Asian Journal of Chemistry; Vol. 23, No. 1 (2011), 363-365

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Synthesis, Characterization and Bioactivity Study of Cyclic Diesters of 4,4'-Cyclohexylidene Bisphenol

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(*Received*: 26 March 2010; *Accepted*: 28 August 2010) AJC-9056

Macrocycles 4,4'-cyclohexylidene bisphenyl butan-1,4-dioate,4,4'-cyclohexylidene bisphenyl hexan-1,6-dioate and 4,4'-cyclohexylidene-bisphenyldecan-1,10-dioate have been synthesized by ring closure using high dilution technique. Structures are characterized by physical, analytical and infrared, ^{1}H , ^{13}C NMR and mass spectral data. Compounds showed positive inhibition against gram positive bacteria *Staphylococcus aurous*.

Key Words: 4,4'-Cyclohexylidene, High dilution, Hexan-1,6-dioate, Butan-1,4-dioate, Decan-1,10-dioate.

INTRODUCTION

Medium cyclic compounds having **8-11** and large cyclic compounds having **12** or more atoms in the ring are referred as macrocycles. Macrocyclic structures with one or more ester linkages are referred to as macrolides[1,2]. Macrolides find application in the field of antitumor activity[3,4] and as antibiotics[5-8]. Synthesis of macrocycles by high dilution are reported by several researchers[9-15]. The formation of macrocycles is favoured at the expense of oligomerization under high dilution conditions. In the present work we report the synthesis of macrocycles 4,4'-cyclohexylidene bis phenyl butan-1,4-dioate,4,4'-cyclohexylidenebisphenyl hexan-1,6-dioate and 4,4'- cyclohexylidenebisphenyl decan 1,10-dioate by high dilution principle.

EXPERIMENTAL

The starting materials and reagents were purchased from commercial suppliers and used after further purification. Melting points were determined on Ajay apparatus and were uncorrected. Micro elemental analysis was carried out on Thermo Finnegan Italy CHNSO analyzer Flash EA 112 series. Infrared spectra were obtained on Magno 550 Nicolet Instrument Corporation, USA, Fourier transform infrared spectrometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on Varian nuclear magnetic resonance spectrometer USA 300 MHZ in $CDCl_3$. Chemical shifts were indicated in δ ppm downfield from internal standard TMS. Mass spectra were recorded on Varian instrument USA.

Synthesis of 4,4'-cyclohexylidene bisphenol (1): Cyclohexanone (16 mL, 0.154 m) was saturated with dry HCl gas for 1 h in a tightly closed container. Phenol (26.4 mL, 0.3 m) was added to it and the flask was tightly stoppered, shaken well and kept in an atmosphere of dry HCl gas for 2 days. White solid obtained was poured into crushed ice, filtered, washed with water and purified by repeated recrystallization from toluene. Purity was tested by commercially available TLC plates. White needles, m.p. 198 ºC yield: (24 g, 58 %).

IR (KBr, ν_{max}, cm^{-1}): 3058, 3027, 1606, 1515, 1016, 827, 624, 598, 562 (aromatic); 3536, 3445 (O-H stretch); 1382 (O-H bend); 1270, 1179 (=C-O stretch); 2935, 2854, 1454 (aliphatic C-H stretch and bend). ^{1}H NMR data (δ ppm $CDCl_3$): 9.3, 9.1 (phenolic OH); 6.6-7.2 (aryl ring), 3.5 (CH_2 protons at C_2, C_6); 2.54-2.10 (CH_2 protons at C_3, C_5); 1.4-1.0 (CH_2 protons at C_4). ^{13}C NMR data (δ ppm $CDCl_3$): 139-115 (aromatic); 56.1, 44.2 (methylene carbon at C_1); 40.3, 40.0 (methylene carbon at C_2, C_6); 36.6-39.7 (methylene carbon at C_3, C_5 and C_4). Mass spectral data: 77, 107, 108, 120, 122, 134, 145, 160, 181, 188, 202, 216, 222, 252, 254, 258, 260, 264, 265, 266, 267, 268 (M^+), 269. Anal. calcd. (%) for $C_{20}H_{18}O_2$; C 80.59; H 7.46; found. (%): C 79.68; H 7.77.

Synthesis of 4,4'-cyclohexylidene bisphenyl butan-1,4-dioate (2): 4,4'-Cyclohexylidene bisphenol (2.68 g, 0.01 m) was dissolved in 100 mL of cyclohexane in a 500 mL, two necked RB flask equipped with water condenser, calcium chloride guard tube and dropping funnel. It was refluxed on a water bath and to the hot solution, pure dry metallic sodium (0.23 g, 0.01 m) was added until it disappears. Butan-1,4-dioyl

chloride (0.16 g, 0.01 m) in cyclohexane (100 mL) was added dropwise to the boiling solution at a rate of approximately 8 drops/min in 10 h. After the addition, the contents were refluxed for 3 h. The clear solution was distilled to separate cyclohexane and the solution was poured into water. Then it was transferred to a separating funnel and ether, sodium hydroxide were added. The ether layer alone was collected and it was dried over anhydrous sodium sulphate and evaporated on a water bath. The white solid 4,4'-cyclohexylidene bisphenyl butan-1,4-dioate obtained was dried and recrystallized from alcohol. Purity tested by TLC. White solid, m.p. 122 ºC, yield: (2.6 g, 74 %).

IR (KBr, ν_{max}, cm^{-1}): 3247-3000, 1612, 1515, 1107, 1010, 822, 587, 562, 532 (aromatic) 1714 (C=O stretch); 1245, 1178 (C-O-C stretch); 2937, 2865 1443 (aliphatic C-H stretch and bend). ^{13}C NMR data (δ ppm, $CDCl_3$): 157.4, 154.7 (C=O): 139.1-114.8 (aromatic carbon); 44.2, 40.3, 40.1 (methylene carbon attached to C=O group); 39.2-39.7 (carbon at C_1); 38.9-36.6 (carbon at C_2 and C_6); 25.9, 22.6,18.6 (carbon at C_3, C_5, C_4). Mass spectral data: 352, 351, 350 (M^+), 345, 340, 338, 336, 322, 320, 295, 287, 226, 214, 197, 174, 159. Anal. calcd. (%) for $C_{22}H_{22}O_4$; C 75.42; H 6.28; found. (%): C 75.63; H 6.84.

Synthesis of 4,4'-cyclohexylidene bisphenol hexan-1,6-dioate (3): 4,4'-Cyclohexylidene bisphenol (2.68 g, 0.01 m) was converted to sodium salt as in 4,4'-cyclohexylidene bisphenyl butan-1,4-dioate. To the sodium salt of 4,4'-cyclohexylidene bisphenol dissolved in cyclohexane (100 mL) was refluxed on a water bath. Hexan-1,6-dioyl chloride (1.96 mL, 0.01 m) in cyclohexane (100 mL) was added drop wise to the boiling solution at a rate of approximately 8 drops/min in 10 h. After the addition, the contents were refluxed for 3 h. After the completion of reaction, the clear solution was poured into water. It was transferred to a separating funnel and was extracted with ether. The ether layer was washed with 1:1 HCl, water, NaOH and again with water and then saturated NaCl solution. Then the ether extract was dried over anhydrous sodium sulphate and evaporated on a water bath. The solid obtained was filtered, dried recrystallized from alcohol. Purity tested by TLC. White solid, m.p. 204 ºC; yield: (2.5 g, 71 %).

IR (KBr, ν_{max}, cm^{-1}): 3027; 1622,1596; 1260-1107; 827, 603, 568, 532 (aromatic); 1718 (C=O stretch); 1230 (C-O-C stretch); 2940, 2864, 1459 (aliphatic). ^1H NMR data (δ ppm $CDCl_3$): 7.2-6.6 (aryl ring); 3.35-3.55, 4.4 (methylene protons nearer to carbonyl group); 2.5 (CH_2 protons at C_2, C_6); 2.1 (CH_2 protons at C_3,C_5); 1.06 (CH_2 protons at C_4). Mass spectral data: 379, 378 (M^+), 374, 351, 336, 308, 293, 292, 285, 280, 248, 223, 217, 196, 179, 168, 165, 158, 153, 148, 144. Anal. calcd. (%) for $C_{24}H_{26}O_4$; C 76.19; H 6.88; found. (%): C 75.64; H 7.12.

Synthesis of 4,4'-cyclohexylidene bisphenyl decan-1,10-dioate (4): 4,4'-Cyclohexylidene bisphenol (2.68 g, 0.01 m) was dissolved in cyclohexane (100 mL) in a 500 mL two necked RB flask equipped with water condenser, calcium chloride tube and dropping funnel. Dry metallic sodium (0.46 g, 0.02 m) was added and refluxed until the reaction of sodium with bisphenol was over. Decan-1,10-dioyl chloride (2.1 g, 0.01 m) in cyclohexane (100 mL) was added to the boiling solution at a rate of approximately 2 drops/min in 4 days at 110 ºC. The clear solution was distilled to separate cyclohexane and the solution is poured into water. It is transferred to a separating funnel and ether extracted with sodium hydroxide. The ether layer is collected and it is dried over anhydrous sodium sulphate and evaporated on a water bath. The crude solid 4,4'-cyclohexylidene bisphenyl decan-1,10-dioate obtained is dried and recrystallized from alcohol. White solid, m.p. 204 ºC; yield: (3.4 g, 78 %).

IR (KBr, ν_{max}, cm^{-1}): 3028; 1571, 1520; 1046; 853, 832, 756, 725, 675, 593, 562 (aromatic); 1713 (C=O); 1245 (C-O-C stretch); 2935, 2854; 1479 (aliphatic C-H). ^1H NMR data (δ ppm $CDCl_3$): 7.2-6.7 (aryl ring); 5.00-3.49 (methylene protons nearer to carbonyl group); 2.6-2.3 (CH_2 protons at C_2, C_6); 2.1-2.2 (CH_2 protons at C_3,C_5); 1.06 (CH_2 protons at C_4). ^{13}C NMR data (δ ppm, $CDCl_3$): 154.2, 175.7 (carbonyl carbon); (139.5-114.7 (aromatic carbon); 77.5-76.6 (methylene carbon attached to C=O group); 40.0-39.2; (carbon at C_1); 37.1 to 30.4 (carbon at C_3 and C_5); 28.7-24.6 (carbon at C_4). Anal. calcd. (%) for $C_{28}H_{34}O_4$; C 77.42; H 7.83; found. (%): C 76.49; H 7.61. Mass spectral data: 154, 176, 140-115, 77.5-76.7, 39, 40, 30-37, 29-25.

Antibacterial activity: Antibacterial activity of the 4,4'-cyclohexylidene bisphenol (**1**), 4,4'-cyclohexylidene bisphenyl butan-1,4-dioate (**2a**), 4,4'-cyclohexylidene bisphenyl hexan-1,6-dioate (**2b**) were determined *in vitro* using paper disc method against gram positive bacteria *Staphylococcus aureus* at 50 and 100 mg/mL concentration in the nutrient agar media. Commercial gentamicin (30 mcg) was used as a standard for comparision. Sterile Muller Hinton Agar (pH 7.3) was poured into petriplates, the depth of the medium should be approximately 4 mm. The plates were dried for 0.5 min in an incubator to remove excess moisture from the surface.

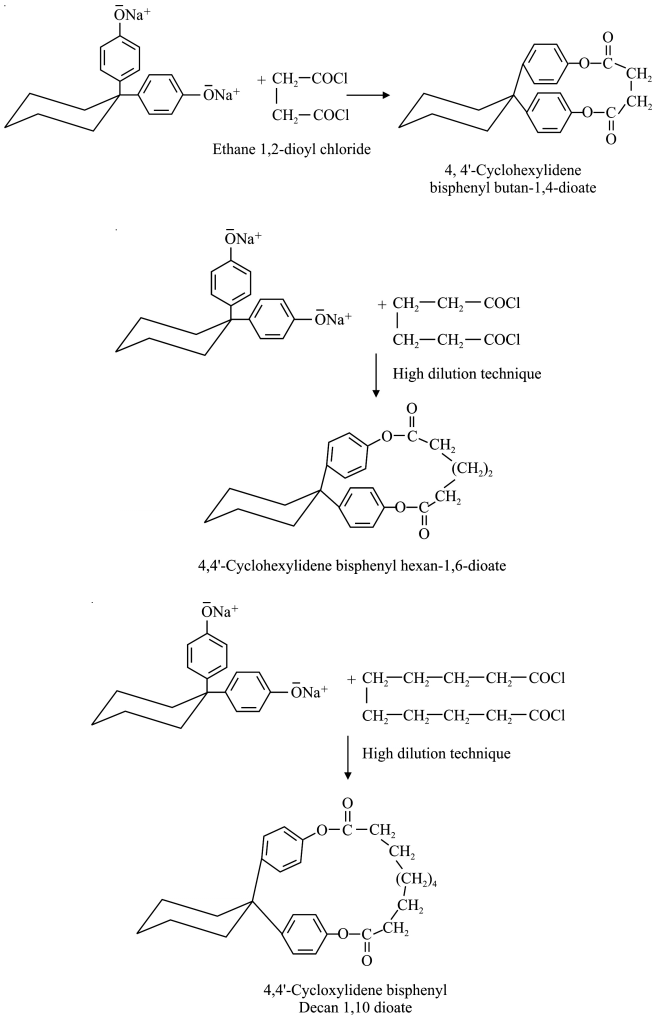
After 24 h the pattern of bacterial growth were observed and zone of inhibition for each compound is measured by using a zone measuring scale and recorded.

RESULTS AND DISCUSSION

The key step in the synthesis of macrolide is the formation of macrocyclic ring. High dilution techniques are generally employed to overcome the problem of polymerization. In high dilution principle[16-18] the reactant or reactants are slowly introduced into the reaction medium over a period of time. The condition is that the starting material flows into the reaction flask at the same rate as the cyclized product is formed. Relatively small volume of the reactants are added over a period of time to establish the stationary concentration of the substrate. Ring contractions of two interacting sites leading to the formation of macro cycles.

Compound **1**, **2a-2c** synthesized as per **Scheme-I**. Macrocycle, **2a-2c** were synthesised under controlled high dilution conditions which causes intramolecular ring closure than intermolecular reaction. Physical, analytical and spectral data are in accordance with proposed structures.

Antibacterial studies: Antibacterial activity of compound **1, 2a-2b** were tested for their *in vitro* growth activity against the bacterial strain *Staphylococcus aureus* ATCC 29213 (gram positive). The inhibition zones are determined disc diffusion



Scheme-I

method. In this method paper discs (6 mm) containing specific amounts of synthesized compounds **1, 2a-2c** (50 and 100 ppm) were placed on the surface of the agar plate inoculated with the standardized suspension of the micro organism *Staphyloccocus aureus*. The plates were incubated at 35 ºC for 24 h. Gentomycin (30 mcg) were used as standard drug. Antibacterial activity of the tested compounds shown in Table-1.

Activity is good for all the compounds and the activity found to increase with increase in concentration of the compound. Compounds **2a-2c** were found to be more active than control.

TABLE-1
ANTIBACTERIAL ACTIVITY OF 4,4′-CYCLOHEXYLIDENE BISPHENOL AND ITS CYCLIC DIESTERS

Compound	Diameter of zone of inhibition (mm) after 24 h of incubation	
	50 ppm	100 ppm
4,4′-Cyclohexylidene bisphenol	22	24
4,4′-Cyclohexylidene bisphenyl butan-1,4-dioate	20	24
4,4′-Cyclohexylidene bisphenyl hexan-1,6-dioate	21	24
Gentamycin (30 mcg)	21	21

Conclusion

Synthesis of macrocycles by intramolecular ring closure employing high dilution an important strategy in organic synthesis were reported.

ACKNOWLEDGEMENTS

This work was supported by UGC under Minor Research Project vide UGC letter No: F MRP-2221/06 (UGC-SERO) Dated 28.06.07 and July '08. The authors thank SAIF, IIT, Mumbai for providing spectral facilities and CHN analyses.

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