

# Synthesis of Diethyl 1,2,3,4-Tetrathiepane-6,6-dicarboxylate: a New Heterocyclic System

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The title compound (**4**) has been identified in the reaction mixture of diethyl bis(*p*-tolylsulfonyloxymethyl)malonate and tetrasulfide ion, along with diethyl 1,2-dithiolane-4,4-dicarboxylate (**2**) and diethyl 1,2,3-trithiane-5,5-dicarboxylate (**3**). Reaction of **2** with elemental sulfur in *N,N*-dimethylformamide at elevated temperatures is a useful synthesis of **4**, giving only **3** as a side-product. Photoelectron spectroscopy indicates that the dihedral angles around the S–S bonds of **4** are comparable to the normal value exhibited by straight-chain disulfides.

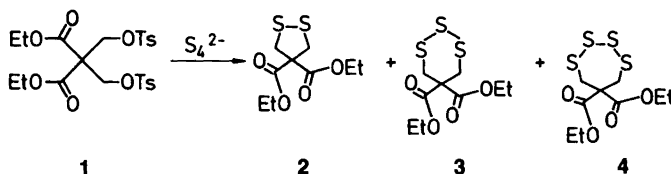
During a search for improved methods for the preparation of 4-substituted 1,2-dithiolanes, the reaction between diethyl bis(*p*-tolylsulfonyloxymethyl)malonate (**1**) and the tetrasulfide ion was investigated<sup>1</sup> with the intent of preparing a precursor of asparagusic acid (1,2-dithiolane-4-carboxylic acid). The method has previously been applied to the preparation of 1,2-dithiolanes<sup>2</sup> and usually produces significant amounts of 1,2,3-trithianes.<sup>1–5</sup> Hence, the reaction mixture is desulfurized prior to isolation, when 1,2-dithiolanes are desired.

This method was eventually abandoned for the synthesis of 1,2-dithiolanes, but because of a longstanding interest also in biologically active 1,2,3-trithianes,<sup>6,7</sup> the reaction mixture was examined prior to desulfurization. The interest in 1,2,3-trithianes originates from the fact that many naturally occurring 1,2-dithiolanes, e.g., 1,2-dithiolan-4-ol,<sup>8</sup> asparagusic acid,<sup>8–12</sup> nereis-

toxin,<sup>13–18</sup> and charatoxin<sup>17–20</sup> have 1,2,3-trithiane counterparts showing similar or enhanced biological activities.

## Results and discussion

<sup>1</sup>H NMR analyses of the product mixture from the reaction of compound **1** and sodium tetrasulfide revealed the presence of three closely related components. Comparison with authentic material allowed the assignment of a characteristic singlet at  $\delta$  3.72 to diethyl 1,2-dithiolane-4,4-dicarboxylate (**2**).<sup>1</sup> Two additional singlets appearing at  $\delta$  3.60 and 3.99 were assigned to diethyl 1,2,3-trithiane-5,5-dicarboxylate (**3**) and diethyl 1,2,3,4-tetrathiepane-6,6-dicarboxylate (**4**), respectively (Scheme 1). In this preparation, these three products were accompanied by a large number of by-products, making the purification of **2–4** quite troublesome. Chromato-



Scheme 1.

graphic purification of the reaction mixture resulted in the isolation of an equimolar mixture of **2** and **3** and a fraction containing almost pure **4** as revealed by NMR spectroscopy and elemental analyses.

Owing to the problems encountered in product purification in the above-mentioned reaction, another preparative procedure was developed in order to gain easier access to **4**. We found that **2** reacts with an excess of elemental sulfur in hot *N,N*-dimethylformamide (DMF). The reaction produced a mixture of **2**, **3** and **4** in the ratio 5:2:2, completely free of side-products. This mixture is separable by TLC. The rather low yield of 1,2,3,4-tetrathiepane **4** (14%) is not a serious limitation since **2** and **3** are recoverable and may be recycled.

Presumably, the S-S dihedral angles in **4** are comparable to the normal value (i.e., ca. 90°) in contrast with those found in 1,2-dithiolanes. The photoelectron spectrum (PES) of **4** contains three separate signals in the low-energy area, two of which, around 10.2 and 11.4 eV, are assigned to the lone pairs on the carbonyl oxygen and the  $\sigma$ -lone pairs on sulfur, respectively. The 3p lone pairs on sulfur give rise to a signal at 8.7 eV without any recognizable splitting, indicating interactions of less than 0.3 eV. This is analogous to the findings for straight chain disulfides.<sup>21,22</sup>

Although 1,2,3,4-tetrahypanes have not previously been described it is entirely possible that they have simply escaped previous notice. One brief report<sup>23</sup> states that 5,5-disubstituted 1,2,3-trithianes formed by the  $S_4^{2-}$ -ion reaction (cf. Ref. 2) may be separated from the simultaneously formed 1,2-dithiolane and thietane analogues by preparative TLC. However, no evidence other than  $R_f$  values is given.<sup>23</sup> The alleged thietanes had the highest  $R_f$  values and were visualized on the plate with UV light (254 nm). We suspect that the latter compounds are in fact 1,2,3,4-tetrathiepanes since the sulfide chromophore does not absorb in this wavelength region.

The 1,2,3,4-tetrathiepane ring system is interesting from a biological point of view, not only because of the relationship with the bioactive 1,2-dithiolanes and 1,2,3-trithianes, but equally because this system may represent a physiologically acceptable form of reactive sulfur. Elemental sulfur is known to exhibit high bioactivity, for instance as an inhibitor of photosynthesis.<sup>18</sup>

These questions, as well as the generality of these preparative methods, are being investigated.

## Experimental

The spectroscopic equipment is described in Ref. 1.

*Diethyl 1,2,3,4-tetrathiepane-6,6-dicarboxylate (4): Method a.* Diethyl 2,2-bis(*p*-tolylsulfonyloxymethyl)malonate (**1**) (10 g, 18.9 mmol) was treated with  $Na_2S_4$  and the crude product mixture was isolated as described in Ref. 2. <sup>1</sup>H NMR (60 MHz;  $CDCl_3$ ) exhibited singlets at  $\delta$  3.60, 3.72 and 3.99. The signal at  $\delta$  3.72 originates from **2**.<sup>1</sup> The mixture was purified twice by silica-gel chromatography using  $CH_2Cl_2$ -hexane (2:3) as the eluent for the first separation and toluene for the second. This procedure resulted in the isolation of nearly pure **4** (0.34 g) 6% yield, based on **1**. Calc. for  $C_9H_{14}O_4S_4$ : C 34.38; H 4.49; S 40.78%; Found: C 34.28; H 4.48; S 42.20%. <sup>1</sup>H NMR (90 MHz;  $CDCl_3$ ):  $\delta$  1.28 (6 H, t,  $CH_3$ ), 3.93 (4 H, s,  $CH_2S$ ), 4.23 (4 H, q,  $CH_2O$ ). <sup>13</sup>C NMR (22 MHz;  $CDCl_3$ ):  $\delta$  14.0 ( $CH_3$ ), 49.6 ( $CH_2S$ ), 62.4 ( $CH_2O$ ), 67.1 (C), 168.7 (CO). Another fraction gave a 1:1 mixture of **2** and **3** as a yellow oil. Yield 0.44 g, 9%, based on **1**. Anal.  $C_9H_{14}O_4S_{2.5}$ : C, H, S. <sup>1</sup>H NMR (60 MHz;  $CDCl_3$ ):  $\delta$  1.30 (12 H, t,  $CH_3$ ), 3.63 [4 H, s,  $CH_2S$  (**3**)], 3.73 [4 H, s,  $CH_2S$  (**2**)], 4.35 (8 H, dq,  $CH_2O$ ).

*Method b.* A solution of **2**<sup>1</sup> (1 g, 4 mmol) and sulfur (3.5 g, 13.6 mmol of  $S_8$ ) in DMF (20 ml) was kept at 120°C for 4 h. The reaction mixture was allowed to cool to room temperature and excess sulfur was removed by filtration. Addition of water (80 ml) followed by extraction with hexane (6×10 ml), washing of the combined hexane extract with water (2×10 ml), drying over  $MgSO_4$ , and evaporation *in vacuo* left the crude product (1.08 g). Purification of this was achieved by applying the crude product dissolved in hexane (7 ml) onto two silica gel plates (silica gel 60, 100×20×0.25 cm; PF 254 and 366 nm). Elution 7 times with diethyl ether-hexane (1:20) produced a well separated upper band (**4**) followed by two poorly separated bands (upper **2**, lower **3**). Elemental sulfur appeared near the front. The components were secured by thorough extraction of the isolated bands with diethyl ether, which was removed by evaporation to

leave residues which were redissolved in a few ml of hexane. Filtration through silica gel (5 g) and elution with  $\text{CH}_2\text{Cl}_2$  gave, after evaporation of the solvent, **4** (195 mg) and **3** (100 mg containing approximately 10% of **2**). After being recrystallised from pentane, **4** was obtained in 14% (176 mg). M.p. 34.5–36°C. Anal.  $\text{C}_9\text{H}_{14}\text{O}_4\text{S}_4$ : C, H, S. MS:  $m/z$  314 ( $\text{M}^+$ ). IR (KBr): 2960 w, 2910 w, 1730 s, 1395 w, 1365 w, 1260 m, 1210  $\text{m cm}^{-1}$ . UV (MeOH):  $\lambda_{\text{max}}$  271 nm ( $\epsilon$   $2.5 \times 10^3$ ). NMR data as described above. PES, 8.7, 10.2, 11.4 eV.

Further purification of **3** was achieved by repetition of the chromatographic procedure (100 mg of the mixture dissolved in 3 ml hexane) to yield 6% (68 mg) of pure **3**.  $^1\text{H NMR}$  (60 MHz;  $\text{CDCl}_3$ ):  $\delta$  1.30 (6 H, t,  $\text{CH}_3$ ), 3.56 (4 H, s,  $\text{CH}_2\text{S}$ ), 4.27 (4 H, q,  $\text{CH}_2\text{O}$ ). UV (MeOH):  $\lambda_{\text{max}}$  264 nm ( $\epsilon$   $1.8 \times 10^3$ ).

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