Synthesis and Characterization of Three Novel Nitrogen-containing Macrolides

Xin Leng, Bingqin Yang, Yuanyuan Liu, Yi Xie, and Jie Tong

Key Laboratory of Synthetic and Natural Chemistry of the Ministry of Education, College of Chemistry and Materials Science, NorthWest University of Xi'an, Taibai Bei Avenue 229, Xi'an 710069, Shaanxi Provice, People's Republic of China

Reprint requests to Prof. Dr. Bingqin Yang. Fax: +86 029 88302217.
E-mail: organic_lengxin@163.com

Z. Naturforsch. **2011**, *66b,* 930 – 934; received July 23, 2011

Three novel nitrogen-containing macrolides have been synthesized by esterification. All of them have been characterized by infrared (IR), elemental analysis, mass spectra (MS), and ^{1}H NMR spectroscopy, and their crystal structures were determined by single-crystal X-ray diffraction. The preparation methods and the intermolecular associations based on C–H$\cdots$O hydrogen bonds and π-π stacking interactions are discussed.

Key words: Macrocycles, Macrolides, Synthesis, X-Ray Crystal Structure, Hydrogen Bonds

Introduction

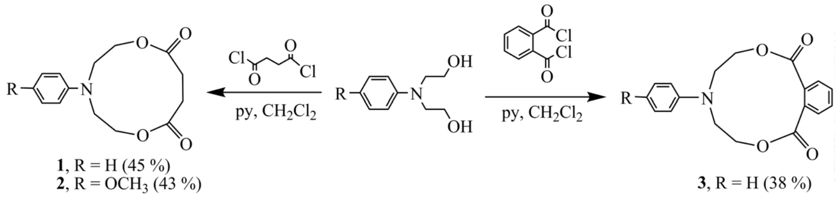
Macrocyclic compouds have attracted increasing attention because of their success in medicinal as well as recognition chemistry and their widespread occurrence in nature [1 – 9].

Among the great number of macrocycles which have been described, macrolides are particularly interesting, which are of high significance in areas as diverse as drug development as well as supramolecular chemistry and application in the perfume industry. Many macrolides are found to be effective as chemotherapeutic agents in the treatment of human and animal diseases, *e. g.*, antibiotics or anticancer agents [9 – 12]. Macrolides are also expected to act as cation receptors which can be used in selective complexation, providing simple models that allow us the molecular understanding of biological processes such as the generation and propagation of the electrical impulse in the nervous system, muscular contraction and the interactions of enzymes with cations.

Macrolides have been synthesized and studied exextensively in organic chemistry [13 – 20]. So far, the preparation of macrolides by relatively easy and economical routes has been described only in a few cases. In this article, some novel macrolides with different ring sizes and annelated with a benzene ring have been synthesized by esterification of acyl chlorides with diols under high-dilution conditions (Scheme 1), and single-crystal structure studies of them are presented.

Results and Discussion

The starting materials 2,2′-(phenylimino)diethanol and 2,2′-[(4-methoxyphenyl)azanediyl]diethanol were prepared according to literature procedures [21]. The most popular way of synthesis of macrocyclic compounds is always under high-dilution condition in order to prevent polymerization. Although metal ions are sometimes used as templates in cyclization, it is always a hard task to remove the ions after the reaction. Macrolides **1**, **2** and **3** were synthesized by condensation reactions in dry dichloromethane under high-dilution. In this way, we finally obtained colorless soluble solids of compounds **1**, **2** and **3**. The preparation is summarized in Scheme 1. All of the products had



Scheme 1.

Table 1. Crystal structure data for **1** – **3**.

	1	**2**	**3**
Formula	$C_{14}H_{17}NO_4$	$C_{18}H_{17}NO_4$	$C_{15}H_{19}NO_5$
M_r	263.29	311.33	293.31
Crystal size, mm^3	$0.35 \times 0.29 \times 0.15$	$0.22 \times 0.20 \times 0.19$	$0.37 \times 0.28 \times 0.21$
Crystal system	monoclinic	orthorhombic	orthorhombic
Space group	$P2_1/c$	*Pbca*	$P2_12_12_1$
a, Å	7.793(2)	8.200(1)	7.467(1)
b, Å	8.954(2)	8.418(1)	8.848(1)
c, Å	18.472(4)	45.418(6)	22.383(3)
β, deg	91.159(3)	90	90
V, Å^3	1288.7(5)	3135.0(7)	1478.7(4)
Z	4	8	4
D_{calcd}, g cm^{-3}	1.36	1.32	1.32
μ(MoKα), cm^{-1}	1.0	0.9	1.0
$F(000)$, e	560	1312	624
hkl range	$-8 \le h \le +9$, $-10 \le k \le +5$, $-21 \le l \le +22$	$-9 \le h \le +9$, $-10 \le k \le +9$, $-34 \le l \le +53$	$-8 \le h \le +5$, $-10 \le k \le +10$ $-26 \le l \le +26$
Temperature, K	293(2)	293(2)	293(2)
$((\sin\theta)/\lambda)_{\max}$, Å^{-1}	0.597	0.597	0.597
Refl. measd / unique / R_{int}	6138 / 2291 / 0.0262	14500 / 2774 / 0.0450	7406 / 2630 / 0.0237
Param. refined	173	208	192
$R1$(F) / $wR2(F^2)^{a,b}$ (all refl.)	0.0563 / 0.1040	0.0738 / 0.1441	0.0430 / 0.0913
A / B (weighting scheme)^b	0.043 / 0.1109	0.083 / 0	0.0432 / 0.0941
x(Flack) [24]	–	–	1.3(12)
GoF $(F^2)^c$	1.082	1.022	1.004
$\Delta\rho_{\text{fin}}$ (max / min), e Å^{-3}	0.193 / −0.139	0.152 / −0.144	0.142 / −0.099

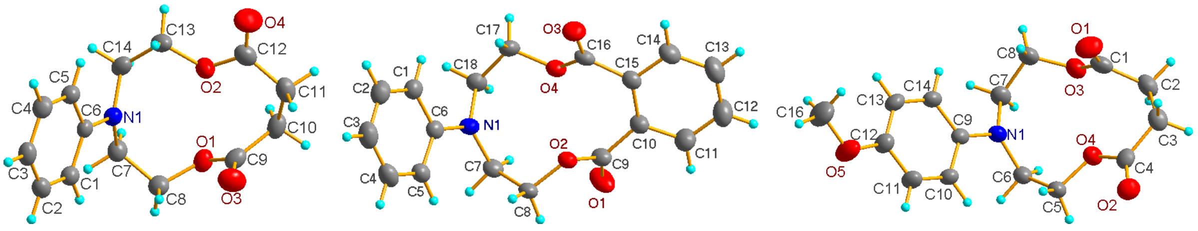
[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; [b] $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\text{Max}(F_o^2,0) + 2F_c^2)/3$; [c] GoF $= [\Sigma w(F_o^2 - F_c^2)^2/(n_{\text{obs}} - n_{\text{param}})]^{1/2}$.

Table 2. Selected bond lengths (Å), angles (deg), and dihedral angles (deg) for **1**, **2**, and **3** with estimated standard deviations in parentheses.

1		**2**		**3**	
O4–C12	1.192(2)	O3–C16	1.207(2)	O1–C1	1.199(2)
O2–C12	1.338(2)	O4–C16	1.332(2)	O3–C1	1.334(2)
O2–C13	1.440(2)	O4–C17	1.445(2)	O3–C8	1.438(2)
O3–C9	1.200(2)	O1–C9	1.194(2)	O2–C4	1.198(2)
O1–C9	1.339(2)	O2–C9	1.339(2)	O4–C4	1.336(2)
O1–C8	1.447(2)	O2–C8	1.444(2)	O4–C5	1.447(2)
C12–O2–C13	118.28(15)	C16–O4–C17	117.43(15)	C1–O3–C8	118.51(17)
O4–C12–C11	125.09(19)	O3–C16–C15	123.71(18)	O1–C1–C2	123.6(2)
O4–C12–O2	123.16(19)	O3–C16–O4	123.72(19)	O1–C1–O3	124.1(2)
O2–C12–C11	111.75(17)	O4–C16–C15	123.71(18)	O3–C1–C2	112.23(18)
O2–C13–C14	107.47(15)	O4–C17–C18	108.31(15)	O3–C8–C7	108.17(18)
C9–O1–C8	117.96(14)	C9–O2–C8	117.01(14)	C4–O4–C5	118.63(16)
O3–C9–C10	124.13(17)	O1–C9–C10	124.44(19)	O2–C4–C3	125.21(18)
O3–C9–O1	123.95(17)	O1–C9–O2	123.93(18)	O2–C4–O4	123.20(19)
O1–C9–C10	111.92(15)	O2–C9–C10	111.55(16)	O4–C4–C3	111.59(18)
O1–C8–C7	109.25(14)	O2–C8–C7	112.76(15)	O4–C5–C6	106.65(15)
C14–N1–C7–C8	113.03(17)	C18–N1–C7–C8	117.38(19)	C7–N1–C6–C5	121.05(18)
C7–N1–C14–C13	−120.75(17)	C7–N1–C8–C17	−103.8(2)	C6–N1–C7–C8	−108.0(2)
C14–N1–C6–C1	14.2(2)	C18–N1–C6–C5	168.13(17)	C7–N1–C9–C10	163.85(18)
C14–N1–C6–C5	−9.6(2)	C18–N1–C6–C1	177.19(16)	C7–N1–C9–C14	−16.8(3)

elemental analyses, IR, MS and ^{1}H NMR spectra which were in accordance with the proposed structures. A view of the molecules **1**, **2** and **3** is shown in Fig. 1. A summary of the crystal data and numbers pertinent to data collection and structure refinement are summarized in Table 1.

All of the macrolides **1**, **2** and **3** were crystallized from dichloromethane. Macrolide **1** crystallized in the monoclinic crystal system, space group $P2_1/c$, with four molecules in the unit cell, while **2** crystallized in the orthorhombic crystal system, space group *Pbca* with eight molecules in the unit cell, and macrolide **3** in



1 **2** **3**

Fig. 1. The molecular structures of **1**, **2** and **3** showing the atom labeling scheme. Displacement ellipsoids are drawn at the 30 % probability level.

Table 3. C–H···O hydrogen bond data for **1**, **2** and **3** (Å, deg).

	D–H···A	D–H	H···A	D···A	D–H···A
1	C8–H8A···O3	0.97	2.28	2.71 (5)	106
2	C18–H18B···O3	0.97	2.56	3.36 (7)	141
	C8–H8B···O1	0.97	2.30	2.71 (2)	105
3	C11–H11···O2	0.93	2.49	3.36 (3)	156

the orthorhombic crystal system, space group $P2_12_12_1$, with four molecules in the unit cell. Selected bond lengths and angles are listed in Table 2.

Macrolide **1** displays offset face-to-face π-π stacking interactions. All three compounds show interesting hydrogen bond patterns built up by weak C–H···O interactions. Characteristic data are listed in Table 3.

In the solid state, macrolide **1** (Fig. 1) displays one ester oxygen (O1) pointing inside the ring, and the other ester oxygen (O2) projecting outwards. Each macrolide uses the oxygen atom of the ester carbonyl (O3) as hydrogen bond acceptor, while the proton H8A acts as the donor. The lattice stabilization is thus achieved through weak C–H···O hydrogen bonds and π-π stacking interactions. Two centrosymmetrically related benzene rings are π-stacked with a shearing in such a way that the benzene centroid-to-centroid distance is 3.855 Å and the interplanar separation between stacked benzene rings in this region is 3.610 Å (Fig. 2).

In the solid-state structure of **2**, each macrolide uses the oxygen of the ester carbonyl (O3) as hydrogen bond acceptor, while the hydrogen H18B acts as the donor. The two benzene rings of the molecule take an approximate perpendicular juxtaposition in which they include an angle of 57.11°.

The major stuctural features of compound **3** are similar to that of macrolide **1**. The methoxy substituent remains almost co-planar with the benzene ring to which it is attached. Each molecule uses the oxygen of the ester carbonyls (O1, O2) as hydrogen bond acceptors, whereas the hydrogen H8B and the aromatic proton H11 act as the donors.

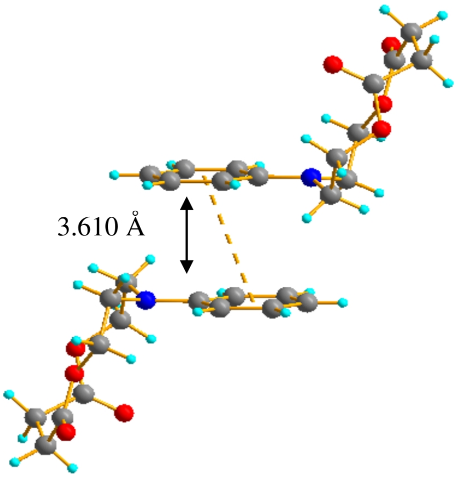


Fig. 2. π-π Interaction in the crystal structure of **1**.

Experimental Section

Solvents and reagents were purified and dried by standard methods. The melting points were determined on a XT4 micro melting point apparatus and are uncorrected. IR spectra were recorded on a EQUINOX-55 spectrometer in a KBr matrix. ^{1}H NMR spectra were recorded on a INOVA-400 NMR spectrometer, using TMS as internal standard and $CDCl_3$ as solvent. Elemental analyses were performed on a Vario EL III CHNOS analyzer. Electrospray mass spectra were obtained with a GC 6890-MS 5973 spectrometer (Agilent). 200 – 300 mesh silica gel was used for column chromatography.

2,2′-(Phenylimino)diethanol and 2,2′-[(4-methoxyphenyl)-azanediyl]diethanol

A mixture of 18.6 g (0.2 mol) of aniline or 24.6 g (0.2 mol) of 4-methoxyaniline, 5 mL of propionic acid and 100 mL of water was stirred vigorously, and to this mixture 25 mL of ethylene oxide was added dropwise at 0 °C in the course of 3 h. The temperature rose gradually to 10 °C, and stirring was continued for an additional 24 h. The organic layer was separated and washed with an aqueous saturated solution of sodium carbonate. All volatiles were evaporated under reduced pressure.

2,2′-(Phenylimino)diethanol: Slightly yellow crystals (30.8 g, 85 %). M. p. 56 – 57 °C (lit.: 55 – 56 °C [21]).

2,2′-[(4-methoxyphenyl)azanediyl]diethanol: Colorless solid (29.1 g, 69 %). M. p. 70 – 71 °C.

*Macrolides **1**, **2** and **3***

A mixture of 0.006 mol of 2,2′-(phenylimino)diethanol or 2,2′-[(4-methoxyphenyl)azanediyl]diethanol, 1000 mL of dry dichloromethane, and 1 mL (0.012 mol) of pyridine was stirred in the dark at r. t. To this solution 0.006 mol of succinyl chloride or 1,2-benzenedicarbonyl chloride in dichloromethane was added dropwise over 4 h. The mixture was stirred overnight at r. t. About 900 mL of the solvent was removed under atmospheric pressure, and the residual solution was washed 4 times with 50 mL of water and dried over $CaCl_2$. The residue was then purified by column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (2 :1).

1: Yield: 45 % . M. p. 82 – 83 °C. – IR (film): ν = 3098, 3032, 1733 (C=O), 1599, 1504, 1259, 1221 755, 694 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (m, 2H, H_{ar}), 6.79 (t, 1H, H_{ar}), 6.62 (d, 2H, H_{ar}), 4.39 [t, 4H, 2(O-CH_2)], 3.67 [t, 4H, 2(N-CH_2)], 2.65 [m, 4H, 2(CH_2-CO)]. – MS (EI, 70 eV): m/z (%) = 263 (100) $[M]^+$. – $C_{14}H_{17}NO_4$ (263.29): calcd. C 63.87, H 6.51, N 5.32; found C 63.83, H 6.53, N 5.31.

2: Yield: 38 % . M. p. 137 – 138. – IR (film): ν = 3062, 3021, 2910, 1712 (C=O), 1598, 1504, 1461, 1290, 1193, 753, 736, 695 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (m, 2H, H_{ar}), 7.59 (m, 2H, H_{ar}), 7.28 (m, 2H, H_{ar}), 6.80 (t, 1H, H_{ar}), 6.62 (d, 2H, H_{ar}), 4.56 [t, 4H, 2(O-CH_2)], 3.83 [t, 4H, 2(N-CH_2)]. – MS (EI, 70 eV): m/z (%) = 311 (100) $[M]^+$. – $C_{18}H_{17}NO_4$ (311.33): calcd. C 69.44, H 5.50, N 4.50; found C 69.41, H 5.49, N 4.52.

3: Yield: 43 %. M. p. 85 – 87 °C. – IR(film): ν = 3065, 2925, 1732 (C=O), 1621, 1515, 1457, 1379, 1275, 1187, 1153, 1043, 813 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 6.85 (t, 2H, H_{ar}), 6.60 (d, 2H, H_{ar}), 4.35 [t, 4H, 2(CH_2-O)], 3.76 (s, 3H, OMe), 3.60 [t, 4H, 2(CH_2-N)], 2.63 [d, 4H, 2(CH_2-CO)]. – MS (EI, 70 eV): m/z (%) = 293 (100) $[M]^+$. – $C_{15}H_{19}NO_5$ (293.31): calcd. C 61.42, H 6.53, N 4.78; found C 61.41, H 6.55, N 4.79.

X-Ray structure determination

X-Ray diffraction data were collected on a Bruker Smart 1000 CCD diffractometer with graphite-monochromatized MoK_α radiation (λ = 0.71073 Å) at r. t. The structures were solved by Direct Methods and refined by full-matrix least-squares methods on F^2 with the programs SHELXS-97 [22] and SHELXL-97 [23]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were treated using a riding model. Due to the lack of heavy atoms, refinement of Flack's x parameter [24] for **3** proved to be inconclusive.

CCDC 833941 – 833943 contain the supplementary crystallograpic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

---

[1] S. Bräse, A. Encinas, J. Keck, C. F. Nising, *Chem. Rev.* **2009**, *109*, 3903 – 3990.

[2] A. Dondoni, A. Marra, *Chem. Rev.* **2010**, *110*, 4949 – 4977.

[3] S. Lee, J. Xie, X. Chen, *Chem. Rev.* **2010**, *110*, 3087 – 3111.

[4] M. Wang, C. N. Boddy, *Biochemistry* **2008**, *47*, 11793 – 11803.

[5] N. Horstmann, S. Essig, S. Bockelmann, H. Wieczorek, M. Huss, F. Sasse, D. Menche, *J. Nat. Prod.* **2011**, *74*, 1100 – 1105.

[6] A. Hamdache, A. Lamarti, J. Aleu, I. G. Collado, *J. Nat. Prod.* **2011**, *74*, 893 – 899.

[7] D. Li, G. Carr, Y. Zhang, D. E. Williams, A. Amlani, H. Bottriell, A. L. -F. Mui, R. J. Anderson, *J. Nat. Prod.* **2011**, *74*, 1093 – 1099.

[8] A. Krunic, A. Vallat, S. Mo, D. D. Lantvit, S. M. Swanson, J. Orjala, *J. Nat. Prod.* **2010**, *73*, 1927 – 1932.

[9] E. Marsault, M. L. Peterson, *J. Med. Chem.* **2011**, *54*, 1961 – 2004.

[10] S. C. Mwakwari, W. Guerrant, V. Patil, S. I. Khan, B. L. Tekwani, Z. A. Gurard-Levin, M. Mrksich, A. K. Oyelere, *J. Med. Chem.* **2010**, *53*, 6100 – 6111.

[11] N. Oku, K. Takada, R. W. Fuller, J. A. Wilson, M. L. Peach, L. K. Pannell, J. B. Mcmahon, K. R. Gustafson, *J. Am. Chem. Soc.* **2010**, *132*, 10278 – 10285.

[12] J. D. Mortison, D. H. Sherman, *J. Org. Chem.* **2010**, *75*, 7041 – 7051.

[13] R. Carrillo, V. S. Martín, M. López, T. Martín, *Tetrahedron* **2005**, *61*, 8177 – 8191.

[14] G. Mehta, K. Srinivas, R. Vidya, R. Uma, A. C. Kunwar, K. Ravi Kumar, M. Vairamani, *Tetrahedron.* **1988**, *54*, 10879 – 10890.

[15] S. Muthusamy, B. Gnanaprakasam, *Tetrahedron* **2007**, *63*, 3355 – 3362.

[16] M. Meyer, J. R. Telford, S. M. Cohen, D. J. White, J. X. K. N. Raymond, *J. Am. Chem. Soc.* **1997**, *119*, 10093 – 10103.

[17] D. G. Rivera, O. Pando, R. Bosch, L. A. Wessjohann, *J. Org. Chem.* **2008**, *73*, 6229 – 6238.

[18] A. Shanzer, J. Libman, S. Lifson, C. E. Felder, *J. Am. Chem. Soc*. **1986**, *108*, 7609 – 7619.

[19] C. Coluccini, D. Pasini, P. Righetti, D. A. Vander Griend, *Tetrahedron* **2009**, *65*, 10436 – 10440.

[20] S. R. Houghton, L. Furst, C. N. Boddy, *J. Org. Chem.* **2009**, *74*, 1454 – 1463

[21] C.-C. Guo, K.-L. Li, R.-B. Tong, L. Chen, X.-B. Zhang, *Chin. J Org. Chem*. **2005**, *25*, 308 – 312.

[22] G. M. Sheldrick, SHELXS-97, Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany) **1997**. See also: G. M. Sheldrick, *Acta Crystallogr.* **1990**, *A46*, 467 – 473.

[23] G. M. Sheldrick, SHELXS-97, Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany) **1997**. See also: G. M. Sheldrick, *Acta Crystallogr.* **1990**, *A46*, 467 – 473.

[24] H. D. Flack, *Acta Crystallogr.* **1983**, *A39*, 876 – 881.