ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 8, pp. 1421–1424. © Pleiades Publishing, Ltd., 2012.
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New Derivatives Obtained from *ortho*-Isobornylphenols and 4,13-Diaza-18-crown-6

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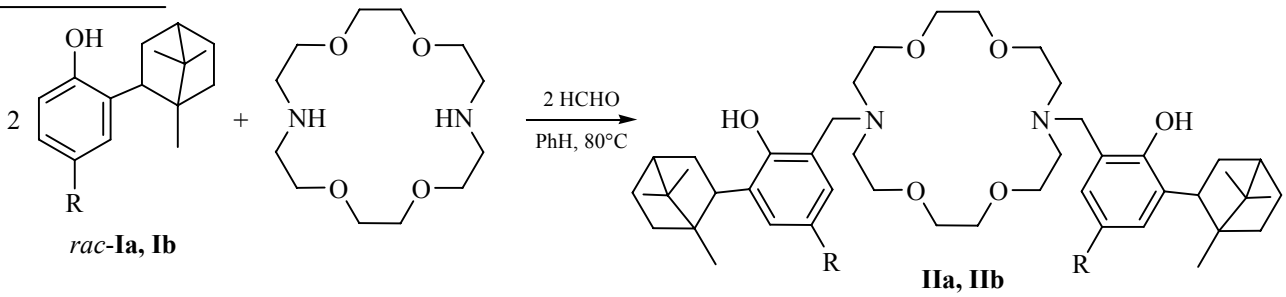
Received June 27, 2011

Abstract—New aminomethyl derivatives were synthesized via Mannich reaction of 4,13-diaza-18-crown-6 with racemic 2-isobornyl-4-methylphenol and 2-isobornylphenol. The diastereoisomers (*meso*-form and racemate) derived from the racemic terpenophenols were detected by the ^{13}C NMR spectroscopy. The signals were assigned by comparison with the ^{13}C NMR spectrum of the enantiomer of one of the derivatives. The optically active disubstituted diaza-crown-ether molecule was studied by the XRD analysis that showed the presence of the intramolecular hydrogen bonds.

DOI: 10.1134/S1070363212080142

Aza-crown ethers are known to be used as complexing agents for heavy metal cations. In addition, the derivatives of aza-crown ethers can possess a biological activity [1]. 4,13-Diaza-18-crown-6 is an interesting object for the synthesis of new macrocyclic structures, including symmetric ones, for it molecule contains two secondary amino groups, which allows involving them in the reaction of the phenols aminomethylation [2, 3]. It was shown in [3] by the XRD analysis data that the derivatives with both nitrogen atoms substituted by phenol may serve as the agents for the axial complex formation. Recently we showed that phenols with terpene fragments and aminomethyl derivatives based on them were effective antioxidants [4].

This work presents the results of the synthesis of new aza-crown ether derivatives based on the phenols containing the isobornyl group in the *ortho*-position relative to the hydroxy moiety. Amines **II** were obtained in 68–82% yields by Mannich reaction of the racemic 2-isobornyl-4-methylphenol **Ia** or 2-isobornylphenol **Ib** with paraformaldehyde and 4,13-diaza-18-crown-6. To obtain the disubstituted amines a slight excess of paraformaldehyde and the starting terpenophenols was used.



rac-**Ia, Ib** **IIa, IIb**

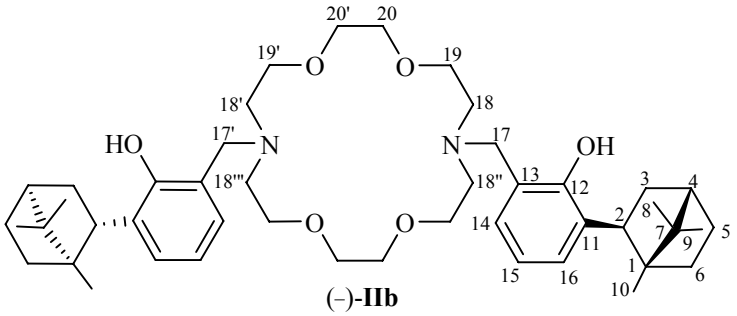
R = CH_3 (**a**), H (**b**).

The structure and composition of compounds **IIa** and **IIb** obtained for the first time were confirmed by the IR, ^1H, and ^{13}C NMR spectroscopy and elemental analysis. In the ^1H and ^{13}C NMR spectra there are the sets of signals characteristic of terpenophenol and aminomethyl fragments. The integral intensity of the signals in the ^1H NMR spectra confirms the formation of disubstituted products. The signal of OH-protons at 10.5–10.8 ppm is a broadened singlet in the ^1H NMR spectra of both amines. In the IR spectrum of the

synthesized products **II** there is no absorption band characteristic of the stretching vibrations of the phenol OH-group (3400–3600 cm^{-1}).

As the racemic phenol *rac*-**Ia** and *rac*-**Ib** were used in the synthesis, the obtained symmetrical diamines **IIa** and **IIb** are the diastereoisomers mixture (*meso*-form and racemate). A confirmation of the presence of these diastereomers is the doubling signals of the carbon atoms of methylene groups of $ArCH_2N$- and $O(CH_2)_2O$-fragments of both products in the ^{13}C NMR spectra.

Under the selected conditions the synthesis was performed of the diaza-crown ether derivative containing a fragment of the optically active (+)-2-isobornylphenol (+)-**Ib**. In the ^{13}C NMR spectra of the product (–)-**IIb** the corresponding signals were attributed to the racemate, other signals to the *meso*-form. The assignement of the signals for a mixture of diastereomers **IIa** was made by analogy with a mixture of diastereoisomers **IIb**.

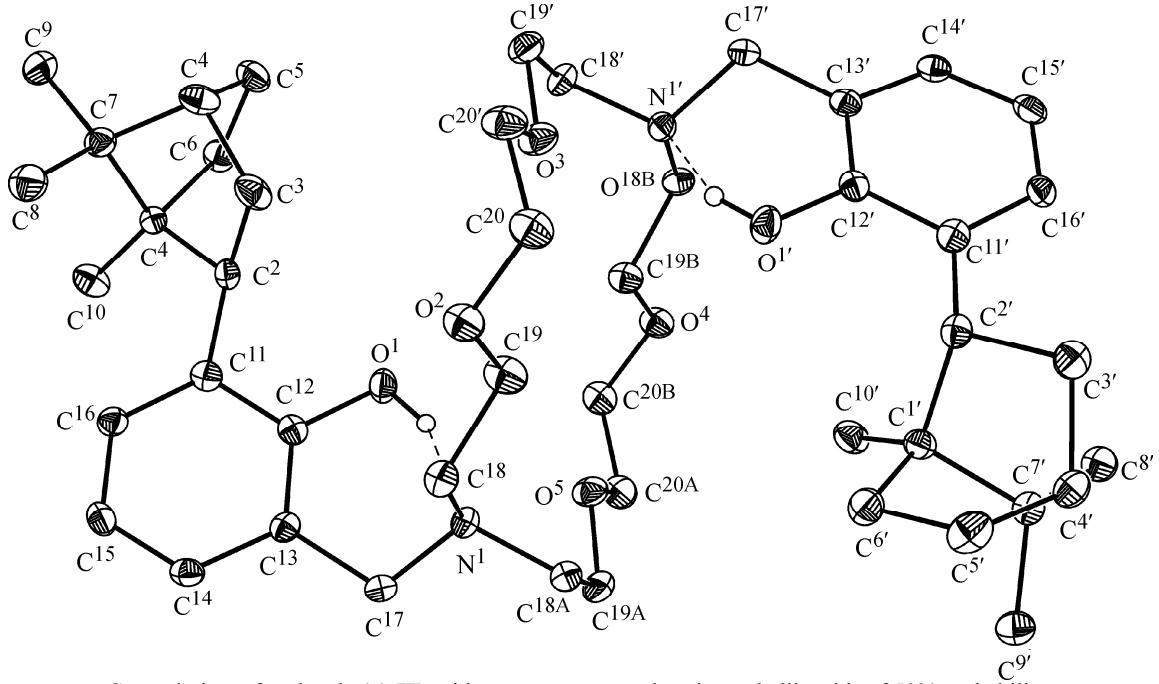


(–)-**IIb**

The numbering of carbon atoms is shown to simplify the interpretation of NMR spectra.

We obtained a single crystals of (–)-**IIb** derivative and subjected it to XRD analysis. Compound (–)-**IIb** crystallizes in a $P2_1$ chiral space group and contains one molecule in the symmetrically independent part of the unit cell (see the figure).

The absolute configuration of the chiral centers of (1*R*,2*S*,4*S*,1'*R*,2'*S*,4'*S*)-isobornyl fragments was determined considering that the configuration of the starting reagent (+)-**Ib** was retained. The nitrogen atoms have a pyramidal coordination [the sum of the angles at the N^1 and $N^{1'}$ atoms is equal to 336.3(6) and 335.2(6)°, respectively]. The isobornylphenol fragments are oppositely directed relative to the median plane of the aza-crown ether and turned around the N^1–C^{17} and $N^{1'}$–$C^{17'}$ bonds toward the macrocycle, hanging over it.



General view of molecule (–)-**IIb** with atoms represented as thermal ellipsoids of 50% probability.

This conformation is stabilized by the relatively strong hydrogen bonds O^1–$H^1\cdots N^1$ [$H^1\cdots N^1$ and $O^1\cdots N^1$ bond lengths are 1.88 Å and 2.661(3) Å, respectively, $\angle O^1H^1N^1$ 152°] and $O^{1'}$–$H^{1'}\cdots N^{1'}$ [$H^{1'}\cdots N^{1'}$ and $O^{1'}\cdots N^{1'}$ bond lengths are 1.96 Å and 2.729(3) Å, respectively, $\angle O^{1'}H^{1'}N^{1'}$ 150°]. At the same time other short intramolecular non-valence contacts in the molecule were not found, i. e., this conformation is additionally stabilized by the van der Waals interactions. The orientation of isobornyl substituents relative to the phenyl rings is different [the torsion angles $C^{12}C^{11}C^2C^3$ and $C^{12'}C^{11'}C^{2'}C^{3'}$ are 75.3(3) and 154.3(2)°, respectively], and differs from the orientation of the previously investigated *ortho*-isobornylphenol derivatives [5, 6] (the corresponding torsion angle is about 20°). Probably, in this case it is caused by the van der Waals intramolecular (between the terpenic fragments and macrocycle) and intermolecular interactions.

The intramolecular hydrogen bonds are retained in solution, as follows from the above data of the IR and ^{1}H NMR spectroscopy, and it is consistent with the data obtained previously for the other tertiary aminomethyl *ortho*-isobornylphenols [5]. The analysis of the Cambridge Structural Database data [7] on the *N*-hydroxybenzyl-substituted diaza-crown ethers shows that in all cases in the crystal structure there are two relatively strong hydrogen bonds (O–H···N) defining the orientation of the phenolic fragment with respect to the aza-crown ethers. Thus, the application of substituted phenols in the synthesis of various macrocycles can purposefully be used to design compounds with a given orientation with respect to the aza-crown ether moiety.

Thus, the new compounds were synthesized for the first time based on 4,13-diaza-18-crown-6 and chiral isobornylphenols. In the case of the starting racemic 2-isobornyl-4-methylphenol and 2-isobornylphenol the reaction products are diastereomers mixture (*meso*-form and racemate), whose presence was detected by the ^{13}C NMR spectroscopy. By an example of (–)-**IIb** the geometry of the molecule and the formation of the intramolecular hydrogen bonds in the synthesized derivatives were considered.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 instrument from KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 300 spectrometer (300 and 75 MHz, respectively) in $CDCl_3$. The signals assignment was done on the basis of two-dimensional spectroscopy (HSQC, COSY, NOESY). The melting points were determined on a Koeffler heating block. The reaction progress was monitored by TLC using Sorbfil plates (eluent petroleum ether–diethyl ether, 3:1), development with a $KMnO_4$ solution (15 g of $KMnO_4$, 300 ml of H_2O, 0.5 ml of conc. H_2SO_4). Benzene was dried over $CaCl_2$ and distilled over metallic sodium. Petroleum ether (bp 65–70°C) and diethyl ether of chemical grade were used. The column chromatography was done using silica gel (Alfa Aesar, 70/230 μ).

The racemic *ortho*-isobornylphenols *rac*-**Ia** and *rac*-**Ib** were prepared according to previously described methods [8]. Phenol (+)-**Ib** {$[\alpha]_D^{23}$ +31.9° (*c* 0.55, $CHCl_3$), enantiomeric purity 98.5% by HPLC on a chiral column} was prepared from *rac*-**Ib** through the diastereomeric camphanates by the method [9]. 4,13-Diaza-18-crown-6 (Alfa Aesar) was used without further purification.

Synthesis of amines (II). To a mixture of 0.5 mmol of phenol **I** and 0.5 mmol of paraformaldehyde dissolved in 3 ml of benzene at 20°C was added 0.2 mmol of 4,13-diaza-18-crown-6. The mixture was refluxed for 12–15 h. The reaction progress was monitored by TLC. After the reaction completion the mixture was separated by the column chromatography (petroleum ether–diethyl ether, 20:1 → 2:1) and recrystallized from a mixture of petroleum ether–diethyl ether.

6,6'-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene)bis{4-methyl-2-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol} (IIa). Yield 82%, diastereomers mixture (racemate/*meso*-form), colorless powder, mp 152–155°C. IR spectrum, ν, cm^{-1}: 2964, 2884, 1464, 1376 (Me, CH_2), 1616 (C=C), 1268 (C–O), 1252 (C–N), 1144 (C–O–C), 860, 780 (=C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79 s (6H, $C^{10}H_3$, $C^{10'}H_3$), 0.84 s (6H, C^9H_3, $C^{9'}H_3$), 0.91 s (6H, C^8H_3, $C^{8'}H_3$), 1.34–1.40 m (2H, H^5, $H^{5'}$), 1.47–1.65 m (6H, H^3, $H^{3'}$, H^6, $H^{6'}$), 1.77–1.89 m (4H, H^4, $H^{4'}$, H^5, $H^{5'}$); 2.10–2.26 m (2H, H^3, $H^{3'}$), 2.27 s (6H, $C^{17}H_3$, $C^{17'}H_3$), 2.77–2.94 m (8H, H^{19}, $H^{19'}$, $H^{19''}$, $H^{19'''}$), 3.32 t (2H, H^2, $H^{2'}$, *J* 9.0), 3.62 s (8H, H^{21}, $H^{21'}$, $H^{21''}$, $H^{21'''}$), 3.68 t (8H, H^{20}, $H^{20'}$, $H^{20''}$, $H^{20'''}$, *J* 5.6), 3.76 and 3.80 two d (4H, H^{18}, $H^{18'}$, *J* 13.7 and *J* 13.7), 6.61 br. s (2H, H^{14}, $H^{14'}$), 7.01 br. s (2H, H^{16}, $H^{16'}$); 10.52 br. s (2H, OH). ^{13}C NMR spectrum, δ_C, ppm: 12.21 (C^{10}, $C^{10'}$), 20.33 (C^9, $C^{9'}$), 20.89 (C^{17}, $C^{17'}$), 21.51 (C^8, $C^{8'}$), 27.60 (C^5, $C^{5'}$), 33.78 (C^3, $C^{3'}$), 39.67 (C^6, $C^{6'}$), 44.70 (C^2, $C^{2'}$), 45.82 (C^4, $C^{4'}$), 47.89 (C^7, $C^{7'}$), 49.85 (C^1, $C^{1'}$), 53.37 (C^{19}, $C^{19'}$, $C^{19''}$, $C^{19'''}$), 58.70 and 58.76 (*meso*-form and

racemate, respectively, C^{18}, $C^{18'}$), 69.27 (C^{20}, $C^{20'}$, $C^{20''}$, $C^{20'''}$), 70.88 and 70.93 (racemate and *meso*-form, respectively, C^{21}, $C^{21'}$, $C^{21''}$, $C^{21'''}$), 121.22, 126.52, 130.39 (C^{11}, $C^{11'}$, C^{13}, $C^{13'}$, $C^{15'}$, $C^{15'}$), 126.59 (C^{14}, $C^{14'}$), 127.81 (C^{16}, $C^{16'}$), 154.71 (C^{12}, $C^{12'}$). Found, %: C 74.51; H 9.53. $C_{48}H_{74}N_2O_6$. Calculated, %: C 74.38; H 9.62.

6,6'-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis((methylene)bis{2-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl}phenol) (IIb). Yield 68%, diastereomers mixture (racemate/*meso*-form), colorless powder, mp 186–188°C. IR spectrum, ν, cm^{-1}: 2952, 2892, 2836, 1456, 1372 (Me, CH_2), 1600 (C=C), 1260 (C–O), 1244 (C–N), 1144 (C–O–C), 844, 752 (=C–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79 s (6H, $C^{10}H_3$, $C^{10'}H_3$), 0.84 s (6H, $C^{9}H_3$, $C^{9'}H_3$), 0.90 s (6H, $C^{8}H_3$, $C^{8'}H_3$), 1.27–1.40 m (2H, H^5, $H^{5'}$), 1.48–1.66 m (6H, H^3, $H^{3'}$, H^6, $H^{6'}$), 1.77–1.94 m (4H, H^4, $H^{4'}$, H^5, $H^{5'}$), 2.12–2.24 m (2H, H^3, $H^{3'}$), 2.75–2.98 m (8H, H^{18}, $H^{18'}$, $H^{18''}$, $H^{18'''}$), 3.34 t (2H, H^2, $H^{2'}$, *J* 9.0), 3.63 s (8H, H^{20}, $H^{20'}$, $H^{20''}$, $H^{20'''}$), 3.69 t (8H, H^{19}, $H^{19'}$, $H^{19''}$, $H^{19'''}$, *J* 5.6), 3.79 and 3.89 two d (4H, H^{17}, $H^{17'}$, *J* 13.7 and *J* 13.7), 6.72 d. d (2H, H^{15}, $H^{15'}$, *J* 7.5), 6.80 d (2H, H^{14}, $H^{14'}$, *J* 6.8), 7.22 d (2H, H^{16}, $H^{16'}$, *J* 7.6), 10.83 br. s (2H, OH). ^{13}C NMR spectrum, δ_C, ppm: 12.20 (C^{10}, $C^{10'}$), 20.28 (C^{9}, $C^{9'}$), 21.48 (C^{8}, $C^{8'}$), 27.58 (C^{5}, $C^{5'}$), 33.80 (C^{3}, $C^{3'}$), 39.66 (C^{6}, $C^{6'}$), 44.69 (C^{2}, $C^{2'}$), 45.76 (C^{4}, $C^{4'}$), 47.86 (C^{7}, $C^{7'}$), 49.85 (C^{1}, $C^{1'}$), 53.32 (C^{18}, $C^{18'}$, $C^{18''}$, $C^{18'''}$), 58.62 and 58.70 (*meso*-form and racemate, respectively, C^{17}, $C^{17'}$), 69.20 (C^{19}, $C^{19'}$, $C^{19''}$, $C^{19'''}$), 70.87 and 70.93 (racemate and *meso*-form, respectively, C^{20}, $C^{20'}$, $C^{20''}$, $C^{20'''}$), 117.79 (C^{15}, $C^{15'}$), 121.48, 130.69 (C^{11}, $C^{11'}$, C^{13}, $C^{13'}$), 126.05 (C^{14}, $C^{14'}$), 127.13 (C^{16}, $C^{16'}$), 157.11 (C^{12}, $C^{12'}$). Found, %: C 74.11; H 9.33. $C_{46}H_{70}N_2O_6$. Calculated, %: C 73.96; H 9.44.

6,6'-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene)bis(2-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl}phenol) [(–)-IIb]. Yield 64%, colorless powder, mp 156–158°C. $[\alpha]_D^{24}$ –14.8° (*c* 0.22, $CHCl_3$). The spectral characteristics are in agreement with those for the diastereomers mixture **IIb**.

X-Ray diffraction analysis of compound (–)-IIb. The single crystals were obtained by the slow evaporation of a solution of compound **(–)-IIb** in chloroform. Colorless plate crystals of **(–)-IIb**, $C_{46}H_{70}N_2O_6$ (*M* 747.04) at 100 K are monoclinic; *a* 11.3279(10), *b* 13.7028(12), *c* 13.5478(11) Å; β 99.570(2)°, *V* 2073.7(3) $Å^3$, space group $P2_1$, *Z* 2, d_{calc} 1.196 g cm^{-3}. The experimental set of 16 651 reflections was obtained on a Bruker SMART APEX2 CCD diffractometer (λMoK_α 0.71073, θ_{max} 29°) using a single-crystal sample of size 0.36 × 0.20 × 0.08 mm. Processing of the source array of the measured intensities was carried out by a SAINT and SADABS programs included into APEX2 software package [10]. The structure was solved by the direct method and refined by a full-matrix anisotropic approximation for the nonhydrogen atoms with respect to F^2_{hkl}. The hydrogen atoms were placed into the geometrically calculated positions, except for the H atoms of the hydroxy groups, whose positions were localized from the difference electron density maps. Further, the O–H distance was normalized to 0.85 Å. All hydrogen atoms were refined using a *rider* model. In the refinement 5716 independent reflections were used (R_{int} 0.0528). The refinements convergence for all the independent reflections wR_2 was 0.1077 [R_1 0.0476 for 4526 reflections with $I > 2\sigma(I)$]. All calculations were performed on an IBM PC using a SHELXTL software package [11]. The atomic coordinates and temperature factors are deposited into the Cambridge structural data base (CCDC 828095).

ACKNOWLEDGMENTS

This work was financially supported by the Federal Agency for Science and Innovations (state contract no. 02.740.11.0081).

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