Mass Spectral Study on Thiazolo[3,2-*a*]benzimidazoles. Studies on Heterocyclic Compounds. IV

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Condensation of α-halocarbonyl compounds and 2-mercaptobenzimidazole gives thiazolo-[3,2-*a*]benzimidazoles. This condensation occurred at the mercapto group of the benzimidazole followed by cyclization to form the thiazole ring. This was confirmed by the examination of the mass spectra of 2- and 3-methylthiazolo[3,2-*a*]benzimidazoles, 2- and 3-phenylthiazolo[3,2-*a*]-benzimidazoles, and their derivatives.

In a previous report, we described the synthesis of the derivatives of thiazolo[3,2-*a*]benzimidazole (I). Synthesis of thiazolo[3,2-*a*]benzimidazoles has also been reported by Alper and Taurins (2). However, the position of the condensation of α-halocarbonyl compounds and 2-mercaptobenzimidazole had not been definitely established.

The present investigation was undertaken to clarify the structure of the condensation product from its mass spectra. Thiazolo[3,2-*a*]benzimidazole (II) was prepared from 3-hydroxythiazolidino[3,2-*a*]benzimidazole (I) by dehydration with polyphosphoric acid (I). 3-Methyl- and 3-phenylthiazolo[3,2-*a*]benzimidazoles (IV and VI) were obtained by the condensation of bromoacetone or phenacyl bromide and 2-mercaptobenzimidazole, followed by dehydration of the intermediates, 3-methyl-3-hydroxythiazolidino[3,2-*a*]benzimidazole (III) (3) or α-(2-benzimidazolylthioacetophenone (V) (2). 2-Methyl- and 2-phenylthiazolo[3,2-*a*]benzimidazoles (VIII and X) were synthesized by the condensation of α-bromopropionaldehyde dimethylacetal or α-bromophenylacetaldehyde dimethylacetal and 2-mercaptobenzimidazole, followed by dehydration of the intermediates, 2-methyl- and 2-phenyl-3-hydroxythiazolidino[3,2-*a*]benzimidazoles (VII and IX). Properties of these compounds are summarized in Table I.

The mass spectra of thiazoles (4,5) and imidazoles (4) have been discussed, however, the effect of increasing side chain length was not described. On the other hand, the mass spectra of benzimidazoles have been reported by Clark-Lewis *et al.* (6) and by Lawesson *et al.* (7), but no survey of thiazolobenzimidazoles has been made. In the thiazolo[3,2-*a*]benzimidazoles, there are four possible directions of cleavage shown by dotted lines, *a*, *b*, *c*, and *d* in Figure II. The first pathway shows a M-S and/or M-SH fragmentation to give an ion of mass M-32 and/or M-33 (Table II). The composition of M-32 was detected by the high resolution measurement (Table III) and metastable transition peaks (8) (Table IV). This observation has not been reported for the fragmentation pattern of thiophenes,

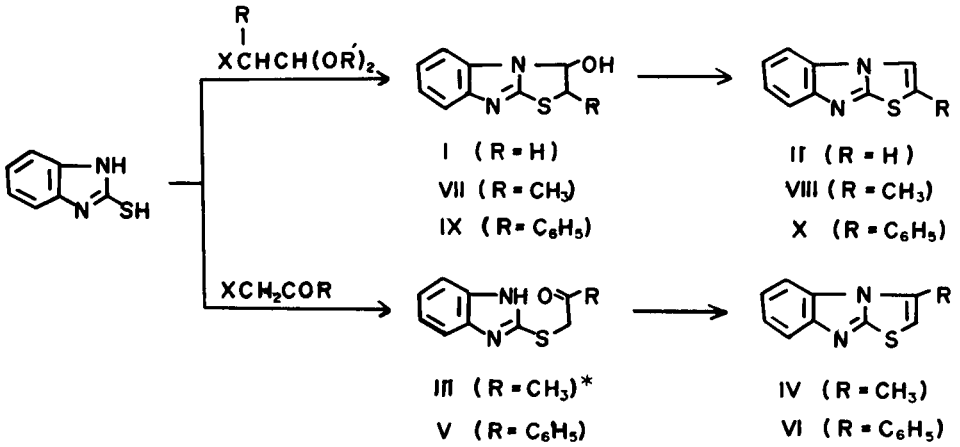

Figure 1

TABLE I

Thiazolo[3,2-*a*]benzimidazoles

Compound	R_1	R_2	M.p. (°C)	Ultraviolet absorption λ max (EtOH), mμ (log ε)	Nuclear magnetic resonance $CDCl_3$, ppm
I	H,H	H, OH	192	250 (3.96), 282 (4.02), 291 (4.06)	
II	H	H	140	250 (3.78), 286 (3.84), 293 (3.94), 306 (7.75)	6.62 (=C*H*-), 6.71 (=C*H*-)
III	H, H	CH_3, OH	110-111	249 (3.99), 284 (4.12), 291 (4.15)	2.01 (CH_3-), 3.90 (-CH_2-)
IV	H	CH_3	163-165	240 (4.17), 247 (4.46), 280 (4.91)	2.59 (CH_3-), 6.11 (=C*H*-)
VI	H	C_6H_5	140-141	235 (4.30), 251 (4.13), 270 (4.15), 285 (4.05, sh)	6.55 (=C*H*-)
VII	H, CH_3	H, OH	198-200	250 (3.98), 284 (4.04), 291 (4.08)	1.80 (CH_3-), 4.95 (-*CH*CH_3), 6.45 (-*CH*OH)
VIII	CH_3	H	158-159	244 (3.89), 250 (3.95), 277 (4.09)	2.53 (CH_3-), 7.0-7.8 (=C*H*-)
IX	H, C_6H_5	H, OH	195-196	250 (4.08), 284 (4.07), 291 (4.10)	5.95 (=C*H*-), 6.85 (=C*H*-)
X	C_6H_5	H	168-170	218 (4.19), 277 (4.14), 311 (4.11)	7.0-7.9 (=C*H*-)

benzothiophenes, and thiazoles (4); moreover, it was not observed in the mass spectra of imidazo[2,1-*b*]thiazoles (9). In the mass spectrum of tetrahydrothiophene, a loss of a sulfhydryl radical was reported (10). Although the mass spectrum of benzothiazole was reported by Millard and Temple (11), a loss of sulfur directly from the molecular ion was not observed. In contrast, the mass spectrum of 2-aminobenzothiazole shows a loss of sulfur directly from the molecular ion in 6% abundance (12). The mass spectra of imidazo[2,1-*b*]benzothiazoles (13) also shows a loss of a sulfur radical to give an ion of mass M-32. Recently, Duffield *et al.* reported the M-S fragmentation in their mass spectral studies on phenothiazine derivatives (14).

The M-H process of 3- and 2-methylthiazolo[3,2-*a*]-benzimidazoles (IV and VIII) involves the second pathway, through the intermediate a and b which cleaved at the α-position due to the preferential cleavage of the C-S bond, yielding the ions *A* (IV, m/e 143; VIII, m/e 129) and *D* (IV, m/e 45; VIII, m/e 59). A similar fragmentation pattern has been observed for alkylfurans, alkylthiophenes (4), oxazoles, and isoxazoles (6,15), and the resulting M-1 cation is stabilized by the resonance (16). In the 3-substituted compound (IV) a strong peak at m/e 143 (*A*) in 40% abundance and m/e 45 (*D*) in 7% abundance was observed, but in the other compound (VIII), very small peaks (2 and 2.5%, respectively) were observed. The 2-substituted compound (VIII) showed strong peaks at m/e 129 (*A*) in 14.6% abundance and m/e 59 (*D*) in 8.6% abundance, while IV showed very small peaks (1.8 and 0.8%, respectively) (Table II). In conclusion, these fragmentations and the relative abundances of ions *A* and *D* indicate the confirmation of the position of the methyl group of IV and VIII. The same conclusion is reached in the 2- or 3-phenyl derivatives (X, VI). In the case of the 3-phenyl derivative (VI), m/e 205 (VI, *A*) a peak is observed in 9.2% abundance. In contrast the 2-phenyl derivative (X) shows only 2.2% in abundance. On the other hand, the corresponding 2-phenyl derivative, m/e 129 (X, *A*) is observed in 9.3% abundance, while the 3-phenyl derivative (VI) shows 0.7% in abundance.

As for the ion *A*, it probably undergoes a rupture of the 4-4a or the 8a-9 bond of the intermediates (b) to two structures, ion m/e 102 (4-4a bond rupture) and ion *B* (IV, m/e 117; VIII, m/e 103) (8a-9 bond rupture). The same results were obtained from the examination of the ion *B*. 3-Substituted compounds (III, IV, and VI) show m/e 117, 117, and 179 peaks in abundances of 3.6, 2.7, and 1.1%, respectively. In contrast, 2-substituted compounds (VII, VIII, IX, and X) show the same ion *B* (R_2 = H) at m/e 103 in abundances of 6.0, 2.7, 6.5, and 5.4%, respectively.

The third cleavage at the positions 3 and 4, 1 and 9a

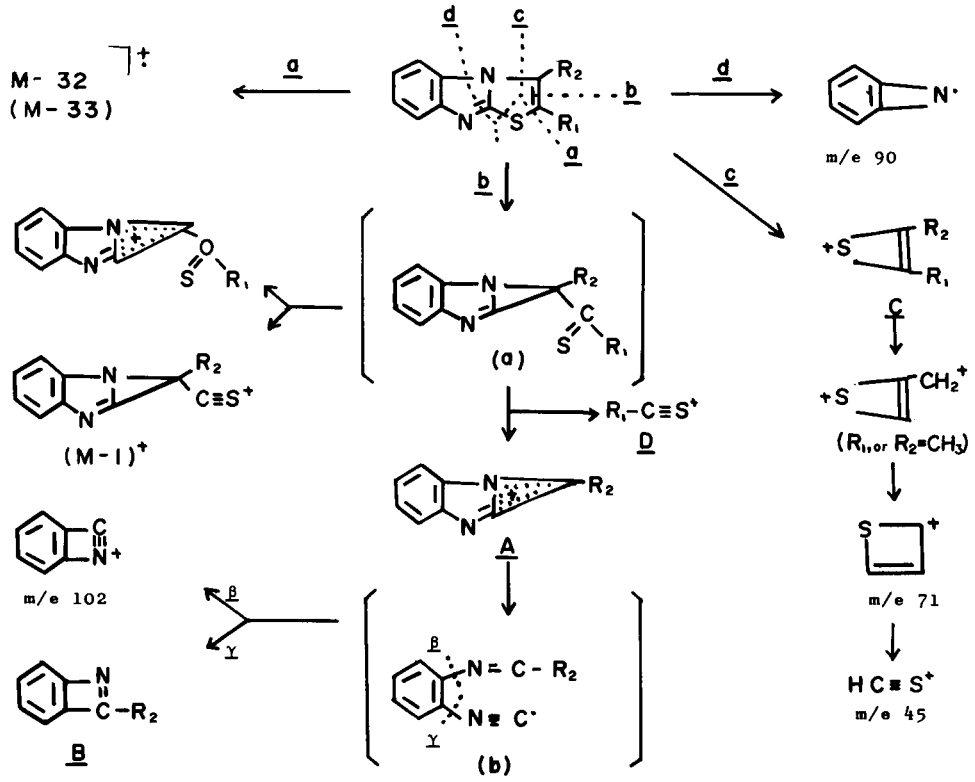

Figure II

also suggests a mode of structural elucidation. When the compounds having no substituent in the position 2 or 3 (I and II), m/e 58 (1.4 and 3.1%) is observed, on the other hand, 2- or 3-methyl derivatives (III, IV, VII, and VIII) show m/e 72 peak (3.7, 1.6, 3.1, and 2.0%), and 2- or 3-phenyl derivatives (VI, IX, and X) show m/e 134 peak (1.6, 13.0, and 2.0%). In the case of the 2- or 3-methyl compounds, the ion *C* was further decomposed to the thietenyl ion (m/e 45) as 4-methylthiazole (4). The metastable transition strongly supports the suggested pathway for the fragmentations (Table IV).

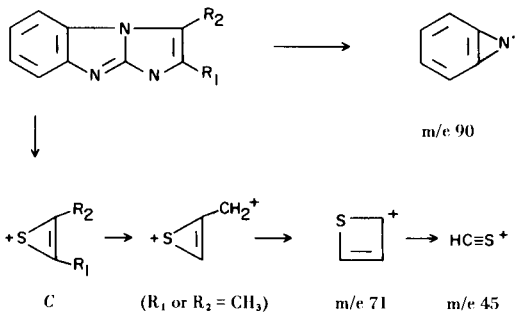

Figure III

In conclusion, the above-mentioned fragmentations confirmed the structure of the 2- or 3-substituted thiazolo[3,2-*a*]benzimidazoles. From this fact, the position of the condensation of 2-mercaptobenzimidazole and α-halocarbonyl compounds was definitely confirmed as occurring at the mercapto group followed by cyclization to a thiazole ring.

EXPERIMENTAL

All melting points are uncorrected. Nuclear magnetic resonance spectra were recorded at 60 Mc with a Hitachi-Perkin Elmer H-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal reference. Mass spectra were taken with a Japan Electron Optics JMS-01S high-resolution spectrometer with a direct inlet system.

2-Methyl-3-hydroxythiazolidino[3,2-*a*]benzimidazole (VII).

To 2-mercaptobenzimidazole (1.5 g., 0.01 mole) in 15 ml. of 4*N* hydrochloric acid was added 2.2 g. (0.012 mole) of α-bromopropionaldehyde dimethylacetal. The mixture was refluxed for 7 hours, cooled, and made alkaline with sodium carbonate and filtered to give 1.8 g. (90%) of 2-methyl-3-hydroxythiazolidino[3,2-*a*]benzimidazole (VII). Two recrystallizations from methanol gave white cubes, m.p. 198-200°. Mass (M^+), 206.054 (Calcd. for $C_{10}H_{10}N_2OS$, 206.051).

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.22; H, 4.88; N, 13.58. Found: C, 58.10; H, 4.93; N, 13.54.

TABLE II

Mass Spectra of Thiazolo[3,2-*a*]benzimidazoles
(Relative Abundances, %)

Compound	M_1^+	M^+	$M-1^+$	$M-32^+$	*A*	*B*	*C*	*D*	m/e102	m/e90
I	192 (100)	174 (26.2)	-	142 (0.4)	129 (6.5)	103 (2.6)	58 (1.4)	45 (4.9)	(5.7)	(12.1)
II		174 (100)	-	142 (0.5)	129 (12.2)	103 (3.1)	58 (3.1)	45 (2.8)	(10.3)	(3.6)
III (a)	206 (50.6)	188 (55.3)	187 (10.6)	156 (1.5) 155 (2.8)	143 (13.3)	117 (3.6)	72 (3.7)	45 (13.3)	(13.3)	(14.6)
IV		188 (100)	187 (13.3)	156 (1.3) 155 (4.3)	143 (40.0)	117 (2.7)	72 (1.6)	45 (7.0)	(20.0)	(5.9)
VI		250 (100)	249 (19.2)	218 (3.2) 217 (1.5)	205 (9.2) [129 (0.7)]	179 (1.1)	134 (1.6)	45 (1.4)	(9.6)	(4.5)
VII	206 (100)	188 (48.9)	187 (16.6)	156 (1.4) 155 (3.1)	129 (7.3)	103 (6.0)	72 (3.1)	59 (9.3)	(9.3)	(30.6)
VIII		188 (100)	187 (36.0)	156 (1.4) 155 (6.0)	129 (14.6)	103 (2.7)	72 (2.0)	59 (8.6)	(14.0)	(6.6)
IX (b)	268 (95.3)	250 (45.3)	249 (6.5)	235 (8.7) 218 (1.5)	129 (6.5)	103 (6.5)	134 (13.0)	121 (48.0)	(8.7)	(21.7)
X		250 (100)	249 (17.6)	218 (7.8) 217 (4.3)	129 (9.3) [205 (2.2)]	103 (5.4)	134 (4.3)	121 (30.2)	(14.1)	(12.8)

(a) base peak m/e 163. (b) base peak m/e 91.

TABLE III

High Resolution Mass Measurement of 2-Methyl- and 3-Methylthiazolo[3,2-*a*]benzimidazoles (VIII and IV)

Elemental composition	IV		VIII	
	Found	Calcd.	Found	Calcd.
$C_{10}H_8N_2S$	188.040	188.041	188.038	188.041
$C_{10}H_7N_2S$	187.033	187.033	187.033	187.033
$C_9H_5N_2S$	173.017	173.017	-	-
$C_{10}H_8N_2$	156.070	156.069	156.068	156.069
$C_{10}H_7N_2$	155.060	155.061	155.062	155.061
$C_9H_7N_2$	143.063	143.061	-	-
C_7H_4NS	134.010	134.006	134.006	134.006
C_9H_7N	129.056	129.058	-	-
$C_8H_5N_2$	-	-	129.050	129.045
C_8H_7N	117.059	117.058	-	-
C_7H_4N	102.036	102.034	102.034	102.034
C_6H_4N	90.032	90.034	90.039	90.034
C_3H_4S	71.998	72.003	72.004	72.003
C_3H_3S	70.990	70.995	70.994	70.995

TABLE IV

Metastable Transitions

Compound	Transition
III	$250^+ \rightarrow 249^+$, $250^+ \rightarrow 218^+$, $250^+ \rightarrow 134^+$, $250^+ \rightarrow 129^+$, $250^+ \rightarrow 121^+$, $129^+ \rightarrow 103^+$, $129^+ \rightarrow 102^+$, $134^+ \rightarrow 45^+$.
IV	$188^+ \rightarrow 155^+$, $188^+ \rightarrow 143^+$, $143^+ \rightarrow 102^+$, $188^+ \rightarrow 90^+$.
VI	$250^+ \rightarrow 249^+$, $250^+ \rightarrow 218^+$, $250^+ \rightarrow 134^+$, $205^+ \rightarrow 179^+$, $205^+ \rightarrow 103^+$, $205^+ \rightarrow 102^+$.
VIII	$188^+ \rightarrow 187^+$, $188^+ \rightarrow 155^+$, $188^+ \rightarrow 129^+$, $129^+ \rightarrow 103^+$, $129^+ \rightarrow 102^+$, $188^+ \rightarrow 90^+$, $188^+ \rightarrow 72^+$.

2-Methylthiazolo[3,2-*a*]benzimidazole (VIII).

To cooled polyphosphoric acid (prepared from 25 g. of phosphorus pentoxide and 20 ml. of 85% phosphoric acid) was added 3.2 g. (0.015 mole) of 2-methyl-3-hydroxythiazolidino[3,2-*a*]-benzimidazole. The reaction mixture was heated at 150-160° for 3 hours. After the addition of water, the reaction mixture was made alkaline with sodium carbonate and filtered to collect the precipitate consisting of 2.6 g. (90%) of 2-methylthiazolo[3,2-*a*]-benzimidazole (VIII). Recrystallization from hexane gave white needles, m.p. 158-159°.

Anal. Calcd. for $C_{10}H_8N_2S$: C, 63.81; H, 4.28; N, 14.88. Found: C, 63.99; H, 4.32; N, 14.96.

2-Phenyl-3-hydroxythiazolidino[3,2-*a*]benzimidazole (IX).

To 2-mercaptobenzimidazole (3.0 g., 0.02 mole) in 25 ml. of 4*N* hydrochloric acid was added 5.1 g. (0.02 mole) of α-bromophenylacetaldehyde dimethylacetal and the mixture was refluxed for 13 hours. When cooled, the mixture was made alkaline with sodium carbonate and filtered to give 4.3 g. (82%) of 2-phenyl-3-hydroxythiazolidino[3,2-*a*]benzimidazole (IX). Recrystallization from methanol gave white cubes, m.p. 195.5-196.5°. Mass (M^+), 268.065 (Calcd. for $C_{15}H_{12}N_2OS$, 268.067.

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.23; H, 4.47; N, 10.49.

2-Phenylthiazolo[3,2-*a*]benzimidazole (X).

To cooled polyphosphoric acid (prepared from 13 g. of phosphorus pentoxide and 10 ml. of 85% phosphoric acid) was added 2.7 g. (0.01 mole) of 2-phenyl-3-hydroxythiazolidino[3,2-*a*]benzimidazole. The reaction mixture was heated at 150-160° for 3 hours. After addition of water, the reaction mixture was made

alkaline with sodium carbonate and filtered to collect the precipitate consisting of 2.2 g. (90%) of 2-phenylthiazolo[3,2-a]benzimidazole (X). Recrystallization from 50% ethanol gave white leaflets, m.p. 168-170°. Mass (M^+), 250.058 (Calcd. for $C_{15}H_{10}N_2S$, 250.056).

Anal. Calcd. for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.02; N, 11.19. Found: C, 71.83; H, 3.98; N, 11.14.

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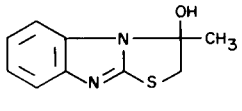
(3) In the case of the condensation of bromoacetone with 2-mercaptobenzimidazole, the intermediate was cyclized to 3-methyl-3-hydroxythiazolidino[3,2-*a*]benzimidazole (i) (1,2).



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