New bis-oxalamides from *trans*-1,2-diaminocyclohexane

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Dedicated to Professor Rosalinda Contreras on the occasion of her 60th anniversary

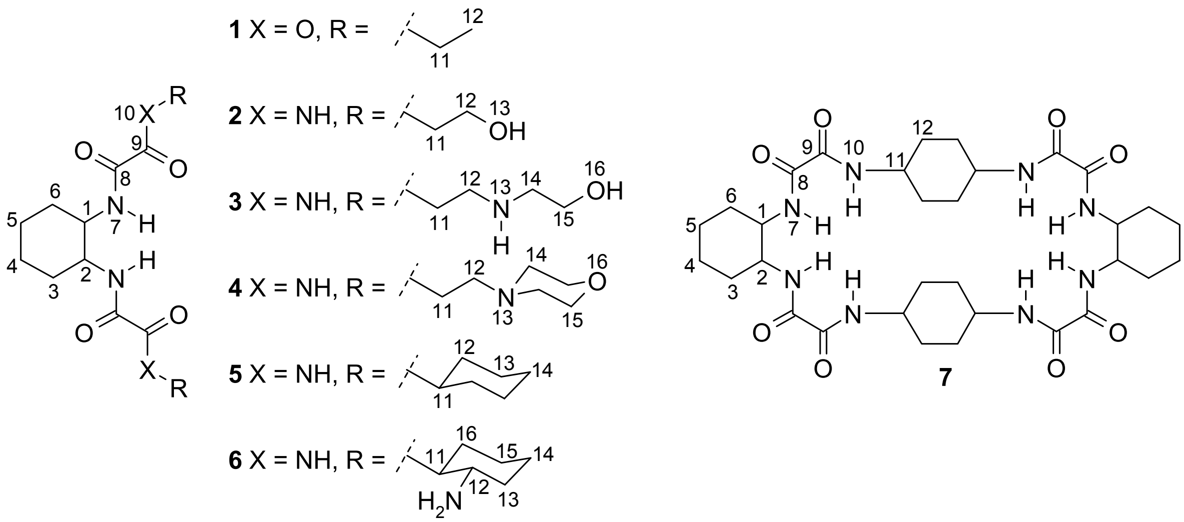
Abstract
The synthesis of six new bis-oxalamides **2-7** derived from *trans*-1,2-diaminocyclohexane and aliphatic amines is reported. These compounds were characterized by IR, MS and ^{1}H and ^{13}C NMR spectroscopy.

Keywords: Bis-oxalamate, bis-oxalamide, macrocycle, ^{1}H and ^{13}C NMR spectroscopy

Introduction

Oxalamides are molecules that possess in their structure acidic protons and O-lone pairs which form inter- and intramolecular hydrogen bonds. Experimental and theoretical studies have demonstrated that intramolecular hydrogen bonds in oxalamides determine their geometry and conformation whereas intermolecular hydrogen bonds increase their stability.[1-3] Due to these interactions, oxalamides are applied in diverse areas such as artificial receptors for biological recognition,[4] in engineering and crystal design[5] and in organogels formation.[6] Recently, oxalamide derivatives were identified as HIV-1 inhibitors.[7] Another important application of these compounds is in coordination chemistry as ligands.[8]

In this paper we report the synthesis and structural characterization by IR, MS and ^{1}H and ^{13}C NMR of six new oxalamides **2-7** derived from *trans*-1,2-diaminocyclohexane (Scheme 1).



Scheme 1

Results and Discussion

Synthesis

Synthesis of bis-oxalamides **2**-**7** started with the preparation of the oxalamate **1** from condensation reaction of *trans*-1,2-diaminocyclohexane and ethyl chlorooxoacetate in the presence of Et_3N as catalyst, according to a procedure reported in the literature.[9] Oxalamate **1** was first prepared by Albano and co-workers from enantiopure (*R,R)*- and (*S,S)*-*trans*-1,2-diaminocyclohexane.[10] Spectroscopic data for oxalamate **1** determined in this study are similar to those reported by Albano, however we observed a melting point of 180-182°C which is 15 ºC higher than that reported. Condensation reaction of **1** and two equivalents of the corresponding alkylamines gave oxalamides **2**-**6**. Under the same conditions **1** and *trans*-1,4-diaminocyclohexane produced the macrocycle **7**. Formation of **7** requires an excess of the diamine, no product formation was observed when the reaction was performed in an equimolar ratio. Macrocycles containing the oxalyl moiety are already known.[11-13] Compounds **2**-**7** were analyzed in solution by ^{1}H and ^{13}C NMR spectroscopy using [^{2}H]TFA as solvent, because they were isolated as very insoluble solids.

Infrared spectra

The IR spectrum of **1** shows characteristic absorption bands at 3248 (νN-H), 1745 (νO=C ester) and 1665 cm^{-1} (νO=C amide), in agreement with reported values[10]. For compounds **2**-**7** the IR spectra show one absorption band in the region of 3282-3276 cm^{-1} for the νN-H and only one strong band with an average value of 1644 cm^{-1} for νO=C due to a similar connectivity in the oxalyl moiety. IR absorptions of **2**-**7** show a high frequency shift for νN-H and a low frequency shift for νC=O with respect to **1**, this behavior indicates that the electronic density of nitrogen is more engaged with carbonyl group in **2**-**7** than in **1**. These values agree with reported data for similar compounds.[9,10,14]

Mass spectra

The analysis by mass spectrometry of compounds **4** and **5** showed the molecular ion, whereas **2**, **3** and **6** showed the $[M+1]^+$ peak. Additionally **2** and **3** present the $[M-OH]^+$characteristic peak for a hydroxyl group. The molecular ion for compound **7** was not observed.

NMR analysis

The ^{1}H and ^{13}C NMR chemical shifts of compounds **1**-**7** are listed in Tables 1 and 2 respectively. The ^{1}H and ^{13}C NMR data determined for oxalamate **1** in this study are similar to those reported by Albano and co-workers.[10] Intramolecular hydrogen bonding between N-H acidic protons and carbonyl oxygen atoms is known to favor the planar conformation and *trans* configuration of the oxalyl moiety.[1] Because **2**-**7** were only soluble in [^{2}H]TFA, which is a solvent that favors deuterium interchange, it was not possible to observe N-H chemical shifts and to conclude about hydrogen bonding in solution. The ^{1}H and ^{13}C NMR spectra of compounds **2**-**6** showed one half of the total expected signals because of the C_2 symmetry axis. H1 was observed as a broad signal between 3.91 - 4.00 ppm and it is in the expected range.[9] H3 and H4 appeared as broad signals. The rigid conformation of 1,2-diaminocyclohexane ring for **1**-**6** in solution, allowed to distinguish equatorial H3 and H4 from axial H3 and H4 at room temperature. We were able to observe that the pendant arm of oxalamate **1** displayed a triplet for methyl protons and a highly symmetric 14 lines multiplet for the methylene protons, in contrast to the quartet triplet multiplicity reported by Albano and co-workers[10] and for the analog oxalamate derived from *trans*-1,4-diaminocyclohexane.[9] In our case, the multiplicity of methylene protons indicates that they have a different chemical environment, probably as a result of slow or no rotation of the pendant arm. The same behavior was observed for compound **2** and is equally expected for **3**-**6** because they gave broad signals. On the other hand, ^{13}C chemical shifts for **2**-**6** are in the characteristic range for this kind of compounds.[9,10,15]

A macrocyclic structure was proposed for compound **7** because its ^{13}C NMR spectrum showed only seven signals, instead of the nine expected if only one NH_2 of *trans*-1,4-diaminecyclohexane had reacted to give an open structure like that showed by **2**-**6**. In the ^{1}H spectrum, compound **7** displayed only six broad signals, which fully correlated with ^{13}C NMR signals in the HETCOR spectrum. ^{1}H and ^{13}C NMR chemical shifts of **7** are similar to those determined for **2-6**.

In future work, we will use the bis-oxalamides reported here as ligands in coordination chemistry.

Table 1. ^{1}H NMR chemical shifts of compounds **1** ($CDCl_3$) and **2-7** in [^{2}H]TFA

Compd.	H1,H2	H3,H6 (eq)	H3,H6 (ax)	H4,H5 (eq)	H4,H5 (ax)	R
1	3.81, *m*	2.08, *m*	1.37, *m*	1.82, *m*	1.37, *m*	7.39, *d,* ^{3}J 6.14, NH; 4.33, *m,* H11; 1.37, *dd*, ^{3}J 7.09, ^{3}J 7.32, H12
2	3.91, *m*	2.07, *m*	1.58, *m*	1.90, *m*	1.43, *m*	3.61, *m*, H11; 3.97, *t*, ^{3}J 4.99, H12
3	3.96, *m*	2.09, *m*	1.55, *m*	1.89, *m*	1.43, *m*	3.73, *m*, H11; 3.58, *m*, H12; 3.50, *m*, H14; 4.17, *m*, H15
4	3.90 - 4.00, *m*	2.10, *m*	1.57, *m*	1.91, *m*	1.45, *m*	3.85, *t*, ^{3}J 11.98, H11; 3.40, *dd*, ^{3}J 11.68, ^{3}J 10.51, H12; 3.62, *m*, $H14_{ax}$; 4.02, *m*, $H14_{eq}$; 4.09, *dm*, ^{2}J 12.86, $H15_{ax}$; 4.36, *dm*, ^{2}J 12.86, $H15_{eq}$
5	3.92, *m*	2.06, *m*	1.65, *m*	1.88, *m*	1.36, *m*	3.71, *m*, H11; 1.88, *m*, $H12_{eq}$, $H13_{eq}$; 1.36, *m*, $H12_{ax}$, $H13_{ax}$, $H14_{ax}$; 1.65, *m*, $H14_{eq}$
6	3.97, *m*	2.26, *m*	1.61, *m*	2.05, *m*	1.42, *m*	3.97, *m,* H11; 3.47, *m*, H12; 2.10, *m*, $H13_{eq}$, $H16_{eq}$; 1.42, *m*, $H13_{ax}$, $H16_{ax}$; 2.05, *m*, $H14_{eq}$, $H15_{eq}$; 1.42, *m*, $H14_{ax}$, $H15_{ax}$
7	3.96, *m*	2.08, *m*	1.57, *m*	1.90, *m*	1.43, *m*	3.80, *m*, H11; 2.08, *m*, $H12_{eq}$; 1.57, *m*, $H12_{ax}$

Table 2. ^{13}C NMR chemical shifts and peak multiplicities of compounds **1** ($CDCl_3$) and **2-7** in [^{2}H]TFA

Compd.	C1, C2	C3, C6	C4, C5	C8	C9	R
1	53.9, *d*	32.1, *t*	24.6, *t*	157.2, *s*	160.4, *s*	63.5, *t*, C11; 14.2, *q*, C12
2	55.5, *d*	31.9, *t*	24.8, *t*	160.8, *s*	161.5, *s*	43.0, *t*, C11; 61.7, *t*, C12
3	55.8, *d*	32.2, *t*	24.9, *t*	160.9, *s*	162.7, *s*	38.2, *t*, C11; 49.3, *t*, C12; 51.5, *t*, C14; 58.8, *t*, C15
4	55.5, *d*	32.1, *t*	24.6, *t*	160.6, *s*	n.o.[a]	35.6, *t*, C11; 58.2, *t*, C12; 54.1, *t*, C14; 65.1, *t*, C15
5	55.7, *d*	31.9, *t*	24.8, *t*	159.9, *s*	161.5, *s*	52.0, *d*, C11; 32.9, *t*, C12; 25.3, *t*, C13; 25.7, *t*, C14
6	54.7, *d*	29.6, *t*	23.0, *t*	159.6, *s*	160.8, *s*	52.7, *d*, C11; 56.2, *d*, C12; 30.9, *t*, C13; 23.5, *t*, C14; 23.5, *t*, C15; 30.9, *t*, C16
7	55.2, *d*	31.6, *t*	24.3, *t*	159.9, *s*	160.9, *s*	50.0, *d*, C11; 30.5, *t*, C12

[a] not observed.

Experimental Section

General Procedures. Melting points were determined on a Melt Temp II apparatus in an open capillary tube and were not corrected. IR spectra were recorded in a Varian 3100 FT-IR Excalibur Series spectrometer equipped with an ATR device in the range of 400-4000 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded in a Varian Mercury 300 (^{1}H, 300.08; ^{13}C, 75.46 MHz) spectrometer in $CDCl_3$ and [^{2}H]TFA solution following standard techniques, chemical shifts are given in ppm and referred to $SiMe_4$ as internal reference. Assignments of ^{1}H and ^{13}C signals were made on the basis of HETCOR experiments and by comparison to the reported values for similar compounds when possible. ^{13}C peak multiplicities were determined by APT experiments. The mass spectra were recorded on a Hewlett-Packard HP 5989A, EI MS, 70 eV. Elemental analyses were carried out in a Flash 1112 Thermo Finnigan analyzer.
Materials. Triethylamine (TEA), tetrahydrofuran (THF), *trans*-1,2-diaminocyclohexane, *trans*-1,4-diaminocyclohexane, ethyl chlorooxoacetate, ethanolamine, cyclohexylamine, 2-(2-aminoethylamino)ethanol and 4-(2-aminoethyl)morpholine, were purchased from commercial suppliers and used as received.

Diethyl *N,N´*-cyclohexane-1,2-diyldioxalamate (1). *trans*-1,2-Diaminocyclohexane (1.05 ml, 1 g, 8.75 mmol) and TEA (2.44 ml, 1.77 g, 17.51 mmol) in THF (40 ml) were treated dropwise under vigorous stirring with ethyl chlorooxoacetate (1.94 ml, 2.39 g, 17.51 mmol) at 0 °C. The reaction mixture was additionally stirred for 4 h at 25 °C. The suspension was filtered and the solid was washed with water. THF solution was evaporated to dryness, washed with water, mixed with the previously obtained solid and dried to give **1** (1.845 g, 67 %) as a white solid. m.p. 180-182 °C (literature 157-165 ºC[10]). IR ν_{max} (cm^{-1}) (s, strong; m, medium; w, weak; br, broad): 3248 (N-H, m); 2937, 2867 (C-H, w); 1745, 1665 (C=O, s); 1197 (O=C-O, s); 1525 (δ N-H, s). MS, m/e (%): $[M+1]^+$ 315.15 (8), M^+ 314.15 (3), 241.20 (84), 197.20 (87), 167.05 (100), 124.05 (45), 81.15 (43).

General synthesis of compounds 2-7
Compounds **3**-**7** were synthesized according to the procedure described for **2**.
***N*-(2-Hydroxy-ethyl)-*N'*-{2-[(2-hydroxy-ethylaminooxalyl)-amino]-cyclohexyl}-oxalamide (2).** **1** (1 g, 3.18 mmol) and TEA (0.88 ml, 0.644 g, 6.36 mmol) in THF (20 ml) were treated dropwise under vigorous stirring with ethanolamine (0.38 ml, 0.38 g, 6.36 mmol) at 25 °C. After refluxing for 5 h, the solid was filtered and washed with hot THF (5 ml) to give **2** (0.8286 g, 75 %) as a white solid. m.p. 286-287 °C. Anal. Calcd. for $C_{14}H_{24}N_4O_6$: C, 48.83; H, 7.02; N, 16.27. Found: C, 48.59; H, 7.22; N, 15.99; IR ν_{max} (cm^{-1}): 3280 (N-H, m); 3200-3000 (O-H, br); 2931, 2859 (C-H, w); 1643 (C=O, s); 1513 (δ N-H, s). MS, m/e (%): $[M+1]^+$ 345.30 (8), $[M-OH]^+$ 327.30 (4), 314.20 (72), 256.20 (86), 238.20 (100), 212.15 (81), 184.20 (72), 167.15 (27), 141.20 (45), 97.20 (44), 81.15 (38).

***N*-[2-(2-Hydroxy-ethylamino)-ethyl]-*N′*-(2-{[2-(3-hydroxy-propylamino)-ethylaminooxalyl]-amino}-cyclohexyl)-oxalamide (3). 1** (1 g, 3.18 mmol), TEA (0.88 ml, 0.644 g, 6.36 mmol) and 2-(2-aminoethylamino)ethanol (0.64 ml, 0.66 g, 6.36 mmol) were refluxed for 3 h. Product **3** (1.36 g, quantitative) was isolated as a white solid. m.p. 209-210 °C. Anal. Calcd. for $C_{18}H_{34}N_6O_6 \cdot 0.5H_2O$: C, 49.19; H, 8.03; N, 19.12. Found: C, 49.38; H, 8.26; N, 19.13; IR ν_{max} (cm^{-1}): 3276 (N-H, m); 3200-3000 (O-H, br); 2928, 2832 (C-H, w); 1644 (C=O, s); 1512 (δ N-H, s). MS, m/e (%): $[M+1]^+$ 431.35 (3), $[M-OH]^+$ 413.30 (2), 399.30 (10), 381.30 (22), 326.25 (54), 199.20 (39), 142.15 (26), 97.15 (29), 74.15 (100).

***N*-(2-Morpholin-4-yl-ethyl)-*N′*-{2-[(2-morpholin-4-yl-ethylaminooxalyl)-amino]-cyclohexyl}-oxalamide (4). 1** (1 g, 3.18 mmol), TEA (0.88 ml, 0.644 g, 6.36 mmol) and 4-(2-aminoethyl)morpholine (0.82 ml, 0.82 g, 6.36 mmol) were refluxed for 7 h. Product **4** (0.99 g, 65%) was isolated as a white solid. m.p. 260-262 °C. Anal. Calcd. for $C_{22}H_{38}N_6O_6$: C, 54.76; H, 7.94; N, 17.41. Found: C, 54.74; H, 8.15; N, 17.31; IR ν_{max} (cm^{-1}): 3282 (N-H, m); 2939, 2859 (C-H, w); 1644 (C=O, s); 1117 (C-O-C, m); 1514 (δ N-H, s). MS, m/e (%): M^+ 482.45 (6), 452.40 (6), 157.05 (3), 100.05 (100).

***N*-Cyclohexyl-*N′*-[2-(cyclohexylaminooxalyl-amino)-cyclohexyl]-oxalamide (5). 1** (1 g, 3.18 mmol), TEA (0.88 ml, 0.644 g, 6.36 mmol) and cyclohexylamine (0.72 ml, 0.63 g, 6.36 mmol) were refluxed for 7 h. Product **5** (1.24 g, 93 %) was isolated as a white solid. m.p. 297-301 °C. Anal. Calcd. for $C_{22}H_{36}N_4O_4 \cdot 0.5H_2O$: C, 61.51; H, 8.68; N, 13.04. Found: C, 61.89; H, 8.94; N, 12.97; IR ν_{max} (cm^{-1}): 3287 (N-H, m); 2932, 2856 (C-H, m); 1645 (C=O, s); 1513 (δ N-H, s). MS, m/e (%): M^+ 420.35 (3), 339.25 (14), 294.15 (94), 250.20 (73), 222.20 (36), 167.15 (67), 141.15 (25), 97.15 (100), 81.15 (19).

***N*-(2-Amino-cyclohexyl)-*N′*-{2-[(2-amino-cyclohexylaminooxalyl)-amino]-cyclohexyl}-oxalamide (6). 1** (1 g, 3.18 mmol), TEA (0.88 ml, 0.644 g, 6.36 mmol) and *trans*-1,2-diaminocyclohexane (0.76 ml, 0.72 g, 6.36 mmol) were refluxed for 7 h. Product **6** (1.30 g, quantitative) was isolated as a white solid. m.p. above 340 °C. Anal. Calcd. for $C_{22}H_{38}N_6O_4 \cdot 1.7H_2O$: C, 54.91; H, 8.60; N, 17.46. Found: C, 55.19; H, 8.53; N, 17.05; IR ν_{max} (cm^{-1}): 3275 (N-H, m); 2925, 2855 (C-H, w); 1643 (C=O, s); 1506 (δ N-H, s). MS, m/e (%): $[M+1]^+$ 451.45 (2), 354.30 (89), 186.25 (10), 97.15 (100), 71.15 (25), 42.15 (54).

2,5,10,13,20,23,28,31-Octaazapentacyclo[30.4.0.0^{14,19}.2^{6,9}.2^{24,27}]tetracontane-3,4,11,12,21,22,29,30-octaone (7). 1 (1 g, 3.18 mmol), TEA (0.88 ml, 0.644 g, 6.36 mmol) and *trans*-1,4-diaminocyclohexane (0.72 g, 6.36 mmol) were refluxed for 2 h. Product **7** (1.05 g, quantitative) was isolated as a white solid. m.p. above 340 °C. Anal. Calcd. for $C_{32}H_{48}N_8O_8 \cdot 3.5H_2O$: C, 52.23; H, 7.53; N, 15.23. Found: C, 52.40; H, 7.90; N, 15.15; IR ν_{max} (cm^{-1}): 3278 (N-H, m); 2931, 2859 (C-H, w); 1644 (C=O, s); 1502 (δ N-H, s). MS, m/e (%): 168.15 (10), 141.15 (18), 113.05 (14), 97.05 (55), 82.15 (13), 71.15 (20), 58.15 (100), 43.15 (53).

Acknowledgements

This work was supported by PROMEP-México and Fondo Ramón Álvarez-Buylla de Aldana 368/05, Universidad de Colima. E. F. M.-V. thanks Conacyt-México for a scholarship.

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