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SYNTHESIS OF 4-METHYLTHIO-1,2-DITHIOLANE AND 5-METHYLTHIO-1,2,3-TRITHIANE. TWO NATURALLY OCCURRING BIOACTIVE COMPOUNDS

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Abstract—Syntheses of the title compounds are described. A method has been developed for the synthesis of 2-methylthio-1,3-propanedithiol, which on treatment with iodine or sulphurdichloride yields 4-methylthio-1,2-dithiolane and 5-methylthio-1,2,3-trithiane respectively.

Recently, naturally occurring 4 - methylthio - 1,2 - dithiolane **1** and 5 - methylthio - 1,2,3 - trithiane **2** have been found to exhibit pronounced photosynthesis inhibiting[1] effects. A number of other 1,2-dithiolanes and 1,2,3-trithianes have been reported to have bioactive properties, such as insecticidal (nereistoxin, 4 - dimethylamino - 1,2 - dithiolane **3**[2] and 5 - dimethylamino - 1,2,3 - trithiane **4**[3]), fungicidal,[4] and plant growth regulating effects (asparagusic acid, 4 - carboxy - 1,2 - dithiolane **5**[5]).

In the present paper we wish to report the synthesis of **1** and **2**, initially isolated from the green alga *Chara globularis*.[1]

Preliminary attempts at the monomethylation of 1,2,3-propanetrithiol **6** led to product mixtures in which the desired isomer 2 - methylthio - 1,3 - propanedithiol **7**, quite expectedly, was only a minor constituent. Likewise, attempts to reverse the selectivity of the 1- and 2-thiol groups towards methylation by reacting the trianion of **6** with methyl iodide were unsuccessful.

1: R = SMe
3: R = NMe_2
5: R = CO_2H

2: R = SMe
4: R = NMe_2

Reaction conditions	7	8	di- and trialkylated
$(MeO)_2SO_2$, NaOH 20%	17%	29%	30%
MeI, BuLi, THF	~0%	24%	33%

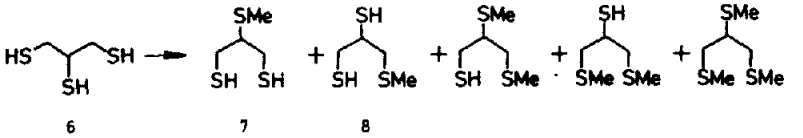
Consequently three different synthetic strategies were explored.

The first attempt was based on the possibility of masking the sulphur atoms in the 1- and 3-positions of **6** in order to allow methylation in the 2-position. Reaction of **6** with phosgene resulted in a 66% yield of 4 - mercaptomethyl - 1,3 - dithiolane - 2 - one and only trace amounts of the desired 5 - methylthio - 1,3 - dithiane - 2 - one. After several futile experiments along these lines[6] we turned our attention towards another strategy.

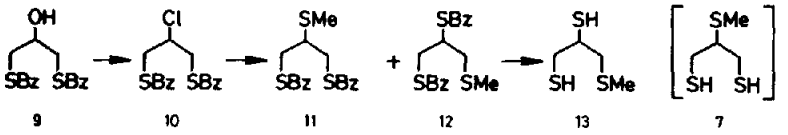
The second attempt centred around the possibility of introducing the 2-methylthio substituent in a framework where the 1- and 3-sulphur functionalities were already established.

Thus, treatment of 1,3 - bisbenzylthio - 2 - chloropropane[7] **10**, readily prepared from 1,3 - bisbenzylthio - 2 - propanol **9**, with methanethiolate gave a mixture, which after reduction with Na/NH_3 contained only trace amounts of **7** while the main product was **13**.

This finding is comparable to the one reported in the synthesis of nereistoxin **3**,[7] except that in our case the



6 7 8



9 10 11 12 13 7

presence of the stronger nucleophile MeS^- as compared to Me_2NH evidently favours the formation of the rearranged product to a degree that precludes the method to be synthetically useful for the desired isomer **7**. Further unsuccessful experiments[8] terminated our devotion to this strategy.

Thirdly, starting with the 2-methylthio group established, attempts to introduce the remaining sulphur functionalities failed. Treatment of 2 - methylthio - 1,3 - propanediol with CCl_4 and Ph_3P[9] yielded 2 - methylthio - 1,3 - dichloropropane. However, this product on attempted substitution of the chlorine atoms gave only the rearranged product **13**.

Finally, we reconsidered the possibility of monomethylating **6**, and found that methylation with methyliodide or dimethylsulphate in relatively non-polar solvents with an insoluble basic catalyst could be controlled to give a 40% yield of **7**. Column chromatography allowed the isolation of pure **7**.

Reaction conditions	7	8	di- and trialkylate
$(MeO)_2SO_2/K_2CO_3$/isopropyl acetate	40%	12%	38%
MeI/KOH on silica gel/CH_2Cl_2	20%	18%	18%

Having secured **7**, the syntheses of **1** and **2** were straightforward. Oxidation with iodine in ether afforded **1** in excellent yield. The thermal stability of **1** does not allow the compound to be handled in a pure state. However, solutions (10% in CH_2Cl_2) could be kept for several days without appreciable decomposition. By analogy with the reported synthesis of 1,2-dithiolane and 1,2,3-trithiane,[10] **7** on reaction with SCl_2 gave a mixture of **1** and **2** (~ 1:1). Column chromatography of the product mixture gave a fair yield (48%) of **2**, while most of **1** present decomposed under these conditions.

The synthetic samples of **1** and **2** proved to be identical with the naturally occurring ones (glc, MS, NMR).

EXPERIMENTAL

Methylation of 1,2,3-*propanetrithiol* **6**

(a) *Aqueous NaOH*: To a solution of **6** (1 mmol) in 20% aqueous NaOH (3 ml) at 0° was added dimethylsulphate (1 mmol). The reaction mixture was stirred at 0° for 1.5 hr. After dilution with water and addition of CH_2Cl_2 the mixture was acidified with dilute aqueous HCl. Extraction of the CH_2Cl_2 phase with 20% aqueous NaOH left the fully methylated derivative in the organic phase. The acidified aqueous phase, on extraction with CH_2Cl_2, yielded the product mixture given in the text (glc analysis).

(b) *BuLi*. A solution of BuLi in hexane (*ca.* 15%, *ca.* 5 ml) was added dropwise at −78° in a N_2-atmosphere to a solution of **6** (2.7 mmol) in tetrahydrofuran (THF, 15 ml), with a small amount of triphenylmethane as indicator, until the reaction mixture showed a red colour. The temperature was raised to 0° and a solution of methyl iodide (2.5 mmol) in THF (2 ml) was added. Stirring for 30 min. followed by heating to room temperature left, after washing with aqueous $NaHCO_3$ (sat.), a solution which according to glc analysis had the composition given in the text.

(c) K_2CO_3: A mixture of **6**, 9.8 g (70 mmol), dimethylsulphate 10.5 g (80 mmol), and finely ground potassium carbonate, 28 g in isopropylacetate (280 ml) was stirred for 2 h. After addition of methylene chloride and filtration, the organic phase was extracted with aqueous NaOH, 20% (400 ml). The aqueous phase was acidified with conc. hydrochloric acid and extracted with CH_2Cl_2, dried and evaporated to give an oil (9.6 g, composition (glc) given in the text). Repeated column chromatography (silica gel) with ether (3%) in hexane gave **7**. Kugelrohr distillation (100°, 0.1 mm Hg) gave pure **7**. (Found: C, 31.0; H, 6.53; S, 62.7%. Calc. for $C_4H_{10}S_3$: C, 31.1; H, 6.53; S, 62.3%. ^{13}C NMR: δ 14.0 ($\underline{C}H_3$), 27.6 ($\underline{C}H_2$), 52.9 ($\underline{C}H$) ppm in CD_2Cl_2).

Almost identical results were obtained using methyl iodide instead of dimethylsulphate.

4-Mercaptomethyl-1,3-dithiolane-2-one. In the course of 1 h, a solution of phosgene (9 mmol) in toluene (13 ml) was added dropwise to a solution of **6** (10 mmol) and triethylamine (20 mmol) in methylene chloride (50 ml) kept at −20 to −30°. The reaction mixture was allowed to reach room temperature (20°) over 1 h. After an additional 30 min. at room temperature conc. hydrochloric acid (5 ml) was added, the organic layer washed with water, dried and evaporated. The residue was subjected to silica gel chromatography with 25% methylene chloride in pentane as eluent, the resulting oil after Kugelrohr distillation (120°, 0.1 mm Hg) yielded 1.1 g (66%) 4 - mercaptomethyl - 1,3 - dithiolane - 2 - one.

Reaction between 1,3 - *bisbenzylthio* - 2 - *chlorpropane and methanethiolate.* A solution of sodium (1.8 g, 75 mmol) in ethanol (100 ml) was saturated with methylmercaptan under cooling. 1,3 - Bisbenzylthio - 2 - chloropropane[7] (24 g, 75 mmol) in abs. ethanol was added with stirring and the solution left overnight. Sodium chloride was filtered off and after evaporation of the ethanol the yellow oil was redissolved in benzene and washed with water. The crude material (M^+ 334. Found: C, 62.7; H, 6.4; S, 27.1%. Calc. for $C_{18}H_{22}S_3$: C, 64.5; H, 6.6; S, 28.7%) was used for the next step without purification.

The procedure for the sodium amide reduction described by Reed *et al.*[11] was followed to give 26% of **13** (^{13}C NMR: δ 16.2, 31.6, 41.0 and 42.2 ppm).

p-Toluenesulphonic acid 1,3 - *bisacetylthio* - 2 - *propylester.* 1,3 - Bisacetylthio - 2 - propanol was prepared from 1,3 - dimercapto - 2 - propanol (0.1 mol) dissolved in CH_2Cl_2 (100 ml) by dropwise addition of pyridine (17 g) while the mixture was cooled in ice. At *ca.* 0° a solution of acetyl chloride (0.2 mol) in CH_2Cl_2 (50 ml) was added dropwise during 175 min. The mixture was stirred for an additional hour at 0° followed by 1 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (250 ml) and washed with water, hydrochloric acid (2*N*) and water. After drying over Na_2SO_4 and evaporation the crude material (20.4 g) was used directly in the tosylation reaction.

A solution of crude product from above (0.07 mol), pyridine (160 ml), and *p*-toluenesulphonylchloride (0.11 mol) was stirred overnight. The reaction mixture was poured on hydrochloric acid (37%, 400 ml) plus ice (300 g) and stirred for 15 min. Extraction with ether (2 × 250 ml), washing of the organic layer with hydrochloric acid, water, and sst. $NaHCO_3$ solution gave a solution which after drying and evaporation left a semicrystalline product (33.7 g). Recrystallisation from methanol (50 ml) gave 12.4 g (31%), m.p. 65–67°. An analytical pure sample was prepared by recrystallisation from hexane: toluene (1:1) m.p. 67–68°. (Found: C, 46.3; H, 4.98; S, 26.8%. Calc. for $C_{14}H_{18}O_5S_3$: C, 46.3; H, 5.01; S, 26.5%).

Reaction of p-*toluenesulphonic acid* 1,3 - *bisacetylthio* - 2 - *propylester with methanethiolate ion.* A solution of methanethiolate was prepared by introducing gaseous methanethiol into a suspension of NaH (50 mmol) in dry DMF (50 ml). The excess methanethiol was removed in a stream of dry N_2. The above solution (15 ml, 15 mmol) was added dropwise into a solution of the tosylate, 40 g, (15 mmol) in DMF (30 ml) at 0°. The reaction mixture was stirred for 1 h at 0° and 1 h at room temperature. The reaction mixture was poured into water (250 ml) and extracted with ether: pentane (1:1, 2 × 100 ml). After washing with water and drying, the organic phase gave on evaporation an oil (2.6 g) which was subjected to Kugelrohr distillation (0.05 mm Hg, 100°) with two successive receivers, the first at room temperature and the second at −78°. The latter receiver contained methylthiolacetate (450 mg, 30%) as evidenced by comparison with an authentic sample, and the former receiver contained 2-(acetylthiomethyl)thiirane (450 mg, 21%) identical (GC/MS, NMR) to an authentic sample.[8]

To a solution of methanethiolate (0.1 mol) prepared from NaH in DMF (50 ml) was added, at room temperature, crude tosylate,

4.0 g (0.011 mol). After stirring for 90 min at room temperature, hydrochloric acid (4*N*, 250 ml) was added dropwise. Extraction with pentane (4*N*, 25 ml) followed by drying and evaporation of the pentane phase left an oil giving 1,3 - bismethylthio - 2 - propanethiol (800 mg, 41%) on Kugelrohr distillation.

Reaction of 1,3 - *dichloro* - 2 - *methylthiopropane with trithiocarbonate ion.* 2 - Methylthio - 1,3 - propanediol was prepared according to Ref. 12. Treatment of the latter product with Ph_3P in CCl_4[9] gave 1,3 - dichloro - 2 - methylthiopropane (45% yield), b.p. 49–50°/1 mm Hg homogeneous in glc, used without further characterisation. Treatment of the dichloro compound with sodium trithiocarbonate, following the procedure of Ref. 12, gave 3 - methylthio - 1,2 - propanedithiol 13 (25% yield), b.p. 59–60°/0.5 mm Hg, identical with the sample described previously.

5 - *Methylthio* - 1,2,3 - *trithiane* 2. A solution of SCl_2 (4.3 mmol in CH_2Cl_2 (15 ml) was added dropwise to a solution of 7 (4 mmol) in CH_2Cl_2 (40 ml) during 12 min. According to glc analysis, all starting material had reacted after an additional 10 min. producing approximately equal amounts of 5 - methylthio - 1,2,3 - trithiane and 4 - methylthio - 1,2 - dithiolane. The yield of the trithiane after column chromatography (silica gel, 5% ether in hexane) was 350 mg (48%). Spectral data were identical with those published for the natural product.[1]

4 - *Methylthio* - 1,2 - *dithiolane* 1. In the course of 5 min. a solution of 7 (1 mmol) in ether (5 ml) was added dropwise to a solution of I_2 (500 mg) in ether (25 ml). After additional stirring for 3 min. sodium thiosulfate (1 g) followed by $NaHCO_3$ solution (sat. 10 ml) was added and the mixture stirred vigorously until colourless. After drying, the organic phase contained 90–100% (glc) of 4 - methylthio - 1,2 - dithiolane. Upon evaporation at 0° the residue decomposed at −20° overnight while a solution (100 mg/ml) in CH_2Cl_2 showed no appreciable decomposition (glc) at room temperature for several days.

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[8]Reaction of 1,3 - dimercapto - 2 - propanol with acetylchloride in pyridine as well as $NaBH_4$ reduction of 1,3 - bisacetylthiopropanone readily afforded 1,3 - bisacetylthio - 2 - propanol, the tosyl derivative of which on reaction with one equivelent MeS^- in DMF afforded *S*-methylthioacetate and 2-(acetylthiomethyl)thiirane (L. W. Miles and L. N. Owen, *J. Chem. Soc.* 817 (1952)) and with excess MeS^- gave a fair yield of 1,3 - bismethylthio - 2 - propanthiol. Various attempts to convert 1,3 - bisbenzylthio - 2 - propanone to 1,3 - bisbenzylthio - 2 - methylthiopropane and 2 - phenyl - 1,3 - dithiane - 5 - ol to 2 - phenyl - 5 - methylthio - 1,3 - dithiane all failed.
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