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Short Note

Octahydro-1*H*,5*H*,7*H*-dipyrrolo[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.

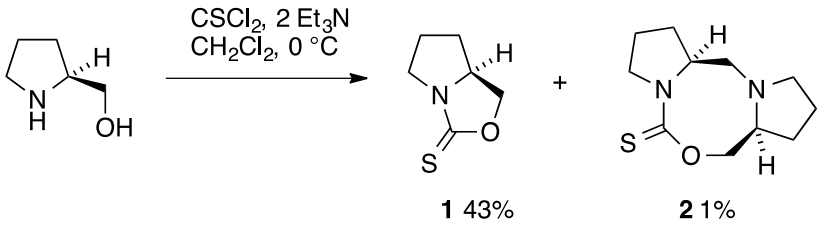
Keywords: 1,3,6-oxadiazocane; 1,3,6-oxadiazocine-2-thione; NMR spectra

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 CH_2Cl_2 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 $CHCl_3$ 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 R_f 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 ^{1}H-NMR spectrum contained signals for 18 hydrogens, clearly indicating that two inequivalent prolinol-derived fragments were present and this was confirmed by the ^{13}C-NMR spectrum with 11 signals including one C=S at 191 ppm, one CH_2O at 79 ppm, two CHNs at 60–65 ppm, three CH_2N signals in the range 50–60 ppm and four CH_2 signals remote from a heteroatom at 20–30 ppm. Particularly the presence of a third CH_2N signal together with only one CH_2O 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).



Scheme 1. Synthetic route to **1** and **2**.

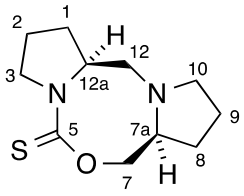


Figure 1. Numbering system for **2**.

Table 1. NMR assignment for **2**.

δ_C	mult. (DEPT)	δ_H (HSQC)	Coupled H (COSY)	Assignment
190.5	C	—		5-C=S
78.9	CH_2	4.08, 4.16		7-CH_2O
62.6	CH	3.10	4.08	7a-CHN
60.0	CH	4.55	2.53, 2.08	12a-CHN
58.3	CH_2	2.53 (2H)		12-CH_2N
56.7	CH_2	3.10, 2.56		10-CH_2N
50.1	CH_2	3.80, 3.66	2.08	3-CH_2N
28.6	CH_2	†		1-CH_2 *
27.2	CH_2	†		8-CH_2 *
24.4	CH_2	†		2-CH_2 *
22.4	CH_2	†		9-CH_2 *

* Assignments may be interchanged, † 2.10, 2.05 (2H), 1.85, 1.75 (2H), 1.70, 1.45—assignment uncertain due to peak overlap.

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** [3] and oxadiazocanone **5** [4] have appeared and the ditosyl oxadiazocane **4** was obtained as a byproduct in azamacrocycle synthesis [5]. The bridged oxadiazocanones **6** were investigated as potential central nervous system-active agents [6], and the benzoxadiazocinone system **7** was obtained by the photochemical rearrangement of a benzodiazepinone [7]. The unsaturated benzoxadiazocine **8** was prepared as a novel heterocycle [8], and reaction of two equivalents of 2*H*-azirines with chlorosulfonyl isocyanate gives the oxadiazocinones **9** [9]. Various ring-fused derivatives are also known including the purine-fused compounds **10** [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 **13** are useful as a component of gel electrolytes [14], and amino acid-derived oxadiazocanediones **14** 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].

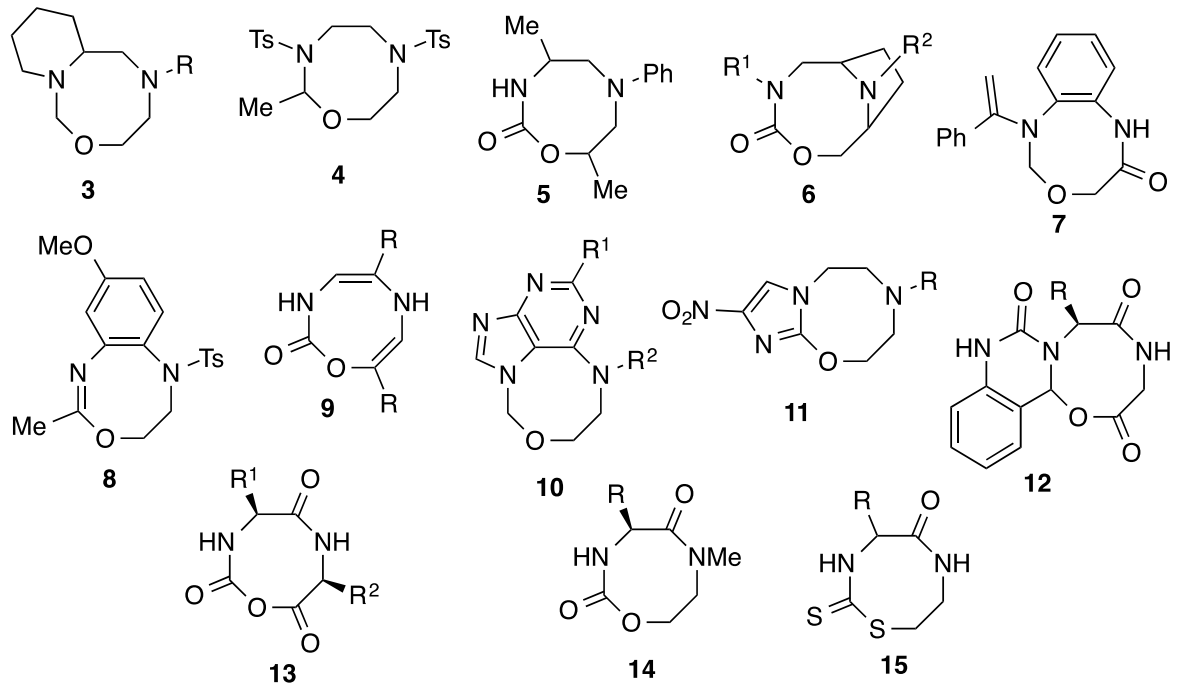
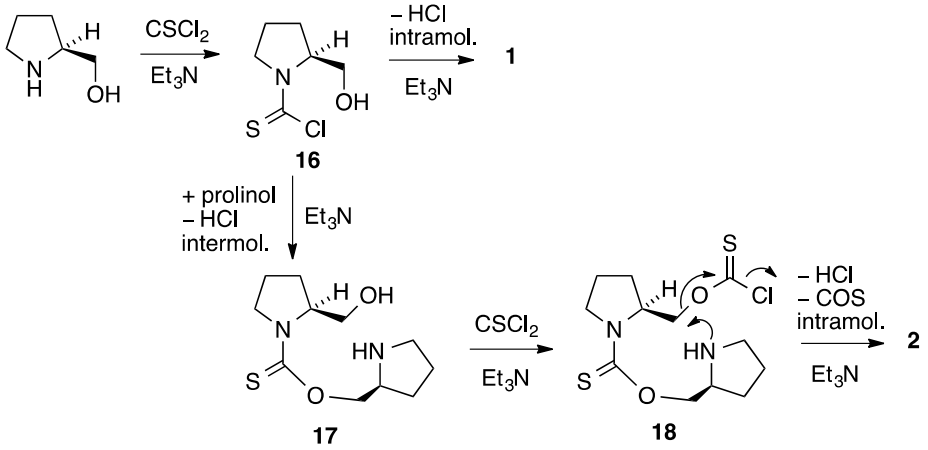


Figure 2. Related 1,3,6-oxadiazocine ring systems.

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 CH_2OH 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 CH_2Cl_2 (250 mL) was stirred at 0 °C while a solution of thiophosgene (5.03 mL, 7.59 g, 66 mmol) in

CH_2Cl_2 (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 R_f 0.28 (*S*)-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-3-thione **1** (3.11 g, 43%) as colourless crystals, m.p. 58–59 °C. $[\alpha]_D^{20}$ + 69 (c = 1.02, CH_2Cl_2) (lit. [2] +55.3); ^{1}H-NMR (300 MHz, $CDCl_3$): 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]); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 189.5 (C=S), 73.2 (CH_2), 63.1 (CH), 47.5 (CH_2), 30.8 (CH_2), 26.6 (CH_2) (good agreement with lit. [2]). Anal. Calcd. for C_6H_9NOS: 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 R_f 0.64, obtained as a pale yellow oil, which proved to be the title compound **2** (56.5 mg, 1%). ^{1}H-NMR (300 MHz, $CDCl_3$): 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), 1.95–1.65 (m, 4H), 1.48–1.40 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 190.6 (C=S), 78.9 (CH_2O), 62.6 (CHN), 60.0 (CHN), 58.3 (CH_2N), 56.7 (CH_2N), 50.1 (CH_2N), 28.6 (CH_2), 27.2 (CH_2), 24.4 (CH_2), 22.4 (CH_2); 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 $C_{11}H_{18}N_2OS$: 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 ^{1}H-NMR spectrum of **2** in $CDCl_3$, Figure S2: 75 MHz normal and DEPT ^{13}C-NMR spectra of **2** in $CDCl_3$, 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.

References

1. Aitken, R.A.; Ali, K.; Mesher, S.T.E. Kinetic resolution of secondary alcohols using proline-derived bicyclic iminium salts. *Tetrahedron Lett.* **1997**, *38*, 4179–4182. [CrossRef]
2. Mahy, W.; Plucinski, P.; Jover, J.; Frost, C.G. Ruthenium-catalyzed O- to S-alkyl migration: A pseudoreversible Barton-McCombie pathway. *Angew. Chem. Int. Ed.* **2015**, *54*, 10944–10948. [CrossRef] [PubMed]
3. Crabb, T.A.; Jackson, G.C. Proton magnetic resonance studies of compounds with bridgehead nitrogen. XXVIII—Stereochemical studies with Perhydropyrido[1,2-*c*][1,6,3]dioxazocines and 2-alkylperhydropyrido[1,2-*c*][1,3,6]oxadiazocines. *Org. Magn. Reson.* **1975**, *7*, 488–495. [CrossRef]
4. Nishiyama, T.; Fujiwara, T.; Miyazaki, S.; Yamada, F. *Cis* and *Trans* 4,8-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,6-oxadiazocin-2-ones: Conformational studies and configurational assignments by NMR. *J. Heterocycl. Chem.* **1992**, *29*, 1529–1533. [CrossRef]
5. Pulacchini, S.; Watkinson, M. An Efficient Route to Symmetrically and Unsymmetrically Substituted Azamacrocyclic Ligands. *Eur. J. Org. Chem.* **2001**, 4233–4238. [CrossRef]
6. Fontanella, L.; Occelli, E. Farmaci potenzialmente attivi sul sistema nervoso centrale derivati del 5-oxa-3,10-diazabiciclo[5.2.1]decano e del 5-oxa-3,10-diazabiciclo[5.2.1]decan-4-one. *Farmaco Ed. Scient.* **1971**, *26*, 685–709. (In Italian)
7. Achour, R.; Essassi, E.M.; Zniber, R.; Desvergne, J.-P.; Bouas-Laurent, H. Réactivité photochimique en solution de 1,5-diazodiazepinones. *Bull. Soc. Chim. Belg.* **1993**, *102*, 479–491. (In French) [CrossRef]
8. Hornyak, G.; Lempert, K. Benzoxadiazocines, benzothiadiazocines and benzotriazocines I: General considerations and the synthesis of two 3,1,6-benzoxadiazocines. *Tetrahedron* **1983**, *39*, 479–481. [CrossRef]
9. Daniel, J.; Dhar, D.N. A facile synthesis of triazocinones and oxadiazocinones. *Synth. Commun.* **1993**, *23*, 2151–2157. [CrossRef]
10. Griengl, H.; Hayden, W.; Plessing, A. C(6)-C(7)-cyclised purines. *J. Heterocycl. Chem.* **1984**, *21*, 333–336. [CrossRef]

11. Musonda, C.C.; Edlin, C.D.; Boyle, G.A. Nitroimidazooxadiazocine Compounds. P.C.T. International Patent Application WO 2013 072903 A1, 23 May 2013.
12. Sonopo, M.S.; Venter, K.; Boyle, G.; Winks, S.; Marjanovic-Painter, B.; Zeevaart, J.R. Carbon-14 radiolabeling and in vivo biodistribution of a potential anti-TB compound. *J. Labelled Compd. Radiopharm.* **2015**, *58*, 23–29. [CrossRef] [PubMed]
13. Diness, F.; Beyer, J.; Meldal, M. Solid-Phase Synthesis of Terahydro-β-carbolines and Tetrahydroisoquinolines by Stereoselective Intramolecular *N*-Carbamyliminium Pictet-Spengler Reactions. *Chem. Eur. J.* **2006**, *12*, 8056–8066. [CrossRef] [PubMed]
14. Horikiri, T.; Yoshihiko, K. Gel Electrolyte, Cell and Electrochemical Element. European Patent EP 0996029 A2, 26 April 2000.
15. Guichard, G.; Lena, G.; Muller, P.; Rognan, D.; Boilard, E.; Lambeau, G. Compositions and Methods for the Inhibition of Phospholipase A2. U.S. Patent 2008 031951 A1, 7 February 2008.
16. Guichard, G.; Lena, G.; Muller, P.; Rognan, D.; Lambeau, G. Compositions and Methods for the Inhibition of Phospholipase A2. P.C.T. International Patent Application WO 2007 074169 A2, 5 July 2007.
17. Guichard, G.; Lena, G.; Lallemand, E.; Renia, L. Compositions and Methods for the Treatment of Disease. P.C.T. International Patent Application WO 2007 074170 A2, 5 July 2007.
18. Guichard, G.; Lena, G.; Lallemand, E.; Renia, L. Aza heterocyclics for the Treatment of Malaria or AIDS. P.C.T. International Patent Application WO 2007 074171 A1, 5 July 2007.
19. Bao, R.; Huang, W.; Zhen, Y.; He, B. One-pot synthesis of 4-substituted 2-thio-5-oxo-1,3,6-thiadiazaoctane. *Synth. Commun.* **1990**, *20*, 2675–2682. [CrossRef]
20. Enders, D.; Eichenauer, H. Asymmetrische Synthesen via metallierte chirale hydrazone. Enantioselektive Alkylierung von cyclischen Ketonen und Aldehyden. *Eur. J. Inorg. Chem.* **1979**, *112*, 2933–2960. [CrossRef]