**Short Note**

**Octahydro-1H,5H,7H-dipyrrrolo[1,2-c:1’,2’-f][1,3,6]oxadiazocine-5-thione**

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**Abstract:** A minor byproduct in the reaction of (S)-prolinol with thiophosgene in the presence of triethylamine is identified as a novel tricyclic dipyrrolidino-1,3,6-oxadiazocane-2-thione, the first example of such a ring system, and a representative of the uncommon, but useful 1,3,6-oxadiazocanes. A mechanism is proposed for its formation.

**Keywords:** 1,3,6-oxadiazocane; 1,3,6-oxadiazocine-2-thione; NMR spectra

1. **Introduction**

Some years ago we reported synthesis of the simple bicyclic 1,3-oxazolidine-2-thione 1 by reaction of (S)-prolinol with thiophosgene in the presence of triethylamine and its conversion into chiral iminium salts useful for the kinetic resolution of alkoxides [1]. The same compound was reported again recently and was shown to be converted by a ruthenium catalyst into the isomeric 1,3-thiazolidin-2-one [2], also mentioned in our earlier publication [1]. We now describe the isolation and identification of a minor byproduct in the synthesis of 1, which has the novel tricyclic structure 2 featuring a central 1,3,6-oxadiazocane ring.

2. **Results**

The synthesis of 1 involved slow addition of thiophosgene to a mixture of prolinol and two equivalents of triethylamine in CH₂Cl₂ at 0 °C (Scheme 1). Chromatographic purification on alumina gave the main product in analytically pure form and moderate yield as fine colourless crystals [1]. In their more recent work, Frost and co-workers conducted the reaction in CHCl₃ at room temperature and obtained 1 in high yield by trituration [2] with a good match in spectroscopic properties. However, in the course of repeated chromatographic purifications we noticed a minor product at much higher Rₜ which was isolated in 1% yield and for which we propose the structure 2 containing the previously unknown 1,3,6-oxadiazocane-2-thione ring system. The ¹H-NMR spectrum contained signals for 18 hydrogens, clearly indicating that two inequivalent prolinol-derived fragments were present and this was confirmed by the ¹³C-NMR spectrum with 11 signals including one C=S at 191 ppm, one CH₂O at 79 ppm, two CHNs at 60–65 ppm, three CH₂N signals in the range 50–60 ppm and four CH₂ signals remote from a heteroatom at 20–30 ppm. Particularly the presence of a third CH₂N signal together with only one CH₂O and a correct high-resolution mass spectrometry measurement leave little doubt as to the structure of 2. By means of COSY and HSQC NMR studies an almost complete assignment of NMR signals was possible (Figure 1, Table 1).
Although it is only formed in low yield, this product is the first 1,3,6-oxadiazocane-2-thione as far as we are aware. Indeed a literature search shows very few publications dealing with 1,3,6-oxadiazocine rings in any state of unsaturation or oxidation. A summary of all such related structures, many of which show potentially useful properties, is shown in Figure 2. NMR studies on the conformation of bicyclic oxadiazocane [3] and oxadiazocanone [4] have appeared and the ditosyl oxadiazocane was obtained as a byproduct in azamacrocyclic synthesis [5]. The bridged oxadiazocanones were investigated as potential central nervous system-active agents [6], and the benzoxadiazocinone system was obtained by the photochemical rearrangement of a benzodiazepinone [7]. The unsaturated benzoxadiazocine was prepared as a novel heterocycle [8], and reaction of two equivalents of 2H-azirines with chlorosulfonyl isocyanate gives the oxadiazocinones [9]. Various ring-fused derivatives are also known including the purine-fused compounds [10], and the imidazo[2,1-b] fused compounds [11] which are active against tuberculosis and a range of other tropical diseases [11,12]. Compound 12 is formed as a byproduct in a Pictet Spengler reaction [13]. A range of amino acid-derived oxadiazocanetriones are useful as a component of gel electrolytes [14], and amino acid-derived oxadiazocanediones are active as phospholipase A2 inhibitors [15,16] and against malaria and AIDS [17,18]. Finally, mention could be made of the closely related 1,3,6-thiadiazocane-2-thione, the only similar system as far as we are aware containing a thione [19].
Figure 2. Related 1,3,6-oxadiazocine ring systems.

The likely mechanism for formation of 2 is shown in Scheme 2. Initial reaction of prolinol with one molecule of thiophosgene and base gives the thiocarbamoyl chloride 16 and, if this simply loses HCl intramolecularly, the major product 1 is formed. If this intermediate is instead attacked intermolecularly by a second molecule of proline, the thiocarbamate 17 is formed containing a free CH₂OH group. This can combine with a second molecule of thiophosgene to give the chlorothioformate 18 and this then undergoes intramolecular attack of the pyrrolidine nitrogen with loss of COS to afford the observed product 2.

Scheme 2. Proposed mechanism for the formation of 2.

3. Experimental Section

Octahydro-1H,5H,7H-dipyrrolo[1,2-c:1′,2′-f][1,3,6]oxadiazocine-5-thione (2)

A solution of (S)-prolinol [20] (5.0 g, 50 mmol) and triethylamine (14.0 mL, 10.12 g, 100 mmol) in CH₂Cl₂ (250 mL) was stirred at 0 °C while a solution of thiophosgene (5.03 mL, 7.59 g, 66 mmol) in
CH₂Cl₂ (100 mL) was added dropwise. The solution was then allowed to warm up to room temperature and stirred for 16 h. The solution was washed with water (2 × 250 mL) and 0.5 M aq. sodium hydroxide (200 mL) and then dried and evaporated to afford a dark coloured oil (6.49 g). This was subjected to column chromatography on alumina (diethyl ether/petroleum, 70:30) to give as the main product at Rf 0.28 (S)-tetrahydro-1H,3H-pyrrolo[1,2-c]oxazole-3-thione 1 (3.11 g, 43%) as colourless crystals, m.p. 58–59 °C. [α]20D + 69 (c = 1.02, CH₂Cl₂) (lit. [2] +55.3); 1H-NMR (300 MHz, CDCl₃): δ 4.80–4.70 (m, 1H), 4.35–4.20 (m, 2H), 3.95–3.75 (m, 1H), 3.55–3.40 (m, 1H), 2.35–2.00 (m, 3H), 1.85–1.55 (m, 1H) (good agreement with lit. [2]); 13C-NMR (75 MHz, CDCl₃): δ 189.5 (C=S), 73.2 (CH₂), 63.1 (CH), 47.5 (CH₂), 30.8 (CH₂), 26.6 (CH₂) (good agreement with lit. [2]). Anal. Calcd. for C₈H₉NOS: C, 50.32; H, 6.34; N, 9.78. Found: C, 50.54; H, 6.36; N, 9.79.

However, this was preceded by a minor component at Rf 0.64, obtained as a pale yellow oil, which proved to be the title compound 2 (56.5 mg, 1%). 1H-NMR (300 MHz, CDCl₃): δ 4.60–4.50 (m, 1H), 4.16 (half AB pattern of d, J 12, 5, 1H), 4.08 (half AB pattern of d, J 12, 12, 1H), 3.85–3.75 (m, 1H), 3.72–3.60 (m, 1H), 3.10–2.98 (m, 2H), 2.58–2.54 (m, 1H), 2.53 (d, J 12, 2H), 2.12–2.00 (m, 3H), 1.95–1.90 (m, 4H), 1.48–1.40 (m, 1H); 13C-NMR (75 MHz, CDCl₃): δ 190.6 (C=S), 78.9 (CH₂O), 62.6 (CHN), 60.0 (CHN), 58.3 (CH₂N), 56.7 (CH₂N), 50.1 (CH₂N), 28.6 (CH₂), 27.2 (CH₂), 24.4 (CH₂), 22.4 (CH₂); MS (EI): m/z 226 (M⁺, 100%), 193 (28), 163 (16), 149 (12), 110 (32), 97 (73), 82 (38), 69 (58), 55 (48). HRMS Calcd. for C₁₁H₁₅N₂OS: 226.1140. Found: 226.1142.

Supplementary Materials: The following are available online: http://www.mdpi.com/1422-8599/2018/M993/s1, Figure S1: 300 MHz ¹H-NMR spectrum of 2 in CDCl₃, Figure S2: 75 MHz normal and DEPT ¹³C-NMR spectra of 2 in CDCl₃, Figure S3: COSY 2D H-H correlation NMR spectrum of 2, Figure S4: HSQC 2D C-H correlation NMR spectrum of 2, Figure S5: Mass spectrum for 2.

Author Contributions: K.A. performed the experiments; R.A.A. designed the experiments, analysed the data and wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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