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

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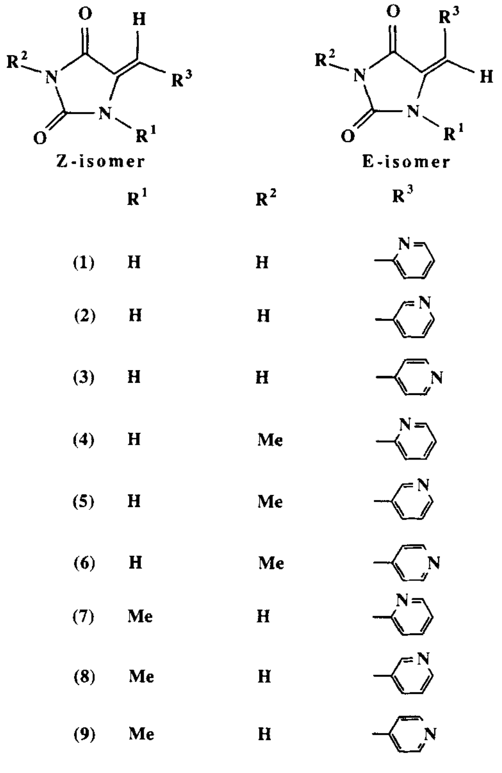
The ionization constants of nine amphoteric 5-pyridylmethylenehydantoins were measured in 80% (w/w) dimethyl sulphoxide–water at 25 °C. The effects of structure and *Z*/*E* configuration on both pK_a^{I} and pK_a^{II} values are discussed. The especially low basicity and acidity of the *Z*-isomers of the *N*-unsubstituted and 3-methyl-substituted 5-(2-pyridylmethylene)hydantoin are attributed to the formation of intramolecular N(1)—H ··· N hydrogen bond in the *s-cis* conformation of these compounds. The existence of N(1)—CH_3···N attraction is also postulated for the *Z*-isomer of 1-methyl-5-(2-pyridylmethylene)hydantoin.

INTRODUCTION

The ionization constants of a series of seventeen 5-arylmethylenehydantoins in 80% (w/w) dimethyl suphoxide–water at 25 °C have been reported previously.[1] The effects of substituents and of stereochemistry on acidity were studied. The ionization constants of a series of nine 5-pyridylmethylenehydantoins (**1**–**9**; Scheme 1) have now been determined in the same solvent. Compared with the aryl compounds, these pyridyl analogues present some additional interesting features. First, they are amphoteric, being not only weakly acidic like the 5-arylmethylenehydantoins but also weakly basic owing to the presence of the pyridyl nitrogen. Second, the pyridine ring may have a 2-, 3- or 4- orientation relative to the methine bridge, and this orientation significantly affects both the acidity and basicity. Further, for the *N*-unsubstituted compounds, the electron-withdrawing effect of the pyridylmethylene group may bring the acidities of the N-1 and N-3 protons sufficiently close so that first deprotonation may produce a mixture of tautomeric monoanions.



Scheme 1

RESULTS AND DISCUSSION

Compounds **1**–**9** were prepared by condensation of hydantoin, 3-methylhydantoin or 1-methylhydantoin with 2-, 3- or 4-pyridinecarboxaldehyde. Compounds **1**–**6** were obtained only in the *Z*-form and **7**–**9** in both *E*- and *Z*-isomeric forms.[2] For each compound, two p*K* values were determined by spectrophotometric methods

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in 80% (w/w) dimethyl sulphoxide–water at 25 °C. The ionization constant of the protonated species, $\mathrm{p}K_\mathrm{a}^\mathrm{I}$, is a measure of basicity and the ionization constant of the neutral form, $\mathrm{p}K_\mathrm{a}^\mathrm{II}$, is a measure of acidity of that compound.

$\mathrm{p}K_\mathrm{a}^\mathrm{I}$

Examination of the results in Table 1 reveals some interesting trends. The $\mathrm{p}K_\mathrm{a}^\mathrm{I}$ values of *N*-unsubstituted compounds (*Z*)-**1** to (*Z*)-**3** parallel closely those of the 3-methyl derivatives (*Z*)-**4** to (*Z*)-**6**, showing that a methyl substituent at N-3 has only a minimal effect on basicity. However, the basicity is very much influenced by orientation of the pyridine ring, so that within each of the groups (*Z*)-**1**–(*Z*)-**3** or (*Z*)-**4**–(*Z*)-**6**, $\mathrm{p}K_\mathrm{a}^\mathrm{I}$ increases sharply from the 2- to the 3-pyridyl and less sharply from the 3- to the 4-pyridyl compounds. The high basicity of the 4-pyridyl compounds (*Z*)-**3** and (*Z*)-**6** can be accounted for by resonance stabilization of the protonated base in which the positive charge is delocalizable from the pyridyl nitrogen into the hydantoin ring. The cations formed on protonation of the 3-pyridyl compounds (*Z*)-**2** and (*Z*)-**5** cannot be similarly stabilized owing to lack of conjugation.

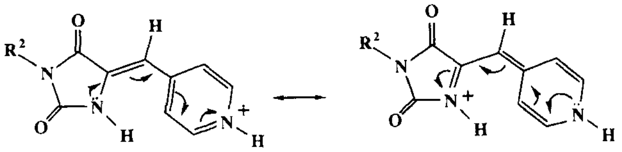
The exceptionally low basicity of the 2-pyridyl compounds (*Z*)-**1** and (*Z*)-**4** may at first appear surprising, since the 2-pyridyl nitrogen, like the 4-pyridyl nitrogen, is obviously conjugated with the hydantoin ring so that its cation should also be resonance-stabilized. For this reason, one may also expect (*Z*)-**1** and (*Z*)-**4** to be stronger bases than the 3-pyridyl analogues (*Z*)-**2** and (*Z*)-**5**. However, the $\mathrm{p}K_\mathrm{a}^\mathrm{I}$ values of (*Z*)-**1** and (*Z*)-**4** are not only much lower than those of the corresponding 4-pyridyl compounds by about 2·15 units but also lower than those of the corresponding 3-pyridyl compounds by about 1·4 units. This apparent anomaly may be rationalized by considering the spatial relationship between the N-1 proton and the pyridyl nitrogen. As the 2-pyridyl ring is unsymmetrical with respect to rotation, two limiting conformations are possible in which the pyridine and hydantoin rings become coplanar to allow for maximum resonance effects. These are the *s*-cis and *s-trans* conformations with the pyridyl nitrogen oriented towards or away from the hydantoin ring, respectively. Preference for the *s-cis* conformation was indicated by the results of NMR studies.[2] In this conformation, the close proximity of the 2-pyridyl nitrogen to the proton at N-1 favours the formation of an intramolecular hydrogen bond, which is strengthened owing to conjugation between the two nitrogen atoms (Scheme 2). Such intramolecular chelation stabilizes the neutral molecule and may be likened to 'internal protonation' rendering the lone pair of the 2-pyridyl nitrogen less available for donation to external protons from solution. This effect is absent in the 3- and 4-pyridyl analogues where the pyridyl nitrogen is too far away to interact intramolecularly with the N-1 proton.

Table 1. $\mathrm{p}K_\mathrm{a}$ values in 80% (w/w) dimethyl sulphoxide–water solvent at 25 °C

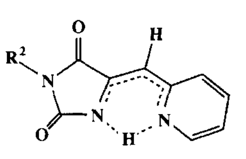
Compound	$\mathrm{p}K_\mathrm{a}^\mathrm{I}$	$\mathrm{p}K_\mathrm{a}^\mathrm{II}$
(*Z*)-**1**	0·89	9·55
(*Z*)-**2**	2·26	9·43
(*Z*)-**3**	3·05	9·15
(*Z*)-**4**	0·80	10·71
(*Z*)-**5**	2·26	9·55
(*Z*)-**6**	2·95	9·16
(*Z*)-**7**	1·82	9·34
(*E*)-**7**	3·22	9·49
(*Z*)-**8**	2·21	9·30
(*E*)-**8**	2·54	9·68
(*Z*)-**9**	2·98	9·09
(*E*)-**9**	3·33	9·31

The differences in basicity among compounds (*Z*)-**1**–(*Z*)-**6** may be correlated with their UV spectra (Table 2). The 4-pyridyl compounds show the largest bathochromic shifts on protonation as a result of enhanced conjugation effects (Figure 1), whereas the smallest shifts are shown by 3-pyridyl compounds. For the 2-pyridyl compounds, the cyclic delocalization of electrons in the six-membered conjugate chelate ring formed by the intramolecular N—H ··· N bond in the neutral form is reflected by the observed longer absorption maximum than those of the neutral 3- or 4-pyridyl analogues.

For the 1-methyl-substituted compounds **7**–**9**, the *E*-isomers are more strongly basic than the *Z*-isomers.



Cationic form
(Z-3) R² = H
(Z-6) R² = Me



Neutral form in the s-cis conformer
(Z-1) R² = H
(Z-4) R² = Me

Scheme 2

Table 2. UV absorptions of compounds **1**–**9** and their cations in 80% (w/w) dimethyl sulphoxide–water

	λ_{max} (nm)	
Compound	Neutral	Cation
(*Z*)-**1**	330	346
(*Z*)-**2**	320	323
(*Z*)-**3**	319	350
(*Z*)-**4**	330	346
(*Z*)-**5**	320	325
(*Z*)-**6**	319	350
(*Z*)-**7**	326	344
(*E*)-**7**	335	370
(*Z*)-**8**	312	317
(*E*)-**8**	335	340
(*Z*)-**9**	313	350
(*E*)-**9**	334	363

Previous x-ray studies of 1-methyl-5-phenylmethylenehydantoin have shown that the phenyl and hydantoin rings are nearly coplanar in the *E*-isomer but not in the *Z*-isomer.[3,4] Although no x-ray data are available for the corresponding pyridyl compounds, it may reasonably be speculated that near coplanarity may be possible for (*E*)-**7**–(*E*)-**9** but not for (*Z*)-**7**–(*Z*)-**9**. Since the pyridine ring is electron-withdrawing with respect to the hydantoin ring, molecular planarity and conjugative effects in the *E*-isomers should enhance the electron density at the pyridyl nitrogen, resulting in increase in basicity relative to the non-planar *Z*-isomers. The order of basicity among the *E*-isomers is found to be (*E*)-**9** > (*E*)-**7** > (*E*)-**8**, consistent with the order of extent of conjugation in these compounds. By contrast, the *Z*-isomers show a different order of basicity: (*Z*)-**9** > (*Z*)-**8** > (*Z*)-**7**. The unexpectedly weaker basicity of (*Z*)-**7** is again attributable to the special position of the 2-pyridyl nitrogen.

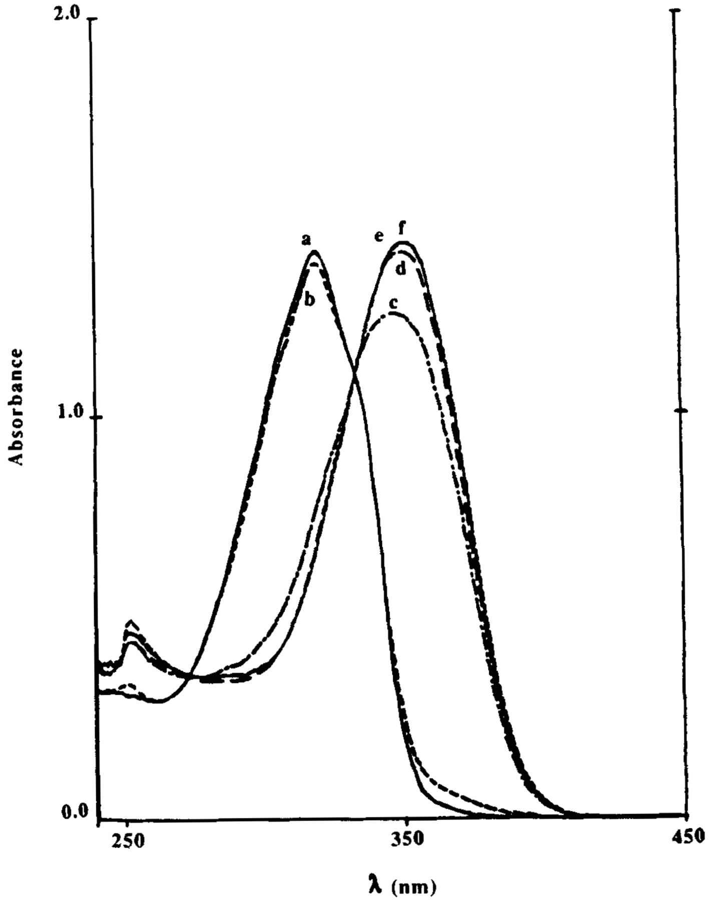


Figure 1. Electronic spectra of $7{\cdot}0\times10^{-5}$ M (*Z*)-**3** in 80% dimethyl sulphoxide–water with (a) 0, (b) $4{\cdot}36\times10^{-5}$, (c) $5{\cdot}34\times10^{-3}$, (d) $5{\cdot}38\times10^{-2}$, (e) $5{\cdot}78\times10^{-1}$ and (f) $9{\cdot}87\times10^{-1}$ M HCl

Intramolecular $CH_3 \cdots N$ interaction

The existence of intermolecular hydrogen bonds between CH groups and N has been well documented.[5–7] In a number of compounds with suitable molecular geometry, the presence of intramolecular CH···N hydrogen bonds has also been demonstrated by spectroscopic and x-ray crystallographic evidence.[8–14] In all cases, the C—H bonds involved are those of a methine, methylene, olefinic or aromatic group which must be suitably activated by electron-withdrawing substituents.

A methyl group is considered to be highly unlikely to participate in similar interactions.[6,8a] However, such an intramolecular $CH_3 \cdots N$ attraction appears to be occurring in (*Z*)-**7**, where a number of contributing factors could concurrently favour its existence. The polarity of the 1-methyl C—H bond is increased by virtue of its attachment to an electronegative nitrogen atom,[7] which is, in turn, conjugated with the two adjacent electron-withdrawing carbonyl and pyridylmethylene groups at positions 2 and 5, respectively. This enhanced polarity may be sufficient for the methyl protons to participate in some weak electrostatic bond if a well placed strong electron donor is present. Moreover, it has been pointed out that the steric requirements of the lone pair on a pyridyl nitrogen are less than those of a hydrogen bonded to an aromatic carbon[15] so that there could be less steric crowding between the 1-methyl group and the 2-pyridyl ring in (*Z*)-**7** in its *s-cis* conformation than between the 1-methyl group and the benzene ring in the otherwise structurally analogous (*Z*)-1-methyl-5-phenylmethylene hydantoin studied previously.[3] With a relatively smaller deviation from molecular planarity, a significant conjugative effect between the hydantoin and pyridyl rings is still possible in (*Z*)-**7** and the 1-methyl group may come close to and interact with the *s-cis*-oriented pyridyl nitrogen.

Such an engagement of the lone pair of this 2-pyridyl nitrogen could explain the observed lower basicity of (*Z*)-**7** compared with (*Z*)-**8** or (*Z*)-**9**, which has a more distant 3- or 4-pyridyl nitrogen atom. Since hydrogen bonds generally cause deshielding of the hydrogen atoms concerned in NMR spectroscopy, the postulation of this hydrogen bond-like $CH_3 \cdots N$ interaction in (*Z*)-**7** is supported by the previously reported downfield shift in its 1-methyl protons relative to those in (*Z*)-**8** and (*Z*)-**9**.[2] Understandably, such an $N—CH_3 \cdots N$ interaction is weaker than the N—H···N hydrogen bond discussed above, as can be seen from comparison of the pK_a^I values of (*Z*)-**7**, (*Z*)-**1** and (*Z*)-**4**.

pK_a^{II}

Deprotonation of hydantoins is known to occur mainly at the N-3 position, although introduction of an unsaturated arylmethylene side chain at C-5 increases the acidity, especially at the N-1 hydrogen.[16,17] Broad comparison of the pK_a^{II} values of the present series of 5-pyridylmethylenehydantoins (Table 1) confirms the higher acidity of the N-3 over the N-1 hydrogen, as shown by the higher acidity of the 1-methyl-substituted compounds (*Z*)-**7**–(*Z*)-**9** than the 3-methyl-substituted analogues (*Z*)-**4**–(*Z*)-**6**, with the corresponding *N*-unsubstituted compounds (*Z*)**1**–(*Z*)-**3** of intermediate acidity. Following the effect of configurations previously found for the geometric isomers of the 1-methyl-5-arylmethylenehydantoins,[1] the *E*-isomers of **7**–**9** are also weaker acids than their *Z*-isomers.

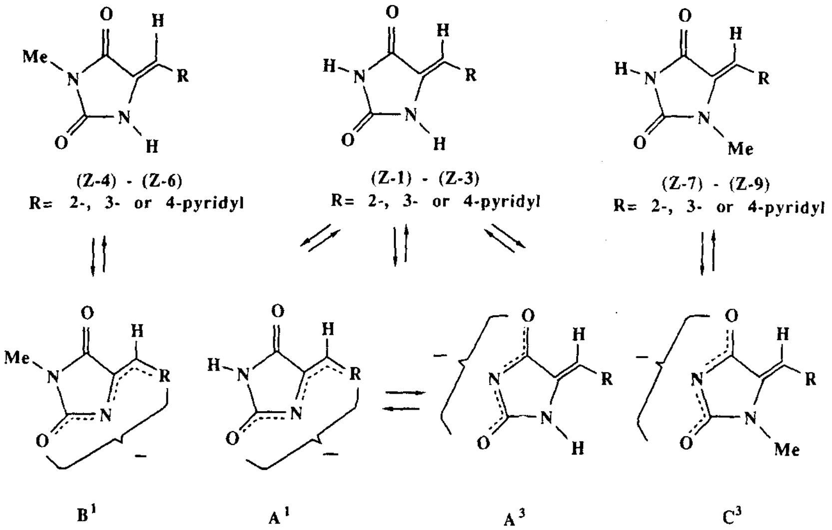
It is noted that within each of the groups (*Z*)-**1**–(*Z*)-**3**, (*Z*)-**4**–(*Z*)-**6** and (*Z*)-**7**–(*Z*)-**9** the order of acidity parallels the order of basicity, that is 4-pyridyl > 3-pyridyl > 2-pyridyl compounds. The electron displacement from the hydantoin to the 4-pyridyl ring through conjugative effects obviously enhances not only the basicity of the pyridine nitrogen but also the acidity of the hydantoin protons. Comparison of the pK_a^{II} values of (*Z*)-**3**, (*Z*)-**6** and (*Z*)-**9** with the previously measured pK_a values of (*Z*)-5-arylmethylenehydantoins indicates that the electron-withdrawing effect of the 4-pyridyl group is intermediate between those of *p*-cyanophenyl and *p*-nitrophenyl groups[1] as far as their acid-strengthening influence on hydantoins is concerned.

Interestingly, the most weakly basic compound, (*Z*)-**4**, is also strikingly the least acidic of those considered. The intramolecular hydrogen bond which makes the lone pair of the 2-pyridyl nitrogen less available to an external proton also makes the N-1 proton less available to an external base from solution. Although a similar interaction is present in (*Z*)-**1**, its effect is less evident because, unlike (*Z*)-**4**, which has only an N-1 hydrogen, ionization of the more labile N-3 proton is the main contributor to the experimentally measured pK_a^{II} value of this *N*-unsubstituted compound.

Tautomeric monoanoins

The observations that the pK_a^{II} values of the *N*-unsubstituted compounds are intermediate between those of the corresponding 3- and 1-methyl derivatives and that the electron-withdrawing character of the pyridyl group is comparable to that of cyanophenyl or nitrophenyl group prompted us to investigate the possible existence of an equilibrium between the monoanions A^1 and A^3 that may be formed from (*Z*)-**1**, (*Z*)-**2** or (*Z*)-**3** on first ionization at the N-1 and N-3 positions respectively (Scheme 3).

It is observed that, on deprotonation, the UV-visible spectra (Table 3) of the 3-methyl compounds (*Z*)-**4**–(*Z*)-**6** show large red shifts of 59–71 nm whereas those of the 1-methyl compounds (*Z*)-**7**–(*Z*)-**9** show relatively smaller red shifts of 15–25 nm. This indicates



Scheme 3

that the negative charge of the N-1 anion, B^1, is more extensively delocalized than that of the N-3 anion, C^3. Although the individual spectra of A^1 and A^3 cannot be obtained directly, the spectra of (Z)-**1**–(Z)-**3** in alkaline medium appear to be a combination of those of B^1 and C^3, with a longer wavelength band attributable to the A^1 anion and a shorter wavelength band to the A^3 anion.

Table 4. Equilibrium percentage of N-1 anions A^1 and equilibrium ratios, $K = \%A^1/(100 - \%A^1)$, in dimethyl sulphoxide (DMSO)–water mixtures

Compound	DMSO		DMSO		DMSO	
	%A^1	K	%A^1	K	%A^1	K
(Z)-**1**	[a]	—	[a]	—	[a]	—
(Z)-**2**	11	0·12	22	0·28	37	0·59
(Z)-**3**	13	0·15	26	0·35	51	1·04

[a] These percentages are very low and could not be determined accurately.

Following the spectrophotometric method used previously to investigate tautomeric monoanions of the 5-arylmethylenehydantoins,[18,19] and using the corresponding B^1 and C^3 as model anions, the absorption maxima and molar absorption coefficients of A^1 and A^3 can be estimated and their relative populations derived. For each compound, this tautomeric equilibrium was determined in 50%, 80% and 95% dimethyl sulphoxide–water solvent. The results (Table 4) show that (Z)-**1** ionizes at the N-1 position to only a very small extent. Increasing the percentage of dimethyl sulphoxide in the solvent produces relatively little

Table 3. UV absorptions of compounds **1**–**9** and their anions in dimethyl sulphoxide (DMSO)–water mixtures

	λ_{max} (nm)								
	50% DMSO			80% DMSO			95% DMSO		
Compound	Neutral	N-3 anion	N-1 anion	Neutral	N-3 anion	N-1 anion	Neutral	N-3 anion	N-1 anion
(Z)-**1**	331	338	372	332	343	382	332	345	391
(Z)-**4**	331	—	372	332	—	382	332	—	391
(Z)-**7**	322	335	—	328	343	—	331	348	—
(Z)-**2**	320	327	369	321	330	380	322	340	388
(Z)-**5**	320	—	369	321	—	380	322	—	388
(Z)-**8**	311	326	—	313	328	—	313	332	—
(Z)-**3**	318	331	379	320	338	391	320	350	399
(Z)-**6**	318	—	379	320	—	391	320	—	399
(Z)-**9**	313	333	—	313	338	—	314	342	—

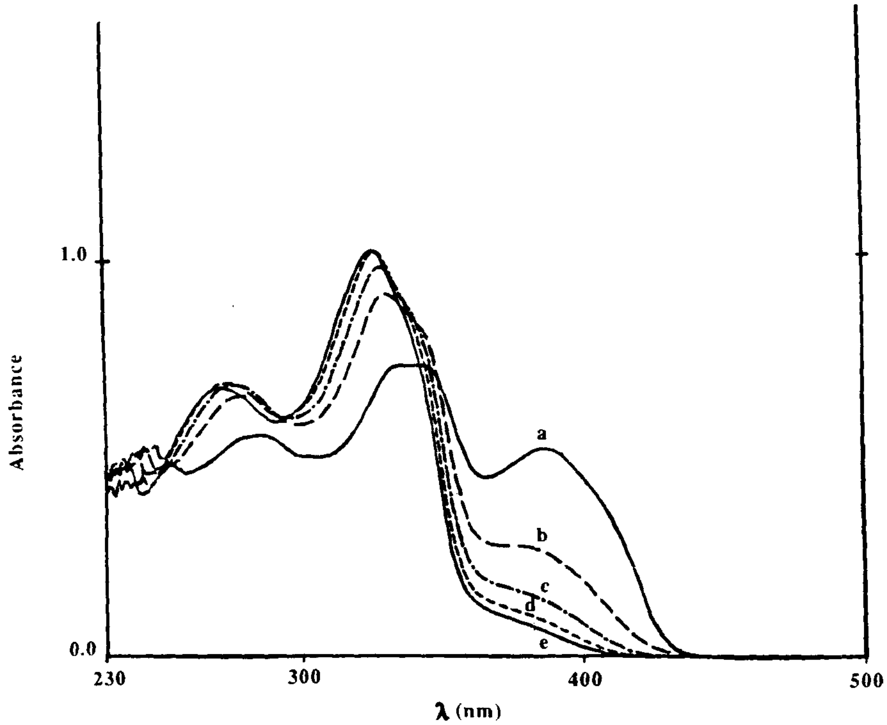


Figure 2. Electronic spectra of $6{\cdot}0\times10^{-5}$ M (*Z*)-**2** in 3×10^{-4} M NaOH in (a) 95%, (b) 80%, (c) 65%, (d) 50% and (e) 35% dimethyl sulphoxide–water mixtures

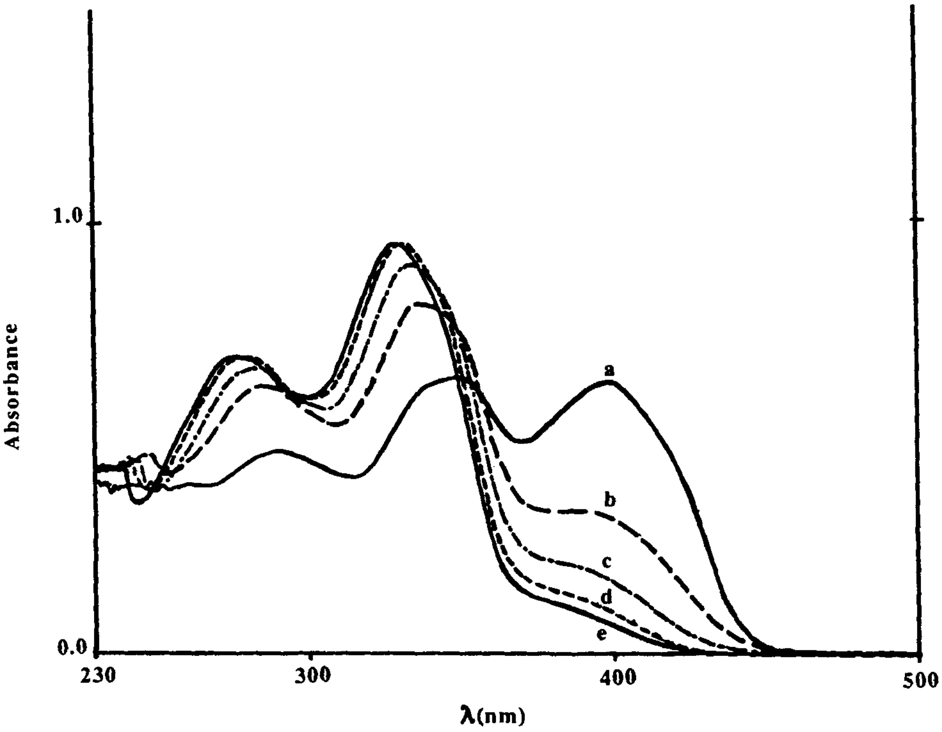


Figure 3. Electronic spectra of $6{\cdot}0\times10^{-5}$ M (*Z*)-**3** in 3×10^{-4} M NaOH in (a) 95%, (b) 80%, (c) 65%, (d) 50% and (e) 35% dimethyl sulphoxide–water mixtures

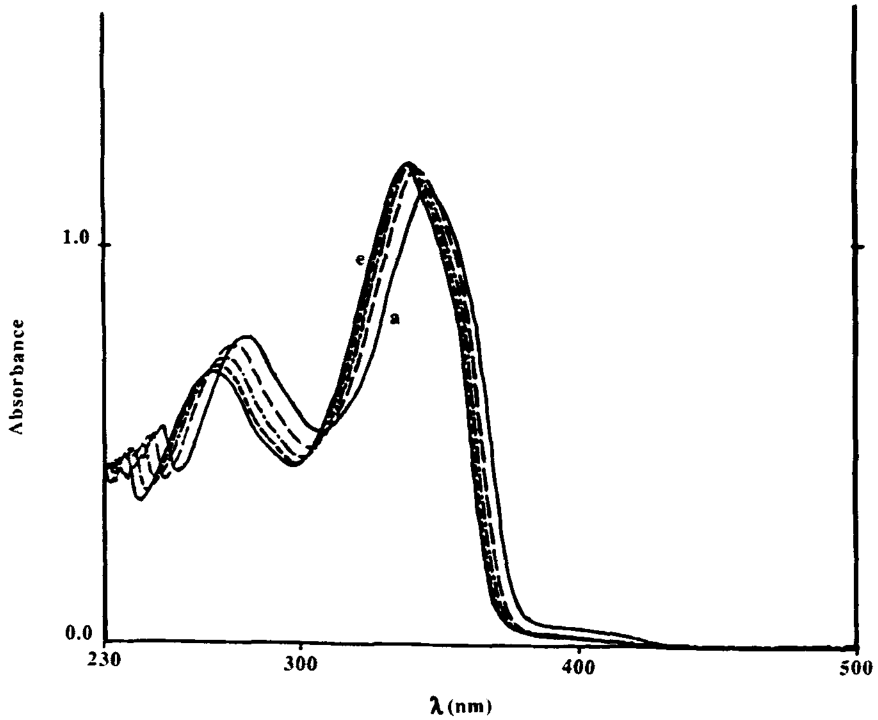


Figure 4. Electronic spectra of $6 \cdot 1 \times 10^{-5}$ M (*Z*)-**1** in 3×10^{-4} M NaOH in (a) 95%, (b) 80%, (c) 65%, (d) 50%, and (e) 35% dimethyl sulphoxide–water mixtures

change in the concentration of A^1. By contrast (*Z*)-**2** and (*Z*)-**3**, even in 50% dimethyl sulphoxide–water, give substantial amounts of A^1, which increase significantly with increase in the percentage of the organic solvent. It is not surprising that among the three compounds, (*Z*)-**3** gives the highest concentration of A^1 on ionization, since this monoanion is the most stabilized through conjugation between N-1 and the 4-pyridyl nitrogen. The equilibrium concentration of A^1 for this compound is comparable to those found for 5-(*p*-cyanophenyl)- and 5-(*p*-nitrophenyl)-methylenehydantoin,[19] in agreement with the similarly strong electron-withdrawing character of the 4-pyridyl and the *p*-cyanophenyl and *p*-nitrophenyl groups.

The changes in the relative populations of A^1 and A^3 with solvent composition may be explained by differences in the solvation characteristics of water and dimethyl sulphoxide. The latter interacts more favourably than the former with the more delocalized A^1 anion, thus enhancing its concentration in a solvent mixture richer in dimethyl sulphoxide. This is shown by the large increase in intensity of the longer wavelength absorption band and the corresponding decrease in the intensity of the band at shorter wavelength in the spectra of the anions of the 3- and 4-pyridyl compounds (Figures 2 and 3). The above emphasized difference for the 2-pyridyl compound is further strikingly demonstrated by the much smaller dependence of the spectra of its anions on solvent composition (Figure 4).

EXPERIMENTAL

Materials. 5-Pyridylmethylenehydantoins **1**–**9** were prepared according to published methods.[2]

Spectrophotometric-grade dimethyl sulphoxide and water purified with a Milli-Q system (Millipore) (freshly boiled and stored under soda lime) were used in preparing the solvent mixtures, hydrochloric acid and carbonate-free sodium hydroxide solutions. Bromothymol Blue and Cresol Red, with suitable known p*K* values in 80% (w/w) dimethyl sulphoxide–water solvent of 8·95 and 10·68, respectively,[20] were used as indicators.

Measurements. Ionization constants were obtained by spectrophotometric methods.[21] Measurements were made using a Shimadzu UV-260 UV–visible recording spectrophotometer with the cell compartment thermostated at 25 ± 0·2 °C. pK_a^{I} values were determined using hydrochloric acid solutions of various concentrations and pK_a^{II} values were measured using the indicator method.

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