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Condensation of Resorcinol with Phosphorylated Acetals, Synthesis of Calix[4]resorcinolarenes with Phosphorus-containing Alkyl Fragments in the Lower Rim

A. R. Burilov*, Yu. M. Volodina*, E. V. Popova*, A. S. Gazizov*, I. R. Knyazeva*, M. A. Pudovik*, V. D. Habicher, and A. I. Konovalov***

** Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center, Russian Academy of Sciences, ul. Arbuzova 8, Kazan, Tatarstan, 420088 Russia*

*** Institute of Organic Chemistry, Technological University of Dresden, Germany*

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Abstract — The reaction of resorcinol with phosphorylated acetals leads to formation of calix[4]resorcinolarenes having phosphonate, phosphinate, or (phosphinothioyl)sulfanylmethyl fragments in the lower rim of the molecule.

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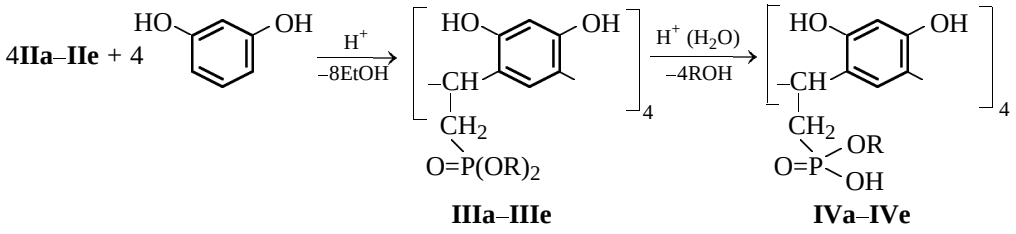
One of the promising and vigorously developing fields of organic chemistry is research into calix[*n*]arenes, specifically calix[4]resorcinolarenes. The interest in these compounds is caused by their synthetic availability, ability to form host–guest complexes with various organic compounds and metal ions, and tendency for self-association leading to formation of supramolecular ensembles. The combination of the above-mentioned properties makes calyx[*n*]arenes promising candidates for creating new types of complex-forming agents, extractants for metal ions, and catalytic systems. One of the most common approaches to forming the calixarene matrix involves reaction of polyphenols with aldehydes or their derivatives. However, it has certain limitations, because the effect of the structure of the starting aldehydes and polyphenols on the structure of the final products is not yet understood completely. It is known that unsubstituted aliphatic and aromatic aldehydes, as well as aliphatic aldehydes with functional substituents separated from the reaction center by 4–8 carbon atoms react with resorcinol in an acid medium to form calix[4]resorcinolarenes [1–3]. At the same time, no such structures are formed in the reaction of α-halo-substituted aliphatic aldehydes with resorcinol [2]. There has been no information on the possibility of calixarene synthesis by the reaction of resorcinol with aldehydes having functional substituents separated from the carbonyl group by 2–3 carbon atoms. In detail, no synthetic approaches have been developed to derivatives of calix[4]resorcinolarenes having alkyl groups with phosphorus-containing structural fragments in the lower rim. This is evidently connected with the fact that phosphorylated aliphatic aldehydes are difficult to prepare. Note also that attempted synthesis of calixarenes with phosphorylated alkyl fragments in the lower rim by means of phosphorylation of a ready calixarene matrix have been unsuccessful. Therefore, to synthesize calixarenes phosphorylated in the lower rim, we decided to use, instead of phosphorus-containing aldehydes, more available phosphonoacetals **IIa**–**IIe**. They latter were prepared by the Arbuzov reaction of trialkyl phosphites with bromoacetaldehyde acetal. Though some of phosphonoacetals were prepared previously [4], we extended this series significantly.

$$\underset{\mathbf{I}}{(RO)_3P} + BrCH_2CH(OEt)_2 \xrightarrow[-EtBr]{} \underset{\mathbf{IIa–IIe}}{(RO)_2P(O)CH_2CH(OEt)_2},$$

R = Et (**a**), Pr (**b**), *i*-Pr (**c**), Bu (**d**), *i*-Bu (**e**).

Phosphonoacetals react with resorcinol in an acid medium at elevated temperature to form in high yield calix[4]resorcinolarenes with phosphoryl groups in the lower rim. The synthetic result of the reaction significantly depends on experimental conditions. Heating of equimolar amounts of resorcinol and acetal for 3–4 h at 50–60°C leads to formation of phosphonates **IIIa**–**IIIe** [δ_P 29.90 ppm for **IIIa**] contaminated with small amounts of their partial hydrolysis products **IVa**–**IVe** (δ_P 32.21 ppm for **IVa**). With time, hydrolytically labile calixarenes **III** completely convert into compounds **IVa**–**IVe**.

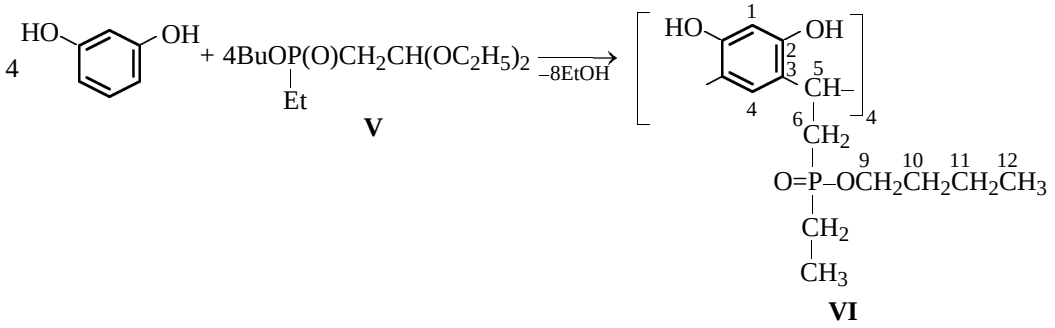


IIIa–**IIIe** **IVa**–**IVe**

III, IV, R = Et (**a**), Pr (**b**), *i*-Pr (**c**), Bu (**d**), *i*-Bu (**e**).

Calixarenes **IVa**–**IVe** are powder-like substances soluble in ethanol and DMF, and also in mixtures of these solvents with water. The ^{31}P NMR spectra of compounds **IVa**–**IVe** contain one signal at 32 ppm. The position of the signal slightly varies depending on the size of substituent R. The ^{1}H NMR spectrum contains proton signals of methyl groups (δ 1.10–1.40 ppm), methylene groups bound with phosphorus (δ 1.63–3.2 ppm), methylene group bound with oxygen (δ 2.70–4.20 ppm), methine groups (δ 5.0–5.90 ppm), and protons in the *ortho* (δ 6.26–6.77 ppm) and *meta* (δ 7.25–7.32 ppm) positions of the aromatic ring. The IR spectra display absorption bands of the OH (3100–3580 cm^{-1}) and P=O groups (1170–1220 cm^{-1}).

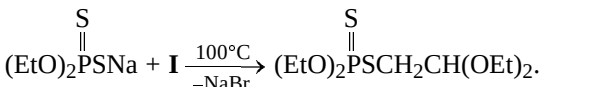
Developed method makes it possible to prepare calixarenes bearing phosphinate fragments in the lower rim. The reaction of resorcinol with acetal **V** gives powder-like product **VI** soluble in ethanol, DMF, and DMSO.



V **VI**

The ^{31}P NMR spectrum of compound **VI** contains one signal at δ_P 59.7 ppm. The ^{1}H NMR spectrum shows signals of methyl (0.83 ppm), methylene (1.24 and 3.72 ppm), metine (4.59 ppm), and hydroxyl protons (9 ppm), as well as the *ortho* (6.26 ppm) and *meta* protons (7.17 ppm) of the aromatic ring. The IR spectrum of this compound contains absorption bands of the OH (3100–3580 cm^{-1}) and P=O groups (1150–1170 cm^{-1}).

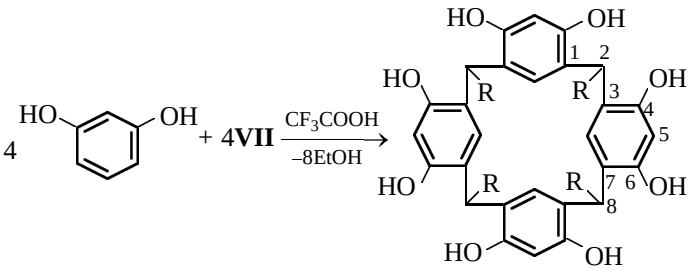
Developing the offered approach, we set ourselves the task to to prepare calixarenes with dithiophosphate fragments in the lower rim. To this end, we synthesized phosphorodithioate **VII** by condensation of *S*-sodium *O*,*O*-diethyl phosphorodithioate with bromoacetal **I**.



VII

The condensation of acetal **VII** with resorcinol under acid catalysis conditions gave a calixarene molecule bearing (phosphinothioyl)sulfanylmethyl fragments in the lower rim.

The structure and composition of product **VIII** were confirmed by IR and ^{1}H and ^{31}P NMR spectroscopy, MALDI–TOF mass spectrometry, and elemental analysis.



R = $CH_2SP(OEt)_2$.

EXPERIMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker MSL-400 spectrometer at 400.13, 100.62, and 166.93 MHz against signals of residual protons of deuterated solvent (DMSO-d_6) and external 85% phosphoric acid. The mass spectra were obtained on a MALDI-2 V-5.2.0 instrument in the 1,8,9-trihydroxyanthracene matrix.

Diethyl (2,2-diethoxyethyl)phosphonate (IIa). A mixture of 19.3 g of triethyl phosphite and 34.3 g of acetal **I** was heated for 4 h at 180°C. The ethyl bromide formed and excess acetal were distilled off. Vacuum distillation gave 21.2 g (72%) of compound **IIa**, bp 92°C (0.03 mm Hg), n_D^{20} 1.4280. ^1H NMR spectrum (CD_3COCD_3), δ, ppm: 1.36 t (12H, CH_3), 3.57 m (8H, OCH_2), 3.98 m (2H, CH_2P), 7.15 t (1H, CH). ^{31}P NMR spectrum: δ_P 22.21 ppm. Found, %: P 12.14. $C_{10}H_{23}O_5P$. Calculated, %: P 12.20.

Dipropyl (2,2-diethoxyethyl)phosphonate (IIb) was obtained analogously from 8.48 g of tripropyl phosphite and 11.82 g of acetal **I**. Yield 6.3 g (55%), bp 102–105°C (0.03 mm Hg), n_D^{20} 1.4330. ^{31}P NMR spectrum: δ_P 26.93 ppm. Found, %: P 10.79. $C_{12}H_{27}O_5P$. Calculated, %: P 10.99.

Diisopropyl (2,2-diethoxyethyl)phosphonate (IIc) was prepared analogously from 4.1 g of triisopropyl phosphite and 5.91 g of acetal **I**. Yield 2.4 g (43%), bp 70–72°C (0.03 mm Hg), n_D^{20} 1.4360. ^1H NMR spectrum ($CDCl_3$), δ_P 0.95 m (18H, CH_3), 3.54 m (6H, OCH_2, OCH), 4.21 m (2H, CH_2P), 6.82 t (1H, CH). ^{31}P NMR spectrum, δ_P 20.64. Found, %: P 10.82. $C_{12}H_{27}O_5P$. Calculated, %: P 10.99.

Dibutyl (2,2-diethoxyethyl)phosphonate (IId) was prepared analogously from 14.3 g of tributyl phosphite and 12 g of acetal **I**. Yield 12.9 g (55%), bp 102–105°C (0.03 mm Hg), n_D^{20} 1.4330. ^{31}P NMR spectrum, δ_P, ppm: 26.93. Found, %: P 9.82. $C_{14}H_{31}O_5P$. Calculated, %: P 10.00.

Diisobutyl (2,2-diethoxyethyl)phosphonate (IIe) was prepared analogously from 11.81 g of triisobutyl phosphite and 9.85 g of acetal **I**. Yield 9.48 g (65%), bp 118–120°C (0.03 mm Hg), n_D^{20} 1.4340. ^1H NMR spectrum (CD_3COCD_3), δ, ppm: 1.14 m (18H, CH_3), 1.5 m (4H, CH_2–C), 3.89 q (4H, OCH_2), 4.13 m (2H, CH_2–P), 5.00 m (1H, CH–O–P), 7.35 t (1H, CH–O). ^{31}P NMR spectrum: δ_P 26.09 ppm. Found, %: P 9.79. $C_{14}H_{31}O_5P$. Calculated, %: P 10.00.

4,6,10,12,16,18,22.24-Octahydroxy-2,8,14,20-tetra[[(ethoxy)hydroxyphosphinoyl]methyl]pentacyclo[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 (IVa). To a mixture of 1.6 g of resorcinol, 10 ml of water, 5 ml of ethanol, and 3.6 ml of conc. HCl acid a solution of 3.55 g of acetal **IIa** in 5 ml of ethanol was added dropwise with stirring. The reaction mixture was stirred for 1 h at 20°C and heated for 1 h at 50°C. The oily layer was decanted, triturated in acetonitrile, filtered, and evaporated in a vacuum (10 mm). The residue was dried in a vacuum (0.04 mm) to give 2.0 g (59%) of compound **IVa**, mp 250°C (decomp.). ^1H NMR spectrum (methanol-d_4), δ, ppm (*J*, Hz): 1.40 t (12H, CH_3, $^3J_{HH}$ 7.0), 1.63 m (8H, CH_2P), 3.95 m (8H, OCH_2), 5.07 br.m (4H, CH), 6.50 s (4H, *o*-CH_{arom}), 7.25 s (4H, *m*-CH_{arom}). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm (*J*, Hz): 17.35 q (CH_3, $^1J_{CH}$ 124.4), 63.45 t (CH_2O, $^1J_{CH}$ 142.6), 79.64 d.d (CH, $^1J_{CH}$ 149.0, $^2J_{CH}$ 149.0, $^2J_{CP}$ 7.0), 102.55 d (*m*-C_{arom}, $^1J_{CH}$ 124.4), 63.45 t (CH_2O, $^1J_{CH}$ 142.6), 79.64 d.d (CH, $^1J_{CH}$ 153.55), 154.37 s ($C_{arom}OH$). ^{31}P NMR spectrum (CD_3OD): δ_P 31.2 ppm. *M* 976. Found, %: C 48.81; H 5.72; P 12.88. $C_{40}H_{52}O_{20}P_4$. Calculated, %: C 49.18; H 5.33; P 12.70.

4,6,10,12,16,18,22,24-Octahydroxy-2,8,14,20-tetra[[hydroxy(propoxy)phosphinoyl]methyl]pentacyclo[19.3.1.1^{3,7}.1^{9,13}.^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (IVb) was obtained analogously from 3.3 g of resorcinol, 50 ml of water, 50 ml of ethanol, 7.75 ml of conc. HCl,

and 8.4 g of acetal **IIb**. Yield 7.31 g (81%), mp > 250°C. IR spectrum (KBr), ν, cm^{-1}: 1160 (P=O), 3100–3580 (OH). ^1H NMR spectrum (methanol-d_4): 1.42 d (24H, CH_3), 1.81 m (8H, CH_2P), 4.01 m (4H, OCH), 5.10 br.m (4H, CH), 6.23 s (4H, *o*-CH_{arom}), 7.30 s (4H, *m*-CH_{arom}). ^{31}P NMR spectrum (CD_3OD): δ_P 33.3 ppm. Found, %: C 50.45; H 5.53; P 10.07. $C_{44}H_{60}O_{20}P_4$. Calculated, %: C 51.16; H 5.81; P 12.02.

4,6,10,12,16,18,22,24-Octahydroxy-2,8,14,20-tetra[[hydroxy(isopropoxy)phosphinoyl]methyl]-pentacyclo[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 (IVc) was obtained analogously from 0.83 g of resorcinol, 10 ml of water, 10 ml of ethanol, 10 ml of conc. HCl, and 2.1 ml of acetal **IIc**. Yield 1.94 g (86%), mp 235°C (decomp.). IR spectrum (KBr), ν, cm^{-1}: 1162 (P=O), 3100–3580 (OH). ^1H NMR spectrum (methanol-d_4), δ, ppm: 1.46 t (12H, CH_3, $^3J_{HH}$ 7.0 Hz), 1.4–1.6 br.m (8H, CH_2), 1.83 m (8H, CH_2P), 3.85 m (8H, OCH_2), 5.17 br.m (4H, CH), 6.26 s (4H, *o*-CH_{arom}), 7.28 s (4H, *m*-CH_{arom}). ^{31}P NMR spectrum (CD_3OD): δ_P 30.82 ppm. Found, %: C 50.97; H 5.56; P 11.57. $C_{44}H_{60}O_{20}P_4$. Calculated, %: C 51.16; H 5.81; P 12.02.

4,6,10,12,16,18,44,24-Octahydroxy-2,8,14,20-tetra[[(butoxy)hydroxyphosphinoyl]methyl]pentacyclo[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 (IVd) was prepared analogously by addition of a solution of 1.75 g of acetal **IId** in 4 ml of ethanol to a mixture of 0.62 g of resorcinol, 8 ml of water, 8 ml of ethanol, and 1.4 ml of conc. HCl. Yield 1.2 g (78%), mp 165–166°C. ^1H NMR spectrum (methanol-d_4), δ, ppm (*J*, Hz): 1.10 t (12H, CH_3, $^3J_{HH}$ 7.0), 1.4–1.70 br.m (16H, CH_2), 1.89 m (8H, CH_2P), 4.20 m (8H, OCH_2), 5.17 m (4H, CH), 6.48 s (4H, *o*-CH_{arom}), 7.32 s (4H, *m*-CH_{arom}). ^{13}C NMR spectrum (methanol-d_4), δ_C, ppm (*J*, Hz): 13.99 q (CH_3, $^1J_{CH}$ 124.4), 19.64 t [$(CH_2)_2$, $^1J_{CH}$ 122.06], 33.48 t (CH_2P, $^1J_{CH}$ 125.60), 66.71 t (CH_2O, $^1J_{CH}$ 142.60), 69.65 d.d (CH, $^1J_{CH}$ 150.90, $^2J_{CP}$ 7.04), 104.05 d (C_m, $^1J_{CH}$ 155.90), 122.53 s ($C_{arom}CH$), 129.96 d (*o*-$C_{arom}CH$, $^1J_{CH}$ 154.60), 154.26 s ($C_{arom}OH$). ^{31}P NMR spectrum (CD_3OD): δ_P 31.14 ppm. *M* 1114. Found, %: C 52.55; H 6.43; P 11.85. $C_{48}H_{68}O_{20}P_4$. Calculated, %: C 52.94; H 4.25; P 11.40.

4,6,10,12.16,18,22,24-Octahydroxy-2,8,14,20-tetra[[hydroxy(isobutoxy)phosphinoyl]pentacyclo-[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 (IVe) was prepared analogously from 3.41 g of resorcinol, 50 ml of water, 50 ml of ethanol, 7.75 ml of conc. HCl, and 9.56 g of acetal **IId**. Yield 6.81 g (67%), mp > 250°C. IR spectrum (KBr), ν, cm^{-1}: 1165 (P=O), 3100–3580 (OH). ^{31}P NMR spectrum (CD_3OD), δ_P 32.90 ppm. Found, %: C 51.60; H 6.15; P 11.04. $C_{48}H_{68}O_{20}P_4$. Calculated, %: C 52.94; H 6.25; P 11.40.

4,6,10,12,16,22,24-Octahydroxy-2,8,14,20-tetra[[(butoxy)ethylphosphinoyl]methyl]pentacyclo-[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 (VI). A mixture of 2.15 g of resorcinol, 20 ml of water, 15 ml of ethanol, and 5.2 ml of conc. HCl was treated dropwise with stirring and cooling with a solution of 5.2 g of acetal **V** in 5 ml of ethanol. The reaction mixture was stirred for 1 h at 50°C and for 5 days at 20°C. The oily layer was decanted, triturated with acetonitrile, and dried in a vacuum (5 h, 90°C, 0.04 mm Hg) to give 4.3 g (77%) of compound **VI** as a white amorphous powder darkening on heating above 250°C (decomp.). IR spectrum, ν, cm^{-1}: 1160 (P=O); 3100–3580 (OH). ^1H NMR spectrum (methanol-d_4), δ, ppm (*J*, Hz): 0.83 m (24H, CH_3), 1.24 m (32H, CH_2), 3.72 m (8H, CH_2), 4.59 m (4H, CH), 6.26 br.s (4H, *o*-H_{arom}), 7.17 br.s (4H, *m*-H_{arom}), 9.0 br.s (8H, OH). ^{13}C NMR spectrum (methanol-d_4), δ_C, ppm (*J*, Hz): 4.27 q [C^8, $^1J_{CH}$ 124.7, $^2J_{CC}$ 6.28), 12.49 q (C^{12}, $^1J_{CH}$ 124.7), 17.28 t (C^{11}, $^1J_{CH}$ 123.74), 19.52 d.t (C^7, $^1J_{PC}$ 90.6, $^1J_{CH}$ 119.8), 31.21 t (C^{10}, $^1J_{CH}$ 120.3), 61.82 t (C^9, $^1J_{CH}$ 125.6, $^2J_{PC}$ 8.97), 101.81 d (C^4, $^1J_{CH}$ 121.73), 120.64 s (C^3), 128.22 d (C^1, $^1J_{CH}$ 145.39), 152.65 s (C^2). ^{31}P NMR spectrum (DMSO): δ_P 59.7 ppm. *M* 1159. Found, %: C 58.64; H 8.22. $C_{56}H_{84}O_{16}P_4$. Calculated, %: C 59.15; H 7.39.

***O,O*-Diethyl *S*-(2,2-diethoxyethyl) phosphorodithioate (VII)**. A mixture of 4.16 g of *S*-sodium *O,O*-diethyl phosphorodithioate and 9.85 g of bromoacetal **I** was heated for 1 h at 100°C, cooled to 20°C, and treated with 10 ml of water and 15 ml of diethyl ether. The ether layer was removed and dried over magnesium sulfate. The ether and excess bromoacetal were removed in a water-jet-pump vacuum to obtain 1.7 g (28%) of compound **VII** as a light yellow oil. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.12 m (12H, CH_3), 2.71 d.d (2H, SCH_2, $^3J_{HH}$ 7.0 Hz, $^3J_{PH}$ 10.2 Hz), 3.48 m (4H, $POCH_2$), 4.07 q (4H, OCH_2, $^3J_{HH}$ 7.0 Hz), 4.51 t (1H, CH, $^3J_{HH}$ 7.0 Hz). ^{31}P NMR spectrum (DMSO): δ_P 93.6 ppm. Found, %: P 9.98. $C_{10}H_{23}O_4PS_2$. Calculated, %: P 10.26.

4,6,10,12,16,18,22,24-Octahydroxy-2,8,14,20-tetrakis[(diethoxyphosphinothioyl)sulfanylmethyl]-pentacyclo[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 (VIII). A solution of 0.72 g of resorcinol in 7 ml of trifluoroacetic acid was quickly treated with a solution of 1.97 g of acetal **VII** in 2 ml of trifluoroacetic acid. The oily layer was decanted and twice precipitated with pentane from chloroform to give 1.61 g (77%) of compound **VIII** as an amorphous white powder, mp 120°C. IR spectrum, ν, cm^{-1}: 750–800 (P=S), 3100-3580 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.36 m (24H, CH_3), 2.10 m (8H, SCH_2), 4.16 m (16H, OCH_2), 4.86 m (4H, CH), 6.46 br.s (4H, *o*-H_{arom}), 7.45 br.s (4H, μ-H_{arom}), 8.33 br.s (8H, OH). ^{31}P NMR spectrum (DMSO-d_6): δ_P 92.8 ppm. Mass spectrum: *m/z* 1305 [*M* + Na]. Found, %: C 44.77; H 5.23; P 10.17. $C_{48}H_{68}O_{16}P_4S_8$. Calculated,: C 45.00; H 5.31; P 9.69.

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