BIS(4-METHYL-2-THIAZOLYL)GUANIDINES. PREPARATION AND PHYSICOCHEMICAL PROPERTIES

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Abstract —— Eighteen N-substituted and N,N-disubstituted N',N''-bis(4-methyl-2-thiazolyl)guanidines were prepared by the reaction of N,N'-bis(4-methyl-2-thiazolyl)-S-methylisothiourea with amines. Their ultraviolet, infrared, ^{1}H- and ^{13}C-nuclear magnetic resonance and mass spectral data supported the structures.

Our previous studies[1-8] have shown that 2-thiazolylthioureas are potentially useful chelating agents for spectrophotometric determination of metal ions. In the course of the studies, we found[9] that the pyrolysis of N-methyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea afforded N-methyl-N',N''-bis(4-methyl-2-thiazolyl)guanidine (1). Similarly the pyrolytic product of N-ethyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea was N-ethyl-N',N''-bis(4-methyl-2-thiazolyl)guanidine (2). For the identification of the compounds, they were prepared separately by the reaction of N,N'-bis(4-methyl-2-thiazolyl)-S-methylisothiourea with methylamine or ethylamine. Use of other mono- or disubstituted amines in the place of methylamine or ethylamine in the reaction gave N-mono- or N,N-disubstitued analogs of 1 and 2. This provides a means of facile synthesis of N,N'-bis(2-thiazolyl)guanidines.

Since there are many guanidine derivatives of biological and medical interests, we prepared a number of bis(4-methyl-2-thiazolyl)guanidines by the reaction and examined their biological activities. This paper describes their physicochemical properties.

EXPERIMENTAL

N,N-bis(4-Methyl-2-thiazolyl)-S-methylisothiourea was prepared by the method of Ledovskikh and Shapovalova.[10] The amines used in the reaction were obtained from commercial sources. Two reactants were mixed without solvent and heated at 120-160°C. Heating was kept for 3-10 min for aliphatic amines and 2-6 h for aromatic amines. Upon cooling to room temperature, part of the products crystallized out of solution. The products were purified through chromatography on silica gel and recrystallization. Yields were in the range of 40-70 %.

A JEOL JMS-D100 mass spectrometer, a JEOL JNM-FX200A FT-nuclear magnetic resonance (NMR) spectrophotometer [270 MHz], a Shimadzu UV-200s double-beam spectrometer and a Hitachi EPI-G3 infrared (IR) spectrometer were used throughout the present study.

RESULTS AND DISCUSSION

Eighteen guanidines were prepared. Compounds **1** and **2** were described in the previous paper.[9] Other sixteen guanidines (**3-18**) have not been described in the literature. Table 1 lists the compounds with analytical data and the absorption maxima in the ultraviolet (uv) region. Ir and ^{1}H-nmr data are tabulated in Table 2. ^{13}C-Nmr and mass spectral data are summarized in Tables 3 and 4, respectively.

The ^{13}C-Nmr spectra were measured in dimethylsulfoxide-d_6 (DMSO-d_6). The assignments of the chemical shifts were confirmed by long-range selective proton decoupling experiments. In mass spectra, all compounds showed the peak assignable to the molecular ion (M^+). The fragmentations characteristic of the series of the compounds are shown in Chart 1. The analytical results and spectral properties shown in Tables support the proposed structures.

Biological activities of the compounds examined were toxicity, metabolism, pharmacological activities on central nervous system, cardiovascular system, gastrointestinal tract and inflammation in experimental animals and antimicrobial activities. The results will be described elsewhere.

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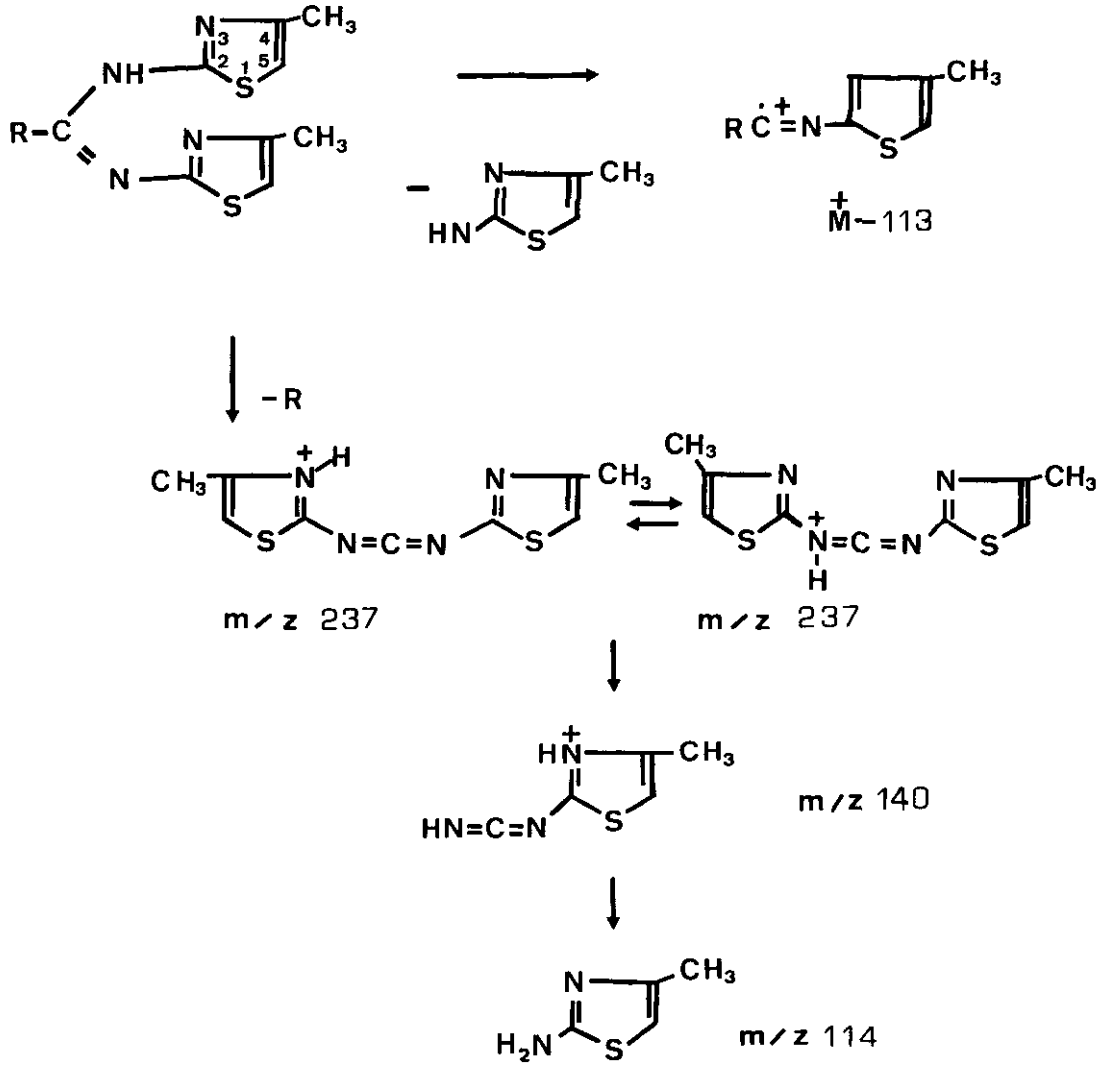
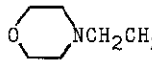
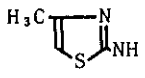
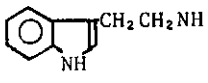
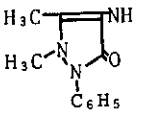


Chart I

Table 1. ANALYTICAL AND ABSORPTION SPECTRAL DATA

Compd.	R	mp(°C) solvent(recryst) Mol. Formula	Elemental analysis Calcd. (Found.)				Absorption maxima[a] nm (ε)
3	$(CH_3)_2N$	163 acetone-cyclohexane $C_{11}H_{15}N_5S_2$	46.95 (46.93	5.37 5.36	24.89 24.58	22.79 22.91)	240sh (6,800) 277sh (9,700) 313 (15,200)
4	$(C_2H_5)_2N$	144 EtOH $C_{13}H_{19}N_5S_2$	50.46 (50.49	6.19 6.08	22.63 22.58	20.72 20.92)	243sh (6,310) 270sh (6,100) 317 (11,800)
5	$(CH_3)_2NCH_2CH_2NH$	80 acetone-H_2O $C_{13}H_{20}N_6S_2$	48.12 (48.05	6.21 6.12	25.90 25.95	19.76 19.67)	271 (11,800) 280sh(11,100) 318 (21,000)
6	$(C_2H_5)_2NCH_2CH_2NH$	58 acetone-H_2O $C_{15}H_{24}N_6S_2$	51.11 (51.10	6.86 6.82	23.84 23.88	18.20 18.49)	271 (14,000) 280sh(13,000) 318 (25,000)
7		148-150 acetone-H_2O $C_{15}H_{22}N_6OS_2$	49.16 (49.22	6.05 6.05	22.93 22.91	17.50 17.55)	271 (11,600) 280sh(10,600) 318 (20,500)
8	C_6H_5NH	123 EtOH-H_2O $C_{15}H_{15}N_5S_2$	54.69 (54.51	4.59 4.44	21.26 21.14	19.47 19.55)	238sh (7,900) 288sh(16,200) 324 (22,500)
9	p-F-C_6H_4NH	167 2-PrOH $C_{15}H_{14}N_5S_2F$	51.85 (52.05	4.06 4.13	20.16 20.10	18.46 18.65)	240 (7,300) 300sh(17,500) 326 (21,400)
10	p-CF_3-C_6H_4NH	175 2-PrOH $C_{16}H_{14}N_5S_2F_3$	48.35 (48.53	3.55 3.72	17.62 17.61)		245 (8,600) 325 (17,500) 355sh(21,400)
11	p-Cl-C_6H_4NH	164 2-PrOH $C_{15}H_{14}N_5S_2Cl$	49.51 (49.61	3.88 3.99	19.25 19.09)		243 (9,000) 300sh(19,400) 327 (24,200)
12	m,p-$(CH_3)_2C_6H_3NH$	147 2-PrOH-H_2O $C_{17}H_{19}N_5S_2$	57.11 (57.25	5.36 5.28	19.59 19.32)		240sh (8,500) 280 (16,200) 322 (23,400)
13	o,m-$(CH_3)_2C_6H_3NH$	133 EtOH-H_2O $C_{17}H_{19}N_5S_2$	57.11 (57.06	5.36 5.44	19.59 19.54	17.94 17.69)	279 (13,900) 318 (19,600)
14	p-(CH_3)-m-(NO_2)-C_6H_3NH	192-193 acetone-H_2O $C_{16}H_{16}N_6O_2S_2$	49.47 (49.38	4.15 4.03	21.63 21.45)		237 (11,000) 323 (20,000) 358 (13,000)
15	o-(CH_3)-m-(NO_2)-C_6H_3NH	182-183 acetone-H_2O $C_{16}H_{16}N_6O_2S_2$	49.47 (49.16	4.15 4.10	21.63 21.06)		240 (11,000) 321 (21,000) 356 (16,000)
16		197 acetone $C_{13}H_{14}N_6S_3$	44.55 (44.39	4.03 4.06	23.98 23.27)		250 (4,900) 331 (20,300) 360 (15,700)
17		144-146 EtOH-H_2O $C_{19}H_{20}N_6S_2$	57.55 (57.35	5.08 5.03	21.19 21.22	16.17 16.12)	273 (16,700) 280 (16,700) 290 (14,500) 318 (20,500)
18		201 acetone-H_2O $C_{20}H_{21}N_7OS_2$	54.65 (54.57	4.82 4.81	22.31 22.37	14.59 14.72)	248 (11,400) 298 (20,700) 323 (18,600)

a) Absorption spectra were measured in 2-propanol (2-PrOH). sh; shoulder.

Table 2. IR AND ^{1}H-NMR DATA

Compd.	IR ν_{max}(KBr)[a] 1700-1400 cm^{-1}		^{1}H-NMR($CDCl_3$, room temp.)[b] thiazole 4-CH_3	thiazole 5-H	other signals
3	1594s 1545vs	1480s 1448s 1405s	2.31 d,3Hx2 (J=1.0Hz)	6.36 d,1Hx2 (J=1.0Hz)	2.97(s,6H,$(CH_3)_2N$)
4	1610s 1580vs 1504s	1475s 1400s	2.33 d,3Hx2 (J=1.0Hz)	6.35 d,1Hx2 (J=1.0Hz)	1.18(t,6H,J=7.3Hz,CH_3x2) 3.40(q,4H,J=7.0Hz,CH_2x2)
5	1630s 1560s	1530m 1510m 1445vs	2.29 6H	6.22 6.33 1Hx2	2.29(6H,$(CH_3)_2N$) 2.56(2H,CH_2) 3.53(2H,CH_2)
6	1635vs 1575vs 1480w 1455m	1440vs 1430s 1405vs	2.28 3Hx2	6.25 6.35 1Hx2	1.07,1.18(6H,$(-CH_2)_3N$) 2.7(6H,$\underline{CH_3}CH_2$) 3.54,3.41(2H,$\underline{CH_2}NH$)
7	1625vs 1565vs 1525vs	1442vs 1428vs	2.29 3Hx2	6.20-6.35 1Hx2	2.34-4.06(m,12H,CH_2x6)
8	1650s 1632s 1595s 1570s	1492s 1450s 1430s	2.33 3Hx2	6.38 1Hx2	7.25-7.71(m,5H,C_6H_5)
9	1659vs 1638vs 1610m 1589vs	1503s 1450s 1410s	2.33 3Hx2	6.31 6.39 1Hx2	7.25-7.65(m,4H,C_6H_4)
10	1660vs 1640vs 1614vs 1572s	1532s 1500s 1445vs	2.34 2.37 3Hx2	6.35 6.40 1Hx2	7.23-7.84(m,4H,C_6H_4)
11	1655vs 1635vs 1590s 1565s	1488s 1445s 1400s	2.34 3Hx2	6.33 6.39 1Hx2	7.30-7.66(m,4H,C_6H_4)
12	1630vs 1596s 1548vs	1500s 1470s 1450vs	2.28 6H	6.36 1Hx2	2.28(CH_3x2) 7.10-7.40(3H,C_6H_3)
13	1640vs 1620vs 1575vs	1525m 1460vs	2.25 2.28 6H	6.37 1Hx2	2.33(CH_3x2) 7.17(3H,C_6H_3)
14	1634vs 1614m 1545m 1525vs	1490m 1460m 1420vs	2.34 3Hx2	6.35 6.41 1Hx2	2.56(s,3H,CH_3) 7.26,7.80,8.40(3H,C_6H_3)
15	1650vs 1618s 1584vs	1558s 1510vs 1455vs	2.34 3Hx2	6.35 6.42 1Hx2	2.52(s,3H,CH_3) 7.54,7.57,8.55(3H,C_6H_3)
16	1630m 1591vs 1537s 1521m	1481m 1462s 1451m 1420vs	2.38 s,3Hx3	6.34 1Hx3	
17	1662vs 1565s	1525s 1440s	2.16 2.29 3Hx2	6.20 6.42 1Hx2	3.12(t,2H,CH_2) 3.83(t,2H,CH_2) 7.0-8.0(m,5H,aromatic H)
18	1635vs 1598s 1560m	1488vs 1432s 1402s	2.32 3Hx2	6.39 1Hx2	2.36(s,3H,CH_3) 3.12(s,3H,CH_2) 7.26-7.45(m,5H,C_6H_5)

a) vs; very strong: s; strong: m; medium: w; weak.
b) Chemical shifts are given in δ-values(ppm) downfield from tetramethylsilane (TMS) as an internal standard. s; singlet: d; doublet: t; triplet: q; quartet: m; multiplet.

Table 3. ^{13}C-NMR DATA[a)]

Compd.	Thiazole Moiety					Other signals
	4-CH_3	2-C	4-C	5-C	N-C(=N)NH	
1	16.54(q)	167.13	144.82	105.22(d)	152.12	27.97(q,CH_3)
2	16.47(q)	167.23	144.55	105.09(d)	151.47	15.16(q,CH_3) 35.80(t,CH_2)
3	16.42(q)	166.12	144.62	104.85(d)	155.54	38.57(q,CH_3)
4	16.15(q)	166.03	143.46	103.76(d)	156.16	13.21(q,CH_3) 42.40(t,CH_2)
5	16.67(q)	166.70	145.37	105.32(d)	151.25	39.73(t,CH_2) 44.80(q,CH_3) 58.79(t,CH_2)
6	16.82(q)	166.62	145.83	103.41(d)	151.05	11.47(q,CH_3) 39.46(t,CH_2) 46.77(t,CH_2) 53.22(t,CH_2)
7	16.70(q)	166.79	145.17	105.44(d)	151.17	38.68(t,CH_2) 53.33(t,CH_2) 58.04(t,CH_2) 66.05(t,CH_2)
8	15.72(q)	168.36	141.73	104.94(d)	151.36	121.59, 122.99, 128.71, 139.26 (C_6H_5)
9	15.69(q)	168.40	141.65	104.96(d)	151.52	115.21, 123.55, 135.58, 144.62, 156.73, 160.28 (C_6H_4F)
11	15.54(q)	168.49	141.30	105.04(d)	151.52	122.82, 126.73, 128.51, 138.36 (C_6H_4Cl)
12	15.81(q)	168.09	142.08	104.96(d)	151.25	18.54(q,CH_3) 19.37(q,CH_3) 119.71, 123.38, 129.75, 131.32, 136.50 (C_6H_3)
14	15.60(q)	168.53	141.41	105.24(d)	151.43	18.43(q,CH_3) 116.13, 125.62, 132.64, 138.51, 149.50 (C_6H_3)
15	15.60(q)	169.24	141.42	105.24(d)	151.56	13.56(q,CH_3) 118.40, 123.46, 126.51, 127.83, 141.72 (C_6H_3)
16	15.89(q)	165.45	143.63	106.55(d)	149.50	
17	16.43(q)	167.16	144.64	104.96(d)	151.43	25.39(t,CH_2) 41.74(t,CH_2) 111.36, 111.48, 118.30, 120.94, 123.00, 127.28, 136.62 (aromatic C)
18	16.63(q)	165	145.52(b)	106.41(d)	149.27	10.35(q,CH_3) 35.57(q,CH_3) 124.73, 127.09, 129.09, 134.65, 148.88 (C_6H_5) 160.83(C=O)

a) The nmr spectra were measured in dimethylsulfoxide-d_6 at 80°C. Chemical shifts are given in δ-values(ppm) downfield from tetramethylsilane (TMS) as an internal standard. d; doublet: t; triplet: q; quartet: b; broad.

Table 4. MASS SPECTRAL DATA

Compd.	Main fragment peaks m/z (rel.int; %)
3	281(68,M^+), 248(40), 237(24,M^+-$(CH_3)_2N$), 168(100,M^+-113), 153(53), 140(33), 114(23)
4	309(68,M^+), 276(19), 237(33,M^+-$(C_2H_5)_2N$), 196(69,M^+-113), 168(34), 140(100), 114(46)
5	324(16,M^+), 266(31,M^+-$(CH_3)_2NCH_2$), 254(97), 253(97), 237(100,M^+-$(CH_3)_2NCH_2CH_2NH$), 140(92), 114(52)
6	352(3,M^+), 266(16,M^+-$(C_2H_5)_2NCH_2$), 254(24), 253(22), 237(100,M^+-$(C_2H_5)_2NCH_2CH_2NH$), 140(12), 114(7), 99(94,$(C_2H_5)_2NCH_2CH$), 86(100,$(C_2H_5)_2NCH_2$)
7	366(7,M^+), 267(47), 266(27,M^+-$(C_4H_8NO)CH_2$), 254(86), 253(86,M^+-113), 237(M^+-$(C_4H_8NO)CH_2CH_2NH$), 140(53), 114(49), 113(75)
8	329(71,M^+), 237(19,M^+-C_6H_5NH), 217(37), 216(100,M^+-113), 215(35), 189(19), 140(4), 139(14), 114(32)
9	347(37,M^+), 237(11,M^+-C_6H_4FNH), 234(100,M^+-113), 207(7), 173(5), 162(3), 140(2), 114(32)
10	397(37,M^+), 280(100,M^+-113), 257(8), 237(8,M^+-$CF_3C_6H_4NH$), 212(4), 145(6), 140(3), 114(20)
11	363(34,M^+), 252(36), 250(100,M^+-113), 237(13,M^+-ClC_6H_4NH), 223(5), 188(7), 140(3), 114(17)
12	357(35,M^+), 244(100,M^+-113), 237(8,M^+-$(CH_3)_2C_6H_3NH$), 217(3), 178(5) 140(2), 121(11), 114(5)
13	357(29,M^+), 244(100,M^+-113), 237(5,M^+-$(CH_3)_2C_6H_3NH$), 217(3), 140(3), 114(12)
14	388(30,M^+), 275(100,M^+-113), 245(11), 237(14,M^+-$(CH_3)(NO_2)C_6H_3NH$), 149(28), 140(6), 114(40)
15	388(35,M^+), 275(100,M^+-113), 237(11,M^+-$(CH_3)(NO_2)C_6H_3NH$), 229(13), 149(12), 140(6), 114(48)
16	350(58,M^+), 317(14), 237(100,M^+-113), 140(14), 114(37)
17	396(32,M^+), 282(8), 254(92), 237(100,M^+-$(C_8H_6N)CH_2CH_2NH$), 149(52), 143(57), 140(50), 130(32), 115(48), 114(37)
18	439(79,,M^+), 326(64,M^+-113), 320(33), 319(32), 237(100,M^+-$(C_{11}H_{11}N_2O)NH$), 203(18), 141(81), 140(58), 114(43)

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