Perhalogenated Thiazoles. Their Synthesis, Reactions and Mass Spectra

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The synthesis of six new mixed perhalogenated thiazoles are reported. Three of these contain a 2-fluoro substituent one of which includes the novel 5-bromo-4-chloro-2-fluorothiazole. The mass spectral fragmentation pattern of the perhalogenated thiazoles was used to elucidate the orientation of the halogen substituents. A novel halogen migration from carbon to nitrogen in the mass spectrum was observed for several of the perhalogenated thiazoles. Nucleophilic displacement of fluoride ion in 4,5-dichloro-2-fluorothiazole (**7**) by cyano, hydroxyl and methoxyl anions and by diethyl amine produced the respective 2-substituted dichlorothiazoles. The ease of electrophilic substitution on carbon in the polyhalogenated thiazoles was observed to be $2 >> 5 > 4$. Sulfur tetrafluoride fluorination of 2-carboxy-4,5-dichlorothiazole, formed by lithiation and carbonation of trichlorothiazole, yielded 4,5-dichloro-2-trifluoromethylthiazole.

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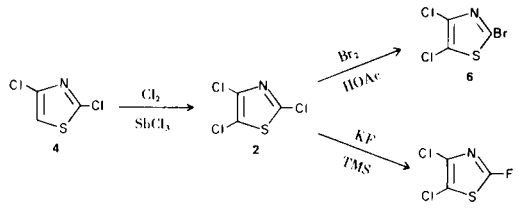
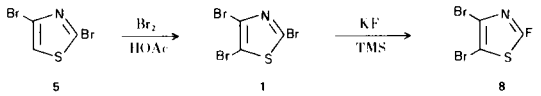
Of the many halogenated thiazoles synthesized, only two perhalogenated derivatives have been reported. Tribromothiazole (**1**), prepared in 85% yield *via* the exhaustive bromination of 2,4-dihydroxythiazole was first reported by Robba, *et al.*, (1) in 1964. The preparation of the trichloro isomer (**2**), recently reported in a U. S. patent (2), involved the thermal cyclization of pentachloroethyl isocyanide dichloride with sulfur. Trichloroisothiazole (**3**) represents the only other documented (3,4) perhalogenated isomeric structure. Our initial interest in the polyhalogenated thiazoles dealt with an understanding of the potential chemical reactivity and thermal stability of the halogens in the 2, 4, and 5 positions. Since only two perhalogenated thiazoles were known, these both being homogeneous for one halogen atom, a program was undertaken to prepare a series of mixed bromo, chloro, and fluoro perhalogenated thiazoles. This report describes their synthesis, reactions, and spectroscopic properties including a detailed analysis of their mass spectra which later proved helpful in several structure elucidations.

2,4-Dichloro- (**4**), and 2,4-dibromothiazole (**5**) (5) were chosen as starting points for the synthesis of all of the mixed perhalogenated thiazoles. Chlorination of neat **4** containing a catalytic amount of antimony trichloride with chlorine at 60° produced **2** in 96% isolated yield. Its physical properties were identical to those previously reported (2). Bromination of **2** in glacial acetic acid at 90° selectively replaced the 2-chlorine affording only 2-bromo-4,5-dichlorothiazole (**6**) in 57% yield. Nucleophilic displacement of the 2-chlorine atom in **2** by fluorine was smoothly accomplished utilizing dry potassium fluoride in tetramethylenesulfone (TMS) at 130° to yield 2-fluoro-



4,5-dichlorothiazole (**7**) in 57% yield.

In analogous fashion **1** was fluorinated to yield 2-fluoro-4,5-dibromothiazole (**8**). Exhaustive bromination of **4**



directly produced 4-chloro-2,5-dibromothiazole (**9**), and subsequent fluorination of **9** yielded the novel multiatom-multihalo derivative, 5-bromo-4-chloro-2-fluorothiazole

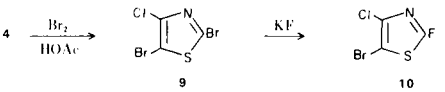


Table I

Mass Spectral Fragmentation of Polyhalogenated Thiazoles (a)

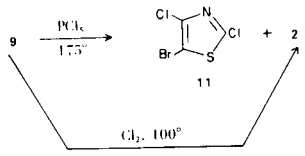
Compound	X	Y	Z											
1	Br	Br	Br	m/e	325	323	321	319	244	242	240	218	216	139
				I%	37	97	97	33	44	100	52	4	7	3
				m/e	137	135	93	91	82	81	79	70	56	38
				I%	68	68	14	14	42	12	12	10	18	30
2	Cl	Cl	Cl	m/e	191	189	187	130	154	152	130	128	126	108
				I%	31	89	90	13	5	7	13	68	100	6
				m/e	96	94	93	91	82	81	79	70	56	49
				I%	2	4	21	56	13	20	56	9	10	10
				m/e	47	44	38							
				I%	31	14	13							
4	Cl	Cl	H	m/e	155	153	128	126	96	94	93	91	82	81
				I%	68	100	56	82	1	4	21	57	6	10
				m/e	79	70	56	49	47	45	44			
				I%	27	3	13	7	20	18	10			
5	Br	Br	H	m/e	245	243	241	140	139	138	137	136	135	125
				I%	52	100	50	2	1	36	4	35	3	8
				m/e	123	106	104	93	91	83	82	57	45	44
				I%	8	4	4	4	4	11	6	36	15	7
6	Br	Cl	Cl	m/e	235	233	231	174	172	170	156	156	152	128
				I%	48	100	60	1	4	3	9	48	70	29
				m/e	126	125	123	117	110	108	93	91	82	81
				I%	42	6	6	10	6	10	19	49	14	10
				m/e	79	70	56	49	47	44				
				I%	21	8	9	6	20	12				
7	F	Cl	Cl	m/e	173	171	128	127	126	112	110	93	91	82
				I%	68	100	14	8	20	10	29	10	27	4
				m/e	81	79	70	63	56	49	47	44		
				I%	26	70	12	33	6	5	14	12		
8	F	Br	Br	m/e	263	261	259	218	216	214	182	180	156	154
				I%	52	100	50	2	4	2	26	25	3	3
				m/e	137	135	125	123	119	117	108	93	91	81
				I%	26	26	12	12	2	3	6	4	5	6
				m/e	79	70	63	56	44					
				I%	6	13	27	6	10					
9	Br	Cl	Br	m/e	281	279	277	275	200	198	196	174	172	170
				I%	16	72	100	43	26	92	70	3	12	9
				m/e	137	135	125	123	119	117	99	98	93	91
				I%	6	6	14	14	9	19	8	6	30	71
				m/e	82	81	79	70	56	47	44	38		
				I%	18	7	9	7	11	13	14	20		
10	F	Cl	Br	m/e	219	217	215	174	173	172	171	170	156	154
				I%	28	100	75	3	5	11	4	8	5	5
				m/e	138	137	136	135	125	123	114	112	110	93
				I%	4	3	7	2	9	9	1	8	21	15
				m/e	91	86	81	79	70	63	56	47	44	31
				I%	38	6	13	30	12	20	7	7	12	23
3(b)	Cl	Cl	Cl	m/e	191	189	187	157	155	154	153	152	145	143
				I%	35	100	100	7	22	10	28	13	4	8
				m/e	141	130	128	126	119	117	110	108	106	96
				I%	6	12	60	88	11	21	8	15	7	3
				m/e	94	93	92	91	85	84	82	81	79	73
				I%	13	20	24	33	7	11	18	15	41	5
				m/e	71	70	67	56	47	44				
				I%	5	5	6	10	22	8				

Table I (continued)

Compound	X	Y	Z										
19(a)	OH	Cl	Cl	m/e	171	170	169	143	141	135	133	108	107	106
				I%	31	3	46	26	38	18	33	12	11	31
				m/e	105	93	91	84	82	81	80	79	76	74
				I%	20	5	15	4	18	19	32	51	4	3
				m/e	72	70	64	62	60	56	49	47	45	44
				I%	9	77	15	47	22	8	6	19	17	100
				m/e	41	40	38	36	35					
				I%	23	11	31	69	26					
12	CF_3	Cl	Cl	m/e	225	223	221	205	204	202	186	162	160	141
				I%	13	70	100	10	9	13	6	24	66	8
				m/e	126	125	117	116	113	112	110	109	106	93
				I%	4	26	5	5	7	7	20	4	9	14
				m/e	91	81	79	75	69	63	56	47	44	
				I%	33	5	14	5	25	11	4	11	7	
25	Cl	F	CF_3	m/e	205	186	170	160	125	110				
				I%	100	22	10	11	12	10				

(a) All peaks having an intensity > 5% are reported. Peaks of lesser significance are included where diagnostic significance was important.
(b) Trichloroisothiazole.

(**10**). The inertness of the 5-halogen for electrophilic substitution was demonstrated in both the bromination of **4** and chlorination of **9**. Chlorination of **9** using phosphorus pentachloride at 175° produced only 5-bromo-2,4-dichlorothiazole (**11**) in low conversion. Under more vigorous conditions, however, **2** could be formed from **9** using chlorine at 100°.



Similarly, in the bromination of **4** only the 4-hydrogen and the 2-chlorine were substituted with bromine.

The perhalogenated derivatives exhibited a characteristic thiazole ring stretching mode (*i.e.*, ν N=C-S) absorption in the infrared at 1466-1550 and 1212-1252 cm^{-1}. Their absorptions show a sizable shift from the parent hydrocarbon (6) as a result of the inductive effect of the halogens. A characteristic absorption of the perhalogenated derivatives in the 825-889 cm^{-1} region was mass-sensitive to the appropriate halogen substitution. With increasing mass of the molecule, a corresponding decrease in the frequency was observed. A similar, although not as great, effect was also observed in the 1466-1550 cm^{-1} region. No assignment to the C-halogen stretching vibration was made because of the mass effect exhibited by halogens on many of the observed absorptions.

The ultraviolet spectra of the perhalogenated and 2-substituted-4,5-dichloro derivatives in ethanol displayed maximum absorptions in the 247-268 nm region (7). The bathochromic shift exhibited by the polyhalogenated thiazoles relative to thiazole and its derivatives appears to result from the inductive effect of the halogens on the nitrogen's basicity. This effect is manifested by a weakening of the nitrogen lone pair interaction with the p-orbitals (*i.e.*, $n \rightarrow \pi^*$ transition) leading to a red shift in the uv spectrum of these compounds. No acid-base relationship in ethanol was observed because of the calculated high p*K*a's of these thiazoles.

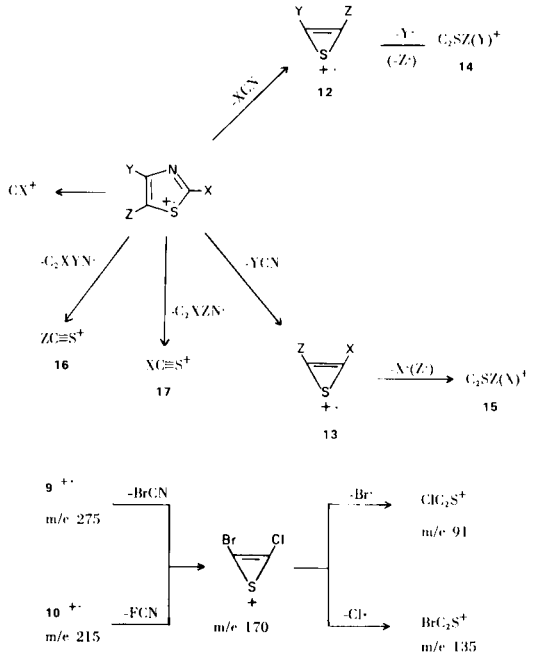
The ^{19}F nmr of **7**, **8**, and **10** displayed singlet absorptions downfield from fluorotrichloromethane at δ 72.6, 69.6, and 70.5, respectively. The relative degree or deshielding of the F-atom was directly related to the electronegativity of the halogens present, *i.e.*, **7** > **10** > **8**. The chemical shifts of **7**, **8** and **9** are similar to those observed for acyl fluorides. The reactivity of the 2-fluorine atom in these derivatives with nucleophiles (see reactions of **7**) is also similar to that observed for acyl fluorides.

Mass Spectra.

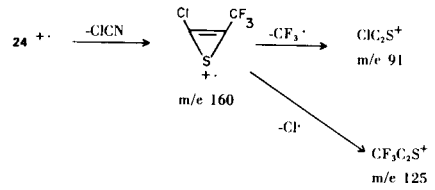
In several instances the mass spectra of the perhalogenated thiazoles were used to assign the orientation of halogen substitution (Table I). The variety of halogen substituents present in these thiazoles provided data on the effect of halogen substitution on the fragmentation pattern of this ring system. Williams (8,9) and Aune (10) have already elucidated the fragmentation process of thiazole and its derivatives, but none of their examples included a poly- or perhalogenated system. The general

decomposition pathways for the perhalogenated thiazoles are illustrated in Scheme I, and in general are similar to those reported earlier (8-10). In most cases the molecular ion is the base peak of the spectrum reflecting the relative stability of aromatics. Loss of a neutral molecule of XCN typical of heterocyclic compounds to give the thiiren radical cation **12** is an important and major decomposition path of most of these compounds. A similar nontrivial loss of YCN to **13** was also observed in **6, 7, 9,** and **11.** In the other perhalogenated derivatives the halogen in positions 2 and 4 are indistinguishable. The ion **13** resulting *via* rupture of the 2,3 and 4,5 bonds appears also to be an important fragment for the polyhalogenated thiazoles. A similar mode of decomposition has been observed for 2-amino- and 2-amino-4-methylthiazole (8). This dual fragmentation pattern provided a basis for further configurational assignment of the halogens. Loss of halogen from **12** produced the cation **14.** In **9** and **10** where two possible losses of halogen from the thiiren radical cation could occur, both were observed. However, in the case of

Scheme I



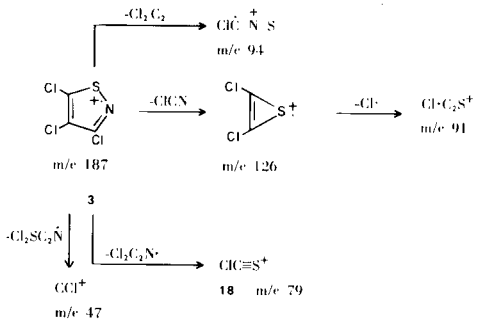
ion **13** only preferential loss of the 2-fluorine radical occurred in compounds (*i.e.*, **7, 8,** and **10**) where **13** contained either a bromine or chlorine atom along with a fluorine substituent. This facile loss of a fluorine radical in ion **13** is also reflected by its high chemical reactivity in the 2-position relative to chlorine or bromine in the perhalogenated thiazoles. When **13** did not contain a fluorine atom, elimination of either bromine or chlorine occurred to produce the ion **15.** Such was observed in the fragmentation of **24.** Loss of either Cl· or CF_3· yielded the corresponding ion **15.**



An additional major fragment observed in the perhalogenated derivatives was the thioformyl cation. Fragmentation of both the 1,2- and 4,5-bonds or alternatively, the 1,5- and 2,3- bonds yielded the ions **16** and **17, respectively,** These decomposition patterns coupled with the above results led to an additional confirmatory assignment of the halogens in the new thiazoles. The only other major ion observed in these spectra was that of C-X^+. Ions for C-Y^+ or C-Z^+ were not detectable (*e.g.*, < .1%). A similar fragment loss of C-Br has been observed by Clarke (8) for for 2-bromothiazole.

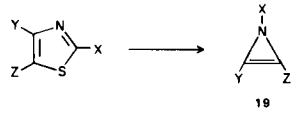
The mass spectrum of **3** was in general similar to that of **2** (Scheme II). Major loss of ClCN occurs from the base parent ion along with decomposition to yield the chlorothioformyl cation (**18**) (11). Loss of a chlorine

Scheme II



radical from the chlorothioformyl cation yielded the ion C_2ClS^+ which is similarly observed in **2.** The presence of C-Cl^+ was also noted in the decomposition of **3.** Loss of dichloroacetylene to produce ClC̈=N=S was observed in **3** but not in the isomeric thiazole **2.**

A rearrangement involving the migration of a halogen



from the 2 carbon to the nitrogen, and subsequent fragmentation to **19** was noted in many of the thiazoles. Although this rearrangement was of little value from a structural elucidation standpoint, it still proved to be of interest. The rearrangement was easily detected, and the

Table II

Mass Spectral Fragmentation Pattern of Rearrangement Ions **19** from Perhalogenated Thiazoles

19

X, Y, Z = Cl

m/e	143,	145,	147
I%	100,	95.5,	30.6

X = Br, Y, Z = Cl

m/e	187,	189,	191
I%	76.1,	100,	43.4

X, Y = Br, Z = Cl

m/e	231,	233,	235
I%	73.8,	100,	70.2

X, Y, Z = Br

m/e	275,	277,	279,	281
I%	33.3,	100,	73.3,	20.0

product ions determined using the chlorine and bromine isotopic abundance patterns. These patterns for **19** from **1, 2, 6,** and **9** are summarized in Table II.

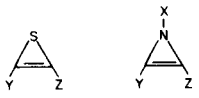
In the case of the 2-fluoro compounds, the rearrangement ions gave a pattern superimposed upon that of the thiiren radical cation. To analyze the contribution of **19** in the overlapping spectra, the thiiren cluster was first subtracted out of the observed mass spectrum, and the resulting pattern matched with that of a computer generated pattern. The data for this analysis are presented in Table III.

In the case of **7,** the composition of **19** (X = F, Y = Z = Cl), was confirmed by high resolution mass spectroscopy. The calculated m/e for $C_2NFC_2^+$ was 126.9392, and the observed value was 126.9394.

High resolution data could not be obtained on **8** and **10** due to their weak intensity of rearrangement ions.

Table III

Mass Spectral Fragmentation Pattern of Rearrangement Ions (19) from 2-Fluorodihalothiazoles



12 **19**

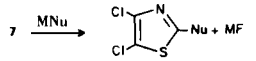
X = F, Y = Cl, Z = Cl

m/e	Observed Net Peak Intensity (a)	(Div) (b)	(Pattern) (c)	(Div) (d)	(Pattern) (e)
126	1006.4	980.5	100.0	---	---
127	423.3	29.6	3.0	377.5	100.0
128	693.2	683.2	67.9	9.8	2.6
129	266.7	20.3	2.1	246.4	65.3
130	137.9	132.8	13.5	6.4	1.7
131	44.0	3.8	3.9	40.2	10.6
X = F, Y = Cl, Z = Br					
170	395.6	390.4	74.2	---	---
171	176.6	11.8	2.2	156.0	76.7
172	530.2	526.2	100.0	4.1	2.0
173	219.1	15.7	3.0	203.4	100.0
174	151.8	147.1	28.0	5.3	2.6
175	54.6	4.3	0.8	49.8	24.5
176	9.8	5.6	1.1	1.3	0.6
X = F, Y = Br, Z = Br					
214	114.6	111.7	50.0	---	---
215	42.6	3.4	1.5	34.8	51.2
216	224.2	223.4	100.0	0.9	1.3
217	74.7	6.7	3.0	68.0	100.0
218	119.1	116.6	52.1	1.8	2.6
219	35.9	3.4	1.5	33.2	48.8
220	7.4	4.8	2.2	0.9	1.3

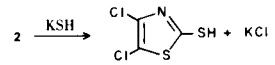
(a) Divisions from analogue chart. (b) Peak intensity in divisions ascribed to **12.** (c) Normalized to base peak of ion cluster. (d) Peak intensity in divisions ascribed to **19.**

Reactions of **7**.

The reaction of **7** was briefly examined since it was the most reactive of the 2-fluorodihalo derivatives. Compound **7** reacted exothermically at 25° with diethylamine to yield the 2-(*N*,*N*-diethylamino) derivative (**20d**), whereas **2** and **6** required several days. Its reactivity is reminiscent of that of acid fluorides with amines. Reaction of **7** with bases such as potassium hydroxide, sodium methoxide, and potassium cyanide afforded only the 2-substituted dichlorothiazole product (**20a-c**). A similar reaction of **2** with potassium hydrogen sulfide afforded 2-mercapto-4,5-dichlorothiazole (**20e**).



20 a, Nu = OH
b, Nu = OCH_3
c, Nu = CN
d, Nu = $N(C_2H_5)_2$



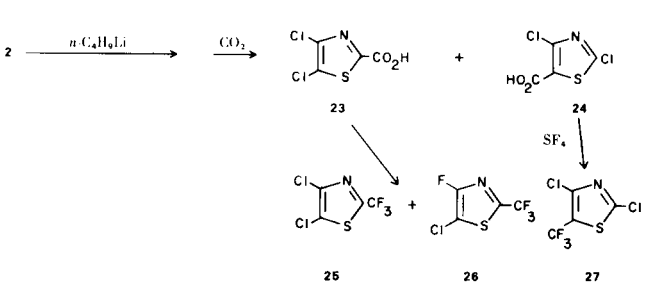
20e

The infrared, ultraviolet, and mass spectra of **20a** and **20e** indicate that they are in equilibrium with their keto tautomers, **21** and **22** (see Experimental).

20a 21

20e 22

Lithiation of **2** with *n*-butyllithium at -78° followed by carbonation gave a 40% yield of isomeric carboxydichlorothiazoles. That a mixture of isomers of dichloro acids was produced was demonstrated by their transformation with sulfur tetrafluoride to the respective trifluoromethyl derivatives. Glpc, ^{19}F nmr, and mass spectral analysis of the product mixture after fluorination of the mixed acids



23 24

25 26 27

indicated two dichloro trifluoromethyl derivatives **25** and **27** along with 5-chloro-4-fluoro-2-trifluoromethylthiazole (**26**) resulting from replacement of chlorine by fluorine in **23**. The ^{19}F nmr spectrum of the mixture showed singlets at δ 55.7 and δ 62.8 for the CF_3-groups in **25** and **27**, respectively. The structure assignment of **26** was made by GC/MS. In addition to its base parent ion of 205, losses of FCN and CF_3CN were observed, characteristic of the polyhalogenated thiazoles.

The major acid **23** was isolated isomerically pure by addition of petroleum ether to the residue after reaction work-up. The 2-acid is more insoluble than the 5-acid, **24**. Fluorination of pure **23** produced a mixture of **25** and **26** in a 91:9 distribution. The assignment of **24** to the minor acid was made from the GC/MS of its trifluoromethyl derivative, **27**. The parent ion (m/e 221) was the base peak and only the loss of ClCN from **27** was observed. Elimination of CF_3CN, which would be expected from the 4-trifluoromethyl analog was not detected in the mass spectrum of **27**.

Competitive halogen metal exchange at the 2 and 5 positions is predicted based on the results of bromination and chlorination and fluorination of the polyhalogenated thiazoles discussed in this study. A similar reactivity trend has been observed in the acid catalyzed Zn reduction of 2,4-dichlorothiazole (5). The only product isolated was the 5-chlorothiazole.

EXPERIMENTAL

Melting and boiling points were measured by DTA. Fluorine nmr spectra were recorded on a Varian Associates A56/60 nmr spectrometer. Chemical shifts are expressed in ppm downfield from internal fluorotrichloromethane. Infrared spectra were recorded on a Perkin-Elmer 21 and the ultraviolet spectra obtained on a Cary 17 spectrometer. The mass spectra of the per- and polyhalogenated thiazoles were run on a CEC-21-103C mass spectrometer at an ionizing potential of 70 eV and ionizing current of 20 μA. Samples were introduced through a glass inlet system maintained at 145°-150°. Glpc analyses were performed on an F & M Model 700 gas chromatograph equipped with a 10 ft x 1/4 in SS column packed with 10% FS1265 on Chromosorb R (Column A) or a 10 ft x 1/8 in column packed with 3% QF-1 on Chromosorb R (Column B). Gas chromatograph mass spectral analyses were performed on a Du Pont 21492 GC/MS Instrument coupled to a 21094 data system.

The dihalothiazoles **4** and **5** were prepared according to the procedure of Reynaud, *et al.*, (5). Their mass spectra are summarized in Table I.

2,4,5-Trichlorothiazole (**2**).

A mixture of 34 g. (0.221 mole) of **4** and 0.3 g. of antimony trichloride was treated continuously with chlorine at 60° for 10-15 hours. The disappearance of **4** (retention time, 8.75 minutes) as well as the appearance of **2** (retention time, 10.75 minutes) was monitored by glpc using Column A at 140° with a flow rate of 30 ml./minute. The cooled mixture was filtered (suction), and the filtrate added to 200 ml. of water in a separatory funnel. The

mixture was extracted with ether (3 x 50 ml.), and the combined extracts washed with 5% sodium bicarbonate (2 x 35 ml.), 5% sodium thiosulfate (2 x 35 ml.), and saturated sodium chloride (2 x 50 ml.). After drying, **2** was distilled on a 38 cm fluorocarbon resin lined spinning band column to give 39.7 g. (96%), b.p. 78°/11 Torr (b.p. 195°, f.p. -13° by DTA); ir (neat): 1488, 1429, 1227, 1060, and 870 cm^{-1}; uv max (ethanol): 217 (ϵ = 2,790) and 265 nm (5,400).

Anal. Calcd. for C_3Cl_3NS: C, 19.15; N, 7.44; Cl, 56.5. Found: C, 19.18; N, 7.48; Cl, 56.8.

2-Bromo-4,5-Dichlorothiazole (**6**).

A solution of 9.3 g. (0.050 mole) of **2** in 125 ml. of glacial acetic acid was treated with 9.5 ml. of bromine over a 15-minute period followed by heating at 90-95° for 30 hours. The light red solution was neutralized with solid sodium carbonate followed by aqueous sodium carbonate. The mixture was extracted with ether (3 x 50 ml.) followed by washing with 5% sodium carbonate (3 x 35 ml.) and water (2 x 35 ml.). After drying and ether removal the residual liquid was vacuum distilled to give 6.6 g. (57%) of **6**, b.p. 91°/6 Torr (b.p. 226°, f.p. 18° by DTA). Glpc on Column A indicated 95% purity; ir (neat): 1486, 1414, 1220, 1047, 1015 and 864 cm^{-1}; uv max (ethanol): 220 (ϵ = 2,890) and 268 nm (5,710).

4,5-Dichloro-2-Fluorothiazole (**7**).

A mixture of 25 g. (0.133 mole) of **2** and 38 g. (0.65 mole) of pulverized dry potassium fluoride in 130 ml. of tetramethylene sulfone (TMS) was stirred, and heated at 130° for 24 hours. After 24 hours, 15 g. of additional potassium fluoride was added, and heating continued for 18 hours. The product was distilled from the mixture at ~ 54°/16 Torr. Redistillation of the distillate gave 12 g. (57%) of **7**, b.p. 50-51°/14 Torr (b.p. 158°, f.p. 34° by DTA); 1440, 1β40, 1$\beta\beta$4, 1168, 1037, 1041, 889 and 747 cm^{-1}; uv max (ethanol): 245 nm (ϵ = 3,420); ^{19}F nmr (deuteriochloroform): δ 72.6 (broad singlet).

Anal. Calcd. for C_3Cl_2FNS: C, 20.95; Cl, 41.23; N, 8.14. Found: C, 21.42; Cl, 41.35; N, 8.11.

2,4,5-Tribromothiazole (1) (**1**).

A mixture of 10 g. (0.0412 mole) of **5** and 15 g. (0.094 mole) of bromine in 100 ml. of glacial acetic acid was refluxed for 20 hours. The cooled light yellow solution was basified with solid sodium carbonate, followed by 5% sodium carbonate. The mixture was extracted with ether (3 x 50 ml.), followed by washing with 5% aqueous sodium bicarbonate and water. Removal of drying agent and solvent gave 11.4 g. (87%) of crude product which was purified by sublimation at 35°/0.22 Torr, m.p. 36°; ir (carbon tetrachloride): 1466, 1401, 1242, 1200, 1015, 1000 and 822 cm^{-1}; uv max (ethanol): 222 (ϵ = 3,700) and 268 nm (6,180).

4,5-Dibromo-2-Fluorothiazole (**8**).

A mixture of 7 g. (0.0278 mole) of **1** and 6.4 g. (0.109 mole) of pulverized dry potassium fluoride in 40 ml. of TMS was vigorously stirred at 125° for 20 hours. The mixture was steam distilled and the distillates extracted with ether (2 x 75 ml.), and dried over magnesium sulfate. Glpc analysis at 155° of the residue after removal of drying agent, and solvent on Column A indicated product and starting material. Distillation of the residue on a 38 cm fluorocarbon resin spinning band column gave 1.0 g. (18% **8**, the rest being starting material), b.p. 198°, f.p. -17° (DTA); ir (neat): 1527, 1244, 1229, 1208, 1000, and 839 cm^{-1}; uv max (ethanol): 215 (ϵ = 3,230) and 247 nm (3,890); ^{19}F nmr (deuteriochloroform): δ 69.6 (singlet).

Anal. Calcd. for C_3Br_2FNS: N, 5.37; Br, 61.24. Found: N, 5.41; Br, 60.11.

4-Chloro-2,5-Dibromothiazole (**9**).

A solution of 10 g. (0.0650 mole) of **4** in 50 ml. of glacial acetic acid was treated dropwise with 16.0 ml. (0.292 mole) of bromine over a 15 minute period. The mixture was stirred and heated at 90° for 30 hours and cooled. The dark solution was basified first with solid sodium carbonate, then with 5% aqueous sodium carbonate. The mixture was extracted with ether (3 x 50 ml.), followed by washing with 5% sodium carbonate and water. The solvent was removed after drying over sodium sulfate to yield a dark liquid residue. Distillation of the residue on a 38 cm fluorocarbon resin lined spinning band column gave 17 g. (73%) of **9**, b.p. 78°/1.1 Torr (b.p. 235°, f.p. 6° by DTA), ir (neat): 1475, 1408, 1212, 1015 and 858 cm^{-1}; uv max (ethanol): 223 (ϵ = 2,680) and 268 nm (5,200); r_D^{20} 1.6412.

5-Bromo-4-Chloro-2 Fluorothiazole (**10**).

A mixture of 15 g. (0.054 mole) of **9** and 13 g. (0.216 mole) of pulverized potassium fluoride in 60 ml. of TMS was stirred at 125° for 22 hours. The dark mixture was vacuum distilled to yield two fractions: (1) b.p. 60-61°/10 Torr 3.97 g., all product; and (2) b.p. 105°/8 Torr; 1 g. of 3:1 starting material:product. Fraction 1 was redistilled on a 38 cm fluorocarbon resin spinning band column at 70-71°/18 Torr to give **10** in 35% yield; $n_D^{24.5}$ 1.5537; b.p. 205°, f.p. -42° (DTA); ir (neat): 1538, 1484, 1252, 1220, 1163, 1006, 881 and 743 cm^{-1}; uv max (ethanol): 215 (ϵ = 2,720) and 247 nm (3,700); ^{19}F nmr (deuteriochloroform): δ 70.5 (singlet).

Anal. Calcd. for $C_3BrClFNS$: C, 16.68; N, 6.47. Found: C, 17.02; N, 6.43.

2,4,5-Trichlorothiazole from **9**.

Five g. (18.1 mmoles) of neat **9** was treated with anhydrous chlorine gas at 100° for 2 hours. The residue was dissolved in 25 ml. of ether, and the ether solution washed with a saturated solution of sodium bicarbonate (2 x 15 ml.), water (2 x 15 ml.) and dried over anhydrous magnesium sulfate. Removal of the drying agent and solvent yielded 2.1 g. (62%, > 98% pure), b.p. 195° and f.p. -13° (DTA).

4,5-Dichloromercaptothiazole (**20c**).

A solution of 5.2 g. (77.5 mmoles) of potassium hydroxide in 25 ml. of ethanol was treated with hydrogen sulfide until colorless with phenophthalolein at -20°. To this clear solution was added 15 g. of **2** in 15 ml. of ethanol at 0°. After stirring 24 hours at 5°, the solids were filtered, and redissolved in 2*N* of sodium hydroxide (50 ml.). The aqueous solution was extracted with ether to remove residual **2**. The aqueous solution was acidified at 5° with 6*N* hydrochloric acid and the solids filtered. Drying at 25° under vacuum over phosphorus pentoxide followed by sublimation at 110°/0.2 Torr yielded 3.7 g. of pure **19c** (73%), m.p. 105° (dec., sealed tube); ir (potassium bromide): 3049, 2985, 2817, 2667, 1575, 1479, 1294, 1215, 1208, 1086, 864, 738, and 672 cm^{-1}; uv max (ethanol): 252 (ϵ = 2,660) and 328 nm (15,400); nmr (DMSO-d_6): δ 10.38 (singlet, -SH); m/e, 185 (M^+).

Anal. Calcd. for $C_3HCl_2NS_2$: C, 19.37; H, 0.54; N, 7.53. Found: C, 19.43; H, 0.57; N, 7.23.

3,4,5-Trichloroisothiazole.

Compound **3** was prepared *via* the route described by Nakagawa,

et al. (3). It had the following properties: b.p. 198°, f.p. 20° (DTA); ir (neat): 1495, 1368, 1304, 938, 813, 791 and 664 cm^{-1}; uv max (ethanol): sh 235 (ϵ = 5,490) and 260 nm (11,900).

Anal. Calcd. for C_3Cl_3NS: C, 19.15; N, 7.44. Found: C, 19.88; N, 7.45.

4,5-Dichloro-2-Hydroxythiazole (**20a**).

A mixture of 1.0 g. (5.8 mmoles) of **7** and 1.22 g. (17.0 moles) of potassium hydroxide in 25 ml. of water was stirred at room temperature for 1 hour. The homogeneous solution was acidified with 6*N* hydrochloric acid and extracted with ether (3 x 50 ml.), and dried. Removal of solvent gave a solid which was sublimed at 115°/0.2 Torr to yield 0.69 g. (69%) of **19a**, m.p. 155° dec.; ir (potassium bromide): 1994, 2817, 1739, 1592, 1198, 1053, 894 and 741 cm^{-1}; uv max (ethanol): sh 220 (ϵ = 4,740) and 250 nm (5,020).

Anal. Calcd. for C_3HCl_2NS: C, 21.19; H, 0.59; N, 8.24. Found: C, 21.41; H, 0.48, 0.58; N, 7.77, 7.68.

4,5-Dichloro-2-Methoxythiazole (**20b**).

A solution of 0.165 g. (3.00 mmoles) of sodium methoxide in 10 ml. of methanol was treated with 0.50 g. (2.90 mmoles) of **7** at 25°. After 15 minutes, the solvent was removed and the residue extracted with ether to yield 0.45 g. (85%) of **19b**. Sublimation at 45°/0.5 Torr gave m.p. 40-42°; ir (potassium bromide): 1548, 1517, 1420, 1269, 1250, 1230, 1055, 1042, 966 and 884 cm^{-1}; uv max (ethanol): 250 nm (ϵ = 5,830).

Anal. Calcd. for $C_4H_3Cl_2NOS$: C, 26.11; H, 1.63; N, 7.57. Found: C, 26.32; H, 1.80; N, 7.77.

4,5-Dichloro-2-Cyanothiazole (**20c**).

A mixture of 1.0 g. (5.9 mmoles) of **7** and 0.39 g. (6.0 mmoles) of potassium cyanide in 20 ml. of anhydrous acetonitrile was stirred 6 hours at 0-10° then 5 days at 25°. The solvent was removed and the dark residue sublimed at 60°/0.5 Torr to yield 0.30 g. (27%) of **19c**, m.p. 57-59°; ir (potassium bromide): 2222, 1456, 1381, 1261, 1155, 1064 and 894 cm^{-1}.

Anal. Calcd. for $C_4Cl_2N_2S$: C, 26.84; N, 15.65; Cl, 39.62. Found: C, 26.65; N, 15.21; Cl, 39.47.

4,5-Dichloro-2-(*N*,*N*-Diethylamino) thiazole (**20d**).

A solution of 0.88 g. (12.0 mmoles) of diethylamine in 20 ml. of ether was added to 1.0 g. (5.8 mmoles) of **7** in 5 ml. of ether at 5°. An immediate precipitate of diethylamine hydrofluoride formed. The mixture was treated with water and the layers separated. Removal of the ether after drying yielded 0.83 g. (80%) of **20d** which darkened in the presence of air; ir (neat): 2959, 1538, 1497, 900 cm^{-1} and others; uv max (ethanol): sh 240 (ϵ = 2,810) and 280 nm (9,100); ^1H nmr (carbon tetrachloride): δ 1.20 (t, CH_3, 6H) and δ 3.40 (q, CH_2, 4H).

2-Carboxy-4,5-Dichlorothiazole (**23**).

A solution of 30 g. (0.159 mole) of **2** in 350 ml. of ether was treated dropwise over a 2 hour period at -78° with *n*-butyllithium (100 ml. of 1.5*M*, 0.160 mole) to produce a dark brown mixture. Carbon dioxide gas was bubbled through the mixture at -78° for 1 hour, and continued while raising the temperature to 0°. The mixture was hydrolyzed with 75 ml. of 6*N* hydrochloric acid at 0°. The layers were separated, and the aqueous layer extracted with ether (2 x 35 ml.). The combined ether extracts were dried, and the solvent removed. Petroleum ether (200 ml., b.p. 40-60°) was added to the black residue, and the mixture stirred 15 minutes. The dark tan solid was filtered, and re-dissolved in 100 ml. of cold 10% sodium hydroxide. The mixture was filtered (gravity) into 50 ml. of cold 6*N* hydrochloric acid to produce a cream-colored solid. The solid was filtered, and dried to yield 7.3 g. (crop 1), m.p. 160-162°. The petroleum-ether filtrate was extracted with 10% sodium hydroxide (4 x 50 ml.), acidified with 6*N* hydrochloric acid and extracted with ether (3 x 100 ml.) to yield an additional 5.2 g. (crop 2, overall 40% yield) which consisted of two isomeric carboxydichlorothiazoles. Crop 1 was found to contain > 91% of **23**; ir (potassium bromide): 2857, 1695, 1504, 1433, 1399, 1274, 1239, 1099, 1067, 906 and 760 cm^{-1}; uv (max ethanol): 233 (ϵ = 3,620), 269 (8,300) and 350 nm; ^1H nmr (DMSO-d_6): δ 12.44 (s, OH).

Anal. Calcd. for $C_4HCl_2NO_2S$: C, 24.26; H, 0.51; N, 7.07. Found: C, 24.74, 24.41; H, 0.80, 0.59; N, 6.65, 6.68.

The structure of the minor acid was assigned the 5-carboxy-2,4-dichlorothiazole (**24**) based on the mass spectrum of its trifluoromethyl derivative (**27**); m/e 221 (M^+), 160 $(M\text{-}ClCN)^+$; ir (Nujol): 3460, 1669, 1701, 1495, 1307, 1272, 1110, 1073, 906, 887, 761 cm^{-1}.

4,5-Dichloro-2-Trifluoromethylthiazole (**25**).

Five g. (25.2 mmoles) of **22** was heated in a closed 80 ml. Hastelloy C reactor with 11.0 g. (100.8 mmoles) of sulfur tetrafluoride and 2.0 g. (100 mmoles) of hydrogen fluoride at 75° for 1 hour and then at 100° for 15 hours. The product mixture was poured into a slurry of sodium fluoride in methylene chloride. The mixture was filtered, and the solvent removed to yield an oil. The oil in 75 ml. of ether was washed with saturated sodium bicarbonate, sodium chloride and dried. Removal of solvent followed by flash distillation gave a colorless liquid, b.p. 152°, f.p. -52° (DTA). Glpc analyses on Column B at 80° showed a mixture consisting of 91% of **25** and 9% 5-chloro-4-fluoro-2-trifluoromethylthiazole (**26**); ir (neat): 1524, 1416, 1307, 1241, 1149, 1070, 1026, 903 and 744 cm^{-1}; uv max (ethanol): 222 (ϵ = 2,830) and 254 nm (4,440); ^{19}F nmr (deuteriochloroform): δ 55.7 (s, CF_3 in **13**) and δ 62.8 (s, CF_3 in **14**). The mass spectra of **25** and **26** are summarized in Table I.

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