Formation of a Stable Adduct of Ethoxycarbonyldithiocarbamic Acid and a Dimer of Ethoxycarbonyl Isothiocyanate

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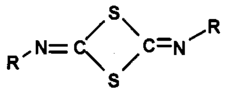
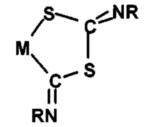
The reaction of ethoxyxcarbonyl isothiocyanate with water in the absence of a solvent has yielded the new compound [$EtO_2CN{=}CS_2C\{N(H)CO_2Et\}\{S_2CN(H)CO_2Et\}$] (**1**) in 76% yield that has been isolated in a crystalline form that contains one equivalent of ethoxyxcarbonyl isothiocyanate. Compound **1** can be viewed as an adduct of a dimer of $EtO_2CN{=}C{=}S$ and the dithiocarbamic acid **2**. Compound **1** dissociates in solution to yield **2** and free ethoxyxcarbonyl isothiocyanate. Compound **2** can be isolated chromatographically, but it is slowly oxidized when allowed to stand in the open air to form the thiuram disulfide **3**. Compounds **1** and **3** were characterized crystallographically. Compound **1** contains an imino-substituted dithietane ring with a dithiocarbamate substitutent bonded to one of the ring carbon atoms. Compound **3** is a thiuram disulfide which has C_2 crystallographic symmetry.

Introduction

Organic isothiocyanates have been used for the synthesis of a variety of new heterocycles.[1] They are also effective ligands for transition metals.[2][3] There are claims that isothiocyanates with electron withdrawing substitutents couple to form dimers **A**,[4] and there is an example of a coupled form **B** of two isothiocyanates coordinated to a transition metal atom that has been verified crystallographically[5]



A



B

Organic isothiocyanates readily react with water to form amines with a release of CO_2 and H_2S (eq. 1).[6] H_2S is known to add to organic isothiocyanates to yield dithiocarbamic acids (eq. 2).[6]

$$RN{=}C{=}S + 2\,H_2O \rightarrow RNH_2 + H_2S + CO_2 \qquad (1)$$

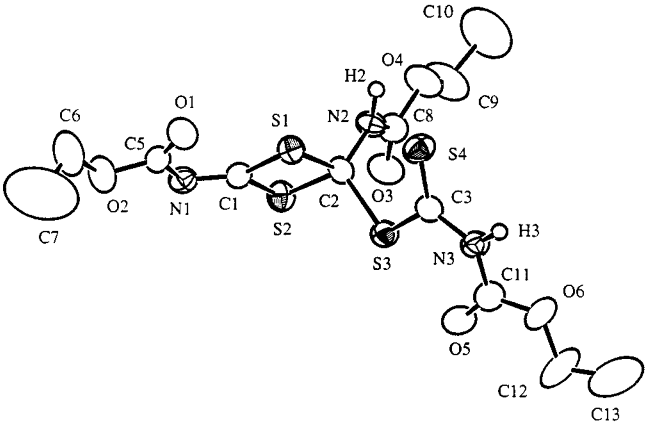
$$RN{=}C{=}S + H_2S \rightarrow RNHCS_2H \qquad (2)$$

Dithiocarbamic acids are generally unstable, but the dithiocarbamate anions are a good ligands for transition metals and a large number of complexes have been made with them.[7] In this report we describe a reaction of the ethoxycarbonyl isothiocyanate with water. We have isolated and structurally characterized the new compound **1** which can be viewed as an adduct of the dimer **A**, and the ethoxycarbonyl dithiocarbamic acid (**2**).

Results and Discussion

When small amounts of water are allowed to mix with pure ethoxycarbonyl isothiocyanate, pale yellow crystals of compound **1** with one equiv. ethoxycarbonyl isothiocyanate are formed in up to 75% yield. The product actually forms crystals suitable for analysis by single crystal X-ray diffraction methods in the reaction mixture. Accordingly, a single crystal X-ray diffraction analysis of **1** was performed. An ORTEP diagram of the molecular structure of **1** is shown in Figure 1.

Figure 1. An ORTEP diagram of {$EtO_2CN{=}CS_2C[N(H)CO_2Et]$-[$S_2CN(H)CO_2Et$]} (**1**) found in the crystal of **1**·$EtO_2CN{=}C{=}S$[a]



[a] Selected interatomic distances (Å) and angles (°): S(1)−C(1) 1.755(8), S(2)−C(1) 1.715(9), S(1)−C(2) 1.831(8), S(2)−C(2) 1.870(7), S(3)−C(2) 1.824(8), S(3)−C(3) 1.762(8), S(4)−C(3) 1.630(8), S(5)−C(4) 1.51(2), C(1)−N(1) 1.28(1), C(2)−N(2) 1.41(1), C(3)−N(3) 1.39(1); S(1)−C(1)−S(2) 102.3(5), S(1)−C(2)−S(2) 93.8(4), S(2)−C(2)−S(3) 103.8(4), S(1)−C(2)−S(3) 115.5(5), N(2)−C(2)−S(1) 113.1(6), N(2)−C(2)−S(2) 112.5(6), N(2)−C(2)−S(3) 115.5(6).

Compound **1** can be viewed as an adduct of the dimer **A** of ethoxycarbonyl isothiocyanate and ethoxycarbonyldithiocarbamic acid. The dimeric ethoxycarbonyl isothiocyanate portion of the molecule is distinguished by a dithiet-

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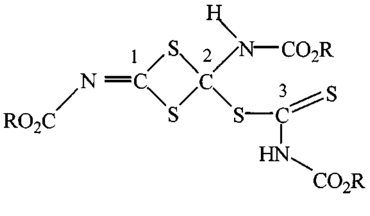
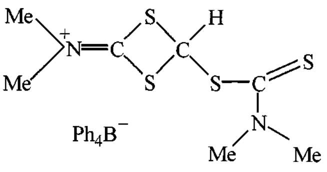
ane ring. One of the sulfur atoms of the ethoxycarbonyldithiocarbamyl grouping S(3) is bonded to one of the imino carbon atoms of the EtO_2CNCS dimer at C(2) atom. Thus, C(2) has three sulfur atoms, S(1), S(2), and S(3) bonded to it with bond lengths typical of C−S single bonds, S(1)−C(2) 1.831(8), S(2)−C(2) 1.870(8), S(3)−C(2) 1.824(8) A. The C−S bonds to C(1) are shorter, S(1)−C(1) 1.755(8) A, S(2)−C(1) 1.715(9) A due to partial multiple bonding character to C(1). A line drawing of the structure is shown below.



1



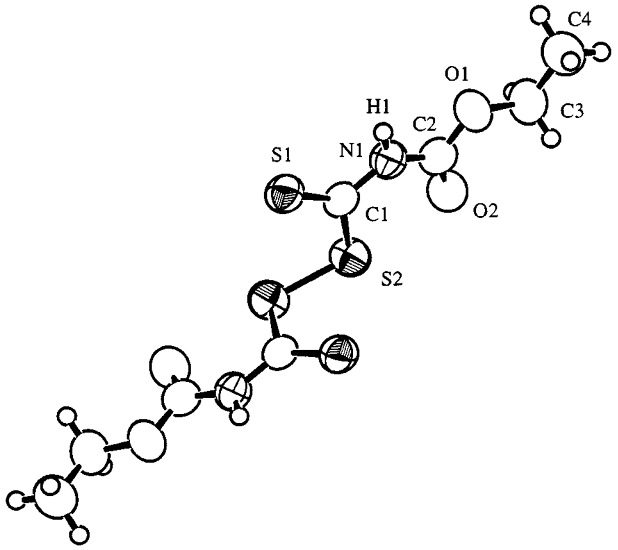
4

The molecule contains an imino-substituted four-membered dithietane ring which imposes a highly distorted tetrahedral structure around atom C(2). There are few molecules that are structurally similar to **1**. Perhaps, its closest relative is the cation of the compound $[Me_2N{=}CS_2C(H)S_2CNMe_2]BPh_4$ (**4**) which contains an amino-substituted dithietane ring.[8] The ^{1}H-NMR spectrum of **1** shows the presence of three ethyl groups, as expected, and two slightly broadened, deshielded resonances of intensity one at $\delta = 9.02$ and 7.23. The latter are attributed to hydrogen atoms that have been assigned to sites on N(2) and N(3) since the C(1)−N(1) bond length is indicative a double bond, C(1)−N(1) 1.283(9) A while the lengths of other two, C(2)−N(2) and C(3)−N(3), 1.41(1) and 1.386(9), respectively, are more consistent with single bond lengths. One equivalent of ethoxycarbonyl isothiocyanate is crystallized with **1** in the same crystal lattice. There are no significant bonding interactions between **1** and the ethoxycarbonyl isothiocyanate solvate.

In solution compound **1** slowly dissociates to form the dithiocarbamic acid **2** and ethoxycarbonyl isothiocyanate as shown by ^{1}H-NMR analysis. Separation of the reaction mixture by column chromatography yielded pale yellow **2** in 85%. Compound **2** was characterized by IR and ^{1}H-NMR spectroscopy. The S−H vibration is observed at 2476 cm^{-1} in the region that is characteristic of this group.[9] Efforts to obtain crystals of **2** suitable for X-ray analysis have been unsuccessful.

Compound **2** decomposes when allowed to stand in the open air, and is converted to a dimer **3** of the dithiocarbamic acid **2**. Crystals of **3** suitable for single crystal X-ray diffraction analysis were obtained and the analysis has been completed. An ORTEP diagram of the molecular structure of **3** is shown in Figure 2.

Figure 2. ORTEP diagram of $[EtO_2CN(H)CS_2]_2$ (**3**)[a]

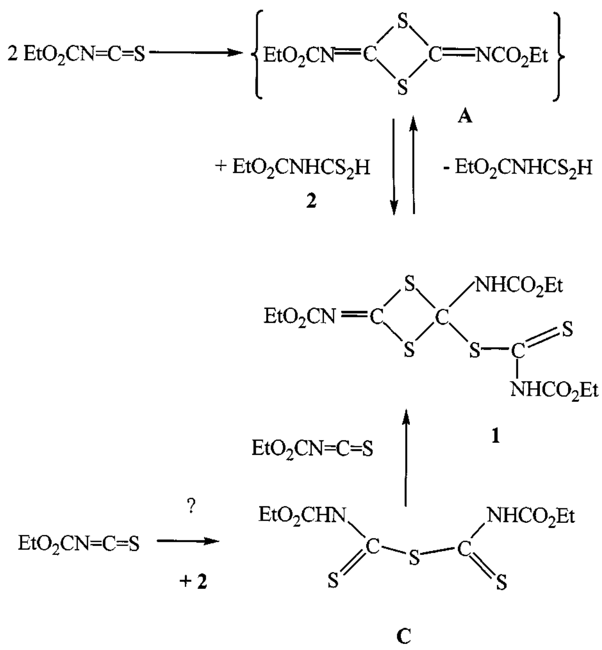


[a] Selected interatomic distances (A) and angles (°): S(2)−S(2′) 2.034(3), S(2)−C(1) 1.780(4), S(1)−C(1) 1.631(4), C(1)−N(1) 1.364(6), C(2)−O(1) 1.330(5), C(2)−O(2) 1.200(5); S(1)−C(1)−S(2) 125.3(3), N(1)−C(1)−S(1) 120.9(3), N(1)−C(1)−S(2) 113.8(3), C(1)−N(1)−C(2) 128.1(5).

Due to crystal symmetry only half of the molecule is present in the asymmetric unit. The two halves are related by a C_2 rotation. A similar situation was observed in both the structure of tetramethylthiuram disulfide and the structure of dipyrrolidylthiuram disulfide (space group *C2/c*).[10a][10b][10c] Compound **3** is a bis(ethoxycarbonyl)thiuram disulfide formed by the oxidation and coupling of two molecules of **2**. The geometry about C(1) of the S_2CN group is essentially planar. These two groups are connected by a S−S single bond with a C−S−S−C torsion angle of −86.2(3)°. The configuration about the S−S bond is similar to that found in the structures of other thiuram disulfides $(S_2CNR_2)_2$ [R_2 = Me_2, Et_2, $(CH_2)_4$, $(CH_2)_5$, Et, cyclo-C_6H_{11}].[10] The S−S bond distance 2.034(2) A, is slightly longer than that found for other thiuram disulfides 1.995−2.009.[11] However, an even longer S−S bond distance, 2.069(1) A, with a *trans*-C−S−S−C torsion angle has been found in a centric thiuram disulfide, tetraisopropylthiuram disulfide.[11] The ^{1}H-NMR spectrum of **3** shows only one set of resonances for the ethyl group and only one deshielded resonance for the hydrogen atoms bonded to nitrogen atoms at $\delta = 9.23$ (s, br, 2 H, NH). This is consistent with the fact that the two halves of the molecule are symmetry equivalent.

The formation of **1** can be explained by the combination of one equivalent of **2** [formed by the series of reactions (1) and (2) of the isothiocyanate with water and H_2S] with two equiv. of the isothiocyanate. Mechanistically, this could occur by either of two mechanisms shown in Scheme 1: (1) The addition of the S−H bond to one of the two C−N double bonds of a dimer such as **A** formed by the combination of two equiv. of the ethoxycarbonyl isothiocyanate. The hydrogen atom is added to the nitrogen atom and the sulfur atom is added to the carbon atom. While there have been several well documented examples of adducts containing four membered rings formed by the addition of carbodiimides to isothiocyanates,[12] the isothiocyanate dimers are not yet well characterized[4]; (2) alternatively the dithiocarbamic acid could combine with the isothiocyanates in a sequential fashion. The combination of **2** with one equiv. of the ethoxycarbonyl isothiocyanate could yield a thiuram monosulfide **C**. A variety of stable thiuram monosulfide derivatives have been characterized.[13]

Scheme 1



The addition of an equivalent of the ethoxycarbonyl isothiocyanate across one of the C=S double bonds in the thiuram monosulfide **C** could give the product **1**. Complex **1** is stable in the solid state, but it is readily dissociated into compound **2** and free isothiocyanate when dissolved in chloroform. This fact would support the first mechanism (microscopic reverse of the dissociation) as the mechanism of the formation of **1**.

Compound **2** can be obtained in a pure form when **1** is passed over a silica gel chromatography column. However, like most dithiocarbamic acids,[9][11][14] it is slowly oxidized upon standing in air to yield the corresponding thiuram disulfide **3**.

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Experimental Section

General: Unless specified otherwise, all reactions were performed under an atmosphere of nitrogen. All solvents were appropriately dried and degassed prior to use. Ethoxycarbonyl isothiocyanate were purchased from Aldrich and freshly distilled prior to use. – TLC separations were performed in air by using silica gel (60 A, F_{254}) on plates (whatman, 0.25 mm). – Elemental analyses were performed by Desert Analytics, Tucson, AZ. – Mass spectra were obtained with a VG Model 70SQ mass spectrometer (direct inlet, electron impact ionization).

Preparation of [$EtO_2CN{=}CS_2C\{N(H)CO_2Et\}\{S_2CN(H)CO_2Et\}$] (**1**): A 60.0-μl amount (3.34 mmol) of distilled H_2O was added to a 200-μl amount (1.70 mmol) of $EtO_2CN{=}C{=}S$ in a small capped vial, and the mixture was simply allowed to stand at room temp. for 2 d. Pale yellow crystals formed and were separated. The crystals were washed with 10 × 1 ml of hexane and dried in vacuo. This yielded 175.6 mg (75%) of **1** with one equiv. of ethoxycarbonyl isothiocyanate. – ^1H NMR ($CDCl_3$): δ = 9.02(s, 1 H, NH), 7.23 (s, 1 H, NH), 4.27(q, $^3J_{H-H}$ = 7.1 Hz, 2 H, OCH_2Me), 4.24 (q, $^3J_{H-H}$ = 7.1 Hz, 2 H, OCH_2Me), 4.15 (q, $^3J_{H-H}$ = 7.1 Hz, 2 H, OCH_2Me), 4.10(q, $^3J_{H-H}$ = 7.1 Hz, 2 H, OCH_2Me), 1.32(t, $^3J_{H-H}$ = 7.1 Hz, 3 H, CH_3), 1.31(t, $^3J_{H-H}$ = 7.1 Hz, 3 H, CH_3), 1.25(t, $^3J_{H-H}$ = 7.1 Hz, 3 H, CH_3), 1.24(t, $^3J_{H-H}$ = 7.1 Hz, 3 H, CH_3). – $C_{16}H_{22}N_4O_8S_5$ (558.67): calcd. (found): C 33.71 (33.16), H 4.01 (4.12), N 9.83 (9.89).

Transformation of **1** *to EtO_2CNHCS_2H* (**2**): (a) A 400.0 mg amount (0.72 mmol) of **1**·(EtO_2CNCS) was dissolved in a minimum amount of CH_2Cl_2. The solution was transferred to a silica gel column and was eluted with a CH_2Cl_2/ethylacetate (6:1) solvent mixture to yield an orange band of EtO_2CNHCS_2H (**2**) (140 mg, 85% yield). – IR (CH_2Cl_2): ν = 3365 cm^{-1} (N–H), 2476(S–H), 1755(C=O). – ^1H NMR ($CDCl_3$): δ = 8.98 (s, br, 1 H, NH), 6.56 (s, br, 1 H, SH), 4.29 (q, $^3J_{H-H}$ = 7.1 Hz, 2 H, OCH_2Me), 1.33 (t, $^3J_{H-H}$ = 7.1 Hz, 3 H, CH_3).

(b) A 5.0 mg amount of **1**·($EtO_2CN{=}C{=}S$) was dissolved in 0.6 ml of $CDCl_3$ and placed in a 5-mm NMR tube at 25°C. The transformation of **1** was followed by ^1H-NMR spectroscopy. After 24 h, compound **1** was converted to **2** and $EtO_2CN{=}C{=}S$ completely.

Transformation of **2** *to ($EtO_2CNHCS_2)_2$* (**3**): A 15.0 mg amount (0.091 mmol) of **2** was dissolved in 5 ml of CH_2Cl_2. The solution was stirred at room temp. in open air for 48 h. After the solvent was removed, the residue was redissolved in a CH_2Cl_2/C_6H_6 (3:1) solvent mixture at room temp. Colorless crystals formed were collected and washed with 5 × 0.5 ml of hexane. This yield 9.2 mg (62%) of $[EtO_2CN(H)CS_2]_2$ (**3**). – ^1H NMR ($CDCl_3$): δ = 9.23 (s, br, 2 H, NH), 4.31 (q, $^3J_{H-H}$ = 7.1 Hz, 4 H, OCH_2Me), 1.35 (t, $^3J_{H-H}$ = 7.1 Hz, 6 H, CH_3). – $C_8H_{12}N_2O_4S_4$ (328.43): calcd. (found): C 29.26 (29.40), H 3.68 (3.44), N 8.53 (8.25).

X-ray Structural Analyses of **1** *and* **3**: Crystals of **1** suitable for X-ray diffraction analysis were obtained by crystallization of an $EtO_2CN{=}C{=}S$ solution at −4°C. Crystals of **3** suitable for X-ray diffraction analysis were obtained by slow evaporation of solvent from a CH_2Cl_2/benzene (3:1) solution at 25°C. The crystals used in intensity measurements were mounted in thin-walled glass capillaries. Diffraction measurements for **1** and **3** were made on a Rigaku AFC6S fully automated four-circle diffractometer using graphite-monochromated Mo-K_α radiation. The unit cells were determined and refined from 15 randomly selected reflections obtained by using the AFC6S or AFC5R automatic search, center, index, and least-squares routines. All data processing was performed on a Silicon Graphics Indigo2 computer by using the TEXSAN structure solving program library obtained from the Molecular Structure Corp., The Woodlands, TX. Neutral atom scattering factors were calculated by the standard procedures.[15a] Anomalous dispersion corrections were applied to all non-hydrogen atoms.[15b] Lorentz-polarization (*Lp*) and absorption corrections were applied in each analysis. Both structures were solved by a combination of direct methods (MITHRIL) and difference Fourier syntheses, and all nonhydrogen atoms were refined with anisotropic thermal parameters. Full matrix least-squares refinements minimized the function: $\Sigma_{hkl}w(|F_o| - |F_c|)^2$, where $w = 1/\sigma(F)^2$, $\sigma(F) = \sigma(F_o^2)/2F_o$, and $\sigma(F_o^2) = [\sigma(I_{raw})^2 + (0.02 \cdot I_{net})^2]^{1/2}/Lp$.

Compound **1** crystallized in the triclinic crystal system. The space group *P*1bar was assumed and confirmed by the successful solution and refinement of the structure. One equiv. of $EtO_2CN{=}C{=}S$ (unreacted reagent) cocrystallized with the product in the lattice. This was included in the calculations employing anisotropic thermal parameters for the sulfur atom S(5), a fixed thermal parameter for the carbon atom C(14) and isotropic thermal parameters for the other nonhydrogen atoms. In all cases, the positions of all hydrogen atoms were calculated by assuming idealized geometries with all C−H distances at 0.95 A. The scattering contributions of calculated hydrogen atoms were added to the structure factor calculations, but their positions were not refined.

Table 1. Crystal data for compounds **1** and **3**

Compound	**1**	**3**
Empirical formula	$S_5O_8N_4C_{16}H_{22}$	$S_4O_4N_2C_8H_{12}$
Molecular mass	558.67	328.43
Crystal system	triclinic	monoclinic
Lattice parameters:		
a (A)	10.168(2)	18.182(5)
b (A)	14.148(3)	5.484(2)
c (A)	9.431(2)	14.211(4)
α (°)	90.84(2)	90.00
β (°)	93.21(2)	90.84(2)
γ (°)	74.53(2)	90.00
V (A^3)	1305.5(5)	1416.7(6)
Space group	*P*1bar(no. 2)	*C2*/*c* (no. 15)
Z value	2	4
ρ_{calc} (g/cm^3)	1.42	1.54
μ(Mo-K_α) (cm^{-1})	4.89	6.76
$2\Theta_{max}$ (°)	45	50
No. obs. ($I > 3\sigma$)	2096	640
No. variables	260	106
Goodness of fit (GOF[a])	3.53	1.40
Max shift in final cycle	0.01	0.01
Residuals*: *R*; R_w	0.066; 0.075	0.037; 0.032
Abs. Cor.	Difabs	Difabs
Transmis coeff max/min	1.29/0.76	1.00/0.53
Largest residual Pk (e/A^3)	0.70	0.20

[a] $R = \Sigma_{hkl}(||F_{obs}| - |F_{calc}||)/\Sigma_{hkl}|F_{obs}|$; $R_w = [\Sigma_{hkl}w(|F_{obs}| - |F_{calc}|)^2/\Sigma_{hkl}wF_{obs}^2]^{1/2}$, $w = 1/\sigma^2(F_{obs})$; $GOF = [\Sigma_{hkl}(w(|F_{obs}| - |F_{calc}|)^2)/(n_{data} - n_{vari})]^{1/2}$.

Compound **3** crystallized in the monoclinic crystal system. The systematic absences were consistent with either of the space groups *C2*/*c* or *Cc*. This structure was solved and refined in the higher symmetry centrosymmetric space group *C2*/*c*. The hydrogen atom H(1) on the nitrogen atom N(1) was located and the positions of other hydrogen atoms were calculated by assuming idealized geometries. These hydrogen atoms were successfully refined with isotropic thermal parameters.[16]

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[16] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101126 (**1**) and CCDC-101149 (**3**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (int. code) +44(1223)336-033, E-mail: deposit@chemcrys.cam.ac.uk, www: http://www.ccdc.cam.ac.uk].

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