

## Action of Nucleophiles on Tetramethylthiuram Monosulphide

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The displacement of dimethyldithiocarbamate from tetramethylthiuram monosulphide by the action of various nucleophiles is reported. These observations substantiate the suggestion that an essential thiol group of aldehyde dehydrogenase reacts with tetramethylthiuram monosulphide in like manner.

THE disulphiram-ethanol reaction<sup>1</sup> refers to the unpleasant symptoms experienced upon drinking alcohol after having previously ingested disulphiram, a drug used in the treatment of alcoholism. The syndrome is primarily caused by inactivation of aldehyde dehydrogenase<sup>2</sup> and accumulation of toxic levels of acetaldehyde.<sup>3</sup> This effect is not limited to disulphiram (tetraethylthiuram disulphide); among other compounds which have a disulphiram-like effect is tetramethylthiuram monosulphide (1).<sup>4</sup> Recently the action of this compound *in vitro* on sheep liver cytoplasmic aldehyde

dehydrogenase was studied,<sup>5</sup> and it was suggested that a covalent interaction between tetramethylthiuram monosulphide and an essential thiolate group on the enzyme occurs according to Scheme 1. However there appears to be little indication in the literature of compound (1) reacting in this way. (The reaction between thiuram disulphides and nucleophiles is well known.<sup>2,6</sup>)

It is now reported that tetramethylthiuram monosulphide does indeed react, in good yield, with a variety of nucleophiles (including thiolate ions) according to the general Scheme 2. The explanation for the effect of

<sup>1</sup> T. M. Kitson, *J. Stud. Alc.*, 1977, in the press.

<sup>2</sup> T. M. Kitson, *Biochem. J.*, 1975, **151**, 407.

<sup>3</sup> E. B. Truitt and M. J. Walsh in 'The Biology of Alcoholism,' eds. B. Kissin and H. Begleiter, Plenum Press, New York and London, 1971, vol. 1, pp. 161—195.

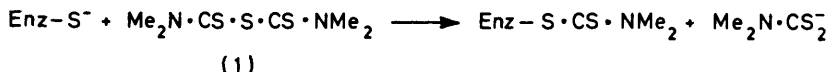
<sup>4</sup> B. A. Barnes and L. E. Fox, *J. Amer. Pharm. Assoc.*, 1955, **44**, 756—759.

<sup>5</sup> T. M. Kitson, *Biochem. J.*, 1976, **155**, 445—448.

<sup>6</sup> J. R. Grunwell, *J. Org. Chem.*, 1970, **35**, 1500—1501.

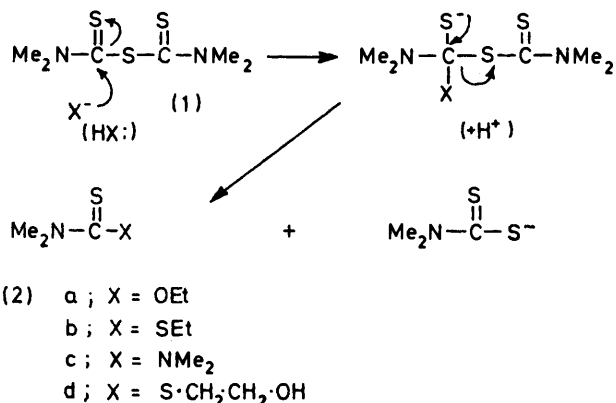
compound (1) on aldehyde dehydrogenase<sup>5</sup> is therefore placed on a sounder footing.

From the reaction between compound (1) and the sodium salt of 2-mercaptoethanol a minor product,

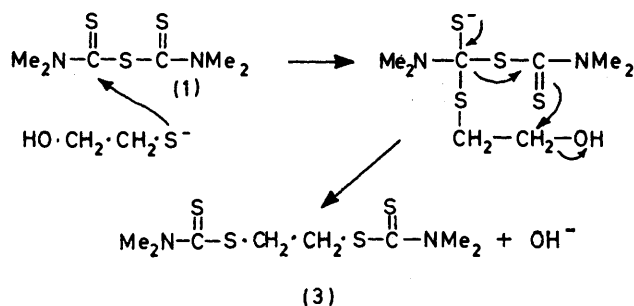


SCHEME 1

obtained in addition to the expected one (2d), was ethylene bis(dimethyldithiocarbamate) (3). How this compound arises is unclear; displacement of hydroxide from compound (2d) by dimethyldithiocarbamate is unlikely, unless perhaps it occurs by a concerted process as suggested in Scheme 3.



SCHEME 2



SCHEME 3

#### EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Mass spectra were determined with an A.E.I. MS9 spectrometer, and <sup>13</sup>C n.m.r. spectra with a JEOL FX 60 spectrometer.

*O-Ethyl Dimethylthiocarbamate* (2a).—Compound (1) (2.08 g, 0.01 mol) was stirred overnight at room temperature in ethanol (75 ml) to which sodium (0.35 g, 0.015 mol) had been added. Water and chloroform were added to the mixture. The chloroform layer was separated, dried (MgSO<sub>4</sub>), and evaporated under reduced pressure to yield the product (2a) as a pale yellow, fuming liquid (1.26 g, 96%), *n*<sub>D</sub><sup>16</sup> 1.521 2 (lit.,<sup>7</sup> *n*<sub>D</sub><sup>14</sup> 1.511 93) (Found: C, 46.2; H, 8.15; N, 10.5; S, 24.2. Calc. for C<sub>5</sub>H<sub>11</sub>NOS: C, 45.1;

H, 8.35; N, 10.5; S, 24.1%); *m/e* 133 (*M*<sup>+</sup>), 105, 88, and 72 (base).

*S-Ethyl Dimethyldithiocarbamate* (2b).—Compound (1) (2.08 g, 0.01 mol) was stirred overnight at room temperature

in ethanol (75 ml) containing ethanethiol (0.62 g, 0.01 mol) and sodium hydroxide (0.4 g, 0.01 mol). Water and chloroform were added to the mixture. The chloroform layer was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure yielding the product (2b) as a pale yellow liquid (1.25 g, 83%), *n*<sub>D</sub><sup>18</sup> 1.593 5 (lit.,<sup>7</sup> *n*<sub>D</sub><sup>18</sup> 1.595 88) (Found: C, 40.0; H, 7.55; N, 9.0; S, 42.4. Calc. for C<sub>5</sub>H<sub>11</sub>NS<sub>2</sub>: C, 40.2; H, 7.45; N, 9.4; S, 42.9%); *m/e* 149 (*M*<sup>+</sup>), 121, and 88 (base).

*Tetramethylthiourea* (2c).—Compound (1) (2.08 g, 0.01 mol) was stirred overnight at room temperature in a mixture of ethanol (75 ml) and aqueous dimethylamine (30% w/v; 2 ml, 0.013 mol). Water and chloroform were added to the mixture. The chloroform layer was dried (MgSO<sub>4</sub>) and evaporated to dryness. The crude product crystallised from ethanol–water (1 : 4) as thin plates (0.82 g, 61%), m.p. 75–78° (lit.,<sup>8</sup> 78°) (Found: C, 45.2; H, 9.05; N, 20.1; S, 24.2. Calc. for C<sub>5</sub>H<sub>12</sub>N<sub>2</sub>S: C, 45.4; H, 9.15; N, 21.2; S, 24.3%); *m/e* 132 (*M*<sup>+</sup>) and 88 (base).

*S-(2-Hydroxyethyl) Dimethyldithiocarbamate* (2d).—Compound (1) (2.08 g, 0.01 mol) was stirred in ethanol (75 ml) to which was added a solution of 2-mercaptoethanol (0.78 g, 0.01 mol) and sodium hydroxide (0.4 g, 0.01 mol) in water (25 ml). The mixture was left overnight at room temperature and then water and chloroform were added. The chloroform layer was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure yielding an oily liquid which partially crystallised. A pale buff crystalline material (0.25 g) was obtained by recrystallisation from chloroform–ethanol (1 : 6); this had the same characteristics (m.p. and mass and n.m.r. spectra) as authentic ethylene bis(dimethyldithiocarbamate) (3) (see below). The mother liquor was evaporated under reduced pressure to give a pale brown viscous liquid (1.3 g), identified by its mass spectrum as being chiefly the expected product (2d); *m/e* 165 (*M*<sup>+</sup>), 121, and 88 (base). Further purification was not undertaken.

*Ethylene Bis(dimethyldithiocarbamate)* (3).—Sodium dimethyldithiocarbamate dihydrate (7.16 g, 0.04 mol) was dissolved in ethanol (75 ml) and 1,2-dibromoethane (3.76 g, 0.02 mol) was added. The mixture was left overnight at room temperature. Water and chloroform were added; the chloroform extract was dried (MgSO<sub>4</sub>) and evaporated to dryness. The crude product (3) was recrystallised from chloroform–ethanol (1 : 6); yield 1.79 g (32%), m.p. 187–190° (lit.,<sup>9</sup> 189°), *m/e* 268 (*M*<sup>+</sup>), 180, 148, 120, and 88 (base), <sup>13</sup>C δ (CDCl<sub>3</sub>; 25 °C) –31.57 and –35.39 (4 Me), –40.91 (2 CH<sub>2</sub>), and 119.3 (C=S) p.p.m. downfield from CDCl<sub>3</sub>. (restricted rotation in similar compounds has been reported<sup>10</sup>).

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<sup>7</sup> M. Delépine, *Ann. Chim. Phys.*, 1912 [8] **25**, 529–574.

<sup>8</sup> P. A. S. Smith in 'Open-chain Nitrogen Compounds,' Benjamin, New York and Amsterdam, 1965, vol. 1, p. 267.

<sup>9</sup> A. W. Campbell and P. F. Tryon, *Ind. and Eng. Chem.*, 1953, **45**, 125–130.

<sup>10</sup> N. K. Wilson, *J. Phys. Chem.*, 1971, **75**, 1067–1072.