2-Aminothiazole Derivatives. II. Mass Spectra of Ethyl *N*-(2-Thiazolyl)-malonamates and Ethyl 2-Thiazolylaminomethylenemalonates (1)

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The fragmentation pattern of the title compounds under electron impact are discussed. During fragmentation in the mass spectrometer, these compounds undergo a rare type of rearrangement involving a long distance transfer of hydrogen.

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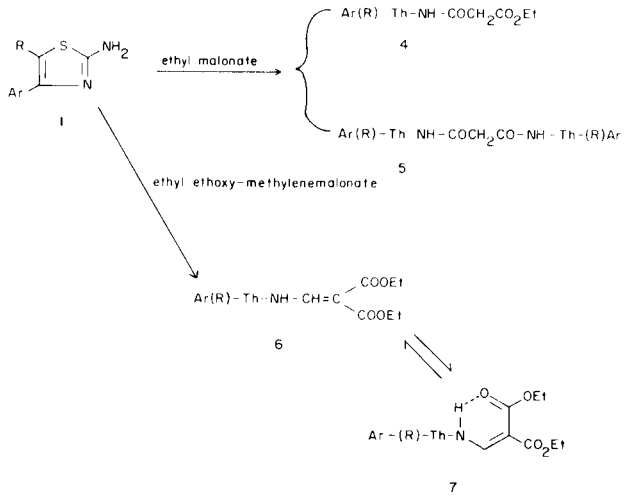
We have previously reported (1) the mass spectral fragmentation patterns of 2-acetylacetamidothiazoles **2** and *N*-(2-thiazolylamino)crotonamides **3**. These 2-aminothiazole derivatives show well defined fragmentation patterns involving a McLafferty-type rearrangement.

Ar-Th-NH-CO-CH_2-CO-Me Ar-Th-NH-CH = C(Me)-NH-Th-Ar

2 (Th = thiazole ring) **3**

The present report is a study of the mass spectra of ethyl-*N*-(2-thiazolyl)malonamates **4** and ethyl-2-thiazolylaminomethylene malonates **6**, synthesized by condensing 2-aminothiazoles with ethyl malonate and ethyl ethoxymethylene malonate, respectively (2). The reaction of ethyl malonate with 2-aminothiazoles yields not only **4**, but also *N,N'*-bis(2-thiazolyl)malonamide **5**. This by-product can also be obtained by reacting equimolar quantities of the amine **1** and **4**.

Two different ethyl groups are shown by the nmr spectra of **6**. In each case, the methylene protons appear as two distinct quadruplets at $\delta \cong 4.2$ and 4.4 ppm, while the methyl protons appear as two triplets at $\delta \cong 1.25$ and 1.45 ppm. A preferential conformation of the molecule, involving an intramolecular hydrogen bond between the NH group and one of the ester carbonyl functions (*cf.* **7**), is probably the reason for this non-equivalence of the two ethyl groups. The addition of trifluoroacetic acid, which ruptures hydrogen bonds, results in the disappearance of this non-equivalence and a common signal for the two ethyl groups is then observed.



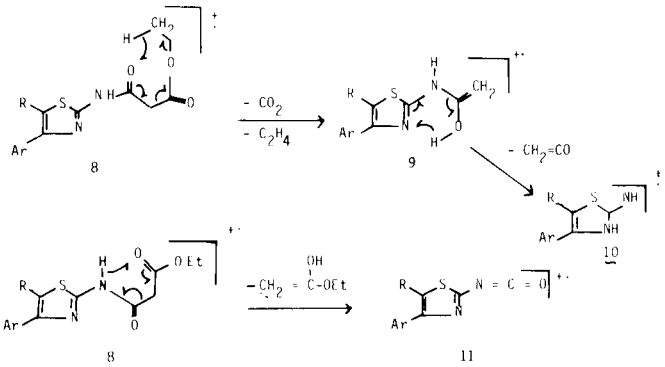
1 4 5 6 7

Mass Spectra.

1. Ethyl Thiazolylmalonamates **4**.

The relative intensities of the peaks corresponding to the molecular ions of the two compounds we studied barely exceed 10% that of the base peaks, demonstrating their instabilites under electron impact (Table 4). The fragmentation patterns (Scheme 1) are dominated by two rearrangements, similar to the McLafferty-type rearrangement

Scheme 1



8 9 10 8 11

we reported in our prior study (1). The first of these rearrangements leads to the enol ion **9** (M-72) by the loss of CO_2 and ethylene from the molecular ion. Ion **9**, in turn, loses vinylketone to give the iminothiazoline ion **10**, which undergoes the well known fragmentation we previously reported (1). The second fragmentation mode, less important than the first, leads to ion **11**, by the elimination of the enol ester CH_2=COH-OEt from the molecular ion.

This type of fragmentation, involving the loss of CO_2, $CH_2=CH_2$ or CH_2CO following a rearrangement involving long distance transfer of hydrogen from an ethoxy group to a carbonyl function, has been reported by Bowie, *et al.* (3), in a study of the spectra of certain β-ketoesters.

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Table 1

Characteristics of Compounds **6**

Ar	R	Formula	M.p. (°C)	Yield (%)	Analyses % Calcd. / % Found C	H	N	Nmr Data (δ) NH (a)	CH = (a)	H5	H. Arom.	CH_2CH_3	CH_2CH_3
C_6H_5	R	$C_{17}H_{18}N_2O_4S$	98	63	59.01	5.24	8.10	11.5 d	8.88 d	7.09 s	7.9 m 2H	4.41 q	1.45 t
					59.07	5.3	8.07				7.45m 3H	4.37 q	1.43 t
p-Cl-C_6H_4	H	$C_{17}H_{17}ClN_2O_4S$	121	70	53.73	4.51	7.7	11.4 d	8.6 d	6.99 s	7.78 d	4.24 q	1.32 t
					53.63	4.58	7.67				7.2 d	4.20 q	1.30 t
p-Me-C_6H_4	H	$C_{18}H_{20}N_2O_4S$	105	80	60.06	5.6	7.78	11.4 d	8.7 d	6.99 s	7.7 d	4.28 q	1.38 t
					60.01	5.6	8.0				7.72 d	4.24 q	1.36 t
p-MeO-C_6H_4	H	$C_{18}H_{20}N_2O_5S$	96	80	57.44	5.30	7.40	11.35 d	8.71 d	6.81 s	7.71 d	4.23 q	1.33 t
					57.57	5.39	7.48				6.8 d	4.19 q	1.31 t
C_6H_5	C_6H_5	$C_{23}H_{22}N_2O_4S$	132	52	65.46	5.25	6.64	11.4 d	8.59 d		7.16 m	4.25 q	1.31 t
					65.50	5.40	6.50					4.20 q	1.25 t
p-C_6H_5-C_6H_4	H	$C_{23}H_{22}N_2O_4S$	148	60	65.46	5.25	6.64	11.5 d	8.75 d	7.0 s	7.64 m	4.32 q	1.35 t
					65.53	5.31	6.49					4.28 q	1.31 t

(a) $J_{NH\text{-}CH} \sim 12$ Hz.

Table 2

Characteristics of the Malonamates **4**

Ar	R	Formula	M.p. (°C)	Yield (%)	% Calcd. C	H	N	% Found C	H	N	Nmr Data (δ, ppm) H5	H4	H Arom.	$COCH_2$	CH_2CH_3	CH_2CH_3
H	H	$C_8H_{10}N_2O_3S$	153 a	33							7.08 d	7.57 d		3.62 s	4.28 q	1.3 t
Me	H	$C_9H_{12}NO_3S$	149 b	30												
Ph	H	$C_{14}H_{14}N_2O_3S$	150	47	57.9	4.9	9.6	57.7	4.8	9.7						
p-ClPh	H	$C_{14}H_{13}ClN_2O_3S$	152	55	51.8	4.0	8.6	51.7	3.9	8.7	7.2 s		7.41 d 7.86 d	3.58 s	4.3 q	1.31 t
p-MePh	H	$C_{15}H_{16}N_2O_3S$	140	30	59.2	5.3	9.2	59.3	5.2	9.1	7.4 s		7.52 d 7.98 d	3.49 s	4.33 q	1.3 t
p-MeOPH	H	$C_{15}H_{16}N_2O_4S$	132	19	56.2	5.0	8.7	56.1	5.1	8.6	7.0 s		6.9 d 7.76 d	3.46 s	4.29 q	1.26 t
												$J_{H4,H5} = 4.8$ Hz				

(a) M.p. 149.5° from reference (3). (b) M.p. 147-148° from reference (11).

Table 3

Malonamides **5**

Ar	R	Formula	M.p. (°C)	Yield (%)	% Calcd. C	H	N	% Found C	H	N
H	H	$C_9H_8N_4O_2S_2$	270 (a)	40						
Me	H	$C_{11}H_{12}N_4O_2S_2$	272 (b)	43						
Ph	H	$C_{21}H_{16}N_4O_2S_2$	264	25	60.0	3.8	13.3	59.9	4.0	13.1
p-ClPh	H	$C_{21}H_{14}Cl_2N_4O_2S_2$	275	18	51.3	2.9	11.4	51.4	2.7	11.2
p-MePh	H	$C_{23}H_{20}N_4O_2S_2$	261	20	61.6	4.5	12.5	61.7	4.6	12.7
p-MeOPH	H	$C_{23}H_{20}N_4O_4S_2$	274	14	57.5	4.2	11.7	57.5	4.1	11.5

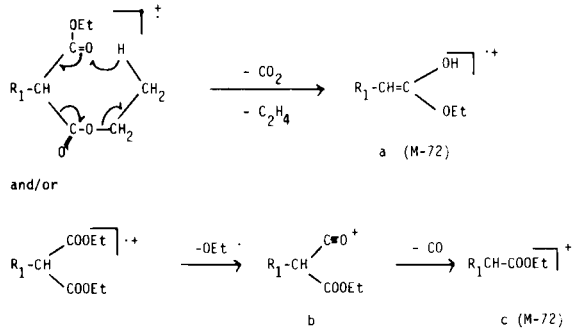
(a) M.p. 271° (reference 6). (b) M.p. 270° dec. (reference 7).

2. Ethyl Thiazolylaminomethylenemalonates **6**.

Bowie, *et al.* (4), examined the mass spectra of a number of monosubstituted ethyl malonate derivatives and concluded that the principal fragmentation mode of these compounds is that illustrated in Scheme 2.

The ions corresponding to M-72 or M-73 were absent in the mass spectra of compound **6**; rather, the loss of OEt constitutes the principal mode of fragmentation. Ion **12** undoubtedly stabilizes in the form of the cyclic thiazolopyrimidinium ion **13**, which in turn loses a CO_2Et group

Scheme 2



followed by a rearrangement involving a hydrogen transfer from the NH function, resulting in the formation of the thiazolopyrimidone ion **14**. This ion, which represents 66 to 100% of the base peak, can lose CO to yield ion **15**, which is present in all the spectra examined. It should be noted that the fragmentation pattern of ions **12** or **13** resembles that we observed with ethyl thiazolopyrimidone carboxylates (5) and this observation argues in favour of the existence of the cyclic ion **14**.

Another large peak present in all the spectra corresponds to the species M^+-44 and probably indicates the intramolecular transfer of hydrogen from one of the ethyl groups to nitrogen, followed by the loss of ethylene oxide to yield ion **16**. The latter then undergoes fragmentation to give the iminothiazoline ion **16**, observed during the electronolysis of **4**. The major peaks and the relative intensities of the compounds are shown in Table 5.

EXPERIMENTAL

Nmr spectra were recorded with a Perkin Elmer R 12 spectrometer in deuterochloroform or in carbon tetrachloride, with tetramethylsilane as internal standard. Mass spectra were recorded with an MS 50 instrument at an ionizing potential of 70 eV. Samples were analysed by direct introduction through a heated inlet system at a temperature near the melting point of each compound. Elemental compositions were obtained by the peak matching method.

Ethyl 2-Thiazolylaminomethylenemalonates (**6**).

An equimolar mixture of the aminothiazole and ethyl ethoxymethylenemalonate was heated for 6 hours at 110° in an oil bath. After cooling, the reaction mixture was triturated with petroleum ether and the solid precipitate was filtered and recrystallized from ethanol. Table 1 summarizes the physical characteristics and nmr data of the products.

Scheme 3

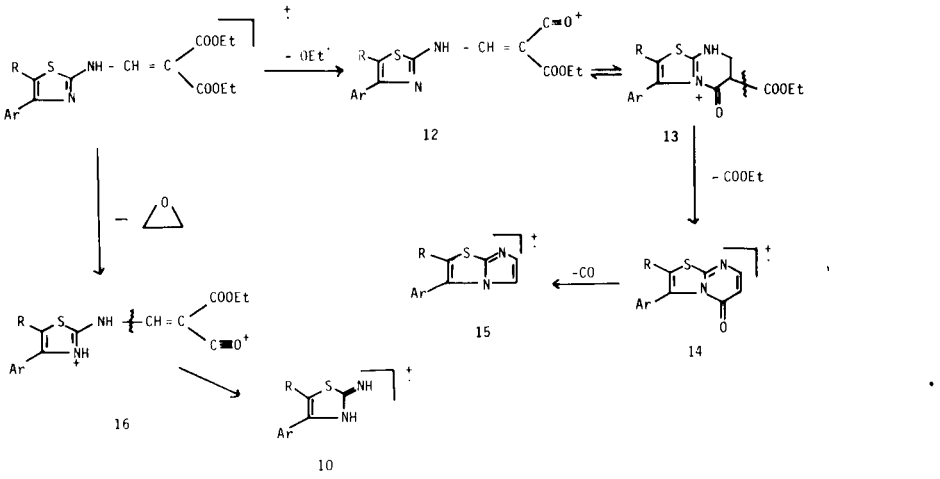


Table 4

Mass Spectral Data of Compounds **4**

Ar	R													
Ph-	H	m/e:	290 (M^+)		286	271	220	219	218	203	202	178	177	176
		I%:	1		35	7	34	86	100	31	29	91	86	86
		m/e:	175	159	149	148	146	136	135	134	133	121	104	103
		I%:	81	7	23	21	13	33	70	99	25	31	98	34
		m/e:	102	90	89	77	76	69	63	51	50	45	43	
		I%:	24	46	64	72	26.7	18.6	22	41	18	38	70	
p-Cl-Ph-	H	m/e:	326 (M^+)		324	254	253	252	213	212	211	210	175	174
		I%:	6		15	28	11	75	12	98	34	100	7	18
		m/e:	170	169	168	138	133	111	102	89	75	43		
		I%:	22	7	63	12.6	9.8	5.7	4.6	10	9	48		

Table 5

Mass Spectral Data of Compounds **6**

Ar	R														
p-Me-Ph	H	m/e:	360 (M^+)		316	315	270	243	241	214	213	201	190		
		I%:	41		22	72	41	20	100	37	28	11	9		
p-MeO-Ph	H	m/e:	377 (M^+)		376	332	331	259	256	239	207	206	193	192	
		I%:	7		30	25	100	15	66	19	87	66	10	26	
		m/e:	191	164	121	103	96	89	77	69	64	45			
		I%:	75	91	76	42	15	23	61	15	23	27			
p-Cl-Ph	H	m/e:	383	381	338	337	336	291	290	289	265	264	263	262	236
		I%:	17	40	40	28	100	25	14	61	53	28	90	14	11
		m/e:	235	234	233	221	210	195	168	159	153	138	136	133	125
		I%:	12	31	17	17	7	5	19	11	5.5	7	15	14	5
		m/e:	123	110	89	75	69	53	44						
		I%:	5	7	12	5	7	18	8						
		I%:	5	7	12	5	7	18	8						
Ph	H	m/e:	423 ($M^+ + 1$)		422 (M^+)		379	378	377	376	332	331	330	329	
		I%:	12.5		38		15	38	100	10	25	95	30	90	
		m/e:	305	304	303	276	275	251	236	234	210	178	165	44	
		I%:	20	67	20	15	21	67	20	25	40	25	75	15	

Ethyl *N*-(2-Thiazolyl)malonates (**4**).

One mole of the amine and 1.5 moles of ethyl malonate were heated at approximately 120-140° for 20 to 40 minutes. After cooling, the reaction mixture was washed with diethyl ether, the residue boiled with ethanol and filtered while hot. The malonamate **4** crystallized out of the filtrate. Table 2 summarizes the physical characteristics and nmr data of these compounds.

The ethanol-insoluble residue consisted almost exclusively of *N,N'*-bis(2-thiazolyl)malonamide **5** and was purified by crystallization from acetic acid. Table 3 summarizes the characteristics of these compounds.

REFERENCES AND NOTES

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