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RESEARCH ARTICLE

Novel propanethiolate—induced transformation of 2,3,5-trithiahexane into some trithiocarbonates

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2,3,5-Trithiahexane reacts with the mercaptide anion derived from 1-propanethiol to furnish, *inter alia*, a family of trithiocarbonates. Key reaction products are identified and their yields determined by GCMS. A complete mechanism is proposed for the unexpected formation of these novel products.

Keywords: Trithiocarbonates; Disulfides as oxidizing agents; Disproportionations

1. Introduction

For quite some time, we have been interested in the synthesis of unsymmetrical disulfides for biological testing against phagocytosis of red blood cells [1], malaria [2], leukemia [3, 4], blood clots [5, 6] and fungi [7–14]. Initially, we established that antifungal activity for molecules related to the biologically-active natural-product, dysoxysulfone **1**, was associated with the α-sulfone disulfide moiety [14].

$$CH_3SO_2CH_2SCH_2SSCH_2SO_2CH_3$$

1

Hence, a principal focus for previous work has been the construction and testing of α-sulfone disulfides.

More recently, we have begun to explore the synthesis and biological testing of another functionality in **1**, namely the α-sulfide disulfide moiety. For this purpose, we have developed and reported a new synthetic reagent: benzoyloxymethyl p-toluenethiosulfonate [15]. Work, described herein, was intended to provide α-sulfide disulfides **2**.

$$CH_3SCH_2SSR$$

2

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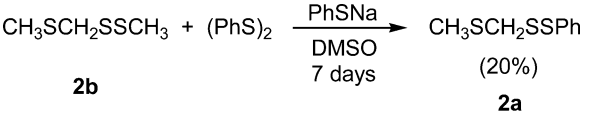
2. Results and discussion

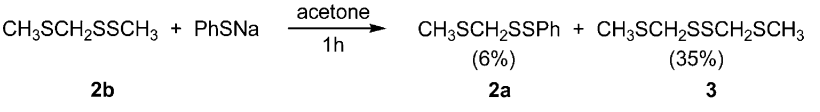
Preliminary exploration of disproportionation as a way to access **2a** (R = Ph) proved to be rather disappointing (see scheme 1).



SCHEME 1

Not only was the yield low, but column chromatography and distillation led to material of unsatisfactory purity.

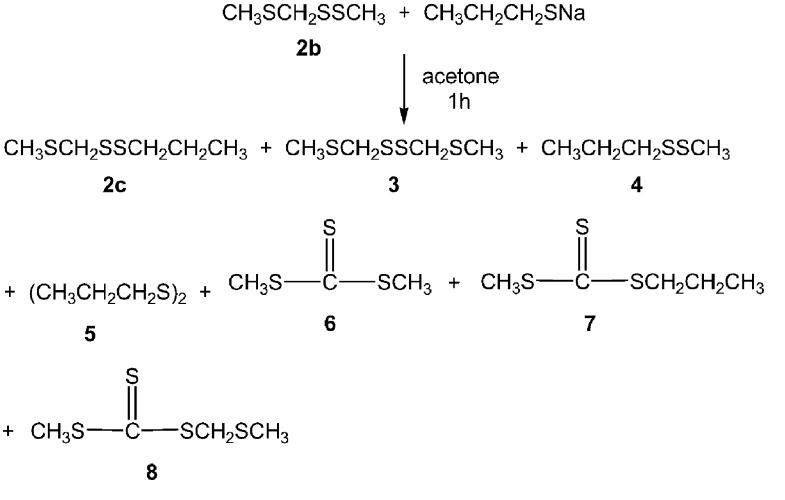
A subsequent effort used completely different conditions (see scheme 2).



SCHEME 2

The lower yield for **2a** depicted in scheme 2, was accompanied by significantly enhanced purity after column chromatography.

We then employed scheme 2 conditions in an attempt to convert **2b** into **2c** (R = $CH_2CH_2CH_3$). As with the scheme 2 reaction, substantial amounts of unchanged **2b** and **3** were isolated. However, in place of the target molecule **2c**, a complex mixture, that included volatile compounds, was obtained. Based on the interpretation of GCMS data, major components in the mixture (except **8**) were assigned the structures shown in scheme 3.

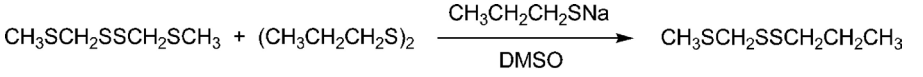


SCHEME 3

In support of the GCMS result, indicating that **6** was present in the mixture, a singlet at δ 2.74 was observed in the 270 MHz proton NMR of the mixture, which corresponds exactly to the chemical shift of the singlet in the 270 MHz NMR of authentic dimethyl trithiocarbonate (Aldrich Chemicals).

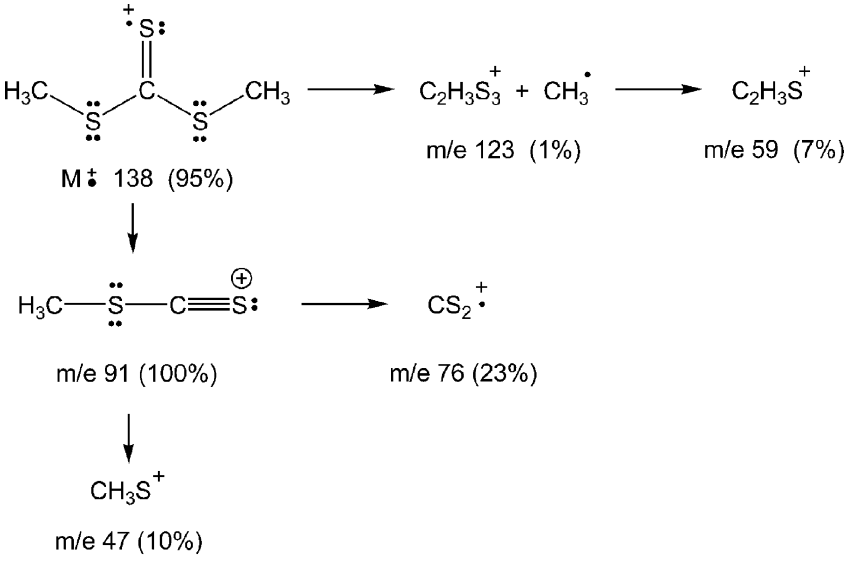
Given that some of the products in scheme 3 were unexpected and that significant amounts of the more volatile components may have been lost during workup, product yields were determined from a second run which was subjected to an abbreviated workup. GCMS analysis was selected as the method to establish yields. Accurate yield determinations with this method require authentic reference materials in order to establish response factors.

Several of the products in scheme 3 were already available to us. Two of those compounds which were not, were prepared for this study. Compound **3** was prepared by Dubs' procedure [16]. Authentic compound **2c** was prepared by disproportionation as depicted in scheme 4. In each case, authentic samples of compounds **2c** → **6** (scheme 3) were identical with reaction products by both their retention times and mass spectra.



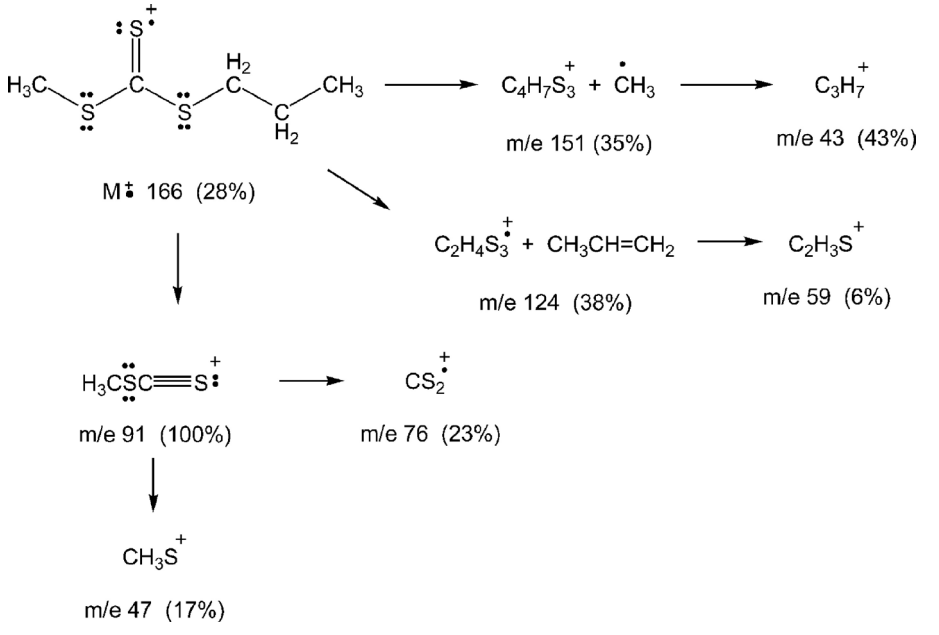
SCHEME 4

No authentic methyl n-propyl trithiocarbonate **7** was obtained, so that (i) its yield was estimated from GCMS results and (ii) its structural assignment rests entirely on the interpretation of its low-resolution mass spectrum. From the natural abundances of ^{32}S and ^{34}S, a molecule containing three sulfur atoms should show a ratio of $M^{+\cdot}/M^{+\cdot}+2$ of about 15:2. Both the molecular ions of the known dimethyl trithiocarbonate ($M^{+\cdot}/M^{+\cdot}+2$: observed ratio 14.1:2) and the molecular ion of the molecule in question, **7**, ($M^{+}/M^{+\cdot}$: observed ratio 14.9:2) conform nicely to this expectation. Major ions in the mass spectrum of authentic dimethyl trithiocarbonate **6** are rationalized in scheme 5.



SCHEME 5

The mass spectrum of compound **7** provides compelling evidence that **6** and **7** are closely related S_3-containing structures and is nicely rationalized with the structure for methyl n-propyl trithiocarbonate (see scheme 6).



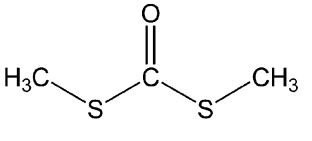
SCHEME 6

A similar analysis supports the structural assignment of compound **8**. The mass spectrum of **8** showed ions at $M^{+\cdot}$ 184 (27%), m/e 169 (16%, $M^{+\cdot} - CH_3$), m/e 137 (50%, $CH_3SC(S)SCH_2^+$), m/e 107(83%, $C_3H_7S_2^+$), m/e 91 (54%, $CH_3SCH_2S^+$), m/e 76 (22%, $CS_2^{+\cdot}$), m/e 61 (100%, $CH_3SCH_2^+$). Compound **8** was not observed in the mixture obtained (by column chromatography) from the first run, but was observed in the second run which was subjected to more careful scrutiny after an abbreviated workup.

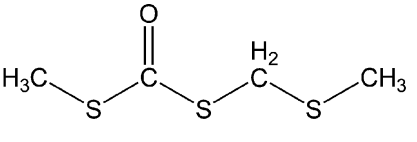
When the reaction, shown in scheme 3, was rerun and subjected to an abbreviated workup, GCMS analysis furnished the yields given in table 1.

The products in scheme 3 and table 1, can all be rationalized by disproportionation reactions, with the exception of the trithiocarbonates **6**, **7** and **8**. A proposed mechanism for the formation of these intriguing products is presented in scheme 7.

A number of components in the product mixture, including those which gave peaks at $R_t = 6.13$ min and $R_t = 8.55$ min, showed a major ion at m/e 75 rather than m/e 91 which is characteristic of methyl trithiocarbonates. Given that the reactions were carried out in acetone which almost certainly contained some moisture and that base-catalyzed hydrolysis of thiocarbonyl groups should not be difficult, we considered the possibility that the methyl dithiocarbonate structures **9** and **10** could be assigned to $R_t = 6.13$ min and $R_t = 8.55$ min, respectively.

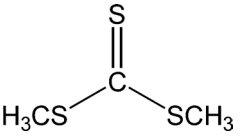
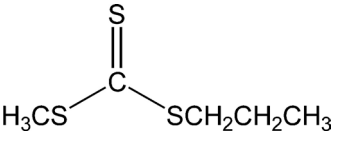
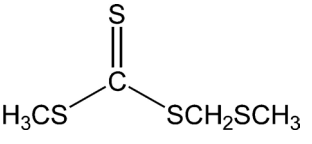


9

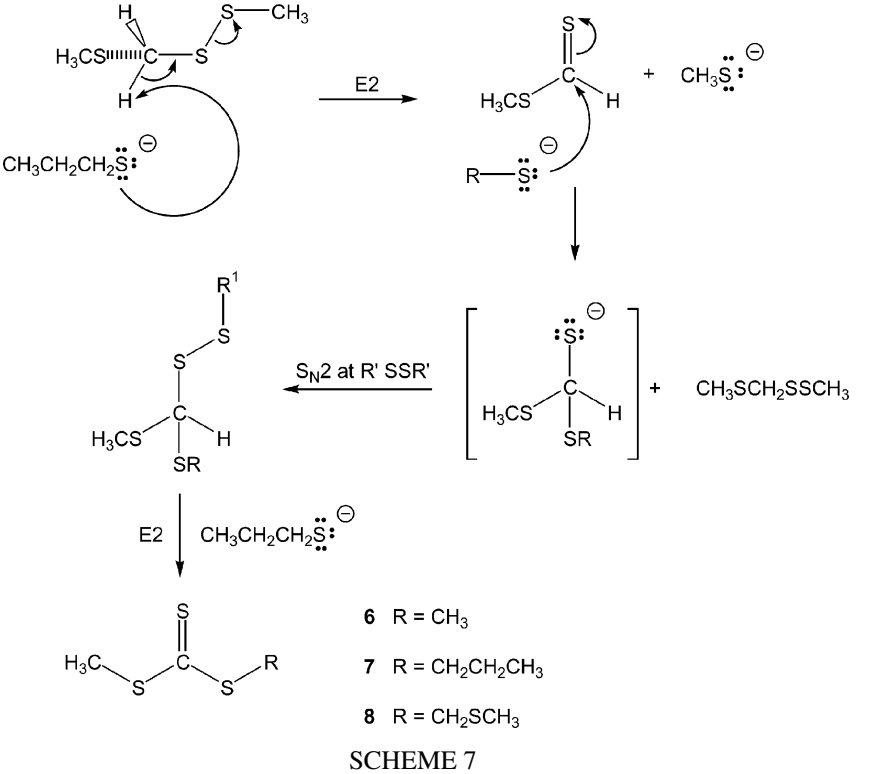


10

Table 1. Yields for scheme 3 determined by GCMS.

Compound		Yield (%)	Retention time (min)
$CH_3SCH_2SSCH_2CH_2CH_3$	**2c**	3.2	7.09
$CH_3SCH_2SSCH_2SCH_3$	**3**	19.4	8.45
$CH_3CH_2CH_2SSCH_3$	**4**	4.6	4.27
$(CH_3CH_2CH_2S)_2$	**5**	0.2	5.69
	**6**	18.7	6.23
	**7**	<2*	7.45
	**8**	<2*	8.79

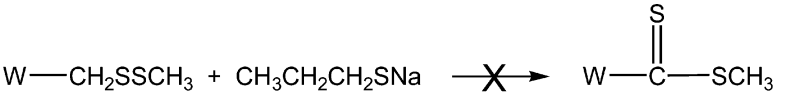
*Authentic material was not available so that response factor is unknown. Yield estimated.



SCHEME 7

While the mass spectrum of authentic **9** (Matrix Scientific) does indeed show an ion at m/e 75 (100%), it also features a major ion at m/e 94 ($M^{+\cdot} - CO$, 60%). This rearrangement ion is reminiscent of the ones arising from facile loss of CH_2O from the molecular ions of α-ester disulfides [17]. Neither of the mass spectra for $R_t = 6.13$ min or $R_t = 8.55$ min showed an ion for $M^{+\cdot} - 28$, which rules out **9** as a component and makes **10** an unlikely structure for $R_t = 8.55$ min. Furthermore, **9** had an R_t of 4.56 min which is entirely inconsistent with the assignment of that structure to the unknown which had $R_t = 6.13$ min.

In a fruitless attempt to construct novel α-carbonyl dithiocarboxylates, the α-ketodisulfide **11** and, separately, the α-ester disulfide **12** were reacted with n-propyl mercaptide anions in acetone (see scheme 8).



11 W = PhC(O)-

12 W = CH_3O_2C-

SCHEME 8

In summary, both direct and circumstantial evidence have been amassed establishing that n-propanethiolate anions catalyze oxidative transformation of an α-sulfide disulfide into several trithiocarbonates. A proposed mechanism is outlined in scheme 7.

3. Experimental

3.1 *General*

^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra were obtained on a JEOL JNM-GSX 270 Fourier-transform NMR system in deutertated chloroform solutions. Routine mass spectra were obtained on a Hewlett-Packard 5988A gas-liquid chromatography mass spectrometer (GLC/MS) system.

Yield determinations reported in table 1 were obtained on a Varian CP-3800 gas chromatograph equipped with a CP-8410 autoinjector, connected to a Saturn 2000 mass selective detector. Analytical details have been provided earlier [7].

3.2 *Preparation of 1-phenyl-1,2,4-trithiapentane 2a*

3.2.1 Disproportionation. Sodium metal (0.013 g, 0.57 mmol) was dissolved in methanol (5 mL) and thiophenol (0.064 g, 0.58 mmol) was added. The solvent was evaporated and the residue dried *in vacuo.* Residual sodium thiophenolate was dissolved in dimethyl sulfoxide (6 mL). 2,3,5-Trithiahexane **2b** (1.32 g, 9.4 mmol) and diphenyl disulfide (6.23 g, 28.5 mmol) were added and the reaction mixture stirred at ambient temperature for 7 days.

2.5% Hydrochloric acid (100 mL) was added and the resultant mixture extracted with diethyl ether (three 100 mL aliquots). The combined organic layers were evaporated. The residue was covered with 2.5% hydrochloric acid (100 mL) and the resultant mixture extracted with diethyl ether (three 100 mL aliquots). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated.

The residue was chromatographed on silica gel (700 g) employing petroleum ether (thirty one 250 mL fractions) and chloroform (250 mL fractions) for elution. Fractions 32–36 were combined and concentrated. The residue was rectified affording 1-phenyl-1,2,4-trithiapentane **2a** (0.38 g, 1.9 mmol, 20%). The foregoing bulb to bulb distillation employed a bath at 220°C and a pressure of 0.8 Torr. **2a** had ^{1}H NMR(270 MHz) δ 2.19 (s, 3H), 3.83 (s, 2H), 7.23 (m, 1H), 7.32 (t, 2H), 7.56 (d, 2H). Signals from impurities were evident in the aromatic region and adjacent to both upfield signals. ^{13}C NMR δ 15.6, 44.1, 127.2, 128.2, 129.1, 136.9. Signals from impurities were evident at δ 15.3, 45.3 and 127.5. GCMS (R_t = 9.14 min) $M^{+\cdot}$ 202 (28%), 109 (29%), 61 (100%). Six other peaks were observed in the GC trace, the major one (R_t = 10.21 min) was from diphenyl disulfide.

3.2.2 Substitution. Sodium metal (0.036 g, 1.56 mmol) was dissolved in methanol (2 mL) and thiophenol (0.172 g, 1.56 mmol) added. The solvent was evaporated and the mixture dried *in vacuo*. The sodium thiophenolate was dissolved in acetone (3 mL) and 2,3,5-trithiahexane **2b** (0.218 g, 1.56 mmol) added. The reaction mixture was stirred at ambient temperature for 1 h. Water (10 mL) was added and the resultant mixture extracted with chloroform (100 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. The residue was chromatographed on silica gel (100 g) employing petroleum ether (thirty one 100 mL fractions) and 9:1 petroleum ether/methylene chloride (100 mL fractions) for elution. Fractions 19–22 were combined and concentrated affording clean **2a** (0.02 g, 0.1 mmol, 6%). Fractions 38–40 were combined and concentrated affording **3** (0.051 g, 0.27 mmol, 35%) [16].

3.3 *Reaction of 2,3,5-trithiahexane 2b with sodium 1-propanethiolate*

3.3.1 Workup with column chromatography. Sodium metal (0.036 g, 1.56 mmol) was dissolved in methanol (2 mL) and 1-propanethiol (0.118 g, 1.56 mmol) was added. The solution was stirred for 10 min and the solvent evaporated. The residue was dried *in vacuo.*

The sodium propanethiolate was dissolved in acetone (20 mL) and the resultant solution added to 2,3,5-trithiahexane **2b** (0.218 g, 1.56 mmol) in acetone (5 mL). The reaction mixture was stirred at ambient temperature for 1 h. Water (10 mL) was added and the resultant mixture extracted with chloroform (100 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. The residue was chromatographed on silica gel (15 g) employing petroleum ether (two 15 mL fractions) and 1:1 petroleum ether/chloroform (15 mL) for elution. Fraction 1 was concentrated affording a mixture (0.030 g) whose components were assigned structures **4**, **5**, **6** and **2c** on the basis of retention times and mass spectra obtained with our Hewlett-Packard instrument. This data was compared with the corresponding information for authentic samples. Fraction 2 furnished unchanged 2,3,5-trithiahexane **2b** (0.031 g). Fraction 3 was concentrated and rechromatographed on silica gel (30 g) employing petroleum ether (thirty one 25 mL fractions) and 9:1 petroleum ether/methylene chloride (25 mL fractions). Fractions 37–43 were combined and concentrated giving 2,4,5,7-tetrathiaoctane **3** (0.03 g).

3.3.2 Analytical determination of yields. The reaction described in part A (above) was repeated. At the end of the one hour reaction time, water (10 mL) was added and the resultant mixture extracted with methylene chloride (100 mL). The organic layer was dried ($MgSO_4$) and filtered. The bulk of the solvent was distilled off at atmospheric pressure leaving a residue of *ca* 2 mL, which was submitted for analysis. Details of the procedure using the Varian/Saturn apparatus have been provided elsewhere [7]. Accurately determined and estimated yields for

compounds **2c** → **8** are given in table 1. Note that details for the mass spectra of **7** and **8** have been provided in scheme 6 and in the text associated with that scheme.

3.4 *Preparation of 2,4,5-trithiaoctane 2c*

Sodium metal (0.036 g) was dissolved in methanol (2 mL) and 1-propanethiol (0.2 mL) was added. The solvent was evaporated and the residue dried *in vacuo*. DMSO (20 mL) was added and the mixture stirred at ambient temperature for 10 min. A portion of the solution (2 mL) was added to a mixture of 2,4,5,7-tetrathiaoctane **3** (1.69 g, 9.08 mmol) in di-n-propyl disulfide (13 mL). The reaction mixture was stirred at ambient temperature for 8 days.

2.5% Hydrochloric acid (150 mL) was added and the resultant mixture extracted with diethyl ether (three 50 mL aliquots). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. Di-n-propyl disulfide was distilled off at 160 °C/18 Torr. The residue was chromatographed on silica gel (110 g) employing petroleum ether (100 mL fractions) for elution. Fractions 11–20 were concentrated and combined affording clean 2,4,5-trithiaoctane **2c** (0.20 g, 1.19 mmol, 13%) which had ^{1}H NMR (270 MHz) δ 0.98 (t, 3H), 1.69 (sex, 2H), 2.21 (s, 3H), 2.73 (t, 2H), 3.80 (s, 2H). ^{13}C NMR δ 13.1, 15.3, 22.6, 41.3, 44.9. GCMS (R_t = 5.55 min) $M^{+\cdot}$ 168 (17%), 61 (100%), 45 (6%).

Acknowledgements

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