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Synthesis of Unsymmetrical Phosphorus-Containing Macrocycles on the Basis of Hydroquinone, 4,4′-(Propane-2,2-diyl)diphenol, and Resorcinol

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Abstract—Bisphosphorylation of hydroquinone and 4,4′-(propane-2,2-diyl)diphenol was performed for the first time in ethyl acetate. The bisphosphorylated products were used in molecular assembly of unsymmetrical phosphorus(III)-containing macrocycles consisting of hydroquinone and 2,2-bis(*p*-hydroxyphenyl)propane or resorcinol fragments. The macrocyclic compound based on hydroquinone and 2,2-bis(*p*-hydroxyphenyl)-propane was subjected to oxidation and sulfurization to obtain the corresponding phosphorus(V) derivatives. Its biological activity was also studied.

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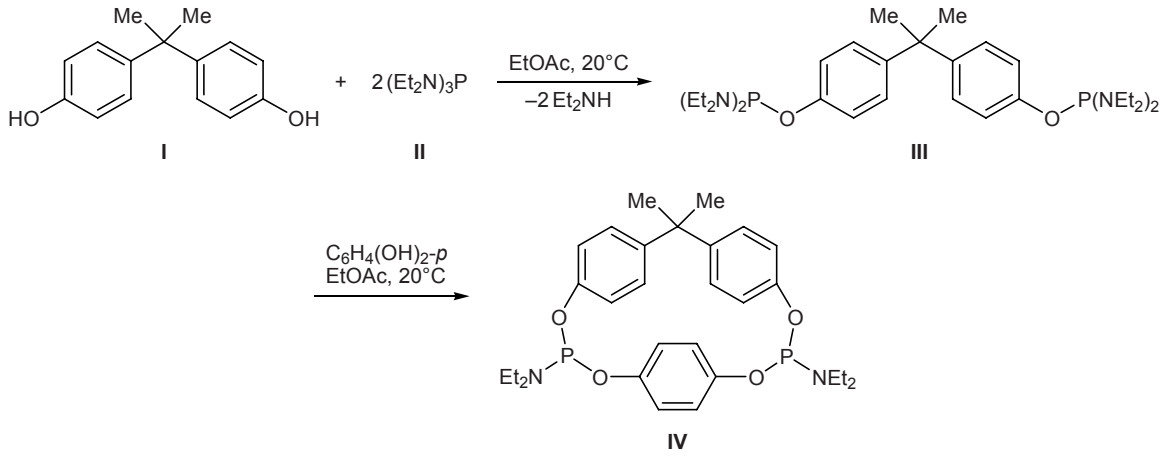
Bisphosphorylation of hydroquinone with hexaethylphosphorous triamide under solvent-free conditions [1], in chlorobenzene [2], and in acetonitrile [3], as well as of 4,4′-(propane-2,2-diyl)diphenol (**I**) in chlorobenzene [2], benzene [4, 5], dioxane [6, 7], and diethyl ether [8], was reported previously. The resulting bisphosphorylated derivatives were used to synthesize the corresponding symmetric macrocycles containing phosphorus atoms in the macroring and hydroquinone [3] or bisphenol **I** fragments [5, 8, 9]. However, unsymmetrical macrocycle containing hydroquinone and 2,2-bis(*p*-hydroxyphenyl)propane fragments was not synthesized so far.

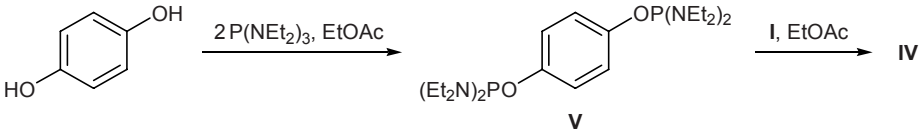
We tried to obtain such compound via molecular assembly. For this purpose, bisphenol **I** was phosphorylated with excess hexaethylphosphorous triamide (**II**) (molar ratio 1:3) with a view to improve the yield and exclude formation of by-products (Scheme 1, method *a*). Nifant'ev et al. [7] erroneously concluded that bisphosphorylated compound **III** could not be isolated as individual substance; however, it was successfully isolated in [4, 5] and subsequently in [8]. In the present work, the synthesis of **III** was performed using ethyl acetate as solvent [10, 11], which ensured higher efficiency. Compound **III** was isolated by removal of the solvent and excess reagent **II**. The reaction time

Scheme 1.

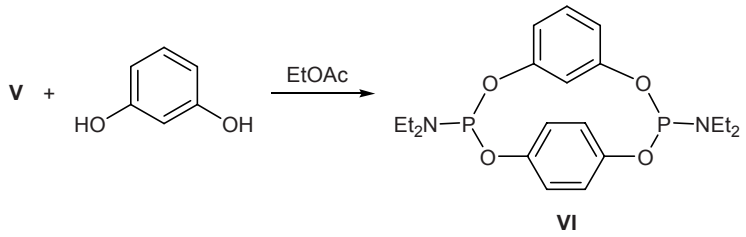


I **II** **III** **IV**

Scheme 2.



Scheme 3.



was 24 h. Bisphosphorylated derivative **III**, as well as macrocyclic compound **IV**, spontaneously separates as an oily material from ethyl acetate solution. The properties of crude product **III** coincided with those reported in [4, 5].

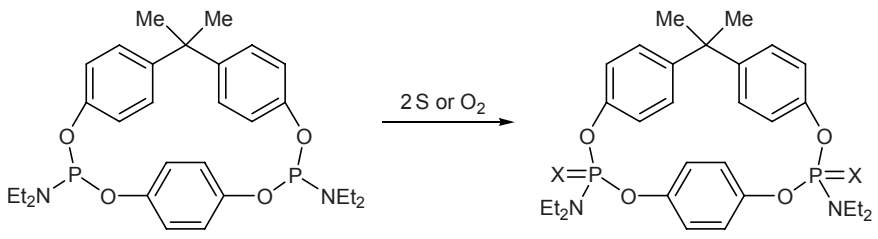
Compound **III** was then brought into reaction with hydroquinone in the same solvent under stirring. After 24 h, a light brown thick oily material separated from the solution. It was chromatographically pure (one spot on a TLC plate), and its ^{31}P NMR spectrum contained two signals at δ_P 141.51 and 142.08 ppm. These data indicated that the reaction followed Scheme 1. Compound **IV** gives two signals in the ^{31}P NMR spectrum due to the presence of two stereoisomers. An analogous pattern was observed previously in the synthesis of symmetric macrocycle based on hydroquinone [3]. In addition, it was shown that symmetric macrocycle derived from compound **I** is also formed as *cis* and *trans* isomers [9]. The structure of **IV** was also confirmed by mass spectrometry (MALDI).

Macrocycle **IV** was also synthesized following another molecular assembly sequence (method *b*). Here, the first step was bisphosphorylation of hydroquinone with 3 equiv of phosphorous triamide **II** (Scheme 2). The use of excess phosphorous triamide **II** favored complete bisphosphorylation. The properties of the isolated bisamide **V** were consistent with those given in [3]. The reaction of **V** with an equimolar amount of **I** in ethyl acetate gave macrocycle **IV** which was identical to the product synthesized as described above from compound **III** and hydroquinone.

By reaction of bisphosphorylated hydroquinone **V** with resorcinol (Scheme 3) we obtained unsymmetrical macrocycle **VI**. In this case, the molecular assembly sequence was the reverse to that reported in [10, 11], where bisphosphorylated resorcinol was brought into reaction with hydroquinone. Macrocycle **VI** synthesized according to Scheme 3 was identical to that described in [11].

The newly synthesized macrocyclic compound **IV** (methods *a* and *b*) was subjected to sulfurization (Scheme 4). After purification by column chromatography we isolated black–red oily compound **VII** in 57 (*a*) and 67% yield (*b*). It displayed in the ^{31}P NMR spectrum two signals at δ_P 67.51 and 67.97 ppm in support of its asymmetric structure. The structure of compound **VII** was also confirmed by ^{1}H NMR and mass spectra.

Scheme 4.



VII, X = S; **VIII**, X = O.

The yields of **IV** indicate that method *b* is more effective than *a*, presumably due to higher rate of phosphorylation of hydroquinone. The oxidation of **IV** gave macrocyclic bis-amidophosphate **VIII** (Scheme 4) which showed one broadened signal at δ_P 2.35 ppm in the ^{31}P NMR spectrum. After purification by column chromatography, compound **VIII** was isolated as a red–brown oily material which thickened on storage. Its structure was confirmed by mass spectrometry.

Biological testing of compounds **VII** and **VIII** for revealed their selective antimicrobial activity [12].

EXPERIMENTAL

Analysis by thin-layer chromatography was performed using Silufol plates and the following eluents: benzene–dioxane, 3:1 (A); hexane–dioxane, 3:1 (B), chloroform–ethanol, 5:1 (C); benzene–dioxane, 5:1 (D); spoys were visualized by treatment with iodine vapor and calcination. The mass spectra (MALDI) were recorded on a Bruker Daltonics Autoflex II mass spectrometer (nitrogen laser, λ = 337 nm; positive ion detection). The ^{31}P NMR spectra were obtained from solutions in ethyl acetate (**IV**) or benzene (**VII**, **VIII**) on a Bruker WP-80SY spectrometer (32.4 MHz) using 85% phosphoric acid as reference. The ^{1}H NMR spectrum was measured in chloroform-*d* on a Bruker AM-400 instrument (400 MHz) relative to TMS.

All syntheses were performed under argon.

***N*,*N*,*N*′,*N*′-Tetraethyl-2,2-dimethyl-4,6,8,10-tetraoxa-5,9-diphospha-1,3,7(1,4)-tribenzenacyclodecaphane-5,9-diamine (IV).** *a*. Hexaethylphosphorous triamide (**II**), 3.35 g (13.5 mmol), was added under vigorous stirring at room temperature to 1.03 g (4.5 mmol) of compound **I** in 40 ml of ethyl acetate. After 24 h, the solvent and excess amide **II** were distilled off under reduced pressure (water-jet pump). Bisphosphorylated product **III** was identified by TLC: R_f 0.83 (A), 0.56 (B); published data [5]: R_f 0.84 (A), 0.61 (B). A solution of 0.52 g (4.5 mmol) of hydroquinone in 45 ml of ethyl acetate was added to the crude product, the mixture was stirred for 24 h at room temperature, and the solvent was distilled off under reduced pressure. Yield 2.60 g, light brown viscous tarry material. R_f 0.65 (A). ^{31}P NMR spectrum, δ_P, ppm: 141.51, 142.08. Mass spectrum, *m*/*z*: 542.02 $[M + H]^+$, 563.87 $[M + Na]^+$, 579.60 $[M + K]^+$.

b. Hexaethylphosphorous triamide (**II**), 2.0 g (7.4 mmol), was added under vigorous stirring at room temperature to 0.2 g (1.8 mmol) of hydroquinone in 8 ml of ethyl acetate. After 24 h, the solvent and excess amide **II** were distilled off under reduced pressure (water-jet pump). Bisphosphorylated hydroquinone **V** was identified by TLC: R_f 0.79 (A); published data [3]: R_f 0.80 (A). A solution of 0.41 g (1.8 mmol) of compound **I** in 13 ml of ethyl acetate was added to the residue, the mixture was stirred for 24 h at room temperature, and the solvent was distilled off under reduced pressure. Yield 1.64 g.

5,9-Bis(diethylamino)-2,2-dimethyl-4,6,8,10-tetraoxa-5λ^5,9λ^5-diphospha-1,3,7(1,4)-tribenzenacyclodecaphane 5,9-disulfide (VII). *a*. A solution of 0.2 g (6.2 mmol) of elemental sulfur in 20 ml of benzene was added to 2.60 g of crude compound **IV** prepared as described above in *a*, the mixture was kept for 24 h, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography using benzene as eluent. The eluate was evaporated, and the product was dried under reduced pressure (10 mm, 50°C, 2 h). Black–red viscous oily substance. Yield 0.92 g (57%). R_f 0.67 (A), 0.63 (D). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.13 t (12H, CH_3), 1.61 s (6H, CH_3), 3.26 m (8H, CH_2, $^3J_{PH}$ = 11.94 Hz), 7.02 d (4H, CH), 7.12 d (4H, CH), 7.26 s (4H, CH). ^{31}P NMR spectrum, δ_P, ppm: 67.51, 67.97. Found, %: C 57.73; H 6.27; P 10.36. Mass spectrum: *m*/*z* 627.70 $[M + Na]^+$. $C_{29}H_{38}N_2O_4P_2S_2$. Calculated, %: C 57.59; H 6.35; P 10.24. *M* 604.70.

b. A solution of 0.18 g (5.6 mmol) of elemental sulfur in 15 ml of benzene was added to 1.64 g of crude compound **IV** prepared as described above in *b*, the mixture was kept for 24 h, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography using benzene as eluent. The eluate was evaporated, and the product was dried under reduced pressure (10 mm, 50°C, 2 h). Black–red viscous oily substance. Yield 0.71 g (67%).

5,9-Bis(diethylamino)-2,2-dimethyl-4,6,8,10-tetraoxa-5λ^5,9λ^5-diphospha-1,3,7(1,4)-tribenzenacyclodecaphane 5,9-dioxide (VIII). Crude compound **IV** prepared as described above in *b*, 1.58 g, was dissolved in 20 ml of ethyl acetate, and the mixture was stirred for 4 h on exposure to air. The originally light yellow mixture turned red–brown. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography using solvent system C as eluent. The eluate was evaporated, and the product was dried under reduced pressure (10 mm, 50°C, 2 h). Yield 0.91 g (51%), red–brown viscous

oily substance, R_f 0.74 (C). ^{31}P NMR spectrum: δ_P 2.35 ppm, br. Found, %: C 60.69; H 6.64; P 10.71. Mass spectrum: m/z 573.60 $[M + H]^+$. $C_{29}H_{38}N_2O_6P_2$. Calculated, %: C 60.82; H 6.70; P 10.82. M 572.60.

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