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Calix[4]resorcinols Bearing γ-Aminoacetal Groups on the Upper Rim. Synthesis and Properties

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Abstract—Synthesis of new calix[4]resorcinol molecules with acetal groups on the upper rim associated with calixarene skeleton through γ-aminoalkyl spacers was performed. The condensation of the compounds studied with 2-methylresorcinol was studied.

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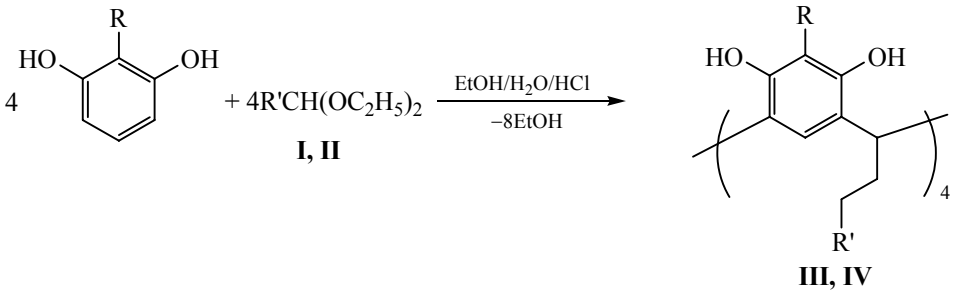
Calix[4]resorcinols are universal macrocyclic compounds capable of forming complexes of the *guest–host* type with both neutral molecules and ions, as well as to form the supramolecular aggregates with a specific supramolecular structure having catalytic activity [1]. Chemical modification of these macrocycles allows varying the size and shape of the molecular cavity to produce compounds that differ in their lability, size, and properties [2].

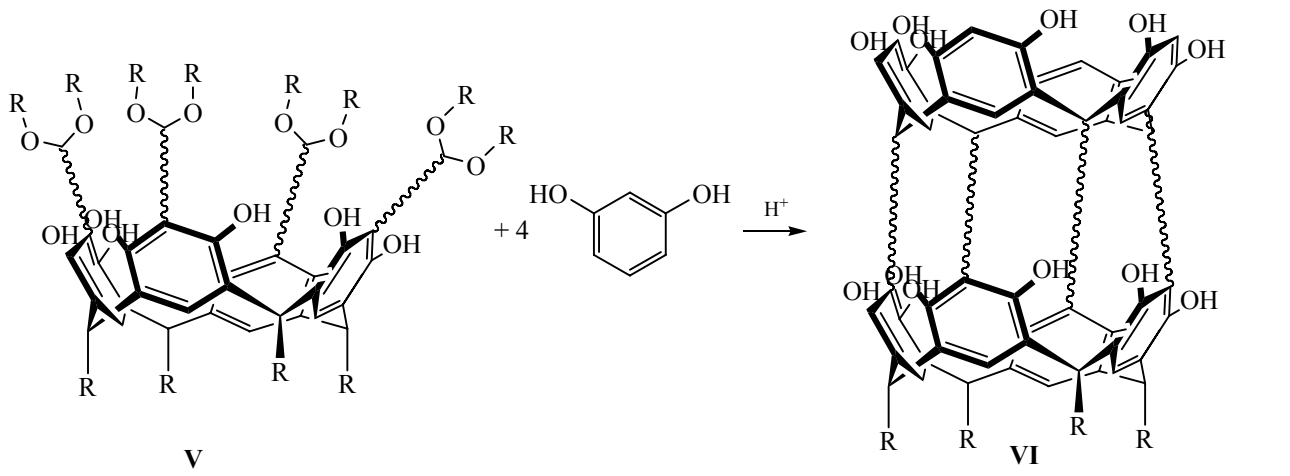
Recently we have developed a simple effective method for synthesis of calix[4]resorcinols consisting in the interaction of functionalized acetals with resorcinol and its derivatives [3, 4].



I, III, R' = $CH_2P(O)(OR'')_2$, R = H; I**I, IV**, R' = $CH_2CH_2NH_2$, R = Me.

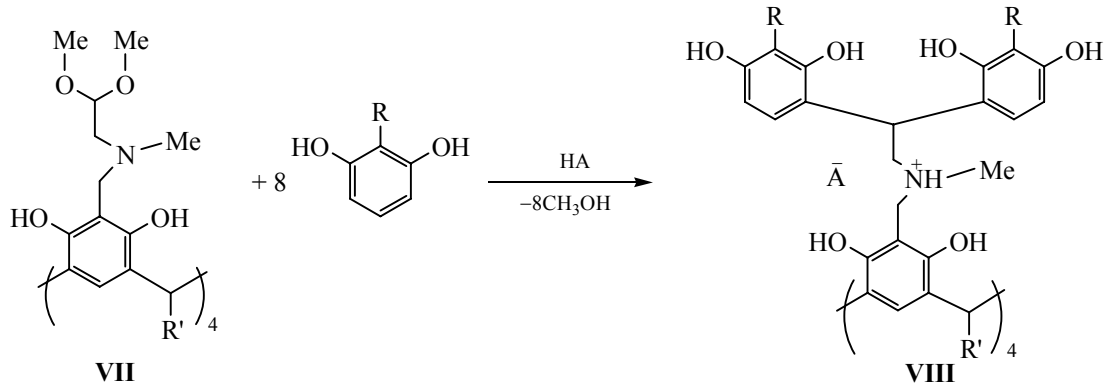
On the other hand, involving the acetals attached to the calix[4]resorcinol scaffold **V** in the condensation reaction with resorcinol and its derivatives opens a possibility of forming a new calix[4]resorcinol core to produce tubular structures **VI**, the bis(calixarenes).

The bis(calixarene) structures are known to be used in analytical chemistry as highly selective complexing agents and extractants, the models of ion channels [5, 6]. However, only a single example of obtaining a bis(calixarene) on the calix[4]resorcinol basis was described in the literature. The synthesis was achieved by reacting the calix[4]resorcinol cavitand containing four *para*-hydroxybenzaldehyde fragments on the upper rim of the molecule with resorcinol and 2-methylresorcinol [7].



V **VI**

We suggest an approach to the formation of bis-(calixarenes) by the condensation of 2-methylresorcinol with the acetal groups attached to the calix[4]resorcinol scaffold. To implement this direction we previously have obtained the first representatives of the calix[4]resorcinols containing α-aminoacetal fragments on the upper rim of the molecule [8, 9]. It was shown that the condensation of these compounds with resorcinol and 2-methylresorcinol led to the formation of compounds **VIII** containing four polyphenol (diarylmethane) fragments on the upper rim of the molecule [10].



VII **VIII**

R = H, Me, R' = Alk.

This synthetic result, apparently, was due to the rigid pre-arrangement of the α-aminoacetal fragments on the calix[4]resorcinol scaffold. Presumably the condensation with 2-methylresorcinol of aminoalkylated calix[4]resorcinols bearing acetal groups connected through a flexible spacer (by three carbon atoms away from the nitrogen atom) will contribute to the formation of bis-calixarenes (**IX**).

To study the possible formation of a structure of this type, we performed its quantum-chemical simulation, which showed that the formation of the structure **IX** is possible in principle. Figure 1 shows an optimized geometry of this structure. We also performed the optimization of the structure with four diarylmethane fragments. Figure 2 shows the optimized geometry of structure **X**.

To estimate quantitatively the feasibility of one or the other structure, we performed the quantum-chemical calculation of their scaffolds, that is, the structures without arylmethane fragments (with the same stoichiometry). As a result of this approximation, it turns out that the scaffolds of structures **IX** and **X** differ in energy by 15.8 kJ mol^{-1} in favor of the latter. Therefore it is logical to assume that the calixarene with the shape of the tube, being sterically more strained than its scaffold, would be even less favorable than the calyx-shaped one. But there are examples in the literature when at the difference between the conformations

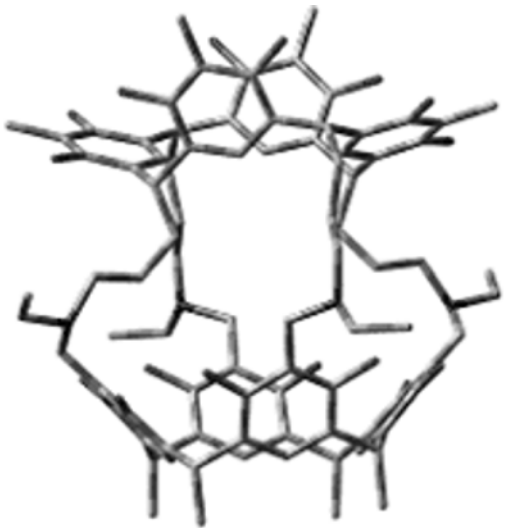


Fig. 1. The optimized geometry of structure **IX.**

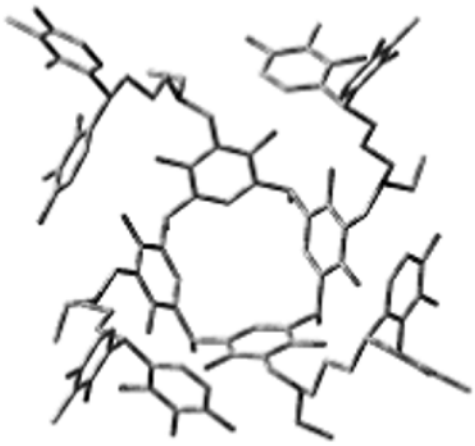


Fig. 2. The optimized geometry of structure **X.**

of 20 kJ mol^{-1} and even more the substances exist as a less favorable form. This is often observed in crystals when the less favorable conformation has a more dense packing [11, 12].

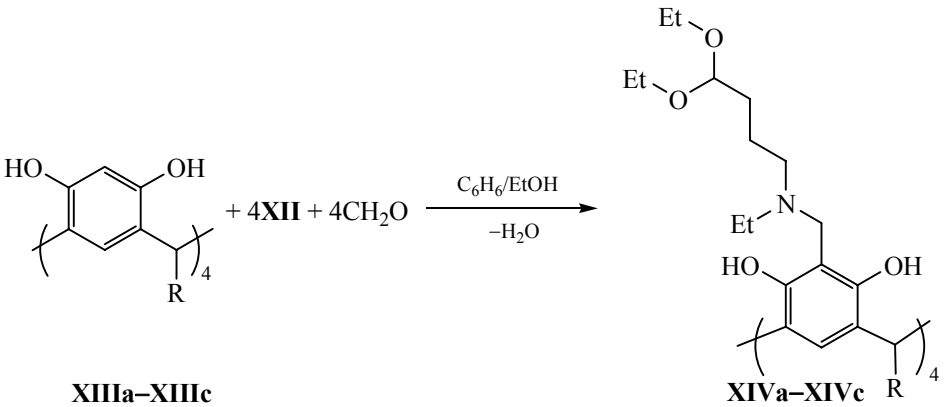
Thus, the quantum-chemical calculations were not able to give clear preference for the choice of a structure. Therefore we had to synthesize new calix[4] resorcinols containing the acetal groups associated with the calixarene core through a γ-aminoalkyl spacer on the upper rim, and to explore their condensation with 2-methylresorcinol.

To achieve the goal, we have synthesized a new secondary γ-aminoacetal **XII** by the reaction of primary γ-aminoacetal **XI** with ethyl bromide in acetonitrile in the presence of potassium carbonate.

$$\underset{\textbf{XI}}{EtBr + NH_2CH_2CH_2CH_2CH(OEt)_2} \xrightarrow{CH_3CN/K_2CO_3} \underset{\textbf{XII}}{EtNHCH_2CH_2CH_2CH(OEt)_2}$$

The structure of compound **XII** was proved using IR and ^{1}H NMR spectroscopy, and elemental analysis confirmed its composition. In the ^{1}H NMR spectrum of compound **XII** the proton signals of the methyl and methylene groups of the ethoxy radicals are doubled, which may indicate the presence of intramolecular hydrogen bonding between the secondary amino group and the oxygen atom of one of the ethoxy groups.

The condensation of the aminoacetal **XII** with calix[4]resorcinols **XIIIa–XIIIc** and formaldehyde water solution in a benzene–ethanol mixture at a ratio of the initial reagents 1:5:5 resulted in 55–75% yield of new aminomethylated derivatives **XIVa–XIVc.** We investigated their condensation with 2-methylresorcinol.

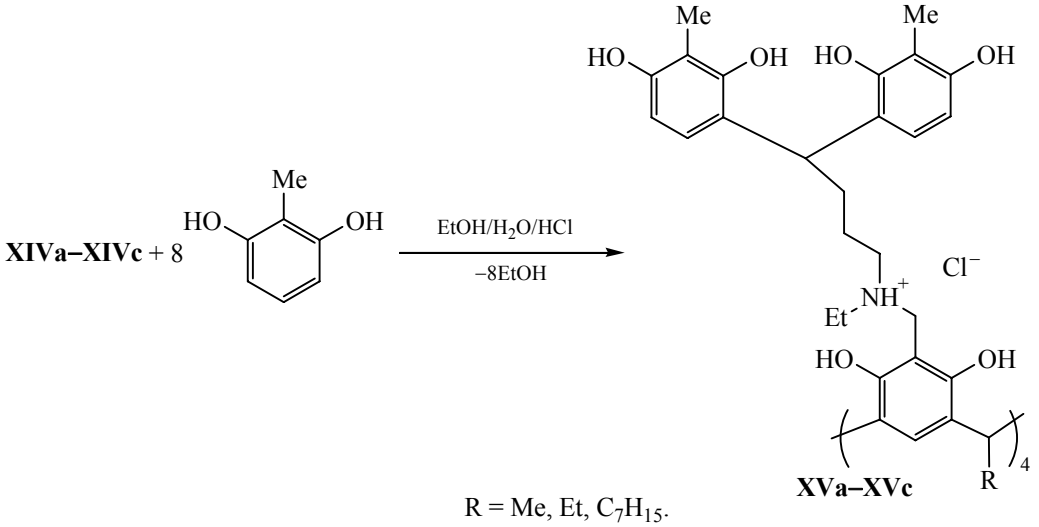


XIIIa–XIIIc **XIVa–XIVc**

R = Me (**a**), Et (**b**), C_7H_{15} (**c**).

Compounds **XIV** are pink powders with melting points from 88 to 126°C. In the ^{1}H NMR spectra of the calix[4]resorcinols **XIVa–XIVc** there are no signals of the protons of the aromatic rings in the *ortho* position to the hydroxy groups, the methylene protons of the etoxy groups are nonequivalent and appear in the spectrum as two multiplets at 3.50 and 3.52 ppm. The proton signals of other groups are broadened, indicating a strong intermolecular association of these compounds.

The reaction of calix[4]resorcinols **XIV** with 2-methylresorcinol was carried out in an ethanol–water medium in the presence of hydrogen chloride at a ratio of initial reagents **XIV**:2-methylresorcinol 1:4 and 1:8. As a result of the reaction the derivatives were isolated containing four diarylmethane fragments on the upper rim **XVa–XVc** with a 23–47% yield. The most part of the product was an intractable solid.



R = Me, Et, C_7H_{15}.

EXPERIMENTAL

Quantum-chemical calculations. The calculations were performed in the framework of the hybrid method of the density functional theory B3LYP with the basis set 6-31G (d), using Gaussian 09 software [13].

The ^{1}H NMR spectra were obtained on a Bruker AVANCE-600 instrument (working frequency 600.13 MHz). The IR spectra of the compounds were taken from suspensions in mineral oil on a UR-20 instrument in the frequency range of 400–3600 cm^{-1}.

Synthesis of (4,4-diethoxybutyl)ethylamine (XII). To a mixture of 15 g aminoacetal **XI** and 54 g of potassium carbonate dissolved in 160 ml of acetonitrile was added dropwise with stirring 10.8 g of ethyl bromide and a catalytic amount of KI (1.5 g). The reaction mixture was heated at reflux for 4–6 h. The precipitate formed was filtered off, the solvent was removed in a vacuum of water-jet pump, in the remaining oily liquid was poured 50 ml of water, the organic portion was separated and the aqueous layer was extracted three times with chloroform. The chloroform extract was combined with the organic part, and the solution was dried over sodium sulfate. After a day, sodium sulfate was filtered off, the solvent was distilled off in a vacuum of water-jet pump, the remaining reaction mixture was distilled in a vacuum of a water-jet pump to obtain 2.11 g (64%) of compound **XII**, bp. 123°C (15 mm Hg), n_D^{20} 1.4300. IR spectrum, ν, cm^{-1}: 1061, 1125 (COC), 3421 (NH). The ^{1}H NMR spectrum (600.13 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 0.83 t (1H, NCH_2Me, $^3J_{HH}$ 7.24), 0.93 t (2H, NCH_2Me, $^3J_{HH}$ 7.24), 1.012 m, 1.016 t (6H , OCH_2CH3, $^3J_{HH}$ 7.04), 1.33–1.37 m (1H, $(CH_2)_2CH$), 1.39–1.48 m (3H, $(CH_2)_2CH$), 2.22–2.26 m (0.5H, NCH_2CH_3), 2.30–2.36 m (1.5 H, NCH_2CH_3), 2.44–2.55 m (2H, NCH_2CH_2), 3.27–3.34 m (2H, OCH_2CH_3), 3.42–3.49 m (2H, OCH_2CH_3), 4.29–4.33 m [1H, CH $(OEt)_2$]. Found, %: C 63.42, H 12.18, N 7.32. $C_{10}H_{23}NO_2$. Calculated, %: C 63.45, H 12.25, N 7.40.

4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[*N*-(4,4-diethoxybutyl)ethylaminomethyl]-2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (XIVa). To a solution of 1.0 g of calixarene **XIIIa** in a mixture of 10 ml ethanol and 10 ml of benzene was added in succession 1.74 g of aminoacetal **XII** and 0.74 g of 37% aqueous solution

of formaldehyde. The reaction mixture was kept at room temperature for two days, the solvent was distilled off in a vacuum of a water-jet pump. The oily residue was triturated in hexane and dried in a vacuum desiccator over P_2O_5. 1.35g (54%) of compound **XIVa** was obtained, mp 87–88°C. IR spectrum, ν, cm^{-1}: 1610 (C=C_{ar}), 1061, 1125 (COC), 3421 (OH). The ^{1}H NMR spectrum (600.13 MHz, CD_3OD) δ, ppm: 1.20–1.23 m (36H, NCH_2CH_3, OCH_2CH_3), 1.63–1.89 m [28H, $CHCH_3$, $(CH_2)_2CH$], 2.58 br.s (8H, NCH_2CH_3), 3.29–3.35 (m, 8H, NCH_2CH_2), 3.51 (m, 8H, OCH_2CH_3), 3.65 m (8H, OCH_2CH_3), 3.87 br.s (8H, $C_{ar}CH_2$), 4.51 br.s [8H, $CH(OEt)_2$, CHEt], 7.28 br.s (4H, $C_{ar}H$). Found,%: C 67.42, H 9.18, N 4.02. $C_{76}H_{124}N_4O_{16}$. Calculated, %: C 67.66, H 9.20, N 4.15.

4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[*N*-(4,4-diethoxybutyl)ethylaminomethyl]-2,8,14,20-tetraethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (XIVb). Similarly to the preceeding experiment, from 1.0 g of calixarene **XIIIb** dissolved in a mixture of 8 ml of ethanol and 8 ml of benzene, 1.65g of aminoacetal, and 0.86 g of 37% aqueous solution of formaldehyde 1.65g (74%) of compound **XIVb** was obtained, mp 116–118°C. IR spectrum, ν, cm^{-1}: 1609 (C=C_{ar}), 1062, 1126 (COC), 3411 (OH). The^{1}H NMR spectrum (600.13 MHz, CD_3OD) δ, ppm: 0.92 br.s (12H, NCH_2CH_3), 1.19–1.23 m (36H, OCH_2CH_3, $CHCH_2CH_3$), 1.63–1.73 m [16H, $(CH_2)_2CH$], 2.19 br.s (8H, CH_2CH_3), 2.66 br.s (8H, NCH_2CH_3), 3.01 br.s (8H, NCH_2CH_2), 3.51 m (8H, OCH_2CH_3), 3.65 m (8H, OCH_2CH_3), 3.9, 4.2 br.s (8H, $C_{ar}CH_2$), 4.51–4.53 br.s (4H, CHEt), 4.89 br.s [4H, CH $(OEt)_2$], 7.28 s (4H, $C_{ar}H$). Found,%: C 68.25, H 9.45, N 3.96. $C_{80}H_{132}N_4O_{16}$. Calculated, %: C 68.38, H 9.4, N 3.99.

4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[*N*-(4,4-diethoxybutyl)ethylaminomethyl]-2,8,14,20-tetraheptylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (XIVc). Similarly to the above from 0.88 g of calixarene **XIIIc**, 0.97 g aminoacetal **XII,** and 0.41g of 37% aqueous solution of formaldehyde 1.29 g (77%) of compound **XIVc** was obtained, mp 123–126°C. IR spectrum, ν, cm^{-1}: 1611 (C=C_{ar}), 1062, 1125 (C–OC), 3409 (OH). The ^{1}H NMR spectrum (600.13 MHz, CD_3OD) δ, ppm: 0.89 m (12H, NCH_2CH_3), 1.20–1.28 m [76H, OCH_2CH_3, $(CH_2)_5CH_3$], 1.63 br.s [16H, $(CH_2)_2CH$] , 1.89 br.s (8H, CH_2 $(CH_2)_5CH_3$), 2.59 br.s (8H, NCH_2CH_3), 3.26–3.28 br.s (8H, NCH_2CH_2), 3.50 m (8H, OCH_2CH_3), 3.65 m (8H, OCH_2CH_3), 3.85–4.2 br.s (8H, $C_{ar}CH_2$), 4.51 br.s [8H, CH $(OEt)_2$, CHEt], 7.09 br.s (4H, $C_{ar}H$). Found, %: C 70.52, H 9.85, N 3.67. $C_{100}H_{172}N_4O_{16}$. Calculated, %: C 71.26, H 10.21, N 3.33.

4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[(*N*-[4,4-bis(2,4-dihydroxy-3-methylphenyl)-butyl]ethylaminomethyl)-N-hydrochloride]-2,8,14,20-tetraethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (XVa). To a stirred solution of 0.9 g of calix [4]resorcinol **XIVa** in a mixture of 5 ml of ethanol, 5 ml of water, and 5 ml of hydrochloric acid, cooled to 10°C, was added dropwise 0.73 g of 2-methylresorcinol dissolved in 2 ml of ethanol. The reaction mixture was heated at 60°C, the separated precipitate was filtered off, washed with diethyl ether, and dried over phosphorus pentoxide. The filtrate was evaporated and the residue was reprecipitated from acetone into diethyl ether. 0.3g (23%) of compound **XVa** was obtained, mp > 300°C. IR spectrum, ν, cm^{-1}: 1606 (C=C_{ar}), 2725 (NH^+), 3201 (OH), 3440 (OH). The ^{1}H NMR spectrum [(CD_3OD), δ, ppm, (J_{HH}, Hz)]: 1.26 br.s (12H, NCH_2CH_3), 1.72 br.s [28H, $(CH_2)_2$, $CHCH_3$], 2.08 s (24H, $C_{ar}CH_3$), 2.96–3.14 br.s (16H, NCH_2), 4.20–4.29 m (8H, $C_{ar}CH_2$) 4.47 q (4H, CHC_{ar}, $^3J_{HH}$. 7.93), 4.64 m (4H, $C_{ar}CH$), 6.37 d (8H, $C_{ar}H$, $^3J_{HH}$ 8.57), 6.89 br.s (8H, $C_{ar}H$, $^3J_{HH}$ 8.57), 7.34–7.56 br.s (4H, H_2). Found, %: C 63.26, H 6.45, Cl 7.28, N 2.74, $C_{116}H_{144}$ $Cl_4N_4O_{24}$. Calculated, %: C 65,71, H 6.85, Cl 6.69, N 2.64.

4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[(*N*-[4,4-bis(2,4-dihydroxy-3-methylphenyl)-butyl]ethylaminomethyl)-*N*-hydrochloride]-2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (XVb). Similarly to the above, from 1.5 g of calix[4]resorcinol **XIVb** and 1.17 g of 2-methylresorcinol was obtained 1.1 g (47%) of compound **XVb**, mp > 300°C. IR spectrum, ν, cm^{-1}: 1606 (C=C_{ar}, 2725 (NH^+), 3201 (OH), 3440 (OH). ^{1}H NMR spectrum [(CD_3OD), δ, ppm, (J_{HH}, Hz)]: 0.92 br.s (24H, CH_3, NCH_2CH_3), 2.07 s [40H, $C_{ar}CH_3$, $(CH_2)_2$], 2.28 br.s (8H, $CHCH_2CH_3$), 2.94–3.15 m (16H, NCH_2), 4.33–4.46 br.s (16H, CHC_{ar}, $C_{ar}CH_2$), 6.46 m (8H, $C_{ar}H$), 7.02 br.s (8H, $C_{ar}H$), 7.43 s (4H, H^2). Found, %: C 63.26, H 6.45, Cl 7.28, N 2.74. $C_{120}H_{152}Cl_4N_4O_{24}$. Calculated,%: C 66.24, H 6.99, Cl 6.53, N 2.58.

4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[(*N*-[4,4-bis(2,4-dihydroxy-3-methylphenyl)-

butyl]ethylaminomethyl)-*N*-hydrochloride]-2,8,14,20-tetraheptylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (XVc). Similarly to the above from 1.29 g of calix[4]resorcinol **XIV** and 0.95 g of 2-methylresorcinol was obtained 0.6 g (32%) of compound **XVc**, mp > 300°C. IR spectrum, ν, cm^{-1}: 1606 (C=C$_{ar}$), 2725 (NH^{+}), 3201 (OH), 3440 (OH). ^{1}H NMR spectrum [(CD$_3$OD), δ, ppm, (J_{HH}, Hz)]: 0.86 br.s (12H, CH$_2$CH$_3$), 1.26 br.s [28H, (CH$_2$)$_2$, NCH$_2$CH$_3$], 2.08 s (24H, C$_{ar}$CH$_3$), 3.14 br.s (16H, NCH$_2$), 4.46 br.s (16H, C$_{ar}$CH$_2$, CHC$_{ar}$, C$_{ar}$CH), 6.43 d (8H, C$_{ar}$H, $^3J_{HH}$ 8.24), 6.79 d (8H, C$_{ar}$H, $^3J_{HH}$ 8.24) , 7.04–7.16 br.s (4H, H$_2$). Found, %: C 67.26, H 7.89, Cl 5.69, N 2.56. C$_{140}$H$_{192}$Cl$_4$N$_4$O$_{24}$. Calculated, %: C 68,46, H 7.82, Cl 5.79, N 2.28.

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