Mass Spectra of Thiazolidines

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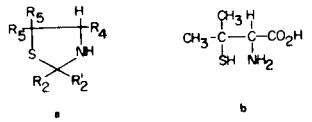
Received July 31, 1974

The electron impact mass spectra of twelve thiazolidines have been measured and the fragmentation patterns examined. The three most intense fragmentations common to all the thiazolidines examined are: (a) the cleavage of the substituent at C-2, (b) 1,4-ring cleavage, and (c) 2,5-ring cleavage. The 1,4- and 2,5-cleavages occur with and without rearrangement of a proton.

Thiazolidines (**a**) are saturated five-membered ring heterocycles with no convenient infrared or visible/ultraviolet characteristics for ready identification or detection.



a **b**

The reported assay (2) involves degradation of the ring. We prepared a series of thiazolidines from biochemically important aminothiols and set out to investigate the use of the mass spectrometer for detection of thiazolidines. Our immediate goal was to identify the characteristic fragmentation patterns of thiazolidines.

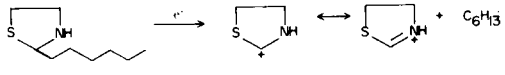
The aminothiols we chose were 2-aminoethanethiol, cysteine, and penicillamine (**b**). All three compounds have been used medicinally. For example, penicillamine has been used in the management of lead poisoning (3), Wilson's Disease (4), and rheumatoid arthritis (5).

The general laboratory synthesis of thiazolidines involves mixing an aminothiol with a carbonyl containing compound usually in the presence of a trace of acid (6). We used this procedure to prepare twelve thiazolidines, all of which have been previously reported. The cyclic nature of our products was clearly demonstrated by nmr; the ring protons being non-equivalent gave a complex splitting pattern which was easily identified. The nmr data for each thiazolidine can be found in the experimental section of this paper (7).

All of the thiazolidines gave molecular ions under electron impact which further supports the structural assignments (see Table I). Only two of the twelve had relative abundances of less than 1%.

We have identified three types of fragmentations as characteristic of thiazolidines. Table I summarizes the data for the three fragmentations.

Cleavage of the substituents at C-2 particularly intrigued us. For the thiazolidines synthesized from heptanal resulting in a C-2 hexyl group (compounds **3**, **7**, **11**), this fragmentation represents the base peak in all three cases. Thiazolidines synthesized from butanone

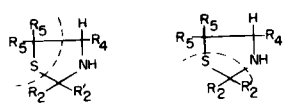


3 Cleavage of the Substituent at C-2

(compounds **2**, **6**, **10**) also gave quite intense $(M\text{-}R_2)^+$ ions. However, when R_2 = phenyl (compounds **4**, **8**, **12**), the intensity of $(M\text{-}R_2)^+$ ions drops off notably (to ~ 15%). The relative stability of the hexyl radical as compared to ethyl and methyl radicals explains the dominance of $(M\text{-}R_2)^+$ ions in compounds **3**, **7**, and **11**. The high energies required for breaking a bond attached to an unsaturated carbon especially when it is part of a benzene ring explains the decreasing importance of $(M\text{-}R_2)^+$ ions in compounds **4**, **8**, and **12**.

Pasto's (8) report of alkyl group cleavage α to both heteroatoms in 2-methyl-2-ethyl-1,3-oxathiolane is in line with our data for thiazolidines. Our data suggest that thiazolidines formed from aminothiol reactions with aliphatic aldehyde groups which are part of a larger molecule, say a peptide, should be identifiable using mass spectrometry.

Ring fragmentations were common to all the thiazolidines examined. Two fragmentations, 1,4- and 2,5-, in which a sulfur and a neighboring carbon are removed, leaving a nitrogen fragment bearing the charge, dominated. The data for 1,4- and 2,5-cleavages is given in Table I.



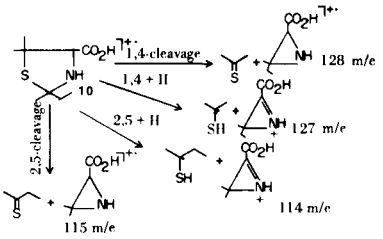
1,4-cleavage 2,5-cleavage

Table I

Thiazolidines	#	R_2	R_2^1	M^+ m/e	M^+ Rel. Abun.	$(M\text{-}R_2)^+$ m/e	$(M\text{-}R_2)^+$ Rel. Abun.	1,4-Cleavage $(M\text{-}SCR_5R_6)^+$ m/e	1,4-Cleavage $(M\text{-}SCR_5R_6)^+$ Rel. Abun.	$(M\text{-}SCR_5R_5H)^+$ m/e	$(M\text{-}SCR_5R_5H)^+$ Rel. Abun.	2,5-Cleavage $(M\text{-}SCR_2R_2)^+$ m/e	2,5-Cleavage $(M\text{-}SCR_2R_2)^+$ Rel. Abun.	$(M\text{-}SCR_2R_2H)^+$ m/e	$(M\text{-}SCR_2R_2H)^+$ Rel. Abun.
From 2-aminoethanethiol	**1** (a)	H	H	89	100	88	36	43	53	42	27	43	53	42	27
	2	CH_2CH_3	CH_3	131	58	102	100	85	20	84	96	43	7	42	70
	3 (a)	$(CH_2)_5CH_3$	H	173	5	88	100	127	2	126	20	43	7	42	5
	4	Ph	H	165	100	88	21	119	23	118	95	43	--	42	2
From cysteine	**5**	H	H	133	19	132	2	87	13	86	15	87	13	86	17
	6	CH_2CH_3	CH_3	175	24	146	100	129	13	128	43	87	2	86	3
	7	$(CH_2)_5CH_3$	H	217	0.6	132	100	171	2	170	18	87	3	86	15
	8	Ph	H	209	7	132	15	163	9	162	10	87	3	86	9
From penicillamine	**9**	H	H	161	10	160	--	87	100	86	2	115	--	114	--
	10	CH_2CH_3	CH_3	203	18	174	93	129	100	128	37	115	16	114	6
	11	$(CH_2)_5CH_3$	H	245	0.04	160	100	171	6	170	2	115	2	114	37
	12	Ph	H	237	36	160	10	163	59	162	11	115	4	114	2

(a) Hydrochloride

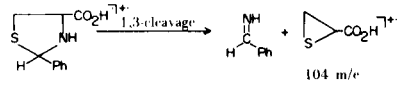
Since all twelve thiazolidine rings fragmented in a 1,4-manner under electron impact, we believe we have observed a significant characteristic for this ring system. The 1,4-cleavage when compared to the 2,5-cleavage was definitely the favored process as judged by relative abundances. The 1,4-cleavage coupled with a hydrogen transfer to the sulfur radical generally leads to intense ions (see Table I). The 2,5-cleavage also occurred coupled with a hydrogen transfer. A possible scheme for compound **10**'s ring fragmentation is outlined below.



The thiazolidines derived from 2-aminoethanethiol (compounds **1-4**) and 2-phenyl-4-thiazolidinecarboxylic acid (compound **8**) had ions which could correspond to 1,3-cleavage where the sulfur fragment retains the charge. Only in one case, compound **8**, was this a relatively intense ion (see Table II).

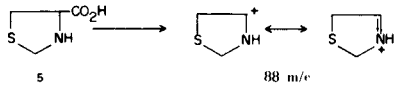
Table II

Thiazolidine	$(M\text{-}NHCR_2R_2^1)^+$ m/e	$(M\text{-}NHCR_2R_2^1)^+$ Rel. Abun.	$(M\text{-}45)^+$ m/e	$(M\text{-}45)^+$ Rel. Abun.	$(M\text{-}33)^+$ m/e	$(M\text{-}33)^+$ Rel. Abun.
1	60	11	--	--	56	2.6
2	60	10	--	--	98	13
3	60	3.2	--	--	140	0.7
4	60	8.7	--	--	132	19
5	104	--	88	100	100	2.1
6	104	--	130	14	142	8.3
7	104	--	172	6.2	184	3.0
8	104	100	164	16.2	176	6.5
9	132	--	116	44	128	2.8
10	132	--	158	1.4	170	6.4
11	132	--	200	1.9	212	1.6
12	132	--	192	11	204	23



8

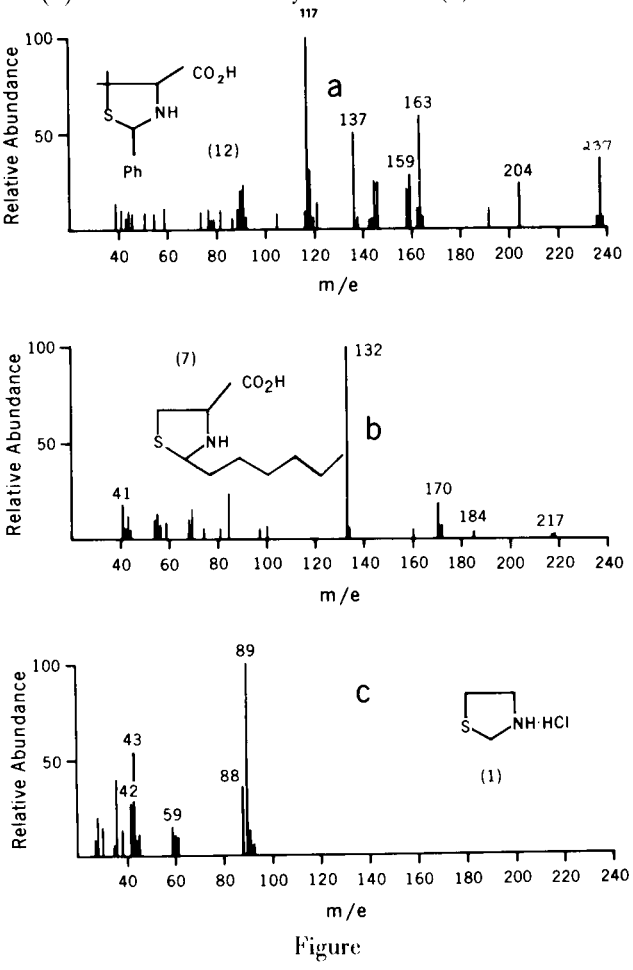
Table II shows two other fragmentation patterns we observed to be common in the thiazolidines we examined. Loss of CO_2H in compounds **5-12** is expected particularly because the resulting charge would be stabilized by the unshared electrons of nitrogen.



5

With all the thiazolidines, we observed a $(M-33)^+$ ion which we assigned to the loss of SH. Djerassi *et al.* (9) noted an ion at $(M-33)^+$ in the spectrum of tetrahydrothiophene, while Williams *et al.* (10) and Gillis and Occolowitz (11) have reported ions corresponding to $(M-SH)^+$ in aromatic and aliphatic sulfides, respectively.

We did not see any $(M-15)^+$ ions, the loss of methyl radical, from the penicillamine derived thiazolidines (compounds **9**, **11**, **12**) which have no methyl in the C-2 position. Our thiazolidine spectra had very few metastable ions. We did not see any metastable ions for several of the compounds. In general, compounds with a 2-phenyl substituent had more complex cracking patterns than did the 2-alkyl ones. Also, the spectra from thiazolidines derived from penicillamine were more complex than the others. The Figure compares graphically the mass spectra of 5,5'-dimethyl-2-phenyl-4-thiazolidinecarboxylic acid (**12**) with 2-hexyl-4-thiazolidinecarboxylic acid (**7**) with thiazolidine hydrochloride (**1**).



Figure

a) 5,5-Dimethyl-2-phenyl-4-thiazolidinecarboxylic acid (**12**), b) 2-Hexyl-4-thiazolidinecarboxylic acid (**7**), and c) Thiazolidine hydrochloride (**1**).

In conclusion, we have identified several electron impact fragmentations of the thiazolidine ring system which should lead to mass spectral procedures for detecting thiazolidines in biochemical systems.

EXPERIMENTAL

Melting points were determined on Fisher-Johns melting blocks and are uncorrected. Ir spectra were obtained using a Beckman Model IR33. Nmr spectra were obtained using a Perkin-Elmer R20B spectrometer. TMS was the internal standard except for spectra run in deuterium oxide. In deuterium oxide, the HDO signal was set at δ 4.61 ppm. The D,L-penicillamine was purchased from Aldrich.

The mass spectra were obtained using a du Pont 21-491 double-focusing mass spectrometer (direct probe, 70 eV, and PFK). The source temperature was at least 50° higher than the melting point of the sample being run. The spectra were collected at temperatures where the ion beam monitor reading remained constant.

Thiazolidine Hydrochloride (**1**).

This compound had m.p. 177-180° [lit. (12) m.p. 180°]; nmr (deuterium oxide): δ 3.5 (m, 2), 3.9 (m, 2), and 4.97 (s, 2) ppm.

2-Ethyl-2-methylthiazolidine Hydrochloride (**2**).

This compound had m.p. 119-123° [lit. (13) m.p. 117-119°]; ir (Nujol): 1590, 1130 cm^{-1}; nmr of free base (deuteriochloroform): δ 1.02 (t, 3), 1.50-1.95 (m, 6), 3.15 (m, 4) ppm, after deuterium oxide wash, the 1.50-1.95 multiplet lost one hydrogen.

2-Hexylthiazolidine Hydrochloride (**3**).

This compound had m.p. 95-97° [lit. (13) m.p. 98-100°]; ir (Nujol): 1583 cm^{-1}; nmr of free base (carbon tetrachloride): δ 1.89 (m), 1.30 (m), 2.18 (s, washed out with deuterium oxide), 2.6-3.6 (m, ring protons), and 4.30 (t) ppm.

2-Phenylthiazolidine (**4**).

This compound had m.p. 105-108° [lit. (14) m.p. 108.3-108.8°]; nmr (deuteriochloroform): δ 1.95 (s, 1, washed out with deuterium oxide), 3.35 (m, 4) 5.53 (s, 1), and 7.4 (m, 5) ppm [lit. (15) nmr spectrum similar].

4-Thiazolidinecarboxylic Acid (**5**).

This compound had m.p. 205-209° [lit. (12) m.p. 196-197°]; ir (Nujol): 1650 cm^{-1}; nmr (deuterium oxide): δ 3.25 (d, 1, J = 1 Hz), 3.35 (d, 1, J = 1 Hz), and 3.38 (m, 3) ppm.

2-Ethyl-2-methyl-4-thiazolidinecarboxylic Acid (**6**).

This compound had m.p. 135-139° [lit. (16) m.p. 132-134° dec.]; ir (potassium bromide): 1650 cm^{-1}; nmr (DMSO-d_6): δ 0.93 (q, 3), 1.6 (m, 5), 3.05 (m, 2), 3.95 (m, 1) and 7.60 (s, 2, Addition of deuterium oxide washed out this peak, the solution became quite cloudy, and the rest of the nmr spectrum was altered.) ppm.

2-Hexyl-4-thiazolidinecarboxylic Acid (**7**).

This compound had m.p. 150-151° [lit. (16) m.p. 150-151°]; ir (potassium bromide): 1640, 1390 cm^{-1}; nmr (DMSO-d_6): δ 0.9 (m, 3), 1.3 (m, 10), 2.7-4.8 (several multiplets, 4), and 7.25 (s, 2, washed out with deuterium oxide) ppm.

2-Phenyl-4-thiazolidinecarboxylic Acid (**8**).

This compound had m.p. 159-161° dec. [lit. (16) m.p. 154-160° dec.]; ir (Nujol): 1600 cm^{-1}; nmr (DMSO-d_6): δ 3.22 (m, 2), 4.04 (m, 1), 5.49 (s, 1/2), 5.66 (s, 1/2), and 7.4 (m, 7) ppm.

5,5-Dimethyl-4-thiazolidinecarboxylic Acid (**9**).

This compound had m.p. 205-206° dec. [lit. (6) m.p. 200-201° dec.]; ir (potassium bromide): 1650, 1580, 1380, and 1340 cm^{-1}; nmr (DMSO-d_6); δ 1.21 (s, 3), 1.58 (s, 3), 3.32 (s, 1), 4.06 (d, 1, J = 15 Hz), 4.23 (d, 1, J = 15 Hz), and 7.72 (s, 2) ppm.

2-Ethyl-2,5,5-trimethyl-4-thiazolidinecarboxylic Acid (**10**).

This compound was prepared by refluxing **D,L-penicillamine** (1.0 g., 0.007 mole), water (16 ml.), and butanone (30 ml.) for 5 hours under nitrogen. The solvents were evaporated under reduced pressure. Recrystallization of the resulting solid, twice from butanone followed by drying *in vacuo* gave the product (0.58 g., 47.5%), m.p. 160-164°; ir (potassium bromide): 1720, 1330, 1240 cm^{-1}; nmr (deuteriochloroform): δ 0.85-2.0 (m), 4.07 + 4.18 (s + s, 1), 9.0 (broad s, 2) ppm. (Reference 6 describes the hydrochloride).

Anal. Calcd. for $C_9H_{17}NO_2S$: C, 53.17; H, 8.43; N, 6.89; S, 15.77. Found: C, 53.11; H, 8.38; N, 6.81; S, 15.91.

5,5-Dimethyl-2-hexyl-4-thiazolidinecarboxylic Acid (**11**).

This compound had m.p. 115-120° [lit. (**6**) m.p. 120-121°]; ir (Nujol): 1650 (broad), 1140 cm^{-1}; nmr (deuteriochloroform): δ 0.8-2.0, 3.8 + 4.05 (s + s, 1), ~ 4.7 (m, 1); and 9.1 (s, 2) ppm.

5,5-Dimethyl-2-phenyl-4-thiazolidinecarboxylic Acid (**12**).

This compound had m.p. 151-152° dec. [lit. (6) m.p. 145-146°]; ir (potassium bromide): 1620, 1420, 1140 cm^{-1}; nmr (deuteriochloroform): δ 1.38 (s, 3), 1.67 (s, 3), 3.85 + 4.03 (s + s, 1), 5.67 + 5.80 (s + s, 1), 6.19 (s, 2, washed out with deuterium oxide), and 7.3 (m, 5) ppm.

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