Designer ligands. Part 11.[1] Electron-ionisation mass spectrometric studies of polydentate malonamide-derived ligands

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(received 31 Jan 03; accepted 26 May 03; published on the web 27 May 03)

Abstract

The mass fragmentations exhibited by a series of *N,N'*-disubstituted malonamides, prepared as potential silver(I)-selective ligands, have been explored using a combination of high-resolution and *B/E* linked-scan mass spectrometric data.

Keywords: Malonamides, silver(I)-selective ligands, fragmentation patterns, electron-ionisation mass spectrometry

Introduction

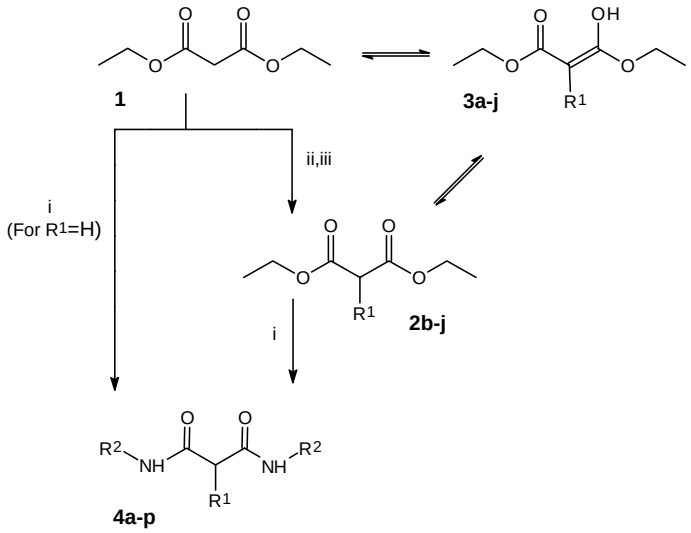
Metal-selective ligands have obvious potential in solvent extraction applications,[2] and Paiva[3] has reviewed numerous examples of silver-selective systems. In our own investigations, aimed at developing ligands capable of extracting silver(I) selectively from ore-leach solutions containing base-metal contaminants, various design criteria were identified. Thus, the target ligands were expected to:-

i) contain a suitable combination of donor atoms, such as nitrogen, sulfur and oxygen, to effect selective and efficient solvent extraction of the metal;
ii) be accessible *via* simple, efficient and cost-effective synthesis;
iii) be capable of extracting the metal ions efficiently at low pH; and
iv) be relatively inert towards acids.

Substituted malonamides were expected to satisfy these criteria, and we have recently reported the microwave-assisted synthesis of series of polydentate malonamide derivatives, designed to effect tetra-coordinate chelation of silver(I).[4] We now discuss the results of electron-ionisation (EI) mass spectrometric studies of these and related ligand systems.

Results and Discussion

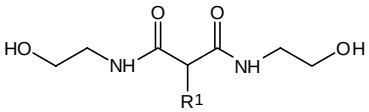
Access to the malonamides was achieved *via* amidation of diethyl malonate **1** and its alkylated derivatives **2b-j** (Scheme 1). Alkylation[5] of the sodium enolate of diethyl malonate **1** with selected alkyl halides (RX) afforded the alkylated derivatives **2b-j** in yields ranging from 47 to 83%. ^{1}H and ^{13}C NMR analysis of these esters revealed the presence of both keto and enol tautomers in $CDCl_3$ solution, the former being dominant under these conditions. Treatment of diethyl malonate **1** and its *C*-alkylated dervatives **2b-j** with ethanolamine[6] at room temperature (for periods of between 2 and 168 hours) gave the corresponding *N,N'*-bis(2-hydroxyethyl)malonamides **4a-j** (Table 1). The products, some of which appear to be new, were all characterised by elemental (high-resolution MS) and spectroscopic (IR and ^{1}H and ^{13}C NMR) analysis. Formation of the amides was clearly evident from a comparison of their ^{1}H NMR spectra with those of their ester precursors. The methyl triplet (at δ *ca.* 1.2 ppm) and the methylene quartet (at δ *ca.* 4.1 ppm), characteristic of the ethyl esters, is replaced by two quartets at *ca.* 3.1 and 3.4 ppm (due to the ethylene protons) and two triplets at *ca.* 4.7 and 8.0 ppm (assigned to the hydroxyl and amide protons, respectively). Unlike their ester precursors **2a-j**, the diamides **3a-j** exhibit no ^{1}H NMR evidence of the enol tautomers. The microwave-assisted synthesis of the more complex *N,N'*-disubstituted analogues **4k-p** has been reported elsewhere.[4] These latter compounds proved to be significantly more efficient ligands, than compounds **4a-j,** for extracting silver(I) from low-pH solutions containing the base metals, copper and lead.[4,7]



	R^1	R^2
a	H	$HOCH_2CH_2$
b	Me	$HOCH_2CH_2$
c	Et	$HOCH_2CH_2$
d	*i*-Pr	$HOCH_2CH_2$
e	Pr	$HOCH_2CH_2$
f	Bu	$HOCH_2CH_2$
g	Bn	$HOCH_2CH_2$
h	$CH_3(CH_2)_3CH_2$	$HOCH_2CH_2$
i	$CH_3(CH_2)_4CH_2$	$HOCH_2CH_2$
j	$CH_3(CH_2)_5CH_2$	$HOCH_2CH_2$
k	H	$CH_3OCH_2CH_2$
l	H	$PhCH_2SCH_2CH_2$
m	H	2-$MeOC_6H_4$
n	H	2-$MeSC_6H_4$
o	CH_2=$CHCH_2$	2-$MeOC_6H_4$
p	H	2-$MeOC_6H_4CH_2$

Scheme 1. Reagents. i, $NH_2CH_2CH_2OH$; ii, EtONa, EtOH; iii, RI or RBr (for **2g**, **2o**).

Table 1. Data the *N*,*N*'-bis(2-hydroxyethyl)malonamides **4a-j**

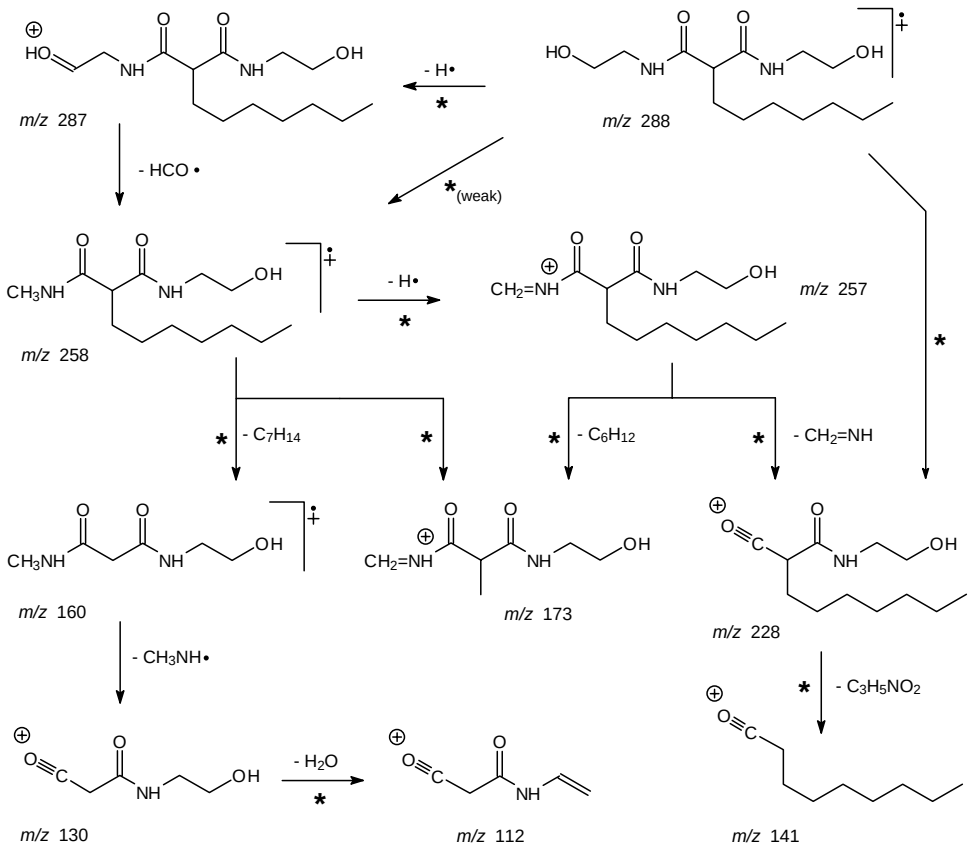


Compound	R^1	Yield [a] / %	Rn. time / h	mp / °C
4a	H	95	2	125-126
4b	Me	88	4	115-117 [b]
4c	Et	81	4	113-114
4d	Pr^i	35	24	120-122
4e	Pr	18	24	117-118
4f	Bu	89	48	123-125
4g	Bn	50	168	130-131 [b]
4h	$CH_3(CH_2)_3CH_2$	45	168	124-126 [b]
4i	$CH_3(CH_2)_4CH_2$	43	168	108-109 [b]
4j	$CH_3(CH_2)_5CH_2$	61	168	111-112 [b]

[a] Based on pure product obtained following recrystallisation. [b] New compound.

With the ligands **4a-p** in hand, the opportunity was taken to explore the major electron-ionisation mass fragmentations exhibited by representative systems. The fragmentation patterns proposed for the malonamides **4j** and **4l** (Schemes 2 and 3) are based on the high-resolution electron-impact (EI) and *B/E* linked-scan data, and correlations between the fragmentation of these compounds and related systems are summarised in Scheme 4.

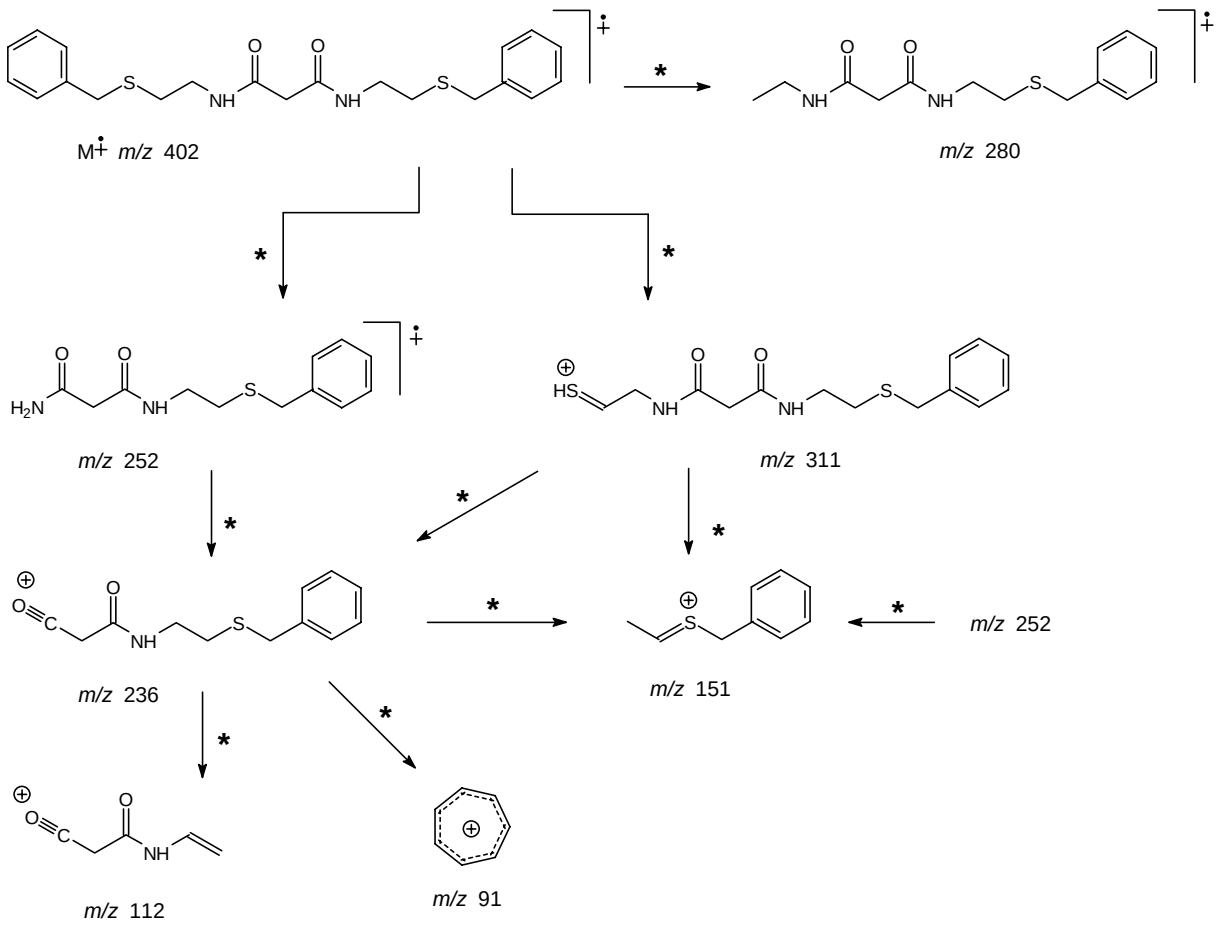
In the mass spectrum of the heptylmalonamide **4j** (Scheme 2), initial fragmentation of the molecular ion (*m/z* 288) proceeds *via* sequential loss of radical species (HX, HCOX and HX) to afford fragments with *m/z* 287, 258 and 257, respectively. The *B/E* linked-scan data also reveal a weak peak corresponding to the fragmentation, *m/z* 288 $\rightarrow$ 258. Further fragmentation of the odd-electron species (*m/z* 258) affords access to fragments formulated as a radical-cation (*m/z* 160), an iminium cation (*m/z* 173) and the acylium cations (*m/z* 130 and 112). Dealkylation of the resonance-stabilised cation (*m/z* 257) also affords the conjugated iminium cation (*m/z* 173), while loss of CH_2=NH leads to an acylium cation (*m/z* 228), which is responsible for the base peak. The latter fragment (*m/z* 228) also appears to be formed directly from the molecular ion and from the odd-electron species (*m/z* 258).



Observed	Formula	Calculated	Relative Abundance / %
288.20543	$C_{14}H_{28}N_2O_4$	288.2049	< 1.5
287 [a]	$C_{14}H_{27}N_2O_4$	287.1971	< 1.5
258.1942	$C_{13}H_{26}N_2O_3$	258.1943	24.32
257.1869	$C_{13}H_{25}N_2O_3$	257.1865	19.78
228.1597	$C_{12}H_{22}NO_3$	228.1600	100
173.0918	$C_7H_{13}N_2O_3$	173.0926	14.73
160.0854	$C_6H_{12}N_2O_3$	160.0848	14.15
141.1282	$C_9H_{17}O$	141.1279	50.06
130.0506	$C_5H_8NO_3$	130.0504	20.64
112.0398	$C_5H_6NO_2$	112.0399	4.11

[a] From the *B/E* linked-scan data.

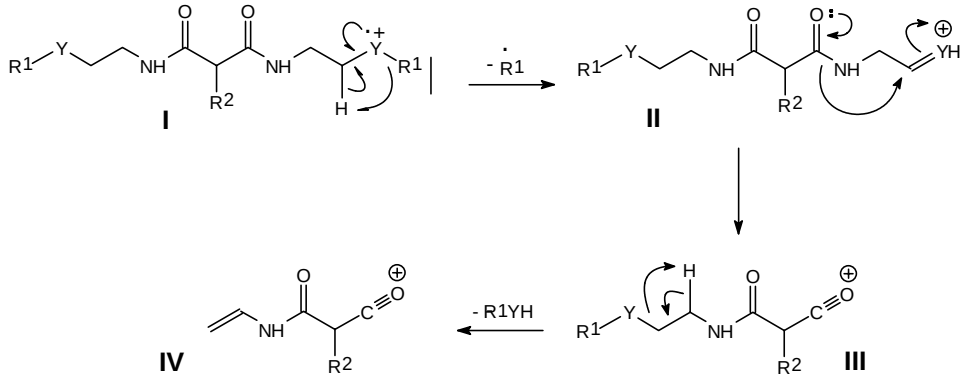
Scheme 2. Proposed fragmentations (*supported by the *B/E* linked-scan data) and the corresponding HRMS and relative abundance data for the malonamide derivative **4j**.



Observed	Formula	Calculated	Relative Abundance / %
402.1444	$C_{21}H_{26}N_2O_2S_2$	402.1436	1.60
311.0895	$C_{14}H_{19}N_2O_2S_2$	311.0888	75.84
280.1247	$C_{14}H_{20}N_2O_2S$	280.1246	1.61
252.0934	$C_{12}H_{16}N_2O_2S$	252.0933	2.02
236.0745	$C_{12}H_{14}NO_2S$	236.0745	4.48
151.0578	$C_9H_{11}S$	151.0582	9.98
112.0399	$C_5H_6NO_2$	112.0399	3.22
91.0549	C_7H_7	91.0548	100

Scheme 3. Proposed fragmentations (*supported by the *B/E* linked-scan data) and the corresponding HRMS and relative abundance data for the malonamide derivative **4l**.

The molecular ion (*m/z* 402; Scheme 3) for *N.N'*-bis(benzylthioethyl)malonamide **4l**, which shows exceptional selectivity for the extraction of silver(I),[4] exhibits initial elimination of radical and/or neutral species to give an even-electron ion (*m/z* 311) and a pair of odd-electron fragments (*m/z* 280 and 252). Sequential fragmentation of the monosubstituted malonamide species (*m/z* 252) leads to the acylium cations (*m/z* 236 and 112). Not surprisingly, certain fragmentations are characteristic of the benzylthioethyl moiety (*e.g.*, *m/z* 402 → 311 → 151); the even-electron species (*m/z* 151) is also produced by fission of the fragments with *m/*z 252 and 236. Fission of the acylium cation (*m/z* 236) affords the tropylium cation (*m/z* 91), which is responsible for the base peak in this case. Fragment types common to all of the "alkyl spacer" compounds examined are illustrated in Scheme 4.



Compound	Y	R^1	R^2	Ion Fragment Types I	II	III	IV
4a	O	H	H	190	189	130	112
4j	O	H	$CH_3(CH_2)_6$	288	287	228	112
4k	O	Me	H	218[a]	203	144	112
4l	S	Bn	H	402	311	236	112

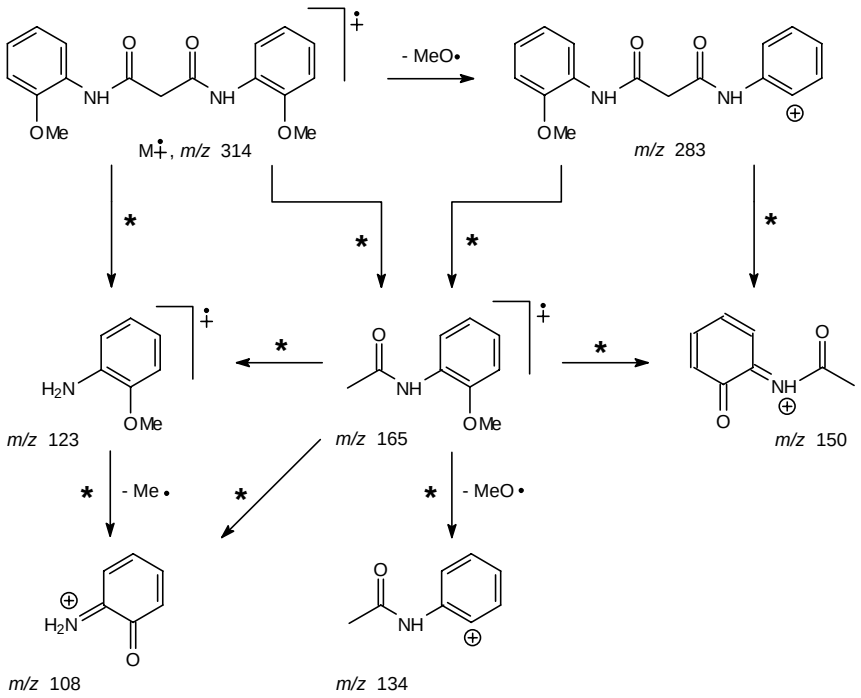
[a] As MH^+ (*m/z* 219)

Scheme 4. Common fragmentation patterns for the malonamides **4a, j-l**; in some cases, fragmentation may involve intermediate species.

The common fragmentations of the malonamides **4a**, **j-l** (Scheme 4) appear to involve loss of a radical species R^1• from the molecular ion **I** to give a resonance-stabilised cation **II**, which

undergoes sequential fission to yield acylium cations of types **III** and **IV**. These fragmentation patterns were observed regardless of the nature of the substituents R^1 and R^2.

The fragmentation patterns exhibited by the "aromatic spacer"-containing compounds **4m-o**, however, are significantly different from those of the "alkyl spacer" analogues **4a, j-l**. Acylium ions, typically detected in the mass spectra of the latter, appear to be absent in the spectra of compounds **4m-o**. Specific fragmentations proposed for the malonamide derivative **4m** are detailed in Scheme 5, while common fragments identified in the mass spectra of the ligands **4m-o** are summarised in Scheme 6.



Observed	Formula	Calculated	Relative Abundance / %
314.1256	$C_{17}H_{18}N_2O_4$	314.1267	93.20
283.1077	$C_{16}H_{15}N_2O_3$	283.1083	< 2
165.0795	$C_9H_{11}NO_2$	165.0790	60.72
150.0550	$C_8H_8NO_2$	150.0555	8.77
134.0604	C_8H_8NO	134.0606	17.27
123.0682	C_7H_9NO	123.0684	100
108.0451	C_6H_6NO	108.0449	56.89

Scheme 5. Proposed fragmentations (*supported by the *B/E* linked-scan data) and the corresponding HRMS and relative abundance data for the malonamide derivative **4m**.

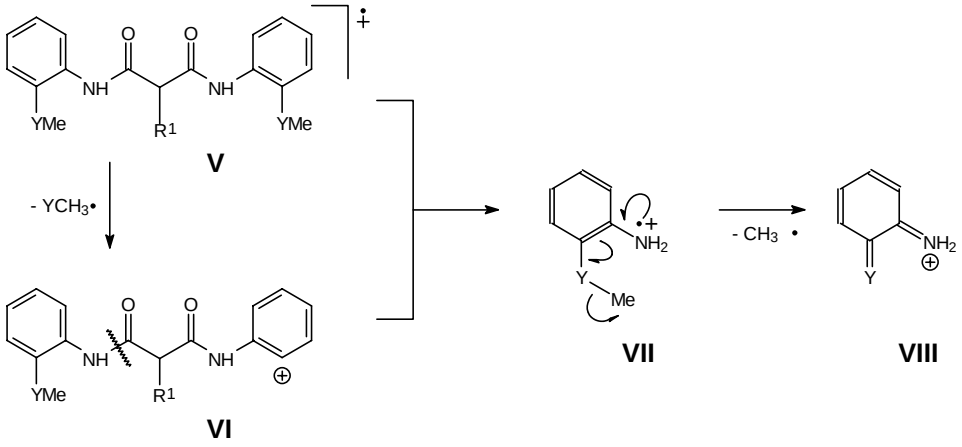
The molecular ion for compound **4m** (*m/z* 314; Scheme 5) undergoes:-

i) loss of MeO•, presumably *via* sequential elimination of HCHO and H•,[8] to afford an even-electron species (*m/z* 283); and

ii) fission of the malonamide skeleton to give two, odd-electron species (*m/z* 165 and 123).

The latter fragment (*m/z* 123) is responsible for the base peak. Fission of the carbocation (*m/z* 283) also affords the acetanilide radical-cation (*m/z* 165) as well as the *ortho*-quinonoid cation (*m/z* 150). Loss of MeO• from the radical-cation (*m/z* 165) and demethylation of the *o*-methoxyaniline species (*m/z* 123) then account for the formation of the acetanilide cation (*m/z* 134) and the *ortho*-quinonoid fragment (*m/z* 108), respectively. The latter fragment also appears to be produced *via* loss of ketene from the odd-electron species with *m/z* 165.

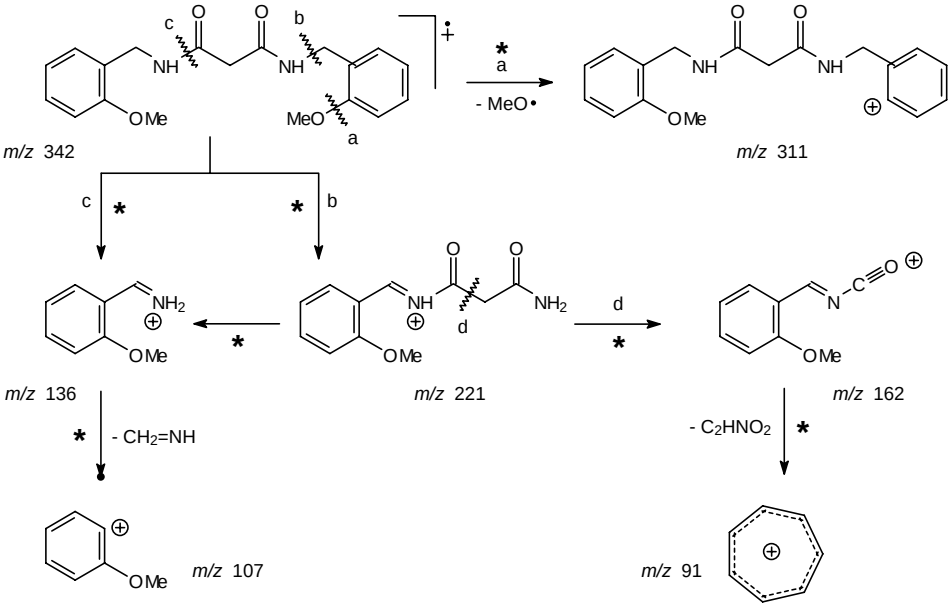
Comparison of the mass spectra of compounds **4m-o** reveals the loss of MeO• or MeS• from the molecular ion **V** (Scheme 6) to afford the corresponding even-electron species **VI**. Both ion types (**V** and **VI**) fragment further to give odd-electron species of type **VII**, which, in turn, undergo demethylation to yield the *ortho*-quinonoid cations of type **VIII**.



			Ion Fragment Types			
Compound	Y	R^1	**V**	**VI**	**VII**	**VIII**
4m	O	H	314	283	123	108
4n	S	H	346	299	139	124
4p	O	CH_2=$CHCH_2$	354	323	123	108

Scheme 6. Common fragmentation patterns for the malonamides **4m-o**; in some cases, fragmentation may involve intermediate species.

Apart from the elimination of MeO• from the molecular ion (*m/z* 342; Scheme 7) to afford a cation (*m/z* 311; cleavage 'a'), *N,N'*-bis(2-methoxybenzyl)malonamide **4p** exhibits somewhat different fragmentation patterns from compounds **4m-o**. Thus, fission ('b' and 'c') of the malonamide back-bone affords resonance-stabilised benzylic carbocations (*m/z* 221 and 136). The former (*m/z* 221) fragments to give a carbamoyl-type cation (*m/z* 162; cleavage 'd'), which then appears to lose C_2HNO_2, *via* an unusual intramolecular rearrangement, to afford the tropylium cation (*m/z* 91). Elimination of CH_2=NH from the cation (*m/z* 136) provides access to an even-electron species (*m/z* 107).



Observed	Formula	Calculated	Relative Abundance / %
342.1588	$C_{19}H_{22}N_2O_4$	342.1580	17.85
311.1381	$C_{18}H_{19}N_2O_3$	311.1396	< 0.5
221.0928	$C_{11}H_{13}N_2O_3$	221.0926	15.57
162.0556	$C_9H_8NO_2$	162.0555	3.17
136.0763	$C_8H_{10}NO$	136.0726	100
107.0495	C_7H_7O	107.0497	2.17
91.0546	C_7H_7	91.0548	23.64

Scheme 7. Proposed fragmentations (*supported by the *B/E* linked-scan data) and the corresponding HRMS and relative abundance data for the malonamide derivative **4p**.

From the foregoing analyses, it is apparent that, while the systems examined exhibit certain common fragmentations, the overall patterns tend to be compound specific.

Experimental Section

General Procedures. Infrared spectra were recorded on Perkin-Elmer Spectrum 2000 spectrophotometer. NMR spectra were recorded on a Bruker 400MHz AVANCE spectrometer, and chemical shifts are reported relative to TMS. Low resolution mass spectra were obtained on a Hewlett-Packard 5988A mass spectrometer, and high resolution and *B/E* linked scan analyses on a VG70-SEQ double-focussing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit); FAB mass spectra were obtained on a VG Micromass 70-70E spectrometer (Iontech B11N FAB-gun), using Xe as the bombarding gas and *m*-nitrobenzyl alcohol as the matrix (University of Potchefstroom).

The malonic esters **2b-k** and the malonamides **4**a-**f** are known compounds; the remaining malonamide derivatives appear to be new. The synthesis of the esters **2** and amides **4** are illustrated by the following examples.

Diethyl methylmalonate (2b)[5]. Diethyl malonate **1** (7.33 g, 45.3 mmol) was added to ethanolic NaOEt [generated *in situ* by reacting sodium (1.1 g, 48 mmol) with dry EtOH (60 ml)], and the resulting mixture was boiled under reflux for 2 h under dry nitrogen. Methyl iodide (6.39 g, 45.0 mmol) was then added dropwise and the mixture was boiled for a further hour. On cooling, water (50 ml) was added, and the resulting mixture was extracted with Et_2O (3 x 50 ml). The Et_2O extracts were combined, washed with brine and dried over anhyd. $MgSO_4$. The solvent was evaporated *in vacuo* to obtain the crude product (7.18 g, 92 %), which was then distilled *in vacuo* using a fractionating column to yield, as a colourless oil, diethyl methylmalonate **2b** (5.10 g, 65 %), bp 104-107 °C / *ca* 20 mmHg (lit.,[9] 198-199 °C).

***N,N´*-Bis(2-hydroxyethyl)malonamide (4a)[6].** Diethyl malonate **1** (1.61 g, 10.0 mmol) was stirred with ethanolamine (1.26 g, 20.6 mmol) for 2 hours. The resultant precipitate was filtered off and recrystallised from EtOH-Et_2O, yielding, as cream flakes, *N,N´*-bis(2-hydroxyethyl)malonamide **4a** (1.81 g, 95 %), mp 125-126 °C (from EtOH)(lit.,[6] 127-127.5 °C).

Analytical data for compounds isolated in this study, and which to our knowledge are new, are as follows.

***N,N´*-Bis(2-hydroxyethyl)-2-methyl-1,3-propanediamide (4b).** Cream flakes, (1.82 g, 88 %), mp 115-117 °C (from EtOH) (Found: MH^+, 205.1331. $C_8H_{16}N_2O_4$ requires *M*+1, 205.1332.); ν_{max}(NaCl)/cm^{-1} 3311 (OH), 3099 (NH) and 1642 (CO); δ_H(400 MHz; DMSO-d_6) 0.91 (3H, d, CH_3CH), 3.04 (1H, q, CHCH$_3$), 3.12 (4H, q, CH_2NH), 3.39 (4H, q, CH_2OH), 4.69 (2H, t, OH) and 8.02 (2H, t, NH); δ_C(100 MHz; DMSO-d_6) 13.2 (*C*H$_3$CH), 41.5 (CH$_2$NH), 53.0 (*C*HCH$_3$), 59.6 (CH$_2$OH) and 169.2 (CO).

2-Benzyl-*N,N´*-bis(2-hydroxyethyl)-1,3-propanediamide (4g). Cream flakes, (1.41 g, 50 %), mp 130-131 °C (from EtOH) (Found: MH^+, 281.1523. $C_{14}H_{20}N_2O_4$ requires *M*+1, 281.1527.); ν_{max}(NaCl)/cm^{-1} 3308 (OH), 3099 (NH) and 1642 (CO); δ_H(400 MHz; DMSO-d_6) 3.09 (2H, d, CHCH_2), 3.12 (4H, q, CH_2NH), 3.24 (1H, t, CHCH$_2$), 3.39 (4H, q, CH_2OH), 4.69 (2H, t, OH), 7.21 (5H, m, ArH) and 8.02 (2H, t, NH); δ_C(100 MHz; DMSO-d_6) 41.5 (CH_2NH), 47.0 (CHCH$_2$), 53.0 (CHCH$_2$), 59.6 (CH_2OH), 128.1, 128.6, 129.9 and 137.7 (ArC) and 168.9 (CO).

***N,N´*-Bis(2-hydroxyethyl)-2-pentyl-1,3-propanediamide (4h).** Cream flakes, (1.18 g, 45 %), mp 124-125 °C (from EtOH) (Found: MH^+, 261.1815. $C_{12}H_{24}N_2O_4$ requires *M*+1, 261.1814.); ν_{max}(NaCl)/cm^{-1} 3283 (OH), 3074 (NH) and 1660 (CO); δ_H(400 MHz; DMSO-d_6) 0.84 [3H, t, CH_3(CH$_2$)$_4$CH], 1.20 [6H, m, CH$_3$(CH_2)$_3$CH$_2$CH], 1.64 [2H, q, CH$_3$(CH$_2$)$_3$CH_2CH], 3.02 [1H, t, CH$_3$(CH$_2$)$_3$CH$_2$CH], 3.12 (4H, q, CH_2NH), 3.38 (4H, q, CH_2OH), 4.69 (2H, t, OH) and 7.86 (2H, t, NH); δ_C(100 MHz; DMSO-d_6) 13.8 [CH$_3$(CH$_2$)$_4$CH], 21.9, 26.4, 30.3, 30.9 [CH$_3$(CH$_2$)$_4$CH], 41.4 (CH_2NH), 53.0 [CH$_3$(CH$_2$)$_4$$C$H], 59.7 ($CH_2$OH) and 169.8 (CO).

2-Hexyl-*N,N´*-bis(2-hydroxyethyl)-1,3-propanediamide (4i). Cream flakes, (1.20 g, 43 %), mp 108-109 °C (from EtOH) (Found: MH^+, 275.1970. $C_{13}H_{26}N_2O_4$ requires *M*+1, 275.1971.); ν_{max}(NaCl)/cm^{-1} 3337 (OH), 3120 (NH) and 1677 (CO); δ_H(400 MHz; DMSO-d_6) 0.85 [3H, t, CH_3(CH$_2$)$_5$CH], 1.22 [8H, m, CH$_3$(CH_2)$_4$CH$_2$CH], 1.64 [2H, q, CH$_3$(CH$_2$)$_4$CH_2CH], 3.02 [1H, t, CH$_3$(CH$_2$)$_4$CH$_2$CH], 3.12 (4H, q, CH_2NH), 3.38 (4H, q, CH_2OH), 4.69 (2H, t, OH) and 7.85 (2H, t, NH); δ_C(100 MHz; DMSO-d_6) 13.9 [CH$_3$(CH$_2$)$_5$CH], 21.9, 26.7, 28.3, 30.4, 31.0 [CH$_3$(CH$_2$)$_5$CH], 41.4 [CH_2NH], 53.0 [CH$_3$(CH$_2$)$_5$$C$H], 59.7 ($CH_2$OH) and 169.8 (CO).

2-Heptyl-*N,N´*-bis(2-hydroxyethyl)-1,3-propanediamide (4j). Cream flakes, (1.75 g, 61 %), mp 111-112 °C (from EtOH) (Found: MH^+, 289.2123. $C_{14}H_{28}N_2O_4$ requires *M*+1, 289.2127.); ν_{max}(NaCl)/cm^{-1} 3337 (OH), 3108 (NH) and 1675 (CO); δ_H(400 MHz; DMSO-d_6) 0.85 [3H, t, CH_3(CH$_2$)$_6$CH], 1.22 [10H, m, CH$_3$(CH_2)$_5$CH$_2$CH], 1.64 [2H, q, CH$_3$(CH$_2$)$_5$CH_2CH], 3.02 [1H, t, CH$_3$(CH$_2$)$_5$CH$_2$CH], 3.12 (4H, q, CH_2NH), 3.38 (4H, q, *J* 5.6 Hz, CH_2OH), 4.70 (2H, s, OH) and 7.86 (2H, t, NH); δ_C(100 MHz; DMSO-d_6) 13.9 [CH$_3$(CH$_2$)$_6$CH], 22.0, 26.8, 28.4, 28.6, 30.4, 31.1 [CH$_3$(CH$_2$)$_6$CH], 41.4 (CH$_2$NH), 53.0 [CH$_3$(CH$_2$)$_6$$C$H], 59.7 ($CH_2$OH) and 169.8 (CO).

Acknowledgements

The authors thank MINTEK, Rhodes University and the National Research Foundation (NRF) for generous financial support, Dr P. Boshoff (Cape Technikon Mass Spectrometry Unit) and Dr L. Fourie (Potchefstroom University) for collecting the high-resolution mass fragmentation data, and Mr A. Sonemann for recording low-resolution spectra.

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