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Products of the Nitration of 2-Thiazolylureas and 2-Thiazolylthioureas

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Products of the nitration of 2-thiazolylurea and 2-thiazolylthiourea derivatives with fuming nitric acid in concentrated sulfuric acid are described. The urea derivatives studied were 3-(4-methyl-2-thiazolyl)urea and -thiourea (**7**), and their 1-methyl (**1** and **2**, respectively) and 1,1-dimethyl analogs. The products were the compounds nitrated at the 5-position of the thiazole moiety. With an excess of nitric acid, 1-methyl-3-(4-methyl-5-nitro-2-thiazolyl)-1-nitrourea was obtained from **1**, while the corresponding 1-nitrosourea was formed from **2**. A pale yellow compound was obtained from the nitration of **7**. Unlike other nitrated thioureas, it did not form a colored Cu(II) chelate and was stable to acid, alkali, and heat. It was concluded to be 6-methyl-2-nitroiminothiazolo[3,2-*b*][1,2,4]thiadiazole from studies of its physicochemical properties, chemical reactions, and the results of X-ray crystallography. Corresponding compounds were obtained from other *N*-(4-alkyl-2-thiazolyl)thioureas.

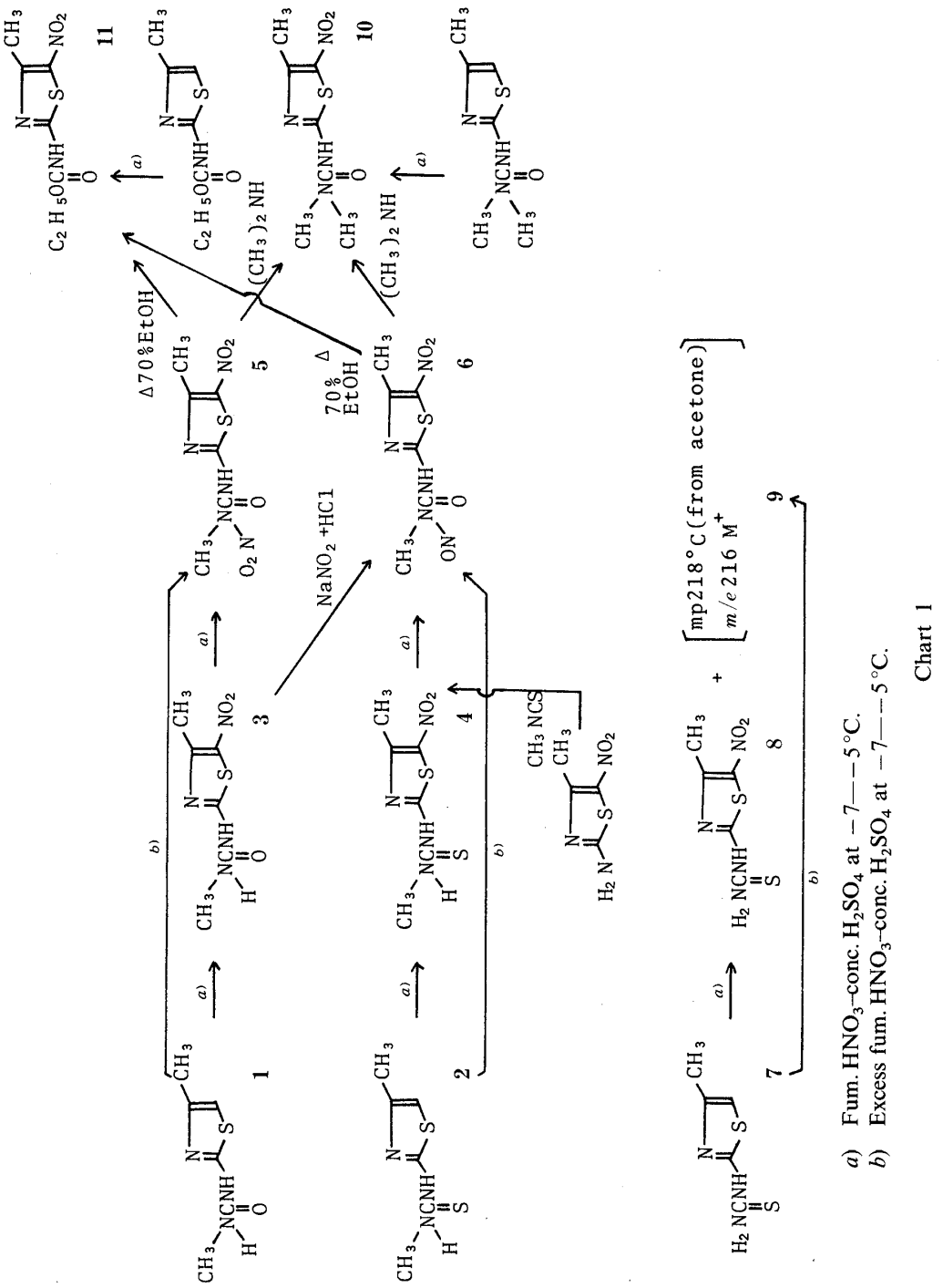
Keywords——nitration; *N*-(2-thiazolyl)urea; *N*-(2-thiazolyl)thiourea; 1-methyl-3-(4-methyl-5-nitro-2-thiazolyl)-1-nitrosourea; 6-methyl-2-nitroiminothiazolo[3,2-*b*][1,2,4]thiadiazole; X-ray analysis

Our recent studies[2)] have shown that 1,1-dimethyl-3-(2-thiazolyl)thioureas are potentially useful chelating reagents for spectrophotometric determination of metal ions. Introduction of a nitro group at the 5-position of the thiazole moiety caused bathochromic and hyperchromic effects on the absorption bands of the thioureas and their metal chelates. This finding prompted us to prepare the corresponding nitro compounds of 3-(2-thiazolyl)thioureas and their 1-methyl analogs by nitration with fuming nitric acid in concentrated sulfuric acid. Contrary to our expectation, a hitherto unknown compound was obtained from the reaction of *N*-(4-methyl-2-thiazolyl)thiourea and it was proved to be 6-methyl-2-nitroiminothiazolo[3,2-*b*][1,2,4]thiadiazole. The present paper deals with this compound as well as the other products formed by the nitration of related thioureas and ureas.

Results and Discussion

Nitration was performed by dropwise addition of fuming nitric acid to a concentrated sulfuric acid solution of a urea or a thiourea at low temperature. Nitration products of 1,1-dimethyl-3-(4-methyl-2-thiazolyl)urea and -thiourea were 5-nitrothiazolyl derivatives.[2b)]

Similarly, 1-methyl-3-(4-methyl-2-thiazolyl)urea (**1**)[3)] and -thiourea (**2**)[4)] gave the corresponding 5-nitrothiazolyl derivatives (**3** and **4**, respectively) (Chart 1). With an excess of fuming nitric acid, another nitrated compound (**5**) was obtained from **1**. The results of elemental analysis and mass spectroscopy indicated that **5** is a dinitro derivative. There are



a) Fum. HNO_3–conc. H_2SO_4 at −7—−5 °C.
b) Excess fum. HNO_3–conc. H_2SO_4 at −7—−5 °C.

Chart 1

four possible sites for nitration in **1**, *i.e.* the two nitrogen atoms of urea and the 3- and 5-positions of the thiazole moiety. The nuclear magnetic resonance (NMR) data indicated the presence of an NH proton and the lack of the 5-thiazolyl proton. The signals of the methyl hydrogens of the urea moiety in **1** and **3** appeared as a doublet and singlet in **5**. The reaction of **5** with dimethylamine gave 1,1-dimethyl-3-(4-methyl-5-nitro-2-thiazolyl)urea (**10**) and that with ethanol gave 2-ethoxycarbonylamino-4-methyl-5-nitrothiazole (**11**). These results indicate that **5** is 1-methyl-3-(4-methyl-5-nitro-2-thiazolyl)-1-nitrourea.

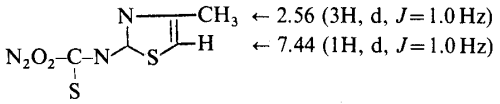
A pale yellow crystalline compound (**6**) was obtained from the reaction of **2** with an excess of fuming nitric acid. The same compound was obtained by treatment of **3** with nitrous acid. In the reactions with dimethylamine or ethanol, the same products were obtained from **6** and **5**. These results and other physicochemical data indicate that **6** is 1-methyl-3-(4-methyl-5-nitro-2-thiazolyl)-1-nitrosourea. This compound has not been described in the literature. The formation of the nitrosourea (**6**) may be explained in terms of an intramolecular redox reaction in a presumed intermediate, 1-methyl-3-(4-methyl-5-nitro-2-thiazolyl)-1-nitrothiourea.

The nitration product of *N*-(4-methyl-2-thiazolyl)urea was the 5-nitrothiazole derivative. Nitration of *N*-(4-methyl-2-thiazolyl)thiourea (**7**) gave a pale yellow crystalline compound (**9**), which was separated with the expected product, *N*-(4-methyl-5-nitro-2-thiazolyl)thiourea (**8**). When excess nitric acid was used, **9** was the main product.

TABLE I. Physicochemical Properties of **9**

Elements	Exact mass measurement *m/e* (Calcd)	*m/e* (Obs.)	E.R. mass unit	
$C_5H_4N_4O_2S_2$	215.9774	215.9793	1.9	M^+
$C_5H_4N_2OS_2$	171.9764	171.9757	−0.7	$\downarrow -N_2O$
$C_5H_4N_2S$	124.0094	124.0085	−0.9	$\downarrow -SO$
$C_4H_4N_3$	94.0404	94.0391	−1.3	Base peak

^{1}H-NMR chemical shifts in DMSO-d_6 (δ, ppm).



The results of elemental analysis and mass spectroscopy showed that the molecular formula **9** was $C_5H_4N_4O_2S_2$. Unlike other thiazolylthiourea derivatives, **9** did not form a colored Cu(II) chelate. The high-resolution mass spectrum (MS) and NMR data are summmarized in Table I. The NMR data indicated that the four hydrogens are those of the 4-methyl group and the 5-position in the thiazole moiety. The four hydrogens were not displaced by deuterium on heating in C_2H_5OD and D_2O. Since the nitro group is absent at 5-position of thiazole, **9** was not derived from **8**, a 5-nitrated compound. Compound **9** was stable to acid, alkali, and heat. It was soluble in aqueous 1 N NaOH, forming a red-colored solution and was recovered upon addition of acid to the solution. Prolonged heating in an aqueous acid solution did not cause any change. No significant change in weight was detected below the melting point in thermal differential analysis.

Nitration of **9** with excess nitric acid in concentrated sulfuric acid gave the 5-nitrothiazolyl derivative fo **9** (**9g**). Reduction of **9** with tin in concentrated hydrochloric acid resulted in recovery of the starting material, **7** (Chart 2).

A yellow-green compound was separated by heating **9** in an alkaline solution. Treatment of the compound with ethanol–water provided 2-ethoxythiocarbonylamino-4-methylthiazole

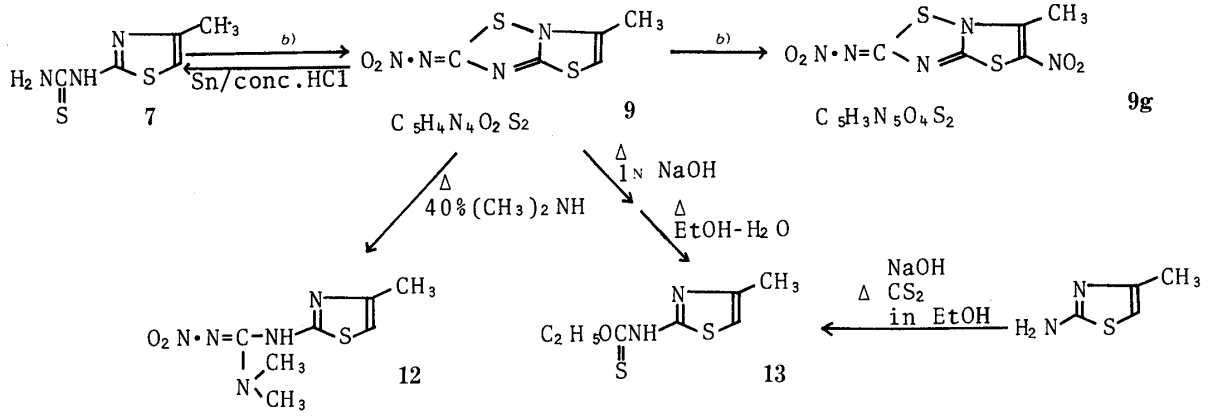


Chart 2

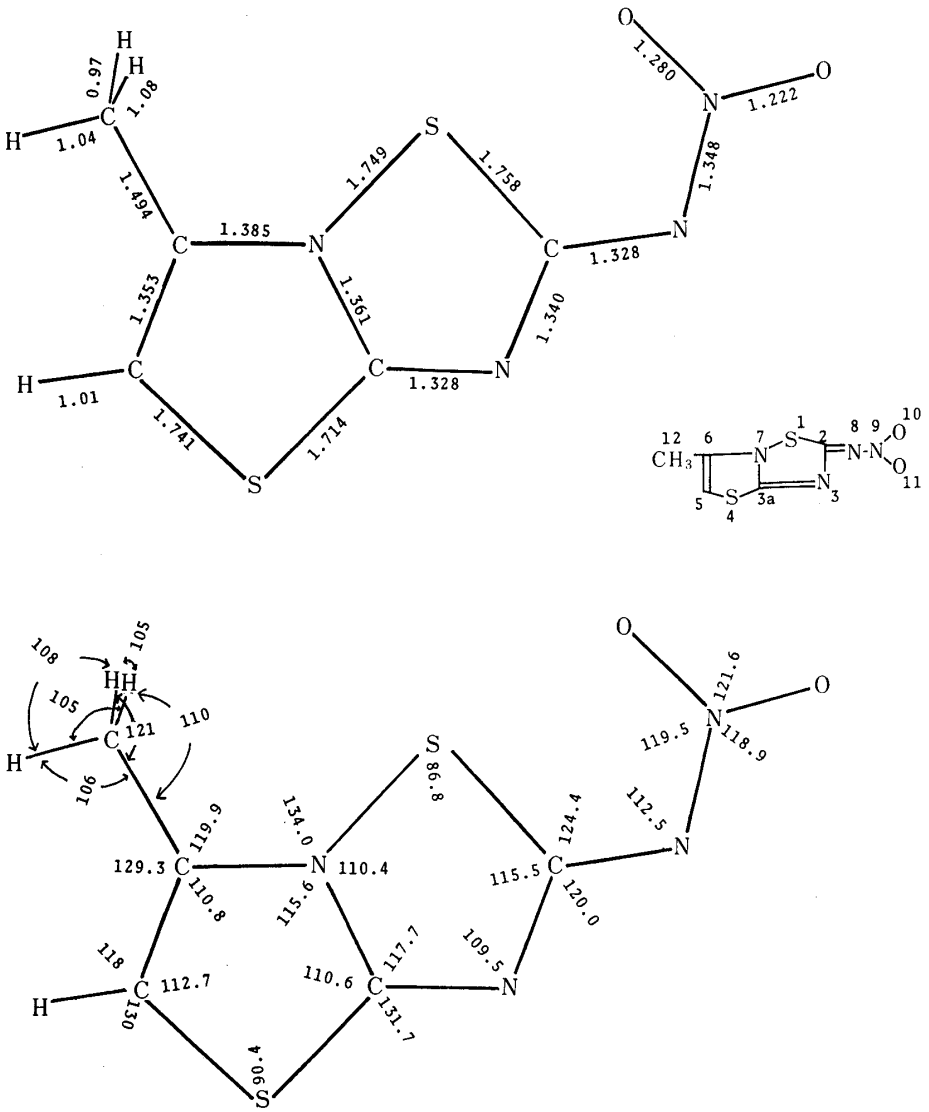
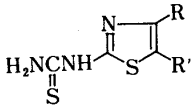
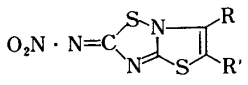
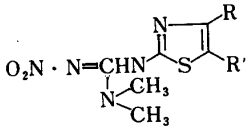


Fig. 1. Bond Lengths (Å) and Bond Angles (Degree) of 6-Methyl-2-nitroiminothiazolo[3,2-*b*][1,2,4]thiadiazole (**9**)

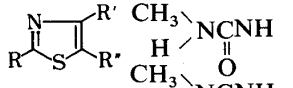
The mean standard deviations of bond lengths and angles are estimated to be 0.008 Å and 0.5°, respectively, for heavier atoms and 0.08 Å and 5°, respectively, for those involving hydrogen atoms.

TABLE II. Derivatives of Thiazolylthiourea

Compd. R	R′	No.	mp (°C)	Recryst. from	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S
										
CH_3	H	**7**[a]	190	EtOH	50	$C_5H_7N_3S_2$				
C_2H_5	H	**7a**	134	EtOH–H_2O	73	$C_6H_9N_3S_2$	38.48 (38.48	4.84 5.46	22.44 22.37)	
C_3H_7	H	**7b**	149	EtOH–H_2O	30	$C_7H_{11}N_3S_2$	41.76 (41.81	5.51 5.79	20.87 20.81)	
iso-C_3H_7	H	**7c**	160	EtOH–H_2O	48	$C_7H_{11}N_3S_2$	41.76 (41.63	5.51 5.50	20.87 20.76)	
C_4H_9	H	**7d**	148	EtOH–H_2O	33	$C_8H_{13}N_3S_2$	44.62 (44.69	6.09 6.01	19.51 19.59)	
C_5H_{11}	H	**7e**	141	EtOH–H_2O	20	$C_9H_{15}N_3S_2$	47.13 (47.18	6.59 6.50	18.32 18.08)	
CH_3	CH_3	**7f**[b]	214—215	EtOH	28	$C_6H_9N_3S_2$	38.48 (38.40	4.84 4.85	22.44 22.39)	
										
CH_3	H	**9**	218	Acetone	21	$C_5H_4N_4O_2S_2$	27.77 (27.76	1.86 1.74	25.91 25.84	29.66 29.35)
C_2H_5	H	**9a**	201	Acetone	16	$C_6H_6N_4O_2S_2$	31.30 (31.39	2.63 2.42	24.33 24.32	27.85 27.61)
C_3H_7	H	**9b**	215	Acetone	17	$C_7H_8N_4O_2S_2$	34.42 (34.42	3.30 3.60	22.93 22.87)	
iso-C_3H_7	H	**9c**	208	Acetone	12	$C_7H_8N_4O_2S_2$	34.42 (34.37	3.30 3.25	22.93 22.82)	
C_4H_9	H	**9d**	168	Acetone	22	$C_8H_{10}N_4O_2S_2$	37.20 (37.18	3.90 3.73	21.69 21.68	24.82 24.59)
C_5H_{11}	H	**9e**	127	Acetone–(H)	22	$C_9H_{12}N_4O_2S_2$	39.69 (39.60	4.44 4.55	20.57 20.38	23.55 23.43)
CH_3	CH_3	**9f**	223—224	Acetone	12	$C_6H_6N_4O_2S_2$	31.30 (31.51	2.63 2.69	24.33 24.31)	
CH_3	NO_2	**9g**	>300	Dioxane–H_2O	58	$C_5H_3N_5O_4S_2$	22.99 (23.34	1.16 1.18	26.80 26.43	24.55 24.15)



CH_3	H	**12**	239—241	2-PrOH	41	$C_7H_{11}N_5O_2S$	36.67	4.84	30.55	13.99
							(36.57	4.79	30.41	14.11)
C_2H_5	H	**12a**	195	2-PrOH	30	$C_8H_{13}N_5O_2S$	39.50	5.39	28.79	
							(39.38	5.32	28.72)	
C_3H_7	H	**12b**	204	MeOH–H_2O	67	$C_9H_{15}N_5O_2S$	42.01	5.88	27.22	
							(41.93	5.95	27.18)	
iso-C_3H_7	H	**12c**	209—210	EtOH	19	$C_9H_{15}N_5O_2S$	42.01	5.88	27.22	12.46
							(41.82	5.65	27.01	12.39)
C_4H_9	H	**12d**	201	MeOH–H_2O	16	$C_{10}H_{17}N_5O_2S$	44.27	6.32	25.81	11.82
							(44.23	6.29	25.78	12.00)
C_5H_{11}	H	**12e**	212	MeOH	21	$C_{11}H_{19}N_5O_2S$	46.30	6.71	24.54	
							(46.24	6.71	24.49)	



R	R′	R″								
$CH_3NHCONH$	CH_3	NO_2	**3**	235	EtOH		$C_6H_8N_4O_3S$	33.33	3.73	25.91	
								(33.38	3.63	26.07)	
$CH_3N(NO_2)CONH$	CH_3	NO_2	**5**	140	Acetone–H		$C_6H_7N_5O_5S$	27.59	2.70	26.81	12.27
								(27.49	2.61	26.36	12.91)
$CH_3N(NO)CONH$	CH_3	NO_2	**6**	125—126	Acetone–H		$C_6H_7N_5O_4S$	29.39	2.88	28.56	13.08
								(29.23	2.90	28.45	13.30)
$(CH_3)_2NCONH$	CH_3	NO_2	**10**	195—200	2-PrOH–H_2O		$C_7H_{10}N_4O_3S$	36.52	4.38	24.33	13.93
								(36.46	4.39	24.19	13.97)
C_2H_5OCONH	CH_3	NO_2	**11**	194—195	70% EtOH		$C_7H_9N_3O_4S$	36.36	3.92	18.17	
								(36.21	3.81	18.16)	
$CH_3NHCSNH$	CH_3	NO_2	**4**	233—234	Acetone–H		$C_6H_8N_4O_2S_2$	31.02	3.47	24.12	
								(31.04	3.47	23.96)	
H_2NCSNH	CH_3	NO_2	**8**	242	Acetone–H		$C_5H_6N_4O_2S_2$	27.52	2.77	25.67	
								(27.27	2.73	25.32)	
H_2NCSNH	C_2H_5	NO_2	**8a**	192—194	Acetone–petroleum ether		$C_6H_8N_4O_2S_2$	31.02	3.47	24.12	
								(30.74	3.28	23.55)	
C_2H_5OCSNH	CH_3	H	**13**	126	EtOH–H_2O		$C_7H_{10}N_2OS_2$	41.56	4.98	13.85	31.70
								(41.54	4.80	13.80	31.94)
H_2NCSN	CH_3	H	**14**	214	EtOH		$C_6H_9N_3S_2$	38.48	4.84	22.44	
								(38.42	4.80	22.42)	
H_2NCSN	CH_3	NO_2	**15**	248	EtOH		$C_6H_8N_4O_2S_2$	31.02	3.47	24.12	
								(31.28	3.51	24.20)	

a) H. Beyer and G. Berg, *Chem. Ber.*, **89**, 1602 (1956).
b) H. Beyer and H. Hantschel, *Chem. Ber.*, **95**, 893 (1962).

TABLE III. Spectral Data for Derivatives of Thiazolylthiourea

Compd. No.	UV $\lambda_{max}^{2\text{-PrOH}}$ nm	ε ($\times 10^3$)	MS *m/e* (R.I%) main peak			IR ν_{max}^{KBr} cm^{-1} 1700—1400
			M^+	$M^+ - NH_3$	Base	
7	252	6.6	173	156	114	1613, 1565, 1530, 1506, 1451sh, 1435
	293	19.7	(77)	(13)		
7a	253	6.2	187	170	128	1640sh, 1625, 1592, 1569, 1528, 1505, 1465sh,
	293	19.1	(78)	(16)		1446sh
7b	253	6.4	201	184	114	1581, 1555, 1517, 1495, 1425
	293	19.5	(60)	(11)		
7c	252	6.8	201	184	128	1617, 1588, 1560, 1512, 1460sh, 1446
	293	20.8	(72)	(12)		
7d	253	6.7	215	198	114	1641, 1610, 1584, 1557, 1522, 1498, 1461sh, 1442
	293	20.1	(36)	(3)		
7e	253	6.7	229	212		1609, 1558, 1527, 1498, 1459, 1447
	293	20.1	(base)	(8)		
7f	253	4.8	187	170	59	1614, 1600, 1572, 1549, 1500, 1424
	298	13.8	(52)	(14)		
			M^+	$M^+ - N_2O$	Base	
9	279	1.4	216	172	124	1565, 1518, 1488, 1450, 1415
	343	15.7	(4)	(47)		
9a	279	1.5	230	186	137	1560, 1516, 1494, 1460, 1413, 1403sh
	343	15.6	(5)	(49)		
9b	280	1.4	244	200	124	1561, 1518, 1500, 1473sh, 1458, 1425, 1403sh
	343	16.6	(2)	(23)		
9c	280	0.7	244	200	137	1555, 1510, 1487, 1462, 1447sh, 1410sh, 1400
	343	12.4	(2)	(10)		
9d	280	1.4	258	214	124	1560, 1515, 1495, 1480sh, 1460sh, 1420
	343	16.3	(2)	(12)		
9e	280	1.7	272	228	124	1555, 1508, 1482sh, 1456, 1441sh, 1414, 1402sh
	343	18.3	(5)	(52)		
9f	242sh	3.4	230	186	138	1589, 1503, 1482, 1450, 1422, 1410sh, 1400
	260sh	1.8	(7)	(38)		
	282sh	1.2				
	348	13.6				
9g	235sh	slightly	—	217	64	1568, 1512, 1489, 1464, 1420
	295	soluble		(35)		
	366					
			M^+	$M^+ - NO_2$	Base	
12	240sh	8.1	229	183	71	1575, 1521, 1475, 1415
	280sh	5.4	(9)	(22)		
	328	19.0				
12a	240sh	7.8	243	197	71	1565, 1530, 1490, 1448, 1427
	280sh	5.5	(11)	(26)		
	327	15.9				
12b	240sh	8.8	257	211	71	1570, 1543sh, 1523, 1477sh, 1464, 1448, 1405
	280sh	5.7	(7)	(18)		
	329	20.1				
12c	240sh	9.3	257	211	71	1570, 1540sh, 1523, 1463, 1415sh
	280sh	6.3	(9)	(24)		
	328	21.1				
12d	240sh	9.7	271	225	71	1596sh, 1570sh, 1560, 1520, 1470, 1444sh, 1400
	283sh	6.6	(7)	(19)		
	329	22.1				
12e	240sh	8.8	285	239	71	1595sh, 1564, 1521, 1463, 1445, 1410, 1400
	283sh	6.0	(8)	(22)		
	329	20.4				

TABLE III. (continued)

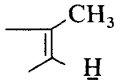
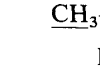
Compd. No.	UV $\lambda_{max}^{2\text{-PrOH}}$ nm	ε ($\times 10^3$)	MS *m/e* (R.I%) main peak	IR ν_{max}^{KBr} cm^{-1} 1700—1400
3	237	6.5	216 (17, M^+)	1710, 1630, 1548
	353	11.9	186 (3, $M^+ - CH_3NHN$)	
	435	0.7	159 (base, $M^+ - CH_3NCO$)	
5	233	12.7	261 (20, M^+)	1703, 1573, 1545sh, 1536, 1485, 1440, 1404
	345	12.9	185 (base, $M^+ - CH_3O_2NNH$)	
	420sh	0.9		
6	235	10.9	245 (21, M^+)	1730, 1550, 1480
	342	11.1	185 (25, $M^+ - CH_3ONNH$)	
	416	7.1	112 (base)	
10	236	8.7	230 (6, M^+)	1675, 1620, 1530, 1490, 1462, 1410
	278	2.8	72 (base)	
	356	13.4		
11	236	7.3	231 (97, M^+)	1740sh, 1725, 1620sh, 1555, 1505, 1475, 1450
	346	13.3	186 (10, $M^+ - C_2H_5O$)	
	420	9.6	159 (base)	
4	240	11.2	232 (70, M^+)	1560, 1525, 1466
	270sh	4.1	198 (18, $M^+ - H_2S$)	
	297	3.0	159 (91, $M^+ - CH_3NCS$)	
	366	10.9	74 (base)	
8	268sh	6.0	218 (99, M^+)	1659, 1609, 1588, 1563, 1527, 1459, 1430
	297sh	4.3	159 (base)	
	364	13.3	60 (56)	
	440	1.0		
8a	238	12.0	232 (88, M^+)	1630, 1620, 1580, 1570sh, 1504, 1444, 1415
	270sh	5.0	215 (15, $M^+ - NH_3$)	
	295sh	3.8	173 (84, $M^+ - NH{=}C{=}S$)	
	366	11.2	60 (base)	
	442	1.5		
13	242sh	5.4	202 (70, M^+)	1608, 1565, 1545, 1445, 1422
	298	10.5	158 (21, $M^+ - C_2H_4O$)	
	335sh	3.7	114 (base)	
14	279	6.6	187 (base, M^+)	1603, 1594, 1495, 1440sh, 1412
	326	14.5	171 (37, $M^+ - NH_2$)	
			154 (22, $M^+ - SH$)	
15	259	2.2	232 (base, M^+)	1648, 1608, 1584, 1570, 1526, 1476, 1410
	297	2.8	216 (35, $M^+ - NH_2$)	
	386	4.2	199 (26, $M^+ - SH$)	

sh: shoulder.

(**13**). Reaction of **9** with dimethylamine gave a compound in which the sulfur atom of **9** was replaced by a dimethylamino group and a hydrogen was added to a nitrogen atom (*N,N*-dimethyl-*N'*-(4-methyl-2-thiazolyl)-*N''*-nitroguanidine, **12**). These results support the partial structure of thiazolyl-N-CS- in **9**.

Nitration of *N*-(4,5-dimethyl-2-thiazolyl)thiourea (**7f**) under similar conditions gave the compound corresponding to **9** (**9f**). *N*-(4-Alkyl-2-thiazolyl)thioureas in which the alkyl group was ethyl, *n*-propyl, isopropyl, *n*-butyl or *n*-pentyl (**7a**—**e**) were nitrated to form the compounds corresponding to **9** (**9a**—**e**). From 4-methyl (**7**) and ethyl thioureas (**7a**), significant amounts of the 5-nitrothiazolyl compounds (**8**, **8a**) were also formed, but the yields of the corresponding nitro compounds from bulkier alkyl thioureas (**7b**—**e**) were poor.

TABLE IV. ^{1}H-NMR Spectral Data for Derivatives of Thiazolylthiourea

Compd. No.	Solvent				$(CH_3)_2N-$		H_2N-	
1	DMSO-d_6	2.18 (3H, d, J=1.0)	6.40 (2H, m)	2.68 (3H, d, J=5.0)		6.40		11.8 (1H, br)
2	DMSO-d_6	2.30 (3H, d, J=1.0)	6.60 (1H, d, J=1.0)	3.10 (3H, d, J=5.0)		9.76 (1H, br)		11.4 (1H, br)
3	DMSO-d_6	2.61 (3H, s)		2.72 (3H, d, J=5.0)		6.66 (1H, br)		Not appear
4	DMSO-d_6	2.61 (3H, s)		2.99 (3H, d, J=5.0)		8.36 (1H, br)		12.3 (1H, br)
5	$CDCl_3$	2.75 (3H, s)		3.74 (3H, s)				11.20 (1H, br)
6	$CDCl_3$	2.74 (3H, s)		3.28 (3H, s)				10.2 (1H, br)
7	DMSO-d_6	2.27 (3H, d, J=1.0)	6.59 (1H, d, J=1.0)				8.96 (2H, br)	11.59 (1H, br)
8	DMSO-d_6	2.63 (3H, s)				7.70 (1H, br)	8.90 (1H, br)	12.39 (1H, br)
9	DMSO-d_6	2.56 (3H, d, J=1.0)	7.44 (1H, d, J=1.0)					
10	$CDCl_3$	2.65 (3H, s)			3.07 (6H, s)			Not appear
12	DMSO-d_6	2.19 (3H, d, J=1.0)	6.67 (1H, d, J=1.0)		3.13 (6H, s)			13.2 (1H, br)

Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; br, broad; J=Hz values.

N-[3,4-Dimethyl-2(3*H*)-thiazolylidene]thiourea (**14**) gave the 5-nitrothiazolyl derivative (**15**), but not the compound corresponding to **9**. The results indicate that the unsubstituted 3-nitrogen atom of the thiazole moiety is required for the formation of **9**. Since there is no hydrogen atom outside the thiazole moiety in the molecule of **9**, the 3-nitrogen may be involved in a condensed-ring system of **9**. The stability of **9** to chemical transformation suggests that the sulfur atom from the thiourea moiety may be contained in the ring system.

Since nitration of **2** (the 1-methyl analog of **7**) took place at the nitrogen atom of the thiourea moiety, the corresponding nitrogen atom of **7** is probably the site of nitration. The 1-nitrated derivative of thiourea may tautomerize to thiol form and subsequent oxidative intramolecular cyclization should lead to the formation of the thiazolothiadiazole compound.

The structure of **9** was confirmed to be 6-methyl-2-nitroiminothiazolo[3,2-*b*][1,2,4]-thiadiazole by an X-ray crystal analysis using CuK_α radiation. The molecular geometry is shown in Fig. 1. Crystal data: $C_5H_4N_4O_2S_2$, MW=216.2. Crystal size, 0.2×0.01×0.5 mm. Monoclinic $P2_1/n$, a=10.786 (5), b=19.447 (10), c=3.892 (2) Å, β=97.89 (5)°, V=808.7 Å^3, Z=4, D_{calc}=1.776 g·cm^{-3}. Observed reflections, 1404 with $I \geq 2\sigma(I)$. The final R factor was 0.069, including the 4 hydrogen atoms.[5]

Physicochemical properties of the compounds which have not been described in the literature are summarized in Tables II, III, and IV.

The structural similarity between **9** and tetramisole, which is used as an antihelmintic and immunopotentiator, prompted us to investigate the biological activities of **9**. The results will be reported elsewhere.

Experimental

A JEOL JMS-D100 mass spectrometer, a JEOL JNM-NH 100 NMR spectrometer [100 MHz], a Shimadzu UV-200s double-beam spectrometer and a Hitachi EPI-G3 infrared spectrometer were used throughout the present study.

Nitration Procedure——One to two equivalents of fuming HNO_3 was added dropwise to a solution of a urea or a thiourea (2 g) in conc. H_2SO_4, in an ice-bath or a freezing mixture. After the addition, the mixture was stirred for 1 h under cooling, allowed to stand at room temperature for 15 min, and then poured into ice-water (*ca.* 100 ml). The yellow precipitate obtained was purified by chromatography on a silica gel column with acetone–$CHCl_3$ (1 : 4). The products were recrystallized from acetone or acetone–cyclohexane.

***N*-(4-Alkyl-2-thiazolyl)thiourea**——Benzoylisothiocyanate was added dropwise to an EtOH solution of 2-amino-4-alkyl(or 2-amino-4,5-dimethyl)thiazole and the mixture was stirred for 4—24 h at room temperature. The precipitate was collected by suction, washed with EtOH, and dissolved in 10% NaOH. The solution was heated for 1 h in a boiling water bath and acidified with HCl after cooling. The white precipitate was treated with aqueous 7% NH_3 and recrystallized from EtOH or EtOH–H_2O.

***N*,*N*-Dimethyl-*N'*-(4-methyl-2-thiazolyl)-*N''*-nitroguanidine (12)**——A solution of **9** in 40% dimethylamine was heated at 70—100 °C for 4—10 h. The mixture was concentrated *in vacuo* and the syrupy residue was chromatographed on a silica gel column with acetone–$CHCl_3$. Pale yellow needles.

2-Ethoxythiocarbonylamino-4-methylthiazole (13)——A 1 N NaOH solution of **9** (0.2 g in 15 ml) was boiled for 2 h, then cooled, and acidified with 1 N H_2SO_4. The yellow precipitate was dissolved in EtOH (15 ml)–H_2O (5 ml) and the solution was boiled for 1.5 h. Yellow needles, mp 126 °C (recrystallized from EtOH–H_2O), yield 200 mg. The crystals were identified as **13** by comparison with an authentic sample.

Reduction of 9——A conc. HCl solution of **9** (1 g in 30 ml) was heated with 4 g of granulated Sn at 100 °C for 1 h, then the mixture was cooled and filtered. The filtrate was neutralized with an aqueous NH_3. The white precipitate was dried and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and the residue was chromatographed on a silica gel column with acetone–$CHCl_3$ (1 : 4) as an eluent. Yellow needles (recrystallized from EtOH, mp 192 °C, yield 166 mg) were separated and identified as **7** by comparison of the physicochemical properties with those of an authentic sample.

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References and Notes

1) Deceased (September 6th, 1983).
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5) The final atomic coordinates will be included in the Cambridge Crystallographic Database. The list of observed and calculated structure factors may be obtained from one of the authors (R. Y.) upon request.