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Synthesis of Some New Ligands as Drug Carrier

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In this research work, the preparation of new biscrown ether and lariat ether compounds as cationic and molecular acceptor are reported. For this purpose first, sulfoxide (**1**) was prepared by reaction of *p*-cresol with $SOCl_2$ in 65 % yield. Then bisphonl (**2**) was prepared by reduction of compound (**1**) with Zn powder and acetic acid. Treatment of bisphenol (**2**) with methyl chloroacetate in the presence of K_2CO_3 and KI by refluxed in dry acetone gave dimethyl ester (**3**) in 98 % yield. Compound (**5**) was prepared by reaction of succinic acid and thionyl dichloride. Macrocyclic diamide (**4**) in 70 % yield was prepared by diamidation of diester (**3**) with diethylentriamine and then purified with recrystallization from methanol. Lariat ether compounds (**8**), (**9**), (**10**) were prepared by reaction of macrocyl (**4**) and henycosanoyl chloride, octanoyl chloride and 4-chloro boutanoyle chloride in 42, 38, 30 % yield. The structure of all prepared compounds has been established by ^{1}H NMR, ^{13}C NMR and IR.

Key Words: Synthesis, Ligand and Drug carrier.

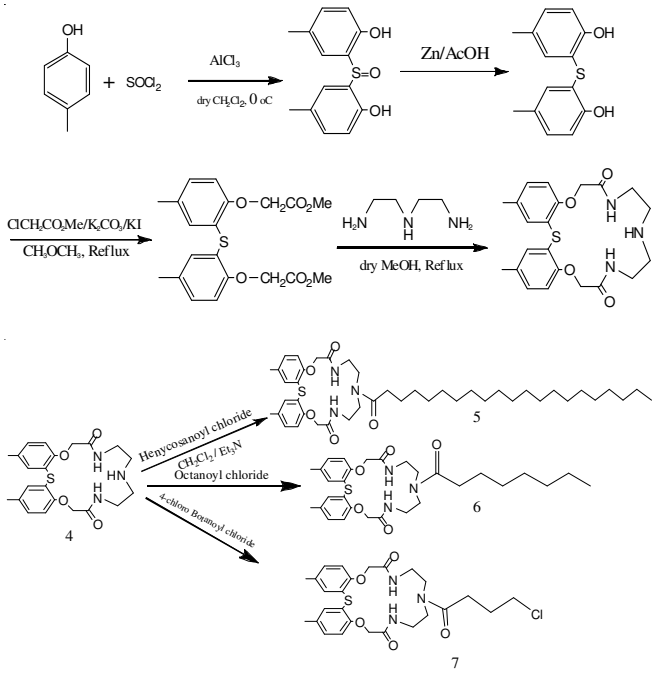
INTRODUCTION

Macrocyclic diamides and corresponding biscrown ether and lariat ether compounds have wide applications in chemistry, nano technology, atomic energy, medicinal, environmental, biology, metal separation and transport, industrial uses and switching agents. Biscrown ether and lariat ether compounds have more complexing ability than corresponding mono crown ethers, because of biscrown ethers can chelate guest molecules with more donor heteroatoms and lariat ethers have flexible structure[1-10].

Colloidal drug carrier systems such as micellar solutions and nano particles all seem to be promising drug delivery systems (DDSs) and have led to increasing attention over the past 20 years. In particular, vesicular systems (liposomes and niosomes) play an increasing important role since they can be used as membrane models, in chemical reactivity studies or in drug delivery and targeting[11,12]. Niosomes are formed by the self-assembly of non-ionic amphiphiles in aqueous media resulting in closed bilayer structures. An increasing number of non-ionic surfactants has been found capable of entrapping hydrophilic and hydrophobic solutes[13]. The greater stability, lower cost of surfactants and less storage problems[14-16] have prompted for the exploitation of these vesicles as an alternative to phospholipids. Liposomes and niosomes have been successfully applied for cosmetic purposes[17,18] and experimentally evaluated as carriers of many antiblastic drugs, such as metotrexate, doxorubicin and cisplatin[19], glucocorticoid[20], hemoglobin, indomethacin[14] and the antipsoriatic dithranol. The encapsulation of pharmaceutical materials in niosomes can decrease drug toxicity, increase drug absorption, stability or activity and retard its removal from the circulation in the case of slow release. Crown ethers belong to the class of macrocycles and possess an outstanding ability to complex ions and small organic molecules and to behave as ionophores capable of transporting ions across lipophilic barriers. Typical applications are provided by devices for the extraction and separation of heavy metals from aqueous solutions and for the stabilization of metal cations in organic media and in crown ether-based sensors. The ability of crown ethers to bind metal cations depends on the cavity size, on the nature of heteroatoms (oxygen, nitrogen or sulphur), on the kind of substituents in the macrocycle and on the particular used solvent. There is also growing interest in the use of crown ethers for their antitumor activity[21]. Herein the synthesis of some of new macrocyclic bisamides containing dibenzosulfide moiety obtained *via* the cyclization reactions of dimethyl ester and diacid chlorides with diamines is reported.

The sulfoxide (**1**) was prepared by reaction *p*-cresol with $SOCl_2$ in 65 % yield. Then bisphonel (**2**) was prepared with reduction compound (**1**) in Zn powder and acetic acid. Also compounde (**2**) gained by reaction *p*-cresol with sulfur dichloride

in 45 % yield. Treatment of bisphenol (**2**) with methyl chloroacetate in the presence of K_2CO_3 and catalytic amount of KI at refluxed in dry acetone gave dimethyl ester (**3**) in 98 % yield. Macrocyclic diamide (**4**) in 70 % yield was prepared by diamidation of diester (**3**) with diethylentriamine and then purified with recrystallization from methanol. Lariat ethers (**5**), (**6**) and (**7**) were synthesized by reaction of macrocylic (**4**) with henycosanoyl, octanoyl chloride and 4-chloro buthanoyl.



EXPERIMENTAL

All the materials purchased from Merck, Fluka and Aldrich chemical companies and used without further purification. The melting points (uncorrected) were measured with a Electrothermal engineering LTD 9100 apparatus. IR spectra were measured on a Perkin-Elmer model 543; the ^{1}H NMR and ^{13}C NMR spectra were obtained using BRUKER AVANCE DRX 400 apparatus. CH_2Cl_2 was dried over P_2O_5 and then distilled from CaH_2. MeOH was dried over CaH_2 and then distilled. Acetone was dried over K_2CO_3 and the distilled.

Preparation of 2,2'-sulfinyl-*bis*[(4-methyl)phenol] or dibenzosulfide (1): *p*-Cresol (10.8 g, 0.1 mol) was dissolved in 50 mL of petroleum ether. A solution of 3.39 mL (0.053 mol) of sulfur dichloride in 6 mL of petroleum ether was dropped in during 1 h.

The mixture was allowed to stand overnight. The petroleum ether layer was then poured off from the brown, semi-solid mass, which was crystallized from toluene/glacial acetic acid yielded colourless crystals of sulfide (**1**) (45 %). m.p. 113.5-114 ºC; IR (KBr, ν_{max}, cm^{-1}): 3400, 3200, 3040, 2920, 1900, 1880, 1760, 1580, 1500, 1480, 1400, 1360, 1280, 1230, 1140, 1060, 940, 880, 820, 760; ^{1}H NMR (60 MHz, $CDCl_3$): δ 204 (s, 6H), 6.1(b, 2H), 6.82 (s, 2H), 6.82 (s, 2H), 7.07 (s, 2H) ppm.

Preparation of 2,2'-sulfinyl-*bis*methyl[(4-methyl phenoxy acetate)] or methyl diester (2): A mixture of (7.5 g, 0.03 mol) of dibenzo sulfide (**1**), (0.03 mol, 6.45 mL) of the methyl chloroacetate, in presence of 15g K_2CO_3 and 0.5 g KI was refluxed in 100 mL of dry acetone for 24 h. The precipitate was filtered off and the filtrate was washed with CH_2Cl_2 and water (2 × 50 mL), 10 % aqueous NaOH solution (50 mL) and then with water (100 mL). Then organic phase was separated and was dried (Na_2SO_4) and evaporated to afford solid products, which was purified with recrystallization from methanol to give 98 % methyl diester (**2**). m.p. 98-100 ºC. IR (KBr ν_{max}, cm^{-1}): 2960, 2940, 1760, 1480, 1280, 1250, 1200, 1150, 1080, 990; ^{1}H NMR (60 MHz, $CDCl_3$) d. 2.2(s, 6H), 3.7 (s, 6H), 4.65 (s, 4H), 6.8(s, 6H) ppm.

Preparation of 7,10,13-triaza-1-thia-4,16-dioxa-2,3,17, 18-dibenzo-20,24-dimethyl cyclooctadecane-6,14-dione or macrocyclic diamides (3): Compound (**3**) was prepared by the cyclization reaction of diester (**2**) (6 g, 0.01 mol) with diethylen triamine (1.68 mL, 0.01 mol) in refluxing dry methanol (120 mL) for 24 h. The solution was cooled, filtered and washed with water (2 × 50 mL), 10 % aqueous HCl solution (100 mL) and then with water (200 mL). The organic layer was dried (Na_2SO_4) and evaporated to afford solid products which was purified with recrystallization from methanol. IR (KBr ν_{max}, cm^{-1}): 3420, 3360, 3010, 2940, 2880, 1680, 1570, 1490, 1280, 1250, 1210, 1080, 1050, 830, 800, 770, 680, 590, 560, 438. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (s, 6H), 2.78-2.8 (m, 4H), 3.39-3.4 (m, 4H), 4.6(s, 4H), 6.82 (d, *J* = 8.29 Hz, 2H), 7.1 (d, *J*=8.17 Hz, 2H), 7.48 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.27, 153.58, 132.61, 132.51, 129.7, 122.19, 112.29, 67.88, 49.33, 39.25, 20.97 ppm; MS (EI) m/e 429 $(M)^+$, 430 $(M+1)^+$, 431 $(M+2)^+$, 386, 360, 316, 303, 257, 241, 228, 180, 178, 164, 151, 121, 108, 105, 91, 85, 84, 56, 49, 43, 30.

General procedure for the lariat ethers: A mixture of macrocyclic diamide (0.01 mol) and chlorides or (0.01 mol, 0.78 g) in dry CH_2Cl_2 or MeOH (80 mL) was refluxed for 24-36 h. The precipitate was filtered off and the filtrate was washed with water (2 × 50 mL), 10 % aqueous NaOH solution (50 mL) and then with water (100 mL). The organic layer was dried (Na_2SO_4) and evaporated to afford solid products which was purified with thin layer chromatography.

Preparation of 11-hencycosanoyl-2,20-dimethyl-9,10,11,12,13,14-hexahydro-6*H*,dibenzo[1,7,4,10,13,16] dioxathiatriazaoctadecin-7,15(8*H*,16*H*)dione: This compound prepared with henycosanoyl and in solvent MeOH and in presence K_2CO_3/KI; Then this compound was purified by thin layer chromatography on silica gel using ethyl acetate/methanol (5:1) as eluent and then recrystallized from C_6H_{13} / $CHCl_3$ to afford lariat ether (**5**) (49 %). m.p. 143-146 ºC; IR (KBr ν_{max}, cm^{-1}): 3503 (m), 3498 (m), 2923 (m), 2841 (w), 1691 (s), 1636 (w), 1509 (vs), 1496 (s), 1443 (m), 1322 (m), 1102 (m), 1009 (w), 811 (m), 771 (m), 662 (m), 480(m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.12, 167.82, 153.28, 131.75, 131.65, 128.79, 121.47, 111.21, 67.08, 52.15, 42.47, 32.13, 31.74, 28.88, 28.31, 21.04, 20.86, 14.75 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.58-0.62 (m: distored ddd, 3H), 1.43-1.49 (m, 34H), 2.18-2.24 (t, 4H), 2.75 (s, 6H), 3.42-3.48 (m: distored ddd, 8H), 4.66 (s, 4H), 6.24-6.25 (d, 2H), 6.43-6.46 (s, 2H), 6.82-6.88 (t, 2H), 7.46 (dd, 2H) ppm.

Preparation of 2,20-dimethyl-11-octanoyl[9,10,11,12, 13,14]hexahydro-6*H*, dibenzo[1,7,4,10,13,16]dioxathia-

triazaoctadecin-7,15(8*H*,16*H*)dione: This compound prepared with octanoyle chloride and in solvent CH_2Cl_2 and in presence of triethylamine. Then this compound was purified by thin layer chromatography on silica gel using ethyl acetate/methanol (3:1) as eluent and then recrystallized from C_6H_{13} / $CHCl_3$ to afford lariat ether (**6**) (39 %). m.p. 260-262 ºC; IR (KBr ν_{max}, cm^{-1}): 3496 (m), 2982 (w), 2938 (m), 1680 (vs), 1628 (vs), 1524 (s), 1490 (s), 1434 (s), 1401 (w), 1355 (w), 1236 (s), 1043 (s), 818 (m), 789 (m), 704 (w), 554 (s), 478 (w), 430 (w). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.12, 179.08, 167.32, 153.13, 131.75, 131.65, 128.78, 121.38, 111.18, 67.01, 52.38, 41.17, 31.71, 30.21, 20.04, 14.81 ppm.

Preparation of 11-(4-chloro butanoyl)-2,20-dimethyl-11-octanoyl[9,10,11,12,13,14]hexahydro-6*H*,dibenzo[1,7,4,10,13,16]dioxathiatriazaoctadecin-7,15(8*H*,16*H*)dione: This compound prepared with 4-chloro butanoyl and in solvent CH_2Cl_2 and in presence of triethylamine. Then this compound was purified by thin layer chromatography on silica gel using ethyl acetate/methanol (3:1) as eluent and then recrystallized from C_6H_{13} /$CHCl_3$ to afford lariat ether (**6**) (55 %). m.p. 143-146 ºC; IR (KBr ν_{max}, cm^{-1}): 3398 (m), 2954 (s), 2932 (vs), 2873 (s), 2742 (s), 1737 (w), 1669 (vs), 1601 (w), 1532 (m), 1498 (s), 1506 (m), 1370 (w), 1255 (s), 1148 (w), 1075 (s), 1040 (w), 875 (m), 802 (s), 700 (m), 664 (w), 757 (s), 557 (w), 436 (w). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.31, 166.47, 135.03, 131.26, 131.16, 128.33, 121.83, 114.87, 114.32, 67.36, 41.23, 21.25 ppm.

RESULTS AND DISCUSSION

Macrocyclic diamides and corresponding aza crown compounds and their bisazacrown have gained a great deal of attention due to their wide applications in chemistry, bio nano technology, environmental, wast water treatment, anti HIV agents, contrast agents for NMR imaging, catalysts for specific cleavage or RNA hydrolysis, stains for fluorescence imaging, responsive luminescent systems or as active agents in cancer radiotherapy, nuclear energy and molecular recognition have prompted considerable interest in lanthanide coordination chemistry.

Macrocycle (**4**) can interlock with the same macrocycle and made a catenane. Therefore this molecule can be used on structure of rotaxanes and catenanes in nano machines[22,23].

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