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Assignment of Isomeric Hydroxyhydantoins: Linked-scan, Tandem and High-resolution Studies

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The mass spectral fragmentation of hydroxyhydantoins was studied by a combination of high-resolution, linked-scan and collisionally activated decomposition (CAD) experiments. This endeavor resulted in the structural assignment of four pairs of synthetic hydroxyhydantoin isomers. A key feature in differentiating 1-methyl-3- aryl-5-hydroxy-2,4-imidazolidinediones from 1-aryl-3-methyl-5-hydroxy-2,4-imidazolidinediones is that under electron ionization (EI) conditions only the 1-methyl-3-aryl-5-hydroxy-2,4-imidazolidinediones yield the [MeNHCHO]$^{+\cdot}$ ion. The analogous [ArNHCHO]$^{+\cdot}$ ion (where Ar is the aryl group) was present in the EI spectra of both isomers and its origins are explained by the linked-scan and CAD experiments performed.

INTRODUCTION

Considerable research concerning the mass spectrometric behavior of hydantoins has been done.[1–3] However, there are no reports on the mass spectrometry of hydroxyhydantoins, even though these compounds are of interest as herbicides. Furthermore, methods for synthesizing this class of compound have been available for some time. Baskakov and co-workers[4] studied the electrochemical reduction of *N*-alkyl-*N*-arylparabanic acid derivatives. They found the formation of two isomeric hydroxyhydantoins which they assigned by independent synthesis of the major product, the 1-aryl-3-alkyl-5-hydroxy-2,4-imidazolidinedione.[5] Metzger and Kurz[6] studied the sodium tetrahydroborate reduction of a parabanic acid derivative and found that the major product was the 1-alkyl-3-aryl-5-hydroxy-2,4-imidazolidinedione derivative.

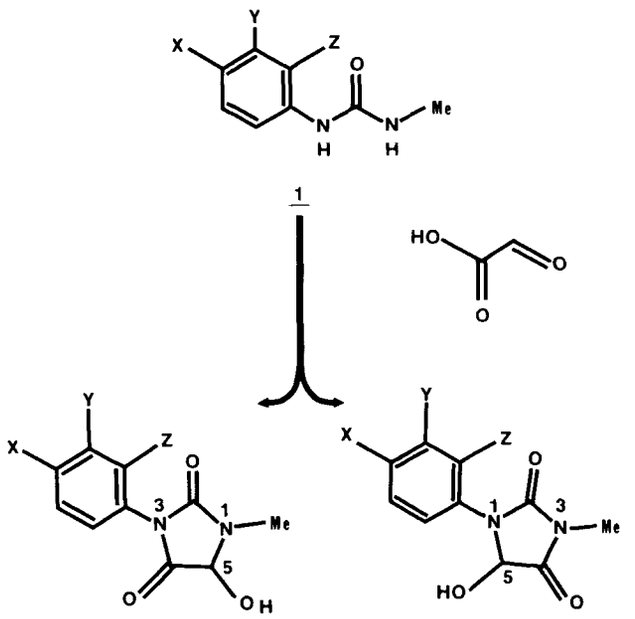
This paper reports mass spectrometric studies that were carried out to elucidate the structures of isomeric hydroxyhydantoins and to understand their electron impact (EI) fragmentation pattern.

EXPERIMENTAL

Materials

The hydroxyhydantoins were synthesized from commercially available anilines (Aldrich Chemical, Milwaukee, WI) by treatment with methyl isocyanate to form 1-methyl-3-arylureas, which were then reacted with glyoxylic acid to give mixtures of the isomeric hydroxyhydantoins (see Scheme 1). The mixtures were separated by column chromatography to give the final products. Thin-layer chromatography and ^{1}H NMR spectroscopy were used to ascertain purity. All materials used in this study were judged to be at least 95% pure.

For example, to a toluene solution (400 cm^3) of 2-fluoroaniline (47.0 g, 0.42 mol) was added dropwise a



2	X=H	Y=H	Z=F	3
4	X=H	Y=CF$_3$	Z=H	5
6	X=H	Y=Cl	Z=H	7
8	X=Cl	Y=Cl	Z=H	9

Scheme 1. Synthesis of isomeric hydroxyhydantoins.

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toluene solution (130 cm^3) of methyl isocyanate (24.1 g, 0.42 mol). The mixture was stirred overnight at room temperature. This produced a white solid that was filtered and washed with a small volume of toluene. The solid was air dried to give 48.3 g (68%) of compound **1** (X = Y = H, Z = F) (IR (KBr pellet), 3350, 1700 and 1650 cm^{-1}; ^1H NMR (DMSO-d_6, 60 MHz), δ 6.0–8.4 (m, 6H), 2.7 (d, J = 5 Hz, 3H); EI mass spectrometry, m/z (relative intensity, %) 168 (8), 150 (2), 137 (5), 111 (100) and 58 (15)).

Compound **1** (X = Y = H, Z = F; 89.0 g, 0.53 mol) and glyoxylic acid monohydrate (47.2 g, 0.51 mol) were suspended in ethanol-free chloroform (600 cm^3) and heated under reflux with a Dean–Stark trap. After refluxing for 4 h the mixture was cooled to room temperature. Solvents were removed by rotary evaporation to give a yellow oil, which was chromatographed on silica gel (230–400 mesh) using 1:1 (v/v) ethyl acetate–hexane as eluent. This gave 8.8 g of compound **2** (m.p. 126–128 °C; IR (KBr pellet), 3320, 1800 and 1710 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz), δ 6.93–7.42 (m, 5H), 5.20 (d, J = 8.5 Hz, 1H), 2.87 (s, 3H)) and 5.4 g of compound **3** (m.p. 113–116 °C; IR (KBr pellet), 3370, 1790 and 1720 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz), δ 7.00–7.50 (m, 5H), 5.47 (d, J = 8.6 Hz, 1H), 2.92 (s, 3H)).

The other hydroxyhydantoins were prepared and purified similarly. This provided compound **4** (m.p. 113–117 °C; IR (KBr pellet), 3310, 1780 and 1710 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz), δ 7.83 (br s, 4H), 7.17 (d, J = 9.0 Hz, 1H), 5.26 (d, J = 9.0 Hz, 1H), 2.97 (s, 3H)), compound **5** (IR (KBr pellet), 3330, 1780 and 1710 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz), δ 7.30–8.00 (m, 5H), 5.80 (br s, 1H), 3.03 (s, 3H)), compound **6** (m.p. 153–155 °C; IR (KBr pellet), 3290, 1790 and 1710 cm^{-1}; ^1H NMR (DMSO-d_6, 60 MHz), δ 7.22–7.38 (m, 4H), 5.80 (br s, 1H), 5.05 (s, 1H), 3.00 (s, 3H)), compound **7** (m.p. 157–161 °C; IR (KBr pellet), 3390, 1790 and 1730 cm^{-1}; ^1H NMR (DMSO-d_6, 60 MHz), δ 7.00–7.70 (m, 5H), 5.62 (br s, 1H), 2.98 (s, 3H)), compound **8** (m.p. 200–202 °C; IR (KBr pellet), 3320, 1790 and 1720 cm^{-1}; ^1H NMR (DMSO-d_6, 60 MHz), δ 7.10–7.70 (m, 3H), 6.90 (d, J = 9 Hz, 1H), 5.10 (d, J = 9 Hz, 1H), 2.86 (s, 3H)) and compound **9** (m.p. 165–168 °C; IR (KBr pellet), 3340, 1780 and 1720 cm^{-1}; ^1H NMR (DMSO-d_6, 60 MHz), δ 7.60–7.80 (m, 3H), 7.4 (br d, J = 9 Hz, 1H), 5.73 (d, J = 9 Hz, 1H), 2.96 (s, 3H)).

Low-resolution mass spectrometry

Samples (1–10 μg) were analyzed on a Finnigan Model 1020 mass spectrometer using the solids probe for sample introduction. The probe was heated from ambient temperature to 300 °C at a rate of 120 °C min^{-1}. Spectra were recorded when the total ion current reached a maximum, which occurred at a nominal probe temperature of about 220 °C. The spectra did not change significantly with temperature. Electron impact mass spectra were obtained using 70 eV electrons. The instrument was tuned and calibrated using perfluorotributylamine to obtain unit mass resolution over the acquisition mass range. The instrument was scanned from m/z 40 to 650 in 4 s. Positively charged ions were observed.

High-resolution mass spectrometry

Samples of about 1 μg were analyzed on a VG Model 7070E-HF mass spectrometer. Samples were evaporated with a solid probe heated from ambient temperature to 330 °C at a rate of 60 °C min^{-1}. Electron impact mass spectra were obtained using 70 eV electrons and a 100 μA trap current. The source potential was 6 kV. The instrument was tuned using perfluorokerosene (PFK) to a resolving power of 6000–10 000 as calculated by the

Table 1. Summary of relative abundances (%) of selected ions

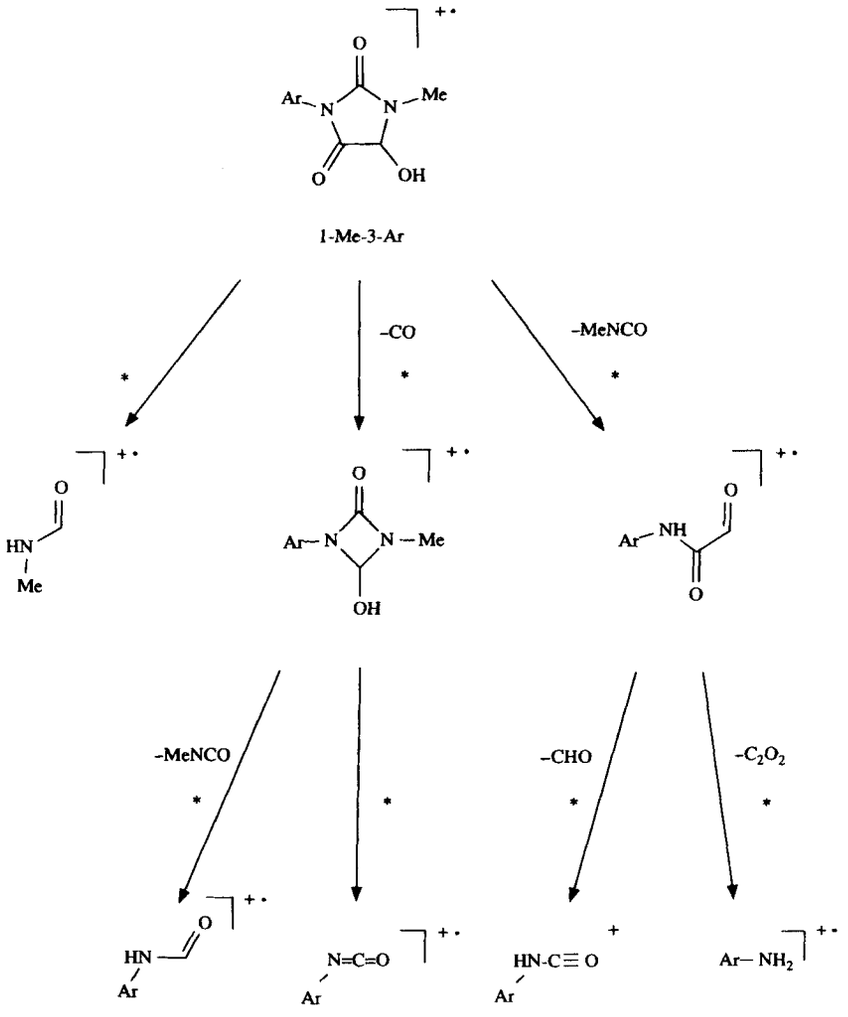
			Compound						
Ion	2	(m/z)[a]	3	4	5	6	7	8	9
$M^{+\cdot}$	25	(224)	23	32	95	60	50	65	37
$M^{+\cdot}$ – CO	25	(196)	—[b]	8	—	10	—	—	—
$M^{+\cdot}$ – MeNCO	8	(167)	—	5	3	15	—	25	—
Ar + 57	—	(152)	5	—	15	—	8	—	5
$[ArNHCHO]^{+\cdot}$ [c]	5	(139)	11	5	36	2[d]	30[d]	3[d]	11[d]
$[ArNHCO]^+$ [e]	36	(138)	3	53	4	42	7	97	3
$[ArNCO]^{+\cdot}$	100	(137)	30	100	50	100	70	100	70
$[ArCO]^+$	—	(123)	25	—	35	—	30	—	20
$[ArNH_2]^{+\cdot}$	18	(111)	100	10	100	20	100	20	100
Ar^+	5	(95)	25	15	30	15	30	10	25
$MeNHCHO^{+\cdot}$ [f]	4	(59)	—	29	—	15	—	15	—
$MeNHCO^+$ [g]	13	(58)	5	22	15	30	36	41	30
$MeNCO^{+\cdot}$	5	(57)	4	3	11	3	9	3	10

[a] Numbers in parentheses are the m/z values for these ions in compounds **2** and **3**. These values are included to aid interpretation of Figs 1–4.
[b] Intensity was less than 1% of base peak intensity.
[c] Corrected for the ^{13}C content of the ArNHCO ion.
[d] Corrected for the ^{37}Cl content of the ArNCO ion.
[e] Corrected for the ^{13}C content of the ArNCO ion.
[f] Corrected for the ^{13}C content of the MeNHCO ion.
[g] Corrected for the ^{13}C content of the MeNCO ion.

Table 2. High-resolution data for selected ions

Ion	Compound 2 Error[a]	2 S.D.[b]	Compound 3 Error	3 S.D.	Compound 4 Error	4 S.D.	Compound 5 Error	5 S.D.
$M^{+\cdot}$	−0.2	1.9	−0.3	3.2	−1.5	2.1	−1.1	1.2
$M^{+\cdot} - CO$	0.6	1.5	—	—	−0.9	1.4	—	—
$M^{+\cdot}$ − MeNCO	2.7	1.0	—	—	−1.9	1.6	—	—
Ar + 57								
$[ArCHN_2O]$	—[c]	—	−1.8	2.1	—	—	8.5	1.8
or								
$[ArC_2H_3NO]$	—[c]	—	−14.3	2.1	—	—	−4.1	1.8
$[ArNHCHO]^{+\cdot}$	2.9	1.7	−0.2	1.4	−4.6	1.4	−1.1	1.8
$[ArNHCO]^{+}$	1.1	1.0	1.0	1.2	−2.5	1.2	−3.0	1.0
$[ArNCO]^{+\cdot}$	0.4	1.3	0.7	1.0	−2.1	1.2	−1.8	0.7
$[ArCO]^{+}$	—	—	0.6	1.7	—	—	0.0	1.2
$[ArNH_2]^{+\cdot}$	0.8	1.1	0.2	1.4	−1.8	1.8	−2.5	1.0
Ar^{+}	1.7	1.2	1.1	1.0	−3.8	0.7	−6.1	4.1
$MeNHCHO^{+\cdot}$	1.1	0.9	—	—	0.1	0.6	—	—
$MeNHCO^{+}$	0.6	0.7	1.4	0.7	−1.0	0.6	0.0	1.1
$MeNCO^{+\cdot}$	4.8	0.9	5.7	1.0	—	—	0.2	3.5

[a] Error equals mean value minus calculated value, in mu.
[b] Standard deviation of the measurements in mu.
[c] Intensity was less than 1% of the base peak intensity.



Scheme 2. Hypothetical structures of fragment ions of 1-methyl-3-aryl-5-hydroxy-2,4-imidazolidinediones. All transitions shown were experimentally verified by either *B/E* linked scans or by CAD studies; such verification is noted by use of an asterisk.

10% valley method. The magnetic field was exponentially scanned from *m/z* 500 to 40 at 5 s per decade. PFK was used as an internal mass standard. Time-domain data from scans containing analyte ions were converted to mass-domain data using a PFK calibration file. The data from 10–20 scans were averaged using a 10 mu mass window.

Linked-scanning experiments

The metastable decomposition studies were done on a VG Model 7070E-HF mass spectrometer operated at a 6 kV source potential. Samples were introduced and ionized as described above in the high-resolution studies. The instrument was tuned and calibrated with PFK to a resolving power of about 2000 and scanned from *m/z* 300 to 40 at 5 s per decade. Linked scans were generated digitally using the 11–250 data system.

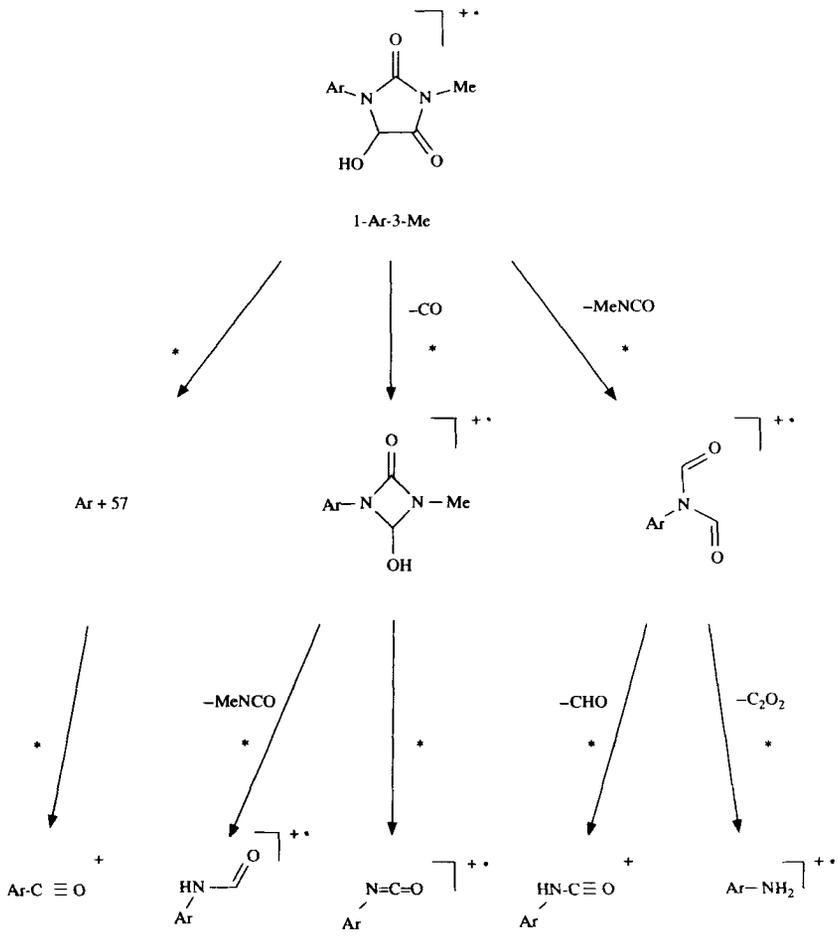
Collision-activated dissociation studies

The collision-activated dissociation (CAD) experiments were done on a Finnigan MAT Model TSQ 70 triple quadrupole mass spectrometer. Samples (~1 μg) were evaporated with a solid probe heated from ambient to 300 °C at 120 °C min^{-1} and then ionized by electron impact at 70 eV. Positive ions were mass-selected and collided with 0.7–1 mTorr argon (1 Torr = 133.3 Pa) at a laboratory-frame collision energy of 35 eV.

RESULTS AND DISCUSSION

Reaction of 1-methyl-3-arylureas with glyoxylic acid (Scheme 1) gives two isomeric products, 1-methyl-3-aryl-5-hydroxy-2,4-imidazolidinediones (1-Me-3-Ar) and 1-aryl-3-methyl-5-hydroxy-2,4-imidazolidinediones (1-Ar-3-Me). Relative abundances of ions found in the positive-ion EI mass spectra of four isomeric pairs of hydroxyhydantoins are summarized in Table 1. The elemental composition of these ions was established by high-resolution experiments which are summarized in Table 2.

By means of accurate mass measurement, linked-scan experiments and tandem mass spectrometric experiments on a triple quadrupole mass spectrometer, fragmentation patterns were obtained as shown in Scheme 2 for the 1-Me-3-Ar isomers and in Scheme 3 for the 1-Ar-3-Me isomers. In the absence of reference spectra of hydroxyhydantoins of known structure, the mass spectrometric assignment of isomeric hydroxyhydantoins is difficult, because the EI mass spectra of



Scheme 3. Hypothetical structures of fragment ions of 1-aryl-3-methyl-5-hydroxy-2,4-imidazolidinediones. All transitions shown were experimentally verified by either *B/E* linked scans or by CAD studies; such verification is noted by use of an asterisk.

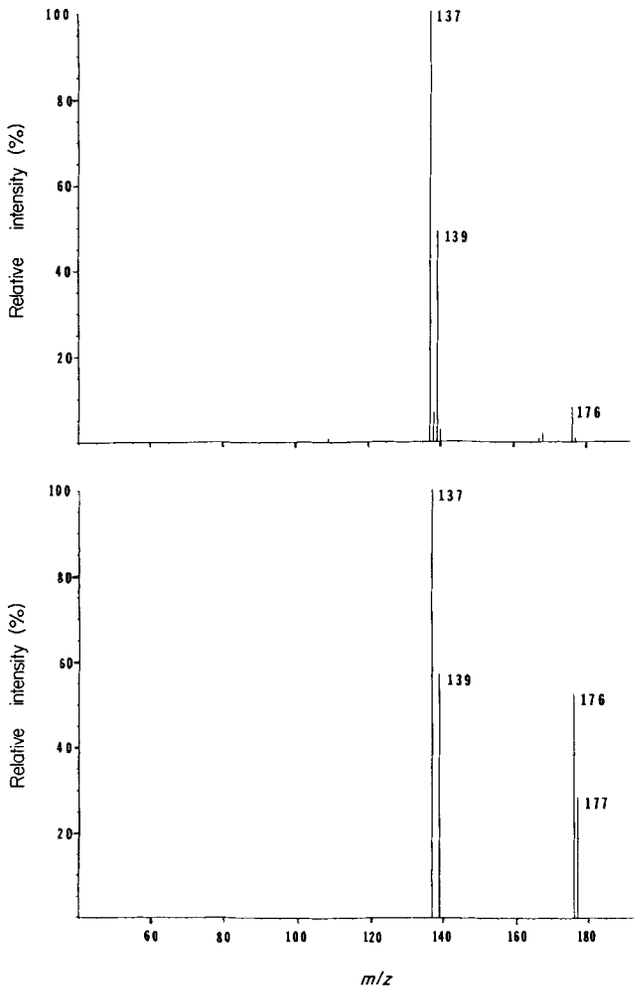


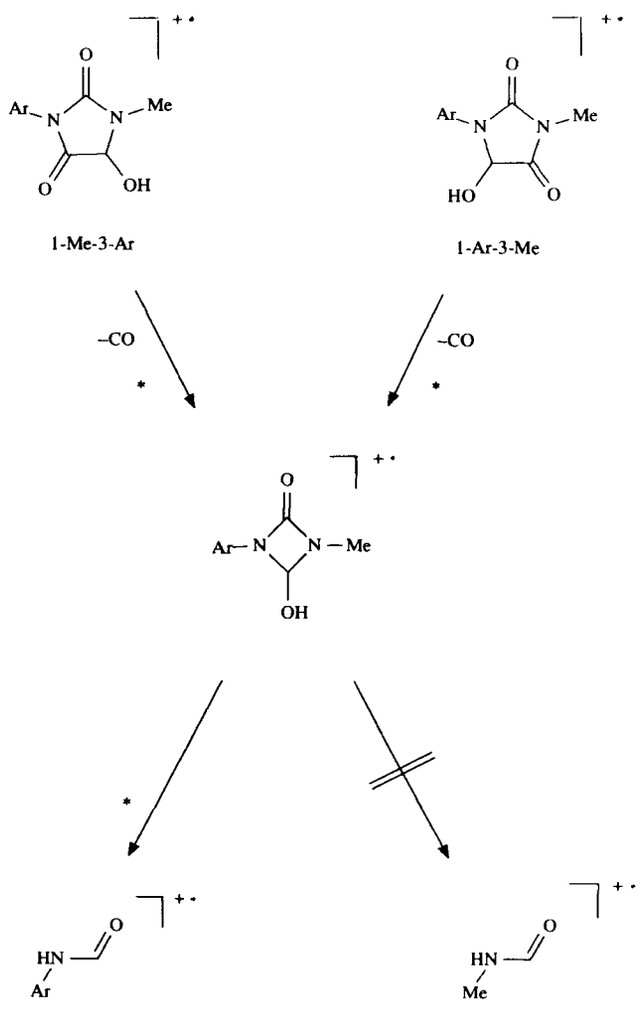
Figure 1. *B/E* linked scan of the $M^{+\cdot} - CO$ ion (*m/z* 196) of compounds **2** (top) and **3** (bottom).

isomeric pairs of compounds are very similar (see Table 1). Differences in abundance can be seen. For example, the $M^{+\cdot} - MeNCO$, $[ArNHCO]^+$ and $[ArNCO]^{+\cdot}$ ions are consistently more abundant in the spectra of 1-Me-3-Ar isomers. Analogously, the $[ArNHCHO]^{+\cdot}$, $[ArNH_2]^{+\cdot}$ and Ar^+ ions are consistently more abundant in the spectra of 1-Ar-3-Me isomers. Because these ions are present in the spectra of both isomers, however, they can not be used to assign isomeric hydroxyhydantoins *a priori*.

The $[MeNHCHO]^{+\cdot}$ ion is only seen in the spectra of 1-Me-3-Ar isomers. This ion can arise from 1-Me-3-Ar isomers by the cleavage of two single bonds. On the other hand, to form the $[MeNHCHO]^{+\cdot}$ ion from 1-Ar-3-Me isomers, two bond cleavages and two hydrogen atom rearrangements would be required. The assignment of hydroxyhydantoins in this paper is based on the observation that the $[MeNHCHO]^{+\cdot}$ ion is only seen in one series of isomers of the compounds synthesized in this work. It seems extremely unlikely that this ion could be formed from the 1-Ar-3-Me isomer exclusively.

For similar mechanistic reasons, the $[ArNHCHO]^{+\cdot}$ ion should be expected from only the 1-Ar-3-Me isomer and similarly be useful in the assignment of these compounds. Although it is true that the $[ArNHCHO]^{+\cdot}$ ion abundance is greater in the spectra of the 1-Ar-3-Me isomers (see Table 1), it is surprising that this ion was observed in the spectra of all of the isomers examined. Linked-scan and tandem experiments offer an explanation. The $[ArNHCHO]^{+\cdot}$ ion from the 1-Me-3-Ar isomer was found to arise from the molecular ion by losses of carbon monoxide and methyl isocyanate. Similarly, the $[ArNHCHO]^{+\cdot}$ ion from the 1-Ar-3-Me isomer arises from the molecular ion by losses of the same two neutral species (see Schemes 2 and 3). This suggests that the $M^{+\cdot} - CO$ ions from the two isomers might have the same structure. This hypothesis is supported by the fact that the metastable decomposition spectra of these ions are very similar (see Fig. 1). Another fragmentation of the $M^{+\cdot} - CO$ ion gives rise to a peak at *m/z* 176. This corresponds to loss of HF and was only observed for compounds **2** and **3**.

A possible structure for the $M^{+\cdot} - CO$ ion is shown in Schemes 2 and 3. Its formation requires the loss of C(4) of the hydantoin ring as carbon monoxide. Two lines of reasoning suggest that it is indeed C(4) that is lost as carbon monoxide: (i) loss of methyl isocyanate from the $M^{+\cdot} - CO$ ion would require considerable structural rearrangement if C(2) were lost as carbon



Scheme 4. Postulated formation of a cyclic $M^{+\cdot} - CO$ ion from 1-Me-3-Ar and 1-Ar-3-Me isomers.

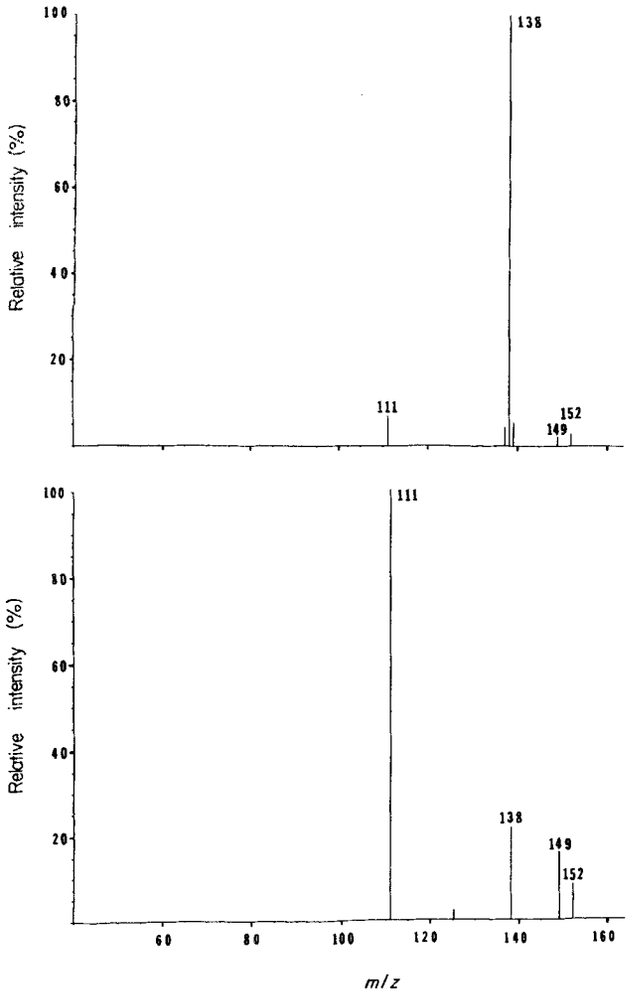


Figure 2. *B/E* linked scan of the $M^{+\cdot}$ – MeNCO ion (*m/z* 167) of compounds **2** (top) and **3** (bottom).

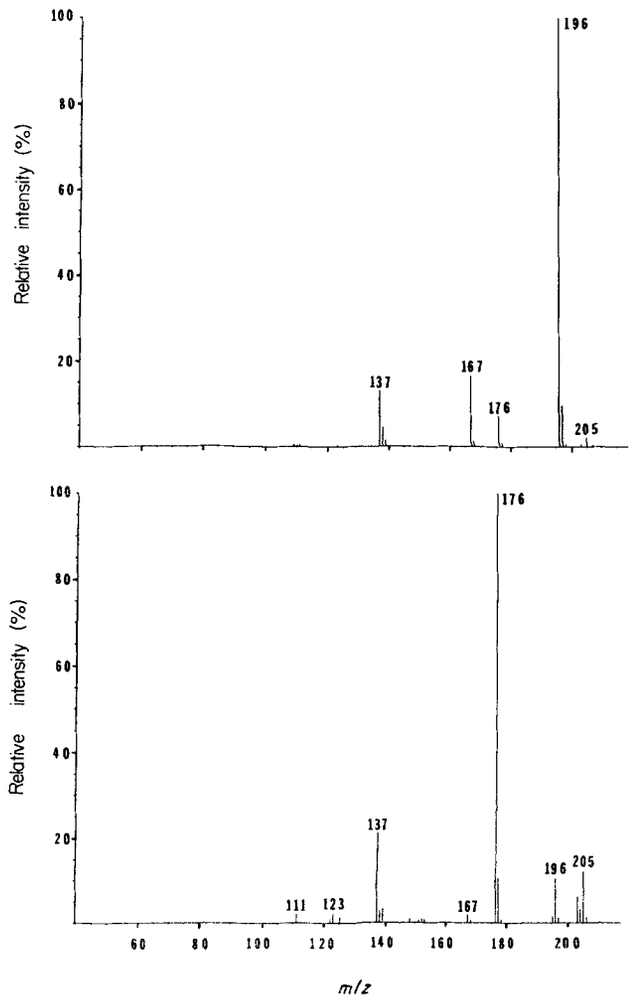


Figure 3. *B/E* linked scan of the molecular ion (*m/z* 224) of compounds **2** (top) and **3** (bottom).

monoxide, whereas the same loss could occur by cleavage of two single bonds if C(4) were lost as carbon monoxide; (ii) when bond energies are conisdered, loss of C(4) should be preferred by ~70 kJ mol^{-1}. This is because loss of C(2) involves breaking two C—N bonds (290 kJ mol^{-1} per bond) and forming one N—N bond (160 kJ mol^{-1}) for a net requirement of about 420 kJ mol^{-1} (2(290) – 160).[7] Loss of C(4) as carbon monoxide requires the cleavage of one C—C bond (350 kJ mol^{-1}) and one C—N bond. After reforming one C—N bond, the net energetic requirement would be about 350 kJ mol^{-1} (350 + 290 – 290).

If a cyclic ion such as that proposed for the $M^{+\cdot}$ – CO ion does exist, then why does it not fragment to give the $[MeNHCHO]^{+\cdot}$ ion from both series of isomers (see Scheme 4)? Charge delocalization in the aryl-substituted ions offers an explanation. Only the more stable product ion is observed.

Significant differences are seen between the *B/E* linked-scan metastable decomposition spectra of the $M^{+\cdot}$ – MeNCO ions from either the 1-Me-3-Ar or the 1-Ar-3-Me isomer (see Fig. 2). Loss of 29 u (probably $H^{\cdot}$ and CO) predominates for decomposition of the $M^{+\cdot}$ – MeNCO ion from the 1-Me-3-Ar isomer whereas loss of 56 u (probably two CO molecules) predominates for decomposition of the $M^{+\cdot}$ – MeNCO ion from the 1-Ar-3-Me isomer. These differences suggest that these ions have different structures although, alternatively, the differences might be due to differences in internal energy. Plausible structures of these ions are shown in Schemes 2 and 3.

Two ions are seen in the spectra of the 1-Ar-3-Me isomers that are not found in the spectra of the 1-Me-3-Ar isomers. These are the Ar + 57 and the $ArCO^{+}$ ions. The composition of the Ar + 57 ion is not known since two very similar compositions exist (see Table 2). Linked-scan and CAD experiments show that the $ArCO^{+}$ ion is a daughter of the Ar + 57 ion, and that the Ar + 57 ion is a daughter of both the molecular ion and an ion 15 u higher (NH or CH_3) than the Ar + 57 ion (see Scheme 3).

A comparison of *B/E* linked-scan metastable decomposition spectra and CAD spectra can be made. Metastable decomposition products of the molecular ions of **2** and **3** (relative molecular mass 224) were obtained by *B/E* linked scans and are shown in Fig. 3. The molecular ions of **2** and **3** were also dissociated by CAD on a triple quadrupole mass spectrometer; the results are shown in Fig. 4. The most notable differences between the two types of analysis is that CAD gave a higher

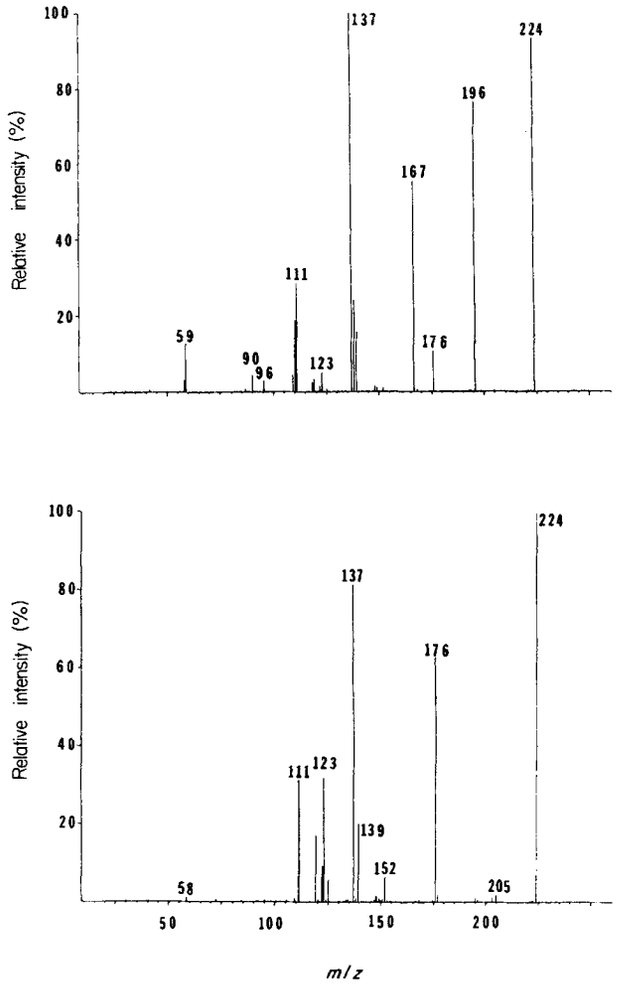


Figure 4. CAD mass spectrum of the molecular ion (*m/z* 224) of compounds **2** (top) and **3** (bottom).

abundance of low-mass fragments than did metastable decomposition. For example, the $[MeNHCHO]^{+\cdot}$ ion was not detected in the *B/E* linked scan of **2**, whereas it was easily seen (18% relative abundance) in the CAD experiment.

The current work is consistent with prior assignments of other hydroxyhydantoins that were based on independent synthesis.[5] Mass spectra were not reported in the previous work, but limited proton NMR data were given so that a direct comparison is possible.[5] For the 1-Me-3-Ar isomers in this study (compounds **2**, **4**, **6** and **8**), the methine proton on C(5) was found between 5.05 and 5.26 ppm. For the 1-Ar-3-Me isomers (compounds **3**, **5**, **7** and **9**), the methine proton of C(5) was found between 5.47 and 5.80 ppm. Baskakov *et al.*[5] reported that the methine proton on C(5) of 1-phenyl-3-methyl-5-hydroxy-2,4-imidazolidinedione resonates at 5.68 ppm. This result is consistent with the values found here and validates the spectroscopic method developed in this work.

In conclusion, we have developed a mass spectrometric method to assign hydroxyhydantoin isomers. The presence of the $[MeNHCHO]^{+\cdot}$ ion in the EI mass spectrum of an unknown would suggest the 1-Me-3-Ar isomer whereas observation of Ar + 57 or $[ArCO]^{+}$ ions would suggest the 1-Ar-3-Me isomer. If both isomers are available, comparison with the relative abundances of other ions (see Table 1) would further support the assignment. The method is expected to be general for other alkyl derivatives apart from the methyl, but caution should be exercised in the extension of its use.

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