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Facile synthesis of 2-*n*-dodecylthio-4-phenylthiomethyl-1,3,4-thiadiazole-5-thione **6**, starting from 2,5-dimercapthothiadiazole *via* 2-*n*-dodecylthio-1,3,4-thiadiazole-5-thione **2**, 2-*n*-dodecylthio-4-hydroxymethyl-1,3,4-thiadiazole-5-thione **4** and 2-*n*-dodecylthio-4-chloromethyl-1,3,4-thiadiazole-5-thione **5** is described.

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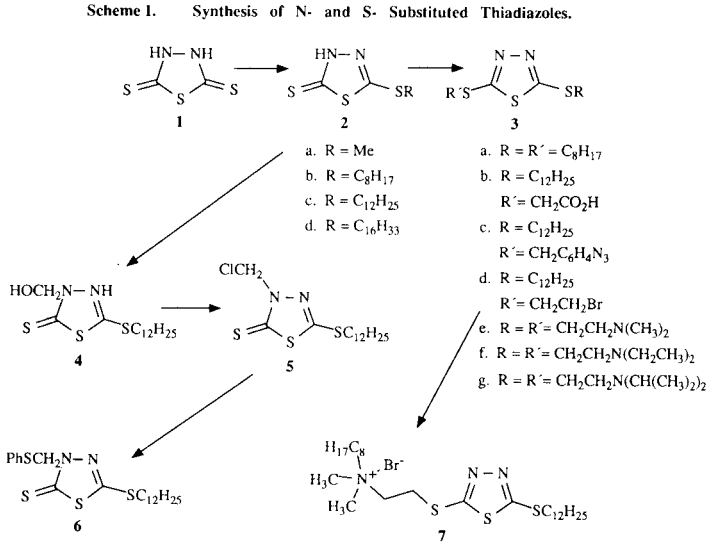
"2,5-Dimercaptothiadiazole" (DMTD) (Scheme 1), which actually exists very predominately in the dithione form **1**, is easily available from hydrazine and carbon disulphide [1,2]. Thioethers of DMTD are prepared in good yields by alkylation of mono- or dipotassium salts of DMTD with alkyl halides in the presence of potassium hydroxide [2-4], or by its reactions with olefins [5] or hydroxymethylphenols [5]. However, although 2-alkylthio-1,3,4-thiadiazole-5-thiones **2** are now well explored [6-8], the analogous 2,5-di(alkylthio)-1,3,4-thiadiazoles [9-11] **3** and 4-substituted-2-alkylthio-1,3,4-thiadiazole-5-thiones [12-16] **6** are much less studied, especially as regards functionalized derivatives.

We now report a variety of compounds of types **2, 3** and **6** (Scheme 1 and Table 1). Compounds of types **2** and **3** were made by standard methods. Our entry to compounds of type **6** was by the hydroxymethylation of **2c** with formaldehyde which readily afforded the hydroxymethyl derivative **4**. Thionyl chloride converted **4** into the reaction chloromethyl intermediate **5** which provided **6** by nucleophilic substitution of the chlorine atom.

Scheme I. Synthesis of N- and S- Substituted Thiadiazoles.



Results and Discussion.

The monoalkyl adducts **2** were prepared (86-98%) by alkylation of **1** with one equivalent of an alkyl halide in

Table 1

Preparation of Thiadiazoles **2** and **3**

Starting Material	Alkylating Agent Nature	Moles	Product	Yield (%)	Cryst. Solvent	Crystal Form	mp (°C)	Literature mp (°C)	Reference
1	CH_3I	1	**2a**	93	Benzene	needles	137-139	138-139	2
1	$C_8H_{17}Br$	1	**2b**	98	Hexane	microcrystal	77-79	77-78	2
1	$C_{12}H_{25}Br$	1	**2c**	86	Hexane	needles	86-88	90, 103	18, 19
1	$C_{16}H_{33}Br$	1	**2d**	86	Hexane	microcrystal	93-95	----- [a]	
1	$C_8H_{17}Br$	2	**3a**	82	EtOH/H_2O	plates	32	32	19
2c	$BrCH_2CO_2H$	1	**3b**	76	EtOH	powder	77-79	----- [b]	
2c	$ClCH_2C_6H_4N_3$	1	**3c**	83	Ethyl Acetate	needles	75-77	----- [c]	
1	$ClCH_2CH_2N(CH_3)_2$ [d]	2	**3e**	80	Hexane	needles	44-46	----- [e]	
1	$ClCH_2CH_2NEt_2$ [d]	2	**3f**	91	-----	oil	----	----- [f]	
1	$ClCH_2CH_2Ni\text{-}Pr_2$ [d]	2	**3g**	91	Hexane	needles	48-50	----- [g]	

[a] *Anal.* Calcd. for $C_{18}H_{34}N_2S_3$: C, 57.71; H, 9.15; N, 7.48. Found: C, 57.77; H, 9.19; N, 7.44. [b] *Anal.* Calcd. for $C_{16}H_{28}N_2O_2S_3 \cdot 0.25\ H_2O$: C, 50.43; H, 7.54; N, 7.35. Found: C, 50.46; H, 7.75; N, 7.11. [c] *Anal.* Calcd. for $C_{21}H_{31}N_5S_3$: C, 56.09; H, 6.95; N, 15.57. Found: C, 55.76; H, 7.11; N, 15.43. [d] As the hydrochloride salt. [e] *Anal.* Calcd. for $C_{10}H_{20}N_4S_3$: C, 41.07; H, 6.89; N, 19.16. Found: C, 40.78; H, 6.89; N, 19.02. [f] *Anal.* Calcd. for $C_{14}H_{28}N_4S_3$: C, 48.24; H, 8.10; N, 16.07. Found: C, 48.14; H, 8.05; N, 16.01. [g] *Anal.* Calcd. for $C_{18}H_{36}N_4S_3$: C, 53.42; H, 8.97; N, 13.84. Found: C, 53.33; H, 9.08; N, 13.82.

Table 2

^{1}H NMR Chemical Shifts (ppm) and J Values (Hz) for Thiadiazoles **2** and **3** [a]

Compound	NH (1H, s)	α-CH_2 2H, t		$(CH_2)_n$ (m)		ω-CH_3 3H, t		Other Signals
		δ	J	δ	H	δ	J	
2a	14.36	----		----		2.68	(s) [b]	----
2b	12.56	3.17	6	2.00-1.08	12	0.89	4	----
2c	11.95	3.17	7	2.07-1.07	20	0.84	4	----
2d	----	3.10	7	2.03-1.03	28	0.84	4	----
3a	----	3.33	4	2.16-1.10	24	0.88	4 [c]	----
3b	----	3.26 4.16 [d]	7	2.00-1.00	20	0.87	4	7.93 (br, 1 H)
3c	----	3.33	7	2.00-1.00	20	0.88	4	8.18 (dd, 1 H, J = 7 Hz, 3 Hz) 8.00-7.33, (m, 3 H), 6.58 (s, 2 H)
3d	----	3.28	9	1.83-1.11 3.78-3.66	20 4	0.88	4	----
3e	----	3.44	7	----		2.28 [e]		2.70 (t, 4 H, J = 7 Hz)
3f	----	3.43 [f]	7	----		1.06	7 [g]	2.86 (t, 4 H, J = 7 Hz), 2.53 (q, 8 H, J = 7 Hz)
3g	----	3.32 [f]	7	----		1.02	7 [h]	2.83 (t, 4 H, 7 Hz), 3.03 (sep, 4 H, J = 7 Hz),

[a] In deuteriochloroform (tetramethylsilane as internal reference δ 0.00) unless noted. [b] Dimethyl sulfoxide-d_6 as solvent, tetramethylsilane as reference (δ 0.00). [c] Integrates for 6 H. [d] Singlet integrates for 2 H. [e] Singlet integrates for 12 H. [f] Integrates for 4 H. [g] Integrates for 12 H. [h] Doublet integrates for 24 H.

Table 3

^{13}C NMR Chemical Shifts (ppm) for Thiadiazoles **2** and **3** [a]

Compound	Thiadiazole Carbons	S-CH_2	ω-CH_3	Other Signals
2a [b]	187.5, 159.4	----	15.5	----
2b	188.6, 160.0	33.7	13.9	31.5, 28.8, 28.7, 28.6, 28.4, 22.5
2c	188.7, 160.0	33.7	14.1	31.8, 29.6, 29.3, 28.9, 28.6, 22.6
2d	188.8, 160.0	33.7	14.1	31.9, 29.7, 29.4, 29.0, 28.6, 22.7
3a	165.1	34.3	14.0	31.7, 29.0, 28.9, 28.8, 28.6, 22.5
3b [b]	165.2, 164.1	36.0, 33.9	13.8	168.8, 31.3, 29.0, 28.9, 28.8, 28.7, 28.4, 27.9, 22.0
3c	168.3, 160.5	49.5, 34.5	14.0	146.2, 132.4, 128.1, 124.4, 120.1, 110.2, 31.8, 29.5 29.4, 29.3, 29.2, 29.0, 28.6. 22.6
3d	166.2, 162.7	34.3, 35.3	14.0	31.8, 29.5, 29.2, 29.1, 28.9, 28.6, 22.6, 14.0
3e	164.2	31.4	44.3	57.0
3f	164.3	31.9	11.3	50.9, 46.2
3g	165.5	35.5	20.8	48.4, 44.2

[a] In deuteriochloroform, (deuteriochloroform as reference, δ 77.0) unless noted. [b] dimethyl sulfoxide-d_6 as solvent, dimethyl sulfoxide-d_6 (δ 39.6) as reference.

refluxing ethanolic potassium ethoxide (see Table 1). The symmetrical bis-adducts **3a,e,f,g** were similarly obtained utilizing two equivalents of potassium hydroxide and the alkylating agent. The unsymmetrical disubstituted compounds **3b-d** were prepared in yields ranging from 74% to 97% by further alkylation of the dodecyl adduct **2b**. For **3e-g** two additional equivalents of potassium hydroxide were added after completion of the reaction to obtain the products as the free bases.

The chloromethyl derivative **5** reacted with sodium thiophenylate in tetrahydrofuran [17] to give 2-*n*-dodecylthio-4-phenylthiomethyl-1,3,4-thiadiazole-5-thione **6**, 91%.

N,N-Dimethyl-*N*-*n*-octyl-*N*-(2-*n*-dodecylthio-1,3,4-thiadiazole-5-thioethyl)ammonium bromide **7** was prepared from 2-*n*-dodecylthio-5-(*N,N*-dimethylaminoethylthio)-1,3,4-thiadiazole by quaternization with *n*-octyl bromide under reflux in 1-propanol in 98% yield.

The compounds were characterized by ^1H and ^{13}C nmr data and their structures confirmed by C,H,N analysis. The ^1H nmr spectra (Table 2) for the simple alkyl derivatives **2b-d** and **3a** showed as their most prominent feature the alkyl resonances at δ 3.10-3.17 (a triplet integrating for 2 H with J = 6-7 Hz) and a multiplet ranging from δ 2.16-1.03. The more highly functionalized derivatives such as **3b** showed an additional resonance for the methylene protons at δ 4.16 while the ^1H nmr spectra for **3c** showed a resonance at δ 6.58 ($-CH_2-$). The resonances for the benzotriazole ring in **3c** ranged from δ 8.18 (1 H) to 8.00-7.33 (3 H) (see Table 2).

The ^{13}C nmr spectra (Table 3) for the monoalkylated derivatives **2** showed resonances for the thione carbons at δ 187.5-188.8, the ring carbon resonances ranged from δ 159.4 to 160.0 and the alkyl resonances from *ca.* δ 33.9 to 13.9. The bis adducts **3** exhibited resonances at δ 160.5-168.3 for the ring carbons and the pattern for the substituents was consistent with that expected. The *S*-, *N*-disubstituted compounds **4-6** exhibited a pattern for the ring carbons similar to that seen in the monoalkylated adducts; the $-CH_2N-$ carbon resonances varied from δ 73.9 to 54.1. The remaining resonances in the spectra were as expected from the substitution pattern.

EXPERIMENTAL

The melting points are uncorrected and were taken on a Thomas-Hoover melting point apparatus equipped with a microscope. The ^1H nmr were recorded on a Varian EM 360 L (60 MHz) or on a Varian VXR 300 nmr spectrometer with tetramethylsilane (TMS) as the internal standard. The ^{13}C nmr spectra were recorded on a JEOL FX-100 (25 MHz) nmr spectrometer or on a Varian VXR 300 nmr spectrometer in deuteriochloroform with deuteriochloroform (δ 77.0) as the internal reference or in dimethyl sulfoxide-d_6 with dimethyl sulfoxide (δ 39.5) as the internal reference. Low and high resolution mass spectra were obtained on an AEI#S30 mass spectrometer. Microanalyses were performed under the supervision of Dr. R. W. King (University of Florida) or by Atlantic Microlabs, Atlanta, GA. Commercially available reagent grade solvents and reagents were used without further purification.

General Method for the Preparation of Mono- and Bis-alkylated Thiadiazoles **2** and **3**.

3*H*,4*H*-1,3,4-Thiadiazolidine-2,5-dithione **1** (22.5 g, 0.15 mole) and potassium hydroxide (9.7 g, 0.15 mole) in 190 ml of absolute ethanol were heated under reflux for 15 minutes and then the alkyl halide (0.15 mole) was added. The reflux was continued for 8 hours, then cooled and diluted threefold with water. The precipitate was filtered and recrystallized to give the thioether (see Table 1).

The bis-adduct **3a** was prepared by adding 3*H*,4*H*-1,3,4-thiadiazolidine-2,5-dithione **1** (22.5 g, 0.15 mole) and potassium hydroxide (19.3 g, 0.30 mole) to 350 ml of absolute ethanol and heating the reaction mixture under reflux for 15 minutes. 1-Bromooctane (58.5 g, 0.3 mole) was added to the reaction mixture and the reflux continued for 8 hours. The mixture was cooled in an ice bath and diluted threefold with water which caused the thioether to separate as a waxy solid. The solid was filtered, recrystallized from absolute ethanol and dried under phosphorus pentoxide to give the product (see Table 1).

2-*n*-Dodecylthio-5-bromoethylthio-1,3,4-thiadiazole-5-thione (**3d**) [22].

Use of 2-bromoethanol in the general procedure gave 2-*n*-dodicylthio-5-(β-hydroxyethylthio)-1,3,4-thiadiazole-5-thione (96%), mp 46-49°, which was treated without purification by adding triphenylphosphine (29.22 g, 0.110 mole) to its stirred solution (20.0 g, 0.055 mole) with carbon tetrabromide (36.96 g, 0.110 mole) in 500 ml anhydrous ethyl ether at 20°. The mixture was stirred for 1 hour at 20° during which time it became slightly yellow. The solution was filtered, the solvent was removed *in vacuo* and the residue was dissolved in 1 ℓ of *n*-pentane. The solution was filtered and the *n*-pentane was removed *in vacuo*. The residue was recrystallized from 150 ml of 95% ethanol giving 15.40 g of the product. Cooling the mother liquor to −4° resulted in an additional 1.80 g of **3d** crystallizing from solution for a total yield of 74% (see Table 1 for spectral data and microanalysis).

2-*n*-Dodecylthio-4-hydroxymethyl-1,3,4-thiadiazole-5-thione (**4**).

The dodecyl adduct **2c** (0.8 g, 2.5 mmoles) was added to a stirred solution of acetic acid (4.4 ml), water (2.8 ml) and ethanol (10 ml) and the mixture heated until the solution became transparent (about 50°). The mixture was cooled to 30° and 37% formaldehyde (0.8 ml) was added dropwise with stirring. The reaction mixture was stirred for 12 hours at room temperature, cooled and the precipitate filtered to give **4** as needles in 93% yield (0.81 g, mp 63-65°). Attempted recrystallization of this product resulted only in decomposition of the compound. The crude material was washed twice with *n*-pentane and dried overnight in a desiccator to give material of suitable purity for the ensuing steps; ^1H nmr data (deuteriochloroform): δ 5.72 (d, 2 H, J = 8 Hz), 4.42 (t, 1 H, J = 8 Hz) 3.15 (t, 2 H, J = 7 Hz), 2.00-1.07 (m, 20 H), 0.88 (t, 3 H, J = 5 Hz); ^{13}C nmr data (deuteriochloroform): δ 187.0, 156.9, 73.9, 33.6, 31.8, 29.5, 29.3, 28.9, 28.6, 22.6, 14.0.

Anal. Calcd. for $C_{15}H_{28}N_2S_3O$: C, 51.69; H, 8.10; N, 8.04. Found: C, 51.72; H, 8.14; N, 8.03.

2-*n*-Dodecylthio-4-chloromethyl-1,3,4-thiadiazole-5-thione (**5**).

Chlorination of **4** (4.0 g) was effected by heating under reflux with 15 ml of thionyl chloride for 10-15 minutes. The thionyl chloride was removed *in vacuo* and the last traces were removed by heating with 1 ml of ethanol for 5 minutes. The residue was diluted with 50 ml of water, extracted with methylene dichloride (2 x 50 ml) and the organic phase separated and dried over magnesium sulfate. The drying agent was removed by filtration, the solvent removed under reduced pressure and the residue crystallized from ethanol/hexane to give 3.33 g (79%) of **5** as needles, mp 42-43°; ^1H nmr data (deuteriochloroform): δ 5.98 (s, 2 H), 3.20 (t, 2 H, J = 6 Hz), 2.00-1.07 (m, 20 H), 0.90 (t, 3 H, J = 4 Hz). ^{13}C nmr data (deuteriochloroform): δ 187.2, 156.8, 55.3, 33.3, 31.7,

29.4, 29.2, 28.8, 28.7, 28.4, 22.5, 14.0.

Anal. Calcd. for $C_{15}H_{27}N_2S_3Cl$: C, 49.09; H, 7.41; N, 7.63. Found: C, 48.69; H, 7.71; N, 7.36.

2-*n*-Dodecylthio-4-phenylthiomethyl-1,3,4-thiadiazole-5-thione (**6**) [17].

A round bottom flask fitted with a condensor and magnetic stirrer was purged with argon, and a solution of thiophenol (0.57 g, 5.1 mmoles) in 5 ml of dry methanol was added. The solution was cooled to 0° and 0.13 g (5.7 mmoles) of sodium was added in small pieces. On complete dissolution of the metal 1.80 g (5 mmoles) of **5** was added in 10 ml of tetrahydrofuran over 10 minutes. The solution was allowed to warm to room temperature and was stirred for 18 hours. The solvent was removed *in vacuo* and the residue dissolved in 20 ml of water and extracted with ethyl acetate (3 x 30 ml). The organic phase was dried, the drying agent removed by filtration and the solvent removed. The crude product could be purified by column chromatography on silica gel using benzene as the eluent to give 2.01 g (91%) of **6** as white prisms: mp 26-28°; ^{1}H nmr data (deuteriochloroform): δ 7.84-7.71 (m, 5 H), 5.63 (s, 2 H), 2.97 (t, 2 H, J = 7 Hz), 2.00-1.07 (m, 20 H), 0.90 (t, 3 H, J = 4 Hz). ^{13}C nmr data (deuteriochloroform): δ 184.8, 155.5, 132.9, 131.9, 128.7, 127.5, 54.1, 33.0, 31.6, 29.3, 29.1, 29.0, 28.7, 28.5, 28.3, 22.4, 13.8.

Anal. Calcd. for $C_{21}H_{32}N_2S_4$: C, 57.23; H, 7.32; N, 6.36. Found: C, 57.32; H, 7.35; N, 6.30.

N,N-Dimethyl-*N*-*n*-octyl-*N*-(2-dodecylthio-1,3,4-thiadiazole-5-thioethyl)ammonium Bromide (**7**).

Use of (β-chloroethyl)dimethylamine hydrochloride in the general procedure gave crude 2-*n*-dodecylthio-5-(β-dimethylaminoethyl)-1,3,4-thiadiazole (1.95 g, 5 mmoles) which with *n*-octyl bromide (0.98 g, 5 mmoles) was refluxed with stirring in 1-propanol (10 ml) for 8 hours. The solvent was removed under reduced pressure. Absolute ethanol was added to the residue to form an azeotropic mixture with a trace of water present and removal of solvents was continued until a solid stock formed. The solid was washed with dry ether twice and dried *in vacuo* to give 2.77 g of **7** as white microcrystals; mp 96-98°; ^{1}H nmr data (deuteriochloroform): δ 4.66-2.66 (m, 14 H), 2.56-0.462 (m, 38 H); ^{13}C nmr data (deuteriochloroform): δ 166.2, 162.8, 64.7, 61.6, 51.2, 43.0, 34.3, 31.5, 31.3, 29.2, 28.9, 28.8, 28.7, 28.3, 25.9, 22.2, 13.7.

Anal. Calcd. for $C_{26}H_{52}BrN_3S_3 \cdot 0.25\ H_2O$: C, 53.17; H, 9.01; N, 7.15. Found: C, 52.83; H, 8.97; N, 7.35.

REFERENCES AND NOTES

[1] S. M. Losanich, *J. Chem. Soc.*, **121**, 2542 (1922).

[2] G. D. Thorn and R. A. Ludwig, *Can. J. Bot.*, **36**, 389 (1958).

[3] M. Pianka, *J. Sci. Fd. Agric.*, **19**, 502 (1968).

[4] L. L. Bambas, "The Chemistry of Heterocyclic Compounds", Vol **4**, Interscience, New York, 1952, pp 177-199.

[5] E. K. Fields, *Ind. Eng. Chem.*, **49**, 1361 (1957).

[6] F. Bottino, S. Caccamese and S. Pappalardo, *Org. Mass Spectrom.*, **17**, 335 (1982).

[7] H. S. Broadbent, R. C. Anderson and M. C. J. Kuchar, *J. Heterocyclic Chem.*, **14**, 289 (1977).

[8] P. Umapathy and A. P. Budhkar, *Synth. React. Inorg. Met.-Org. Chem.*, **16**, 1289 (1986).

[9] S. Pappalardo, F. Bottino and C. Tringali, *J. Org. Chem.*, **52**, 3409 (1987).

[10] F. Bottino and S. Pappalardo, *Org. Magn. Reson.*, **16**, 1 (1981).

[11] F. Bottino and S. Pappalardo, *Tetrahedron*, **38**, 665 (1982).

[12] M. M. Sidky, M. R. Mahran, M. F. Zayed, W. M. Abdou and T. S. Hafez, *Org. Prep. Proced. Int.*, **14**, 225 (1982).

[13] S. Pappalardo, F. Bottino and C. Tringali, *Heterocycles*, **22**, 1339 (1984).

[14] S. Pappalardo, F. Bottino and C. Tringali, *J. Org. Chem.*, **52**, 405 (1987).

[15] U. Anthoni, B. M. Dahl, H. Eggert, C. Larsen and P. H. Nielsen, *Acta. Chem. Scand. B*, **30**, 71 (1976).

[16] R. Kada, V. Knoppova and J. Kovac, *Collect. Czech. Chem. Commun.*, **43**, 160 (1978).

[17] A. R. Katritzky, S. Rachwal, K. C. Caster, F. Mahni, K. W. Law and O. Rubio, *J. Chem. Soc., Perkin Trans. I*, 781 (1987).

[18] A.-G. AGFA, British Patent 940,169 (cl. c o3c), 1963; *Chem. Abstr.*, **60**, 2951a (1964).

[19] H. Krzikalla and H. Pohlemann, U. S. Patent 2,736,729, 1956; *Chem. Abstr.*, **51**, P489e (1957).