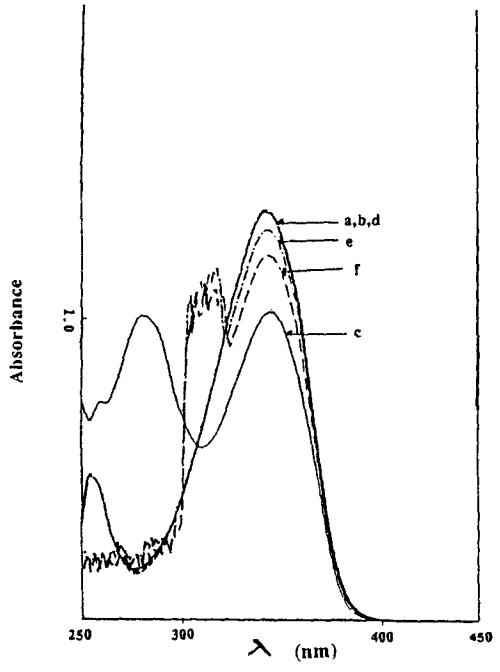


Figure 3. Electronic spectra of $1{\cdot}4 \times 10^{-4}$ M (*E*)-**12** in 80% (w/w) dimethyl sulphoxide–water: (a) neutral; (b) with 1×10^{-2} M HCl; (c) with 1×10^{-2} M NaOH; (d) with acetic acid buffer of pH 8·07; (e) and (f) with *p*-cyanophenol buffer of pH 9·79 and 10·16, respectively

proton is more acidic than the N-1 proton.[4] However, closer examination of the alkaline spectrum reveals the appearance at a longer wavelength of an additional band of much lower intensity, which may be attributed to the possible presence of a small concentration of the N-1 anion.

Representative spectra of the three groups of compounds are shown in Figures 1–3.

Ionization constants

The p*K* values of compounds **1**–**12** measured by spectrophotometric methods[5,6] are presented in Table 2. To facilitate discussion, some of the previously determined p*K* values of the aryl and pyridyl compounds are also included for comparison.

Among the 5-arylmethylenehydantoins, such as **A1**–**A12**, the effects of substituents in the phenyl ring on the relative acidities of the two hydrogens at N-1 and N-3 of the hydantoin ring have been estimated by using, as models, the 1-methyl and 3-methyl derivatives each with only one ionizable proton. While good Hammett correlations were found for each of the *N*-unsubstituted, 1-methyl- and 3-methyl-substituted series of compounds, the difference between the ease of deprotonation at N-1 and N-3 narrows as the phenyl substituent becomes more electron withdrawing so that the first ionization of the *N*-unsubstituted compounds gives rise to mixtures of tautomeric monoanions.[7] The effect of replacing the benzene ring with the π-deficient pyridine ring is qualitatively similar to that of introducing electron-withdrawing substituents in the 5-arylmethylenehydantoins so that the 5-pyridylmethylenehydantoins **B1**–**B9** are significantly stronger acids. The extent of this acid-strengthening effect is dependent on the position of the pyridyl nitrogen atom.

Thus, the p*K* values of the 4-pyridyl compounds **B3**, **B6** and **B9** are close to those of the aryl compounds with a *p*-cyano group, **A3**, **A7** and **A11**, or a *p*-nitro

Table 2. p*K* values in 80% (w/w) dimethyl sulphoxide–water at 25 °C

Furyl/thienyl compounds	p*K*	Phenyl compounds	p*K*[a]	Pyridyl compounds	pK[b]
(*Z*)-**1**	9·91	(*Z*)-**A1**	9·97	(*Z*)-**B1**	9·55
(*Z*)-**2**	10·06	(*Z*)-**A2**	10·13	(*Z*)-**B2**	9·43
(*Z*)-**3**	9·71	(*Z*)-**A3**	9·22	(*Z*)-**B3**	9·15
(*Z*)-**4**	10·01	(*Z*)-**A4**	9·01		
(*Z*)-**5**	10·95	(*Z*)-**A5**	10·49	(*Z*)-**B4**	10·71
(*Z*)-**6**	10·88	(*Z*)-**A6**	10·70	(*Z*)-**B5**	9·55
(*Z*)-**7**	9·94	(*Z*)-**A7**	9·28	(*Z*)-**B6**	9·16
(*Z*)-**8**	10·59	(*Z*)-**A8**	9·15		
(*Z*)-**9**	9·48	(*Z*)-**A9**	9·62	(*Z*)-**B7**	9·34
(*E*)-**9**	9·74	(*E*)-**A9**	10·15	(*E*)-**B7**	9·49
(*Z*)-**10**	9·73	(*Z*)-**A10**	9·72	(*Z*)-**B8**	9·30
(*E*)-**10**	10·12	(*E*)-**A10**	10·30	(*E*)-**B8**	9·68
(*Z*)-**11**	9·35	(*Z*)-**A11**	9·17	(*Z*)-**B9**	9·09
(*E*)-**11**	10·01	(*E*)-**A11**	9·49	(*E*)-**B9**	9·31
(*Z*)-**12**	9·59				
(*E*)-**12**	10·14	(*E*)-**A12**	9·44		

[a] Values from Ref. 1.
[b] Values from Ref. 2.

group, **A4**, **A8** and **A12**, respectively. The 3-pyridyl analogues **B2**, **B5** and **B8** are noticeably less acidic. Unexpectedly, the 2-pyridyl compound **B4** is the weakest acid in the whole series and is even less acidic than the phenyl analogue **A5** in spite of the expected acid-strengthening effect of the pyridyl group. Its high pK has been attributed to intramolecular hydrogen bonding between the only ionizable N-1 proton and the basic 2-pyridyl nitrogen atom which comes into close proximity when the molecule adopts the *s-cis* conformation.[2]

Unlike pyridine, furan and thiophene are π-rich heteroaromatics. Therefore, all the compounds in the furyl and thienyl series are less acidic than those in the pyridyl series. When compared with 5-phenylmethylenehydantoin, the replacement of the benzene with the furan or thiophene ring may be expected to produce an acid-weakening effect. However, this expectation is only partially borne out by the present results. Analysis of the experimental data reveals the interplay of a number of interesting factors, some of which will be discussed below.

Effect of Z/E configuration and of methyl substitution

The Z-isomers of each of the 1-methyl-substituted compounds **9**–**12** are more strongly acidic than the corresponding E-isomers and are also more acidic than the 3-methyl-substituted compounds (Z)-**5**–(Z)-**8**, with the N-unsubstituted compounds (Z)-**1**–(Z)-**4** having intermediate acidity. These observations again reflect the generally higher acidity of the N-3 than the N-1 proton of hydantoin.

Effect of the position of O/S heteroatom

There are significant differences in the pK values of the 2-furyl/thienyl and the 3-furyl/thienyl compounds. With only one exception, the former group are more acidic than the latter group of compounds. Compared with the N-unsubstituted and the 3-methyl-substituted 5-phenylmethylenehydantoins **A1** and **A5**, the corresponding 3-furyl/thienyl compounds **2**/**4** and **6**/**8**, respectively, are indeed weaker acids, as expected from the more electron-rich character of the furan/thiophene ring relative to benzene. Their pK values are closer to those of **A2** and **A6**, which bear an electron-releasing p-methyl substituent in the benzene ring. By contrast, the 2-furyl compound **1** and the 2-thienyl compounds **3** and **7** are more strongly acidic than their 3-furyl and 3-thienyl analogues and the phenyl compounds **A1** and **A5**. This dependence of acidity on the position of the O/S heteroatom may be rationalized by noting that two opposing electronic effects are operative in furan and thiophene. The involvement of an electron pair of the O/S heteroatom in aromatic delocalization implies electron release which is more effective at the β- than at the α-position. At the same time, the heteroatom also exerts an electron-withdrawing inductive effect, more strongly at the α- than at the β-position.[8] Thus, it is observed that the presence of the furyl or thienyl group produces an acid-strengthening or acid-weakening effect relative to the phenyl compound depending on whether the methylenehydantoin residue is attached to the heteroaromatic ring at the α- or β-position.

Interestingly, the pK of 3-methyl-5-(2-furyl) methylenehydantoin (**5**) does not follow the trend mentioned above. This 2-furyl compound is a weaker acid than both its 3-furyl analogue **6** and the phenyl compound **A5**. In fact, it is the weakest acid among the present two series of compounds. This exceptional behaviour is reminiscent of the strikingly low acidity of its 2-pyridyl analogue **B4**, which has been interpreted as evidence for the presence of intramolecular N-1-H···N hydrogen bond. This may suggest the possibility of similar intramolecular interaction between the N-1-H group and the 2-furyl oxygen atom if the molecules of **5** adopts the favourable s-cis conformation. However, it should be noted that the difference between the pK values of **5** and **6** is much smaller in magnitude than that between the pK values of the 2-pyridyl (**B4**) and its 3- or 4-pyridyl analogue (**B5** or **B6**), indicating that such N-1-H···O interaction, if present, must be correspondingly weaker. This could be partly due to the greater distance between the N-1-H and O as a result of the smaller five-membered heteroaromatic ring. Moreover, as a result of electron drift from the oxygen atom towards the ring, furan is much less basic than pyridine and is only a poor hydrogen bond acceptor, as shown by its lower solubility in water relative to tetrahydrofuran.[9] Recent x-ray crystallographic analysis of **5** has revealed that, in the solid state, the furan ring is indeed orientated *s-cis* with respect to the hydantoin ring.[10] Although the distance between the proton at N-1 and the furyl oxygen of 2·47 Å is too large to indicate the existence of a strong hydrogen bond, the presence of some weak attractive interaction could be one of the reasons for the preference for the *s-cis* conformation. On the other hand, 3-methyl-5-(2-thienyl)methylenehydantoin (**7**) does not exhibit parallel behaviour. It is more acidic than its phenyl and 3-thienyl analogues, as expected from the electron-withdrawing effect of the 2-thienyl group. Sulphides are known to be less basic than ethers. The greater resonance effect and aromatic character of thiophene compared with furan[11,12] further lowers the inclination of the thiophene sulphur to interact with proton. Hence, intramolecular N-1-H···S interaction is likely to be absent.

When the hydantoin ring is 1-methyl substituted, deprotonation occurs only at the N-3 position which is not directly conjugated with the furan/thiophene ring. Hence, the resonance effect will be minimal but the

inductive effect could still be present. It is observed that both *Z*- and *E*-isomers of the 2-furyl/thienyl compounds are more acidic than the corresponding phenyl compound of the same configuration. The inductive effect becomes further attenuated in the 3-furyl/thienyl compounds which are found to be of comparable acidity to their phenyl analogues.

Comparison of furyl and thienyl compounds

No clear trend is observed when the acidities of the two series of compounds are compared. Furan and thiophene differ in several respects. The higher electronegativity of oxygen relative to sulphur may lead to the expectation of higher acidity for the furyl than the thienyl compounds. On the other hand, the higher polarizability of sulphur than oxygen and the higher aromaticity of thiophene relative to furan result in different distributions of electron density at various positions around the two ring systems. These could lead to effects on acidity different from those deduced from consideration of electronegativity alone. Thus, it is found that among the *E*-isomers of the 1-methyl-substituted compounds, the furyl are more acidic than the thienyl analogues, but the reverse is true for the pairs of the *Z*-isomers of the *N*-unsubstituted and the 3-methyl substituted compounds. These apparently contradictory trends suggest different factors influencing the acidity of the N-1 and the N-3 protons. The largest difference in p*K* between a pair of furyl and thienyl compounds is observed for **5** and **7** and is attributable, at least partly, to the acid-weakening effect of some weak intramolecular N-1-H···O interaction in the case of the 2-furyl compound but lack of similar N-1-H···S interaction in the 2-thienyl compound since N-1-H is the only acidic proton here. A smaller difference is found for the pair of compounds **1** and **3** where deprotonation occurs mainly at the N-3 position.

EXPERIMENTAL

Materials. Compounds **1–12** were prepared according to methods reported earlier.[3] The solvent mixture was prepared with Baker spectrophotometric-grade dimethyl sulphoxide and water which had been purified with a Milli-Q system (Millipore), freshly boiled and stored under soda-lime. Carbonate-free sodium hydroxide solutions were prepared as described by Bassett[13] and standardized. All solutions for measurement were carefully adjusted so that the final solvent composition corresponded to 80% (w/w) dimethyl sulphoxide–water. AnalaR-grade cresol red and bromothymol blue, with suitable known p*K* values in this solvent system of 10·68 and 8·95,[5] were further recrystallized and checked by elemental analysis before use as indicators.

Measurements. Electronic spectral measurements were carried out using a Shimadzu UV-260 UV–visible spectrophotometer with the cell compartment thermostated at 25 ± 0·2 °C. Indicator methods were used for p*K* determinations.

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