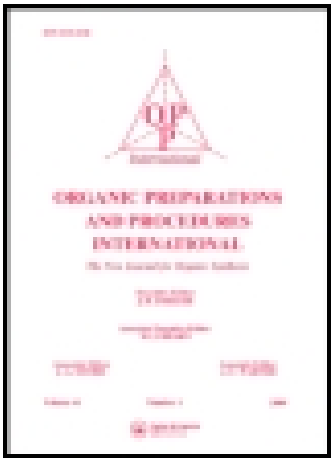

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FACILE ONE-STEP SYNTHESIS OF DITHIAALKANEDIOLS

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(12/13/04)

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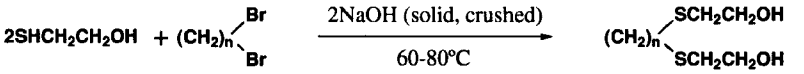
Dithiaalkanediols are important intermediates for the synthesis and degradation of the chemical warfare agents (CWA), such as sesquimustard (Q)[1,2] and sulfur mustard (HD).[2,3] the strong organic sulfur vesicants. They also serve as potential biomarkers as well as suitable models for verifying the use of sulfur vesicants either in war or by any terrorist group. Dithiaalkanediols are also potentially versatile intermediates for the synthesis of diesters of fatty acids, which act as heat stabilizers for polymers.[4] They also find application as emulsifying agents[5] in photographic silver halide systems,[6] cross linking agents for polymers and polyurethane,[4,7] in cosmetic compositions,[8] and in lubricant additives.[9] Because of their potential synthetic utility and our interest in their properties and characterization and in the development of new detection methods, we decided to reinvestigate their synthesis. Among the reported methods,[1,10,11] the following deserve mention as convenient laboratory routes. The first method is through the interaction of ethylene dibromide and monothioglycol in alcoholic sodium ethoxide or by the reaction of ethylene chlorohydrin on the sodium salt of ethylene dithioglycol. The second route involves the addition of dichloroalkanes to a solution prepared from aqueous sodium hydroxide and mercaptoethanol. However, the reported methods invariably result in the contamination of products with starting materials, and the use of sodium metal requires stringent precautions in its handling. Moreover, these routes often involve tedious work-up giving poor yields with low purity. They also require refluxing for hours, and the extreme volatility of materials necessitates distillation under low vacuum. Furthermore, not much information is available in the literature on the synthesis and characterization (spectroscopic data) of dithiaalkanediols.



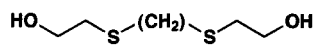
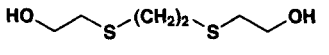
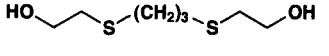
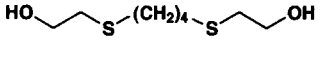
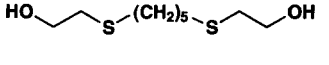
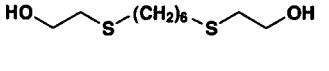
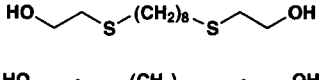
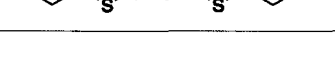
n = 1-6, 8, 10

Scheme 1

Owning to the scanty literature, we were interested in a procedure, which could allow us to easily prepare the dithiaalkanediols and to characterize them. Herein we describe a more convenient method for the synthesis of these compounds with high purity of the products and reduced reaction time from several hours to 1-2 hours and quantitative yields. The formation of

dithiaalkanediols is thought to proceed *via* the formation of the thiolate salt followed by reaction with the dibromoalkane.

Table 1. Preparation and Properties of Dithiaalkanediols

Entry	Dithiaalkanediol	mp/bp (°C/mmHg)	Time (hrs)	Yield (%)
1		115/0.5	1	80
2		64	1	80
3		200/4	1	82
4		207/3	1	84
5		210/3	1.5	90
6		45	2	95
7		61	2	96
8		70	2	98

To the best of our knowledge, little information is available on the synthesis and characterization of dithiaalkanediols. Dithiaalkanediols have now been prepared by the condensation of mercaptoethanol with dibromoalkanes $Br(CH_2)_nBr$ in the presence of solid crushed sodium hydroxide. The reaction was exothermic, and due care was taken during the addition of the dibromoalkanes. Many factors, such as changes in the structure of the dibromoalkanes, the temperature of the reaction mixture, and the solvent profoundly influence the course of the reaction. For example, the reactivity of the dibromoalkanes decreases in the order of $BrCH_2Br$ > $Br(CH_2)_2Br$ > $Br(CH_2)_3Br$ > $Br(CH_2)_4Br$ > $Br(CH_2)_5Br$ > $Br(CH_2)_6Br$ > $Br(CH_2)_8Br$ > $Br(CH_2)_{10}Br$. It was evident that the more hydrophobic the dibromoalkane, the slower the reaction. The temperature of the reaction also shows some trends. While the less hydrophobic dibromoalkanes [$Br(CH_2)_nBr$, n = 1-5] reacted more rapidly with a rise in temperature (highly exothermic reaction), the more hydrophobic dibromoalkanes $Br((CH_2)_nBr$, n = 6,8,10) reacted slowly; the latter reaction had to be heated to 60-70°C for 30 min for completion. Similarly, the effect of solubility of materials in dichloromethane had a profound effect on the recovery of the product. The yields were higher where n = 6,8,10 (*Table 1, Entries 6-8*) in comparison to those compounds where n = 1-5 (*Table 1, Entries 1-5*). This is essentially because of the relatively high solubility of higher homologues in dichloromethane in comparison to that of lower homologues of the dithiaalkanediols.

In conclusion a simple, mild, and efficient method has been developed for the synthesis of dithiaalkanediols. The operational simplicity, rapid reaction rate, and formation of pure products in high yields at moderate temperatures make this one-pot method superior to many existing protocols.

EXPERIMENTAL SECTION

Melting points were determined on a hot stage microscope and are uncorrected. Proton NMR spectra were recorded in $CDCl_3$ on Bruker 400 MHz instrument with TMS as an internal standard. IR spectra were obtained on a Perkin Elmer 577 Spectrophotometer using TMS as an internal standard. Elemental analyses were performed on a Carlo Erba elemental analyser Model 1106. The HPLC instrument-ation consists of a Waters 600E pump, a Rheodyne injector with 5 µl loop, and Waters 486 tunable UV detector. Waters Symmetry C18 (4.6x 150 mm, 5 µm) column was used for analysis. The detector was tuned at 200 nm. HPLC grade methanol was procured from S. D. Fine Chemicals, Mumbai, India. Water was triply distilled from an all glass distillation apparatus. The aqueous methanol mobile phases were prepared by filtering the solvents through 0.45 µ membrane filters. Dithiaalkanediols were prepared by the general method described below. (***Note***: *This procedure should be carried out in an efficient hood*).

General Procedure.- Mercaptoethanol (0.1 mmol, 7.8 g) and crushed solid sodium hydroxide (0.1 mmol, 4.0 g) were taken in a 100 mL, two-necked, round-bottomed flask equipped with a condenser and a guard tube. The flask was cooled to 0°C in an ice bath, and the dibromoalkane (0.05 mmol) was then added dropwise *via* a addition funnel at such a rate that the temperature of the reaction mixture did not exceed to 60°C. The mixture was brought to room temperature and then stirred at 60-80°C for 1-2 h. The progress of reaction was monitored by thin layer chromatography (TLC) (silica plates, 10% acetone in toluene). The resulting solid was extracted with dichloromethane and filtered. After removal of solvent from the filtrate *in vacuo*, the residue was washed with and recrystallized from petroleum ether to afford the dithiaalkanediols in 80-98% yields. The purity of compounds was verified by TLC (silica plates, 10% acetone in toluene) and high performance liquid chromatography (HPLC).[12] All the dithiaalkanediols were characterized by spectroscopic techniques and the details are given below.

***bis*(2-Hydroxyethylthio)methane (1)**, colorless oily viscous liquid, bp.115°C (0.5 mm); IR (neat): 3365, 2918, 2875, 1465, 1063, 647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.7 (t, 4H), 3.6 (s, 2H,), 2.8 (t, 4H), 2.2 (bs, 2H); MS (EI) m/z: 168 (M^+), 151, 124, 105, 91, 61.

Anal. Calcd for $C_5H_{12}O_2S_2$: C, 35.71; H, 7.14. Found: C, 35.76; H, 7.17

1,2- *bis*(2-Hydroxyethylthio)ethane (2), colorless solid, mp. 64°C. IR (KBr): 3284, 2958, 2931, 1477, 1050, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.7 (t, 4H), 2.7 (m, 8H), 2.2 (bs, 2H); MS (EI) m/z: 182 (M^+), 164, 138, 105, 91, 61.

Anal. Calcd for $C_6H_{14}O_2S_2$: C, 39.56; H, 7.69. Found: C, 39.60; H, 7.71

1,3- *bis*(2-Hydroxyethylthio)propane (3), pale yellow viscous liquid, bp. 200°C (4 mm), IR (KBr): 3367, 2921, 2872, 1418, 1046, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.7 (t, 4H), 2.7

(t, 4H), 2.6 (t, 4H), 2.1 (bs, 2H), 1.7 (m,2H); MS (EI) m/z: 196 (M^+), 178, 151, 119, 107, 61.

Anal. Calcd for $C_7H_{16}O_2S_2$: C, 42.85; H, 8.16. Found: C, 42.90; H 8.21

1,4- *bis*(2-Hydroxyethylthio)butane (4), pale yellow viscous liquid, bp. 207°C (3 mm). IR (KBr): 3368, 2923, 2869, 1422, 1045, 722, 655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.6 (t, 4H), 2.6 (t, 4H), 2.4 (m, 4H), 1.9 (bs, 2H), 1.6 (m, 4H); MS (EI) m/z 210 (M^+): 192, 165, 133, 115, 87, 61.

Anal. Calcd for $C_8H_{18}O_2S_2$: C, 45.71; H, 8.57. Found: C, 45.73; H, 8.60

1,5- *bis*(2-Hydroxyethylthio)pentane (5), pale yellow viscous liquid, bp. 210°C (3 mm). IR (KBr): 3361, 2926, 2856, 1458, 1045, 725, 655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.6 (t, 4H), 2.6 (t, 4H) 2.4 (t, 4H), 2.2 (bs, 2H), 1.5 (m, 4H), 1.4 (m, 2H); MS (EI) m/z: 224 (M^+), 207, 179, 147, 129, 101, 61.

Anal. Calcd for $C_9H_{20}O_2S_2$: C, 48.21; H, 8.92. Found: C, 48.25; H 8.96

1,6- *bis*(2-Hydroxyethylthio)hexane (6), white solid, mp 45°C. IR (KBr): 3337, 2923, 2853, 1461, 1047, 773, 726 cm^{-1}; ^1H NMR (400 MHz,$CDCl_3$): δ 3.6 (t, 4H), 2.6 (t, 4H), 2.4 (t, 4H) 2.3 (bs, 2H), 1.5 (m, 4H), 1.3 (m, 4H); MS (EI) m/z: 238 (M^+), 220, 161, 143, 115, 91, 87, 82, 67, 61, 55.

Anal. Calcd. for $C_{10}H_{22}O_2S_2$: C, 50.42; H, 9.24. Found: C, 50.45; H, 9.28

1,8- *bis*(2-Hydroxyethylthio)octane (7), white solid, mp 61°C. IR (KBr): 3340, 2921, 2851, 1461, 1048, 723, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.6 (t, 4H), 2.6 (t, 4H), 2.4 (t, 4H), 2.1 (bs, 2H), 1.5 (m, 4H), 1.3 (m, 4H), 1.2 (m, 4H); MS (EI) m/z: 248 ($M^+ - H_2O$), 189, 171, 143, 115, 101, 87, 61, 55.

Anal. Calcd for $C_{12}H_{26}O_2S_2$: C, 54.13; H, 9.77. Found: C, 54.18; H, 9.80

1,10- *bis*(2-Hydroxyethylthio)decane (8), white solid, mp. 70°C. IR (KBr): 3339, 2920, 2850, 1461, 723, 618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.6 (t, 4H), 2.6 (t, 4H), 2.4 (t, 4H), 1.9 (bs, 2H), 1.5 (m, 4H), 1.2 (m, 12H); MS (EI) m/z: 276 ($M^+ - H_2O$), 233, 199, 171, 136, 115, 101, 87, 61, 55;

Anal. Calcd for $C_{14}H_{30}O_2S_2$: C, 57.14; H, 10.20. Found: C, 57.18; H, 10.24

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REFERENCES

1. E. J. Glasson, H. C. McCombie, A. H. Williams and F. N. Woodward, *J. Chem. Soc.*, 44 (**1948**).

2. P. A. D. Agostino and L. R. Provost, *J. Chromatogr.*, **645,** 283 (1993).

3. C.D. Raghuveeran, R. C. Malhotra and R. S. Dangi, *J. Liquid Chromatogr.*, **16**, 1615 (1993).

4. F. W. Kuepper, H. W. Voges and W. Paetzold, R. Schaaf, Ger. DE 3,639,339; *Chem. Abstr.*, **109**, 150718y (1988).

5. Kodak, *Soc. Anon Belg.* 595,533 (**1960**); [*Chem. Abstr.*, **55**, 14140i (1961)].

6. J. Calcines, H. M. Dolan, K. R. Falkensterns, C. D. Kellys, E. P. Murphys, R. L. Klinger, B. E. Kahn, A. G. Difrancesco and R. K. Hailstone, *J. Imaging Science & Technology*, **46**, 101 (2002).

7. K. Abe and T. Sakurai, *Japan Kokai* 77 59 782 (**1977**); *Chem. Abstr.*, **87**, 137245z (1977).

8. C. Bouillon and J. Maignan, *Chem. Abstr.*, **94,** 46780y (1981),

9. C. A. Audeh, *US Patent Ger. Offen.,* 3,002,878, 4,759,873 (**1988**); *Chem. Abstr.*, **109**, 131946e (1988).

10. (a) R. Rosen and E. E. Reid, *J. Am. Chem. Soc.*, **44**, 634 (1922); (b) G. M. Bennett and E. M. Whincop. *J. Chem. Soc.*, **120**, 422 (1921).

11. J. E. Shaw, *US Patent*, 5,162,585 (**1992**); *Chem. Abstr.,* **118**, 41198u (1993).

12. B. N. Acharya, H. Rana, J. Acharya and M. P. Kaushik , *J. Liquid Chrom. and Rel. Technol.,* **27**, 2945 (2004).

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A NOVEL AND CONVENIENT METHOD FOR THE SYNTHESIS OF PHENSTATIN

Submitted by (02/28/05) Maojiang Wu, Qinggang Ji, Chunhao Yang* and Yuyuan Xie

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Phenstatin (**4**), a combretastatin A-4 (CA-4) derivative designed from the CA-4 skeleton by replacement of the olefin group with a carbonyl group, was found to be a potent anti-tubulin agent by the Pettit's group and displays excellent anticancer and antimitotic activities comparable to those of CA-4.[1] It is used as standard for antitublin test and is now under preclinical studies[2-9] with the potential to be developed as a drug.[10,11] Pettit's group reported the synthesis of phenstatin starting from 3-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzaldehyde by