Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 3337–3340

TETRAHEDRON: *ASYMMETRY*

On the easy oxidation of (*R*)-2-[*N*-(1-phenylethyl)amino]-1-cyclopentenedithiocarboxylic acid to its disulfide dimer

Raymundo Cea-Olivares,[a,*] Verónica García-Montalvo,[a] Simón Hernández-Ortega,[a] Cristina Rodríguez-Narváez,[b] Patricia García y García,[b] Marcela López-Cardoso,[b] Pedro de March,[c] Lluïsa González,[c] Laia Elias,[c] Marta Figueredo [c] and Josep Font [c]

[a]*Instituto de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Mexico 04510 D.F., Mexico*
[b]*Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, Chamilpa, Cuernavaca, 62210 Morelos, Mexico*
[c]*Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain*

Received 23 June 1999; accepted 22 July 1999

Abstract

The physical and spectroscopic data of (*R*)-2-[*N*-(1-phenylethyl)amino]-1-cyclopentenedithiocarboxylic acid are reviewed and the synthesis of (*R*)-di-[2-(*N*-(1-phenylethyl)amino]-1-cyclopentenedithiocarboxylic acid disulfide is described. The product resulting from the conjugate addition of the dithioacid to 2(5*H*)-furanone is also characterised. © 1999 Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

We have recently reported the preparation of (*R*)-2-[*N*-(1-phenylethyl)amino]-1-cyclopentenedithiocarboxylic acid, **1**,[1] that is one of the small number of known enantiopure dithioacids. This molecule was synthesised for the purpose of using it as a chiral equivalent of hydrogen sulfide on the conjugate addition to α,β-unsaturated carbonyl compounds. In addition, it could be interesting to test **1** as a chiral ligand, since *N*- and *S*-bonded main groups and transition metal complexes of *N*-alkyl and ester derivatives of 2-amino-1-cyclopentenedithiocarboxylic acid present a remarkable diversity in their co-ordination behaviour and have important bioorganic implications.[2,3] Dithioacid **1** was obtained by the well-known amine exchange reaction[4] between (*R*)-(+)-*N*-(1-phenylethyl)amine and 2-amino-1-cyclopentenedithiocarboxylic acid. Flash chromatography of the crude material allowed the isolation of **1** in ca. 50% yield as a thick yellow-orange oil. Although it was quite difficult, we were able to grow some crystals from this material, but unfortunately, as we can now demonstrate, these

* Corresponding author. Tel: 52 5 6224505; fax: 52 5 6162217; e-mail: cea@servidor.unam.mx

0957-4166/99/$ - see front matter © 1999 Published by Elsevier Science Ltd. All rights reserved.
PII: S0957-4166(99)00354-7

crystals did not correspond to the acid **1**, but to the disulfide **2** instead (Fig. 1). The easy oxidation of 2-amino-1-cyclopentenedithiocarboxylic acids to disulfides has already been described[5] and accordingly **2** is formed by leaving a sample of **1** in contact with air for a few days. We report herein irrefutable proof of the formation of **1** along with the corrected physical and spectroscopic data of both compounds **1** and **2**.

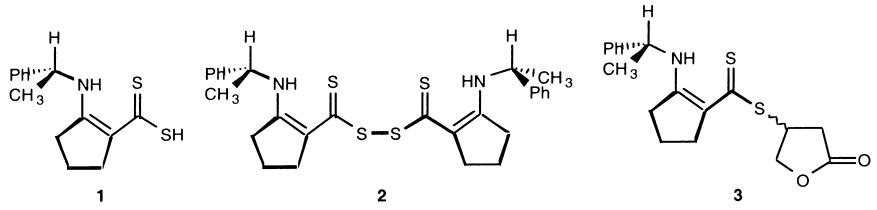

Figure 1.

Purified **1**, as an oil, reacted nicely with α,β-butenolide in methylene chloride solution at room temperature in the presence of catalytic amounts of triethylamine. Purification of the crude material by flash chromatography afforded 65% yield of the conjugate addition product **3** as an inseparable 1:1 mixture of diastereoisomers that was fully characterised by its spectroscopic data and correct elemental analysis. The structural identification of **3** is mainly based on the following features: (i) the mass spectrum presents the molecular ion at *m/z*=347; (ii) its ^{1}H NMR spectrum shows two double doublets at δ 3.03 and 3.02, corresponding to one of the protons H-3 of each diastereoisomer and another double doublet at δ 4.30, assigned to one of the protons H-5 of each stereoisomer; and (iii) the IR spectrum clearly indicates the presence of a saturated five-membered lactone at 1778 cm^{-1}, as well as the electron rich carbon–carbon double bond (1588 cm^{-1}) and the thiocarbonyl group (1278 cm^{-1}). The isolation and identification of lactone **3** in good yield is chemical proof of the structure of the dithioacid **1**.

In addition, the crop of crystals isolated in the attempted crystallisation of **1** have also been fully characterised by its spectroscopic data and X-ray analysis as the disulfide **2**. Table 1 presents selected bond distances and angles, while the molecular structure with the atom numbering appears in Fig. 2. The five-membered ring is quite similar to that described for amino-1-cyclopentenedithiocarboxylic acid and its derivatives.[2,6] The molecule presents the expected N–H···S hydrogen bonds, and all the distances and angles agree well with the dimensions reported for related structures.

Table 1
Selected bond distances (Å) and angles (°) for **2**

Bond distances		Bond angles	
C(1)-C(2)	1.412(7)	C(1)-C(2)-C(3)	111.0(5)
C(2)-C(3)	1.494(9)	C(2)-C(3)-C(4)	105.3(5)
C(3)-C(4)	1.502(10)	C(3)-C(4)-C(5)	106.7(7)
C(4)-C(5)	1.514(9)	C(4)-C(5)-C(1)	105.2(4)
C(1)-C(5)	1.527(9)	C(3)-C(2)-N(1)	123.9(5)
C(2)-N(1)	1.326(7)	C(5)-C(1)-C(6)	125.9(4)
C(6)-S(1)	1.668(6)	C(1)-C(6)-S(1)	128.8(4)
C(6)-S(2)	1.817(5)	C(1)-C(6)-S(2)	110.9(4)
S(2)-S(3)	2.009(3)	C(6)-S(2)-S(3)	105.4(2)
C(7)-N(1)	1.469(6)	C(2)-N(1)-C(7)	122.8(5)

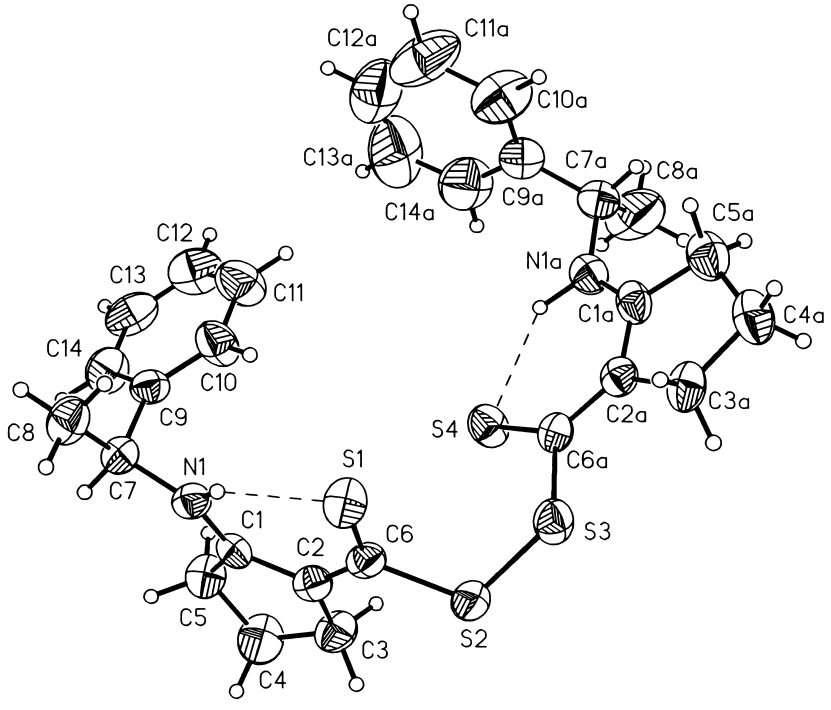

Figure 2. ORTEP view of **2**, with the atom numbering scheme

2. Experimental

*2.1. Dithioacid **1***

IR (film) 2966, 2931, 1588, 1489, 1271 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.10 (br s, mobile signal), 7.30–7.15 (m, 5H), 4.65 (q, *J*=7.3 Hz, 1H), 3.90 (br s, mobile signal), 2.71–2.50 (m, 3H), 2.40–2.22 (m, 1H), 1.90–1.55 (m, 2H), 1.57 (d, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 190.1 (CS), 170.5 (C-2), 142.2/128.8/127.5/125.7 (Ph), 118.8 (C-1), 56.2 (*C*HNH), 33.8/33.5 (C-3/C-5), 24.3 (Me), 20.0 (C-4); $[\alpha]_D^{20}$ −1371 (*c* 0.35, $CHCl_3$).

*2.2. Disulfide **2***

Mp 165–167°C (ethyl acetate–hexane); IR (film) 2966, 2931, 1588, 1489, 1271 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.30–7.15 (m, 5H), 4.70 (q, *J*=7.3 Hz, 1H), 3.15–2.95 (m, 2H), 2.80–2.60 (m, 1H), 2.45–2.30 (m, 1H), 1.95–1.50 (m, 2H), 1.45 (d, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 170.2 (C-2), 142.6/128.9/127.6/125.8 (Ph), 118.4 (C-1), 56.1 (*C*HNH), 33.2/32.3 (C-3/C-5), 24.5 (Me), 21.1 (C-4); FAB-MS (*m/z*): 524 (M^+, 9), 523 (7), 262 (25), 230 (100), 105 (38). $[\alpha]_D^{20}$ −2102 (*c* 0.37, $CHCl_3$). Anal. calcd for $C_{28}H_{32}N_2S_4$: C, 64.08; H, 6.15; N, 5.34; S, 24.44. Found: C, 63.71; H, 6.49; N, 5.27; S, 24.30.

*2.3. Reaction between dithioacid **1** and 2(5*H*)-furanone*

To a magnetically stirred solution of 2(5*H*)-furanone (100 mL, 1.5 mmol) in methylene chloride (4 mL) at room temperature, dithioacid **1** (440 mg, 1.7 mmol) and a catalytic amount of triethylamine were

added. The mixture was maintained at the same temperature for 24 h, washed with water (4 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under vacuum to yield 580 mg of an oil. Purification of this crude material by flash chromatography on silica gel (230–400 mesh) using hexane:ethyl acetate (3:1) as eluent afforded a 1:1 mixture of (4*R*)- and (4*S*)-4,5-dihydro-4-{[2′-((*R*)-*N*-α-methylbenzylamino)-1′-cyclopenten-1′-yl](thiocarbonyl)thio}-2(3*H*)-furanone, **3** (342 mg, 1.0 mmol, 65% yield), as an oil: IR (film) 2966, 2946, 2818, 1778, 1588, 1489, 1278, 1166, 1018, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.15 (m, 5H), 4.79 (m, 1H, H-5), 4.71 (m, 2H, H-4, C*H*-NH), 4.30 (dd, $J_{5,5}$=9.8 Hz, $J_{5,4}$=4.9 Hz, 1H, H-5), 3.03 (dd, $J_{3,3}$=18.3 Hz, $J_{3,4}$=8.8 Hz) and 3.02 (dd, $J_{3,3}$=18.3 Hz, $J_{3,4}$=8.8 Hz) (1H, H-3), 2.75–2.62 (m, 3H), 2.59 (dd, $J_{3,3}$=18.3 Hz, $J_{3,4}$=5.8 Hz, 1H, H-3), 2.40–2.25 (m, 1H), 1.90–1.60 (m, 2H, H-4′), 1.54 (d, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 192.3 (CS), 175.4 (CO), 170.1 (C-2′), 142.4/130.0/127.7/125.7 (Ph), 118.6 (C-1′), 73.5 and 73.4 (C-5), 55.9 (*C*HNH), 39.6 (C-4), 33.4/32.4 (C-3/C-3′/C-5′), 24.2 (CH_3), 20.4 (C-4′); MS (*m/z*): 347 (M^+, 2), 261 (8), 230 (8), 126 (13), 105 (100), 79 (23), 77 (25). Anal. calcd for $C_{18}H_{21}NO_2S_2$: C, 62.21; H, 6.09; N, 4.03; S, 18.45. Found: C, 62.37; H, 6.20; N, 4.04; S, 18.18.

2.4. X-Ray determination

Suitable crystals for X-ray single crystal structural determination of disulfide **2** were obtained by layering a solution of the compound in CH_2Cl_2 with hexane at room temperature. Data collections were carried out on a Siemens-P4 diffractometer at room temperature, with graphite-monochromated Cu-Kα radiation (λ=1.54178). Crystal cell parameters were obtained from 33 reflections in the range $20.03<2\theta<36.28$. Data were corrected for background and Lorentz-polarisation effects, and a semi-empirical absorption correction was applied (min/max transmission factors 0.3392/0.7791). The structures were solved by direct methods and refined by full-matrix least-squares calculation using SHELXL-97[7]. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were calculated in idealised positions, except for the hydrogen atom bonded to nitrogen. Final difference Fourier map was 0.235 and -0.3 eA^{-3}.

Acknowledgements

We gratefully acknowledge CONACYT for financial support Grant (0109P-E) and CRN for a fellowship.

References

1. de March, P.; Figueredo, M.; Font, J.; González, L.; Salgado, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2603–2606.
2. (a) Singh, S. K.; Singh, Y.; Rai, A. K.; Mehrotra, R. C. *Polyhedron* **1989**, *8*, 633–639; (b) Martin, E. M.; Bereman, R. D. *Inorg. Chem. Acta* **1991**, *188*, 221–231, and references cited therein.
3. Cea-Olivares, R.; Toscano, R. A.; Estrada, M.; Silvestru, C.; García y García, P.; López-Cardoso, M.; Blass-Amador, G. *Appl. Organomet. Chem*. **1995**, *9*, 133–140.
4. Bordás, B.; Sohár, P.; Matolcsy, G.; Berencsi, P. *J. Org. Chem*. **1972**, *11*, 1727–1730.
5. Takeshima, T.; Yokoyama, M.; Imamoto, T.; Akano, M.; Asaba, H. K. *J. Org. Chem*. **1969**, *34*, 730–732.
6. Miyamae, H.; Oikawa, T. *Acta Cryst*. **1985**, *C41*, 1489–1490.
7. SHELXL-97, University of Goettingen.