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Synthesis of Bifunctional Ligands Based on Azaheterocycles and Fragments of 12-Crown-4

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Abstract—Bifunctional ligands synthesized in this study are of interest for developing sensors based on SERS (Surface Enhanced Raman Spectroscopy). The function of 2,2'-bipyridyl and 1,10-phenanthroline fragments consists in formation of complexes with the metal surface, and the crown-fragment is meant for selective sensing of cations.

We report here on the synthesis of a series of heterocyclic crown ethers containing fragments of 2,2'-bipyridyl and 1,10-phenanthroline. Compounds obtained are distinguished by the ability to rotate of the aromatic rings of the heterocycle, by the nature of the donor atoms in the crown-fragment, and by the mode of junction of these parts of the bifunctional ligand. A crown ether with four complexing atoms best fit to form complexes with lithium cations was chosen for selective moiety.

The ion Li^+ is held in the cavities of crown ethers with the ring dimensions in the range from 12-crown-4 to 15-crown-4. However the simple crown ethers are not selective toward Li^+ ions in the presence of larger ions. This is caused by formation of sandwich complexes between the supporting ions (e.g., Na^+) and two molecules of the crown ether. To pervent the complexing at the stoichiometric ratio 1:2 in solution or on the membrane bulky substituents are included into the molecule of the crown ether [1]. Under the SERS conditions the molecules of bifunctional ligands are sorbed on a metal surface (for instance, on silver or gold) with the aid of heteroatoms (nitrogen, sulfur). If the heterocyclic part of the molecule of the bifunctional ligand is rigidly fixed on the surface the sandwich complexing with crown fragments would presumably be avoided.

The crown derivatives of 2,2'-bipyridyl were first synthesized in 1979 [2]. Later a synthesis was proposed of bipyridyl-crowns with a carbonyl group included into the conjugation chain [3].

The preparation of the crown derivatives of 2,2'-bipyridyl and 1,10-phenanthroline is a multistage process. The common stage of the syntheses is the production of ditosylate **II** of the corresponding glycol **I** which constitutes the crown-building element. The other intermediate stages aim at preparation of compounds based on 2,2'-bipyridyl and 1,10-phenanthroline capable to react with the ditosylate affording the crown derivatives.

EXPERIMENTAL

NMR spectra were registered at room temperature on a spectrometer Bruker DPX 300 (^1H and ^{13}C NMR spectra at operating frequencies 300 and 75 MHz respectively). Elemental analyses were carried out on a CHN-analyzer HP-185B.

Triethylene glycol ditosylate (II). To a solution of 10 ml (0.06 mol) of triethylene glycol (**I**) in 50 ml of freshly distilled anhydrous THF cooled to 0°C in the presence of 10.86 g (0.194 mol) of KOH was added dropwise at stirring within 1.5 h a solution of 26.1 g (0.137 mol) of tosyl chloride in 43 ml of THF. The mixture obtained was stirred for 5 h at 0°C, then for 24 h at room temperature. The precipitate was filtered off. On removing the solvents we isolated from the filtrate 19.8 g (72%) of compound **II**. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.81 d (4H), 7.36 d (4H), 4.15 t (4H), 3.67 t (4H), 3.55 s (4H), 2.47 s (6H).

1,10-Phenanthroline-5,6-dione (IV) was prepared by procedure described in [4]. A cooled mixture of 40 ml of concn. H_2SO_4 and 20 ml of concn. HNO_3 was added to 4 g (0.022 mol) of 1,10-phenanthroline and 4 g (0.033 mol) of KBr. The mixture was stirred at 130°C for 3 h, then the hot yellow solution was poured into 500 ml of ice and cautiously neutralized with NaOH solution. The separated precipitate of 1,10-phenanthroline-5,6-dione was filtered off, washed with distilled water,

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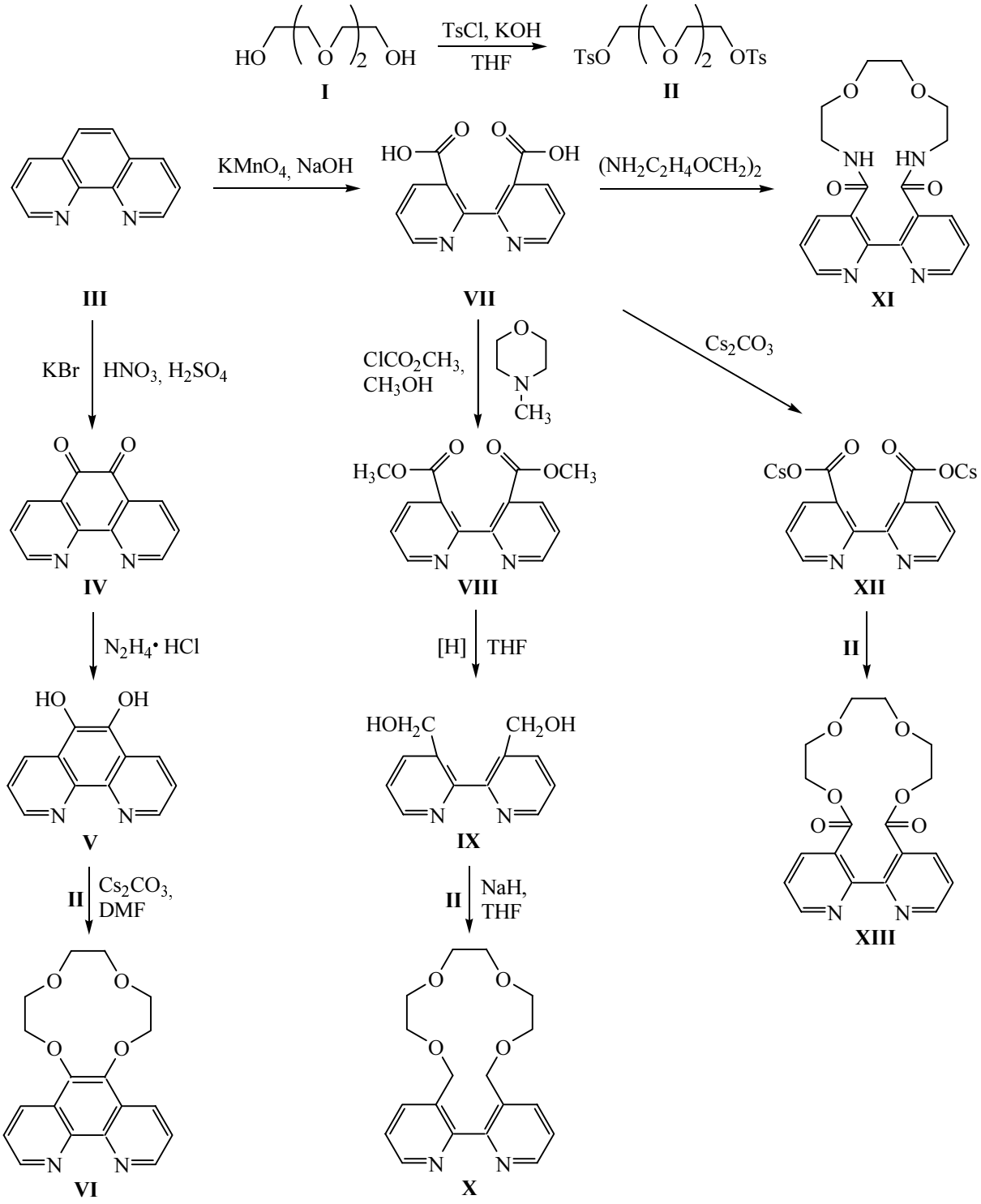

and dried. The rest of the product was extracted with CH_2Cl_2 (3×100 ml) from the water phase, and then the solvent was distilled off. Overall yield 4.5 g (96%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 9.15 d.d (2H), 8.53 d.d (2H), 7.62 d.d (2H).

1,10-Phenanthroline-5,6-diol (V). In keeping with procedure described in [5] a solution of 4.4 g (0.021 mol) of compound **IV** in 100 ml of distilled water heated on a water bath was treated with a solution of hydrazine hydrochloride till the end of gas evolution. The obtained

water-soluble salt form of 1,10-phenanthroline-5,6-diol was precipitated by a careful addition of a concn. solution of NaOH (till pH 5–6). The yellow precipitate was filtered off,washed with water, and dried. Yield 3.7 g (83%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.40 s (2H), 8.94 d.d (2H), 8.62 d.d (2H), 7.74 m (2H).

2,3,5,6,8,9-Hexahydro[1,4,7,10]tetraoxacyclododecino[2,3-f][1,10]phenanthroline (VI). In 180 ml of freshly distilled DMF was stirred for 10 min in a flow of N_2 a mixture of 6.4 g (0.014 mol) of triethylene glycol ditosylate and 46 g (0.141 mol) of cesium carbonate; then 2.7 g (0.0127 mol) of 1,10-phenanthroline-5,6-diol was added. The reaction mixture was stirred at 60°C under a nitrogen atmosphere for 5 days. The precipitate was filtered off and washed with CH_2Cl_2. The solvents were distilled off from the combined organic solutions. The mixture of the reaction products was separated by column chromatography on aluminum oxide, eluent CH_2Cl_2. We obtained 0.629 g (14%) of 1,10-phenanthroline-12-crown-4, colorless rhombic crystals. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 9.96 d.d (2H), 8.58 d.d (2H), 7.67 m (2H), 4.48 m (4H), 3.93 s (4H). ^{13}C NMR spectrum (CDCl3), δ, ppm: 150, 145, 143, 131, 126, 123, 78, 74, 72. Found, %: C 65.99; H 5.30; N 8.41. $C_{18}H_{18}N_2O_4$. Calculated, %: C 66.26; H 5.52; N 8.59. M 326.

2,2'-Bipyridyl-3,3'-dicarboxylic acid (VII). The oxidation of 1,10-phenanthroline (**III**) to 2,2'-bipyridyl-3,3'-dicaboxylic acid (**VII**) was carried out by procedure [6]. Into 1 l of water containing 4.4 g (0.11 mol) of NaOH was charged 10.9 g (0.055 mol) of 1,10-phenanthroline·H_2O. In the course of stirring at room temperature was added within 2 h 24.2 g (0.153 mol) of potassium permanganate. Then the solution was stirred for 2 h at heating. The hot mixture was filtered from MnO_2 and evaporated to a volume of 100 ml. In distinction from the procedure [6] the solution was neutralized and compound **VII** was converted from the salt into an acid form on a chromatographic column packed with cation-exchange resin KU-2·8 in the H+-form. At the output of the column we obtained a water solution of 2,2'-bipyridyl-3,3'-dicarboxylic acid. The acid low soluble in water was partially detained in the column and was separated from the grains of resin by decanting. On evaporation of water and decanting we obtained 8.2 g (61.1%) of white powdery substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 12.93 s (2H), 8.68 d.d (2H), 8.27 d.d (2H), 7.54 d.d (2H).

Dimethyl 2,2'-bipyridyl-3,3'-dicarboxylate (VIII). In 150 ml of freshly distilled methanol containing 4.5 ml (0.04 mol) of N-methylmorpholine was dissolved 4.9 g (0.02 mol) of acid **VII**. The solution was cooled for 10 min on an ice bath to 0°C, and 3.2 ml (0.04 mol) of methyl chloroformate was added dropwise within 30 min. The mixture was stirred for 1 h. On distilling off the methanol the separated colorless precipitate was dissolved in 100 ml of CH_2Cl_2. The solution was washed with a saturated solution of sodium hydrogen carbonate (2×10 ml). On removing the solvent compound **VIII** was obtained in a 4.13 g (76%) yield. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.79 d.d (2H), 8.39 d.d (2H), 7.47 d.d (2H), 3.71 s (6H).

2,2'-Bipyridyl-3,3'-dimethanol (IX). In 255 ml of freshly distilled THF under the nitrogen atmosphere was dissolved 2.56 g (0.0094 mol) of ester **VIII**. The solution was cooled for 10 min on an ice bath. A suspension of sodium bis(2-methoxyethoxy)alumohydride in toluene containing 0.041 mol of the reductant was dissolved in 39 ml of THF and added dropwise to the reaction mixture. After stirring for 1 h at 0°C the unreacted reductant was decomposed by cautious adding water solution of NH_4Cl. The solution was decanted, the precipitate was washed with 50 ml of CH_2Cl_2. The organic solutions were combined, and the solvents were distilled off. The separated precipitate was washed with ethyl acetate and filtered off. We obtained 1.2 g (59%) of compound **IX**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.51 d.d (2H), 8.04 d.d (2H), 7.47 d.d (2H), 5.30 s (2H), 4.39 s (4H).

9,11,12,14,15,17,18,20-Octahydropyrido-[2',3':14,15][1,4,7,10]tetraoxacyclohexadecino-[13,12-b]pyridine (2,2'-bipyridyl-12-crown-4) (X). A solution of 1.27 g (0.0059 mol) of diol **IX** in 200 ml of anhydrous THF was stirred with 2 g (0.05 mol) of 60% suspension of NaH in mineral oil for 20 h at 70°C under the nitrogen atmosphere. To the reaction mixture cooled to room temperature was added dropwise within 4 h a solution of 3.12 g (0.0068 mol) of triethylene glycol ditosylate in 60 ml of anhydrous THF. The reaction mixture was boiled for 16 h. The precipitate was filtered off, the solvent was distilled off. To the remaining 20 ml of the solution 5 ml of H_2O was added. The mixture was dissolved in 150 ml of CH_2Cl_2 and washed with 1 N HCl (3×50 ml). The combined water solutions were neutralized with a concn. solution of NaOH and extracted with CH_2Cl_2 (3×100 ml). The combined organic solutions were evaporated to a volume of 20 ml and subjected to chromatography on a column packed with aluminum oxide (eluent acetone–CH_2Cl_2, 3:7). We obtained 0.508 g (40%) of powdery 2,2'-bipyridyl-12-crown-4. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.57 d.d (2H), 7.96 d.d (2H), 7.35 d.d (2H), 4.53 d.d (4H), 3.58 m (8H), 3.34 m (4H).

Found, %: C 65.50; H 6.75; N 8.34. $C_{18}H_{22}N_2O_4$. Calculated, %: C 65.45; H 6.67; N 8.48. M 330.

9,10,11,12,14,15,18,19-Decahydrodipyrido[3,2-i: 2,3-*k*][1,4,7,14]dioxadiazacyclohexadecine-9,20-dione (XI). To 1.46 g (0.006 mol) of acid **VIII** in 40 ml of water was added 0.9 ml (0.006 mol) of 3,6-dioxaoctane-1,8-diamine. The clear solution containing compound **XI** was evaporated on a water bath till a volume of 5 ml. The reaction product was precipitated by adding 20 ml of CH_3CN. After stirring for 40 min from the organic phase a colorless precipitate separated that was filtered off and washed with ethanol. We obtained 1 g (42%) of solvate $C_{16}H_{20}N_4O_4 \cdot C_2H_5OH$. ^1H NMR spectrum (D_2O), δ, ppm: 8.44 d.d (2H), 8.03 d.d (2H), 7.43 d.d (2H), 3.65 m (8H), 3.07 m (4H). ^{13}C NMR spectrum (D_2O), δ, ppm: 148.7, 138.1 123.8, 69.9, 66.8, 39.4. Found, %: C 52.90; H 6.45; N 13.38. $C_{18}H_{26}N_4O_5$. Calculated, %: C 53.73; H 6,47; N 13.93. M 402.

9,11,12,14,15,17,18,20-Octahydropyrido [2',3': 14,15][1,4,7,10]tetraoxacyclohexadecino[13,12-*b*]-pyridine-9,20-dione (dioxo-2,2'-bipyridyl-12-crown-4) (XIII). In 180 ml of DMF was stirred 5.97 g (0.013 mol) of triethylene glycol ditosylate and 6.6 g (0.013 mol) of cesium salt of compound **XII** for 4 days at 65°C under the nitrogen atmosphere. Then the brown mixture was filtered, the solvent was distilled off, and the reaction products were subjected to column chromatography on aluminum oxide (eluent CH_2Cl_2). On evaporating the solvent we obtained 1.1 g (24%) of colorless powdery dioxobipyridyl-12-crown-4. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 8.80 d.d (2H), 8.53 d.d (2H), 7.49 d.d (2H), 4.26 m (4H), 3.55 m (8H). Found, %: C 61.11; H 5.06; N 7.65. $C_{18}H_{18}N_2O_6$. Calculated, %: C 60.33; H 5.03; N 7.82. M 358.

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