New phosphorus-containing analog of calix[4]resorcinarene based on 2,6-dihydroxypyridine

A. R. Burilov,[a] I. R. Knyazeva,[a] M. A. Pudovik,[a]★ V. V. Syakaev,[a] Sh. K. Latypov,[a] I. Baier,[b] W. D. Habicher,[b] and A. I. Konovalov[a]

[a]*A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center, Russian Academy of Sciences, 8 ul. Akad. Arbuzova, 420088 Kazan, Russian Federation. Fax: +7 (843 2) 75 2253. E-mail: pudovik@iopc.knc.ru*

[b]*Institute of Organic Chemistry, Dresden Technical University, 13 Mommsenstrasse, D-01062 Dresden, Germany. Fax: +49 (351) 463 4093*

Acid-catalyzed reaction of 2,6-dihydroxypyridine hydrochloride with diethyl 2,2-diethoxyethylphosphonate or 2-ethoxyvinylphosphonyl dichloride in aqueous ethanol furnished a tetramer, phosphorus-containing analog of calix[4]resorcinarene with pyridine fragments in the molecule.

Key words: 2,6-dihydroxypyridine, diethyl 2,2-diethoxyethylphosphonate, condensation, tetramer.

Chemistry of calix[*n*]arenes, in particular of calix[4]resorcinarenes,[1—3] is one of the most promising and fast developing branches of organic chemistry. The simplicity of their synthesis and the ability to form complexes of the type "guest—host" with various organic compounds and metal ions, as well as the tendency to form supramolecular ensembles by self-association make the conditions for it. For all the properties described above, this class of compounds is considered as very prospective for the creation of new types of complex-forming compounds, extracting agents for metal ions, and catalytic systems. The functionalized derivatives of calixarenes, especially the phosphorylated ones, are of particular interest. Analysis of the literature data shows that plenty of *O*-phosphorylated derivatives of different composition and structure has been prepared by now, while there is actually no information on calixarenes *C*-phosphorylated along the lower rim of the molecule.[4] This is not a surprise, since the direct phosphorylation of the calixarene framework would not be likely to lead to the target products. It is known[5,6] that the most simple and widely used method for the synthesis of calix[4]resorcinarenes includes a condensation of resorcinol with aldehydes in acidic aqueous alcohols. It is logically to suppose that the calixarenes *C*-phosphorylated along the lower rim can be produced by reaction of resorcinol or its analogs with phosphorylated aldehydes. However, synthesis of such derivatives is not simple. Recently, we first accomplished the formation of phosphorus-containing calixarene matrix by the one-step acid-catalyzed reaction of resorcinol with easily produced phosphorus-containing acetals. As a result, the calix[4]resorcinarenes with phosphorylalkyl fragments on the lower rim of the molecule were synthesized for the first time.[7] It turned out that calixarenes of this type with acidic phosphonate fragments are efficient extracting agents of the metal ions of the lanthanum group from acidic solutions.

To further explore this area of investigation, we made an effort to synthesize compounds, the calixarene matrix of which includes the pyridine fragments instead of benzene ones. The *N*-protonation or alkylation of such cyclic tetramers would allow one to obtain charged structures of a new type, including water-soluble ones. The insertion of the acidic phosphonate or phosphinate fragments into the lower rim of the molecule might lead to the compounds with the structure of the intramolecular salts. There are just few literature[8,9] examples of the formation of cyclic tetramers by the reaction of 2,6-dihydroxypyridine with aldehydes in acidic media.

The acid-catalyzed condensation of 2,6-dihydroxypyridine hydrochloride (**1**) with diethyl 2,2-diethoxyethylphosphonate (**2**) has been carried out upon prolonged heating in aqueous alcohol (Scheme 1). As a result, the water-soluble pyridinocalixarene **3** with four fragments of phosphonic acid (a product of full hydrolysis of the corresponding ester) on the lower rim of the molecule was obtained.

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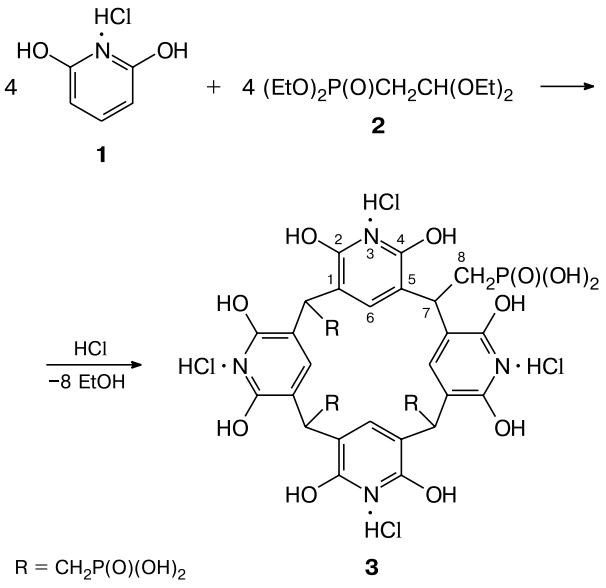
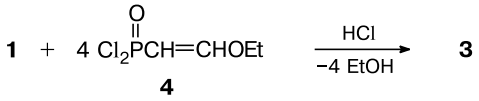
Scheme 1



There is a singlet at δ 21.14 in the ^{31}P NMR spectrum of compound **3**. The structure of compound **3** was established by ^{1}H and ^{13}C NMR spectroscopy as well as by HSQC, HMBC and 1D NOESY experiments. In the ^{1}H NMR spectrum, protons in the methylene fragments reveal themselves as a well resolved doublet of doublets at δ 2.63 ($^{3}J_{H,H}$ = 7.7 Hz, $^{2}J_{P,H}$ = 17.9 Hz), the methyne protons, as doublet of triplets at δ 4.42 ($^{3}J_{H,H}$ = 7.7 Hz, $^{3}J_{P,H}$ = 11.2 Hz), and the aromatic methyne protons resonate at δ 7.75 as a singlet. The given spectral data point out a high symmetry in the structure of the product. There are five signals in the ^{13}C NMR spectrum of compound **3**, which were assigned based on HSQC and HMBC experiments. The single signals for all the atoms in the NMR spectra indicate the presence of only one isomer with C_{4v} or D_{4h} symmetry. The 1D DPFGSE-NOE experiments[10] were carried out to assign the configuration of compound **3**. The negative nuclear Overhauser effects (NOE) were observed, since the sample has a high molecular weight; the NOE between *ortho*-proton in the aromatic ring and proton in the methylene group (59.3%) is three times as intense as the analogous interaction between protons in the methyne and in the methylene groups (17.4%). The obtained values attest the fact that the methylene protons are closer in space to the aromatic protons then methyne ones and that, consequently, the methylene groups occupy axial position, namely *cis* relatively to *ortho*-protons of the aromatic rings. Taking into account the literature data,[11,12] it is safe to say that compound **3** has the cone (C_{4v}) configuration. The structure and composition of calixarene **3** were also confirmed by mass-spectral and analytical data.

The calixarene **3** was also alternatively obtained by the reaction of dihydroxypyridine hydrochloride **1** with 2-ethoxyvinylphosphonyl dichloride **4** instead of the phosphorylated acetal **2** (Scheme 2). The physical and spectral characteristics of both products are identical.

Scheme 2



Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-600 spectrometer (600 and 150 MHz, respectively) in $(CD_3)_2SO$, ^{31}P NMR spectra were recorded on a Bruker MSL-400 NMR-Fourier spectrometer (100.62 MHz). NMR-experiments were carried out in solutions (10 mmol L^{-1}) at 303 K with the use of the inverse data unit with a z-gradient coil (5 mm). 1D DPFGSE-NOE spectra were recorded with the mixing times from 50 to 600 ms. The δ values are given relatively to the residual signals from the deuterated solvent (^{1}H, ^{13}C) or relatively to the external standart (^{31}P), 85% H_3PO_4. Mass-spectra were recorded on a Esquire-LC 00084 instrument.

2,6-Dihydroxypyridine hydrochloride (**1**) was purchased from Aldrich. Phosphonate **2** and vinylphosphonate **4** were obtained by known procedures.[13]

4,6,10,12,16,18,22,24-Octahydroxy-2,8,14,20-tetrakis[(dihydroxyphosphoryl)methyl]-5,11,17,23-tetraazapentacyclo[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 (3). ***A.*** Phosphonic acetal **2** (4.57 g, 18.0 mmol) was added dropwise to a stirred mixture of hydrochloride **1** (2.65 g, 18.0 mmol), ethanol (13 mL), water (13 mL), and conc. HCl (7.0 mL). The reaction mixture was heated under stirring for 7 days at 70—80 °C. The precipitate formed was filtered off, washed sequentially with ethanol and acetone, and kept *in vacuo* (40 °C, 0.06 Torr) until the weight was constant. Compound **3** (1.96 g, 43%) was obtained as light yellow powder, soluble in water and DMSO. The substance turns black under heating over 165 °C.

B. Phosphonyl dichloride **4** (3.84 g, 20.3 mmol) was added dropwise to a stirred mixture of hydrochloride **1** (3 g, 20.3 mmol), ethanol (15 mL), water (15 mL), and conc. HCl (7.5 mL). The reaction mixture was first kept for 2 days at 20 °C, then heated under stirring for 5 days at 70—80 °C. The precipitate formed was filtered off, washed sequentially with ethanol and acetone, and kept *in vacuo* (40 °C, 0.06 Torr) until the weight was constant. Compound **3** (2.75 g, 53%) was obtained (the substance turns black under heating over 165 °C). Found (%): C, 33.44; H, 4.12; N, 5.59. $C_{28}H_{36}Cl_4N_4O_{20}P_4$. Calculated (%): C, 33.14; H, 3.55; N, 5.52. ^{13}C NMR, δ*: 157.67 (C(4)); 137.1 (C(6)); 116.1 (C(1), C(5)); 28.6 (C(7)); 28.5 (C(8)). ^{31}P NMR, δ: 21.14. Mass-spectrum (ESI-MS), *m/z*: 869 ([M – 4 HCl] + H).

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* With the heteronuclear correlation considered.

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