Synthesis of novel phosphorus-containing sterically hindered phenols by the reaction of diphenyl (3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)methylphosphonate with phenols

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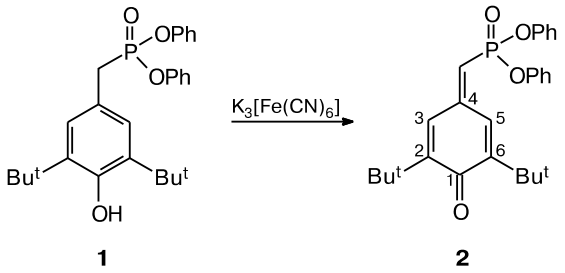
Diphenyl (3,5-di-*tert*-butyl-4-hydroxybenzyl)phosphonate was oxidized to the corresponding methylidenequinonoid derivative. The addition of phenols to the exocyclic double bond of this compound gave phosphonates with two phenol moieties.

Key words: diphenyl (3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)methylphosphonate, oxidation, phenols, phosphonates.

Derivatives of 2,6-di-*tert*-butylphenols are efficient antioxidants, which are widely used as inhibitors of thermooxidative destruction of polymers, oils, fats, fuels, *etc.* and as correctors of oxidant pathologies in living biological systems.[1] The contemporary approach to the development of new types of antioxidants is the design of hybrid molecules containing combinations of several reaction centers capable of inhibiting oxidation *via* various mechanisms.[2,3] From this point of view it is interesting to obtain structures containing simultaneously phosphorus atoms and a fragment of sterically hindered phenol.[4,5] Similar structures can be synthesized using a phosphorus-containing derivative of 2,6-di-*tert*-butyl-4-methylidenecyclohexa-2,5-dienone.[6—8] High reactivity of phosphorylated methylidene quinones makes it possible to use them successfully for synthesis of diverse sterically hindered phenols, and in some cases the abovementioned approach is most optimum.

In the framework of the synthesis and study of the properties of phosphorylated methylidene quinones,[8—10] we developed the method of preparation of diphenyl (3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)-methylphosphonate (**2**) by oxidation of diphenyl (3,5-di-*tert*-butyl-4-hydroxybenzyl)phosphonate (**1**) with an alkaline solution of potassium ferricyanide (Scheme 1).

Scheme 1



The structure of compound **2** was confirmed by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, IR spectroscopy, mass spectrometry, and X-ray diffraction analysis. In the ^{1}H NMR spectrum, signals of the aromatic H(3) and H(5) protons neighboring to the 2,6-di-*tert*-butyl moieties appear as two singlets at δ 7.20 and 7.88, respectively. According to the X-ray structure data, the bond lengths and bond angles in the molecule are within the values standard for each type of the bond. The coordination polyhedron of the pentavalent phosphorus atom is a distorted tetrahedron, the phenoxyl substituents are turned mutually perpendicularly and are localized at different sides from the plane of the molecule (Fig. 1).

For the purpose of synthesizing phosphoryl-containing sterically hindered phenols, we carried out the reactions of methylidene quinone **2** with phenol, pyrocatechol, resorcinol, and hydroquinone. It is known[10,11] that phosphorylated methylidene quinones react with aliphatic alcohols in the presence of catalytic amounts of mineral acids to form dialkyl (α-alkoxy-3,5-di-*tert*-butyl-4-hydroxybenzyl)phosphonates. When optimizing the conditions for the reaction between phosphorylated methylidene quinone **2** and phenol (Scheme 2), it turned out to be efficient to use trifluoromethanesulfonic acid as a catalyst: in the presence of its catalytic amounts, reaction product **3** formed in 87% yield in acetonitrile at room temperature.

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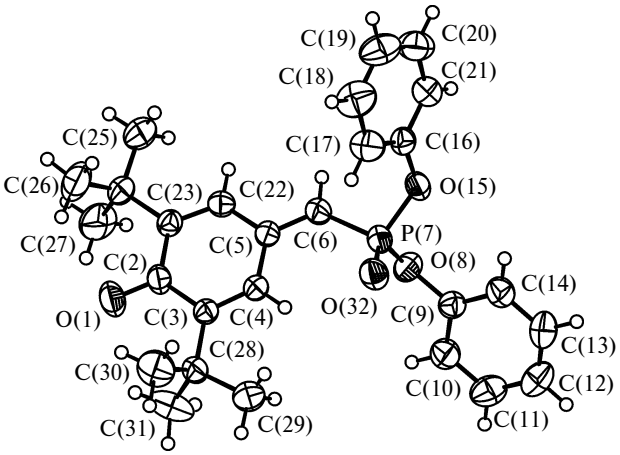
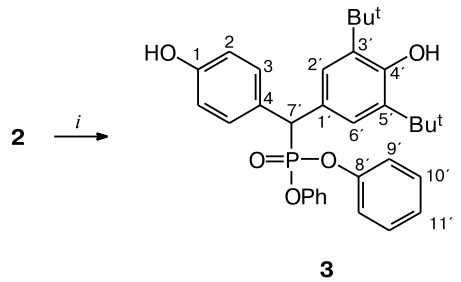


Fig. 1. Crystal structure of molecule **2**. Thermal vibrational ellipsoids of non-hydrogen atoms are shown with 50% probability.

Scheme 2



3

i. PhOH, CF_3SO_3H, MeCN.

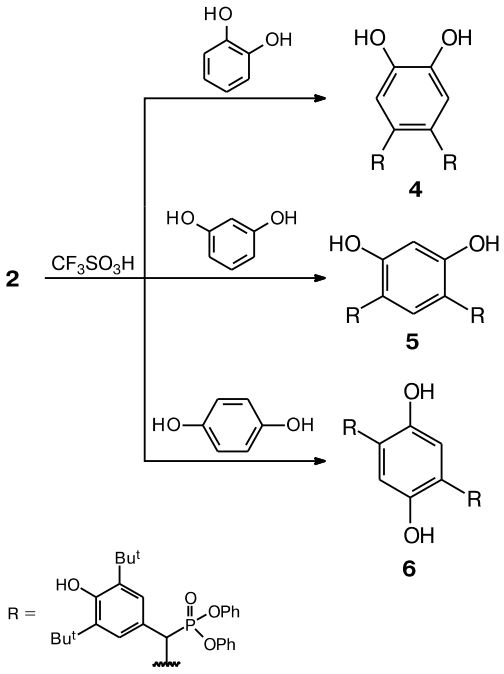
The structure and composition of compound **3** were established from the data of ^1H and ^{31}P NMR spectroscopy, IR spectroscopy, mass spectrometry (MALDI-TOF), and elemental analysis.

Diatomic phenols, such as pyrocatechol, hydroquinone, and resorcinol, react with methylidene quinone **2** in the ratio 1 : 2 to form the corresponding bis-adducts **4**—**6** (Scheme 3).

Compounds **4**—**6** are mixtures of diastereomers, which is confirmed by doubling of all signals in the ^{31}P and ^1H NMR spectra. The signal of the proton at the C_α carbon atom appears in compounds **4**—**6** in the region δ 5.0—5.25 as two doublets of the diastereomeric pair with spin-spin coupling constants $^2J_{P,H}$ = 23.0—26.0 Hz. In the ^{13}C NMR spectrum, the signal from the carbon atom at the phosphorus atom for compounds **4** and **5** lies in the region δ 41.82—46.6 with the spin-spin coupling constants $^1J_{P,C}$ = 148—150 Hz.

In summary, the reaction of diphenyl (3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)methylphosphonate with phenols can serve as a convenient method for the preparation of novel phosphorylated polyphenols containing sterically hindered moieties. The synthesized products are promising as potential antioxidants.

Scheme 3



Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 600 instrument at working frequencies of 600 and 150 MHz, respectively, using residual signals of the deuterated solvent (DMSO-d_6) as standards. ^{31}P NMR spectra were obtained on a Bruker MSL-400 instrument with a working frequency of 166.93 MHz relative to 85% H_3PO_4 as the external standard. IR spectra were recorded on a Vector 22 FTIR spectrometer (Bruker) in the range from 400 to 4000 cm^{-1}. The matrix-activated laser desorption/ionization mass spectra were obtained on a MALDI TOF/TOF time-of-flight mass spectrometer (Bruker Daltonics). Elemental analyses were carried out on a Carlo Erba EA 1108 elemental analyzer.

Single crystals of compound **2** were grown in DMSO. The X-ray structure analysis of compound **2** was carried out at 20 °C on a Bruker Smart APEX2 automated diffractometer (Mo-Kα radiation, graphite monochromator, ω scan mode, θ_{max} = 28.80°). The crystal of compound **2** is monoclinic, $C_{27}H_{31}O_4P$, M = 450.49, space group $P2_1/c$, at T = 296 °C: a = 8.918(2) Å, b = 24.427(6) Å, c = 11.670(3) Å, β = 104.554(3)°, V = 2460.7(11) $Å^3$, Z = 4, $F(000)$ = 960, d_{calc} = 1.216 g cm^{-3}, μ = 0.141 mm^{-1}. The structure was solved by a direct method using the SIR program[12] and refined first in the isotropic and then in the anisotropic approximation using the SHELXL-97 program.[13] The positions of hydrogen atoms were calculated geometrically and refined in the isotropic approximation. The final R factors were R_1 = 0.0442 for 2829 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.1031 for all 5916 independent reflections.

All calculations were performed using the WinGX (see Ref. 14) and APEX2 (see Ref. 15) programs. The figures of molecules and analysis of intermolecular interactions were made using the ORTEP3 and PLATON programs.[16,17] The crystallo-

graphic data were deposited with the Cambridge Crystallographic Data Centre (CCDC 832621).

Solvents were purified and dehydrated using known procedures.[18] Diphenyl (3,5-di-*tert*-butyl-4-hydroxybenzyl)phosphonate was synthesized by a published procedure.[19]

Diphenyl (3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)-methylphosphonate (2). A solution of diphenyl (3,5-di-*tert*-butyl-4-hydroxybenzyl)phosphonate (**1**) (4.5 g, 1 mmol) in benzene (160 mL) was stirred with a solution of $K_3Fe(CN)_6$ (19.8 g, 0.06 mol) in 2 *M* KOH (180 mL) at room temperature for 3 h. A colored benzene solution was separated, washed with water to neutral pH, and dried with Na_2SO_4. Benzene was removed *in vacuo* of a water-jet pump. The yellow crystalline product was isolated in a yield of 3.1 g (67%), m.p. 76 °C. Found (%): C, 69.74; H, 7.14; P, 6.95. $C_{27}H_{31}O_4P$. Calculated (%): C, 71.98; H, 6.94; P, 6.88. ^{1}H NMR, δ: 1.15, 1.22 (both s, 18 H each, $(CH_3)_3C$); 6.92 (d, 1 H, PCH, $J_{P,H}$ = 16.8 Hz); 7.19 (s, 1 H, H(3)); 7.23 (t, 2 H, H(11), J = 7.6 Hz); 7.26 (t, 4 H, H(9), J = 8.4 Hz); 7.41 (t, 4 H, H(10), J = 8.05 Hz); 7.87 (s, 1 H, H(5)). ^{13}C NMR, δ: 29.71 (q, $(\underline{C}H_3)_3C$, J = 128 Hz); 35.6 (s, $(CH_3)_3\underline{C}$)); 121.13 (d, C(9), J = 160.94 Hz); 126.26 (d, C(11), J = 160.21 Hz); 125.40 (d, C(7), $J_{P,C}$ = 182.9 Hz); 128.54 (d, C(3), $J_{P,C}$ = 7.18 Hz, J = 160.03 Hz); 130.78 (d, C(10), J = 160.58 Hz); 134.3 (d, C(5), $J_{P,C}$ = 26.81 Hz, J = 163.48 Hz); 147.00 (s, C(4)); 150.05 (s, C(2)); 150.66 (s, C(8), $J_{P,C}$ = 23.77 Hz); 186.39 (s, C(O)). ^{31}P NMR acetone), δ: 6.7. IR, ν/cm^{-1}: 1648 (C_{arom}); 1631 (C=O); 1593 (C=CH); 1253 (P=O); 932 (POC). MS (MALDI), *m/z*: 450.45 $[M]^+$.

Diphenyl (3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-hydroxyphenyl)methylphosphonate (3). A solution of phenol (0.1 g, 1.1 mmol) in acetonitrile (1 mL) was added to a solution of methylidene quinone **2** (0.5 g, 1.1 mmol) in acetonitrile (2 mL). Then trifluoromethanesulfonic acid (0.002 mL, 0.02 mol) was added. The reaction mixture was kept at room temperature for 4 h, and the white precipitate that formed was filtered off and washed with pentane. The product was dried in a vacuum of an oil pump (1 h, 20 °C, 1 Torr), the yield was 0.52 g (87%), m.p. 138—140 °C (from pentane). Found (%): C, 70.34; H, 6.47; P, 5.41. $C_{33}H_{37}O_5P$. Calculated (%): C, 72.78; H, 6.85; P, 5.69. ^{1}H NMR, δ: 1.40 (s, 18 H, $C(CH_3)_3$); 4.65 (d, 1 H, PCH, $J_{P,H}$ = = 25.90 Hz); 5.95 (br.s, 2 H, OH); 6.61 (d, 2 H, H(2), J = 8.20 Hz); 6.73 (d, 2 H, H(3), J = 8.20 Hz); 6.87 (d, 2 H, H(9′), J = 8.00 Hz); 7.05, 7.08 (both t, 2 H, H(11′) J = 7.50 Hz), 7.15, 7.20 (both t, 2 H each, H(10′) J = 8.00 Hz); 7.33 (d, 2 H, H(9′), J = 8.00 Hz); 7.35 (s, 2 H, H(2′)). ^{31}P NMR ($CHCl_3$), δ: 19.65. IR, ν/cm^{-1}: 3563 (OH); 3440 (OH); 1613, 1516 (C_{arom}); 1210 (P=O); 1036 (POC). MS (MALDI), *m/z*: 544.68 $[M]^+$.

4,5-Bis[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(diphenoxyphosphoryl)methyl]pyrocatechol (4) was synthesized similarly to compound **3** from methylidene quinone (1 g, 2.2 mmol) and pyrocatechol (0.12 g, 1.1 mmol) in a yield of 0.95 g (94%), m.p. 129—130 °C (from pentane). Found (%): C, 69.68; H, 7.14; P, 6.56. $C_{60}H_{68}O_{10}P_2$. Calculated (%): C, 71.27; H, 6.78; P, 6.13. ^{1}H NMR, δ: 1.23, 1.30 (both s, 18 H each, $C(CH_3)_3$); 5.01, 5.21 (both d, 1 H each, PCH, $J_{P,H}$ = 27.00 Hz); 6.05 (br.s, 4 H, OH); 6.50, 6.52 (both d, 2 H each, H(9′), J = 8.00 Hz); 6.66, 6.82 (both d, 2 H each, H(9′), J = 8.0 Hz); 7.05 (s, 2 H, H(2′)); 7.07—7.17 (m, 8 H, H(10′); 7.19—7.22 (m, 4 H, H(11′)); 7.41 (s, 2 H, H(6′)); 7.43 (s, 1 H, H(3)); 7.60 (s, 1 H, H(6)). ^{13}C NMR, δ: 30.76, 30.86 (both q, $(\underline{C}H_3)_3C$, J = 125 Hz); 34.96, 35.12 (both s, $(CH_3)_3\underline{C}$)); 45.16, 46.49 (both d, CHP, $^1J_{C,P}$ = 148 Hz); 115.86, 116.00 (both s, C(4)); 117.84, 118.32 (both d, C(3), J = 155 Hz); 120.43, 120.68, 120.92, 121.07 (all d, C(9′), J = 162 Hz); 125.93—126.89 (m, C(10′)); 130.02, 130.09 (both d, C(2′), J = 162 Hz); 139.45, 139.84 (both s, C(3′)); 144.86, 144.98 (both s, C(1′)); 150.43, 150.50, 150.56, 150.63 (all s, C(8′)); 150.99, 151.05 (both s, C(4′)); 153.86, 153.92 (both s, C(1)). ^{31}P NMR (C_6H_6), δ: 22.42, 22.80. IR, ν/cm^{-1}: 3628 (OH); 3123 (OH); 1614, 1533 (C_{arom}); 1204 (P=O); 1059 (POC). MS (MALDI), *m/z*: 1011.43 $[M]^+$, 1034.56 $[M + Na]^+$, 1051.07 $[M + K]^+$.

4,6-Bis[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(diphenoxyphosphoryl)methyl]resorcinol (5) was synthesized similarly to the previous compound from methylidene quinone **2** (1 g, 2.2 mmol) and resorcinol (0.12 g, 1.1 mmol) in a yield of 0.98 g (97%), m.p. 195—197 °C (from pentane). Found (%): C, 70.52; H, 6.94; P, 6.28. $C_{60}H_{68}O_{10}P_2$. Calculated (%): C, 71.27; H, 6.78; P, 6.13. ^{1}H NMR, δ: 1.24, 1.30 (both s, 18 H each, $C(CH_3)_3$); 5.15, 5.20 (both d, 1 H each, PCH, $J_{P,H}$ = 26.00 Hz); 6.40 (br.s, 2 H, OH); 6.46 (s, 1 H, H(2)); 6.69 (d, 2 H, H(9′), J = 8.05 Hz); 6.78, 6.82 (both d, 2 H each, H(9′), J = 8.30 Hz); 6.94 (d, 2 H, H(9′), J = 8.05 Hz); 7.05—7.16 (m, 8 H, H(10′)); 7.20 (t, 4 H, H(11′), J = 7.90 Hz); 7.26 (s, 4 H, H(2′)); 7.46 (s, 1 H, H(5)); 9.64 (s, 2 H, OH). ^{31}P NMR (C_6H_6), δ: 21.89, 22.06. ^{13}C NMR, δ: 30.86 (q, $(\underline{C}H_3)_3C$, J = 125 Hz); 34.97, 35.02 (both s, $(CH_3)_3\underline{C}$)); 41.82, 42.75 (both d, CHP, $^1J_{C,P}$ = 150 Hz); 102.99 (d, C(2), J = 153 Hz); 114.75 (s, C(5)); 115.88, 119.32 (both d, C(4), J = 155 Hz); 120.43—121.07 (m, C(9′)); 125.93—126.89 (m, C(10′)); 130.02, 130.09 (both d, C(2′), J = 162 Hz); 139.45, 139.84 (both s, C(3′)); 144.86, 144.98 (both s, C(1′)); 150.43—150.63 (m, C(8′)); 150.99, 151.05 (both s, C(4′)); 153.86, 153.92 (both s, C(1)). IR, ν/cm^{-1}: 3646 (OH); 3134 (OH); 1621, 1542 (arom.); 1218 (P=O); 1061 (POC). MS (MALDI), *m/z*: 1011.67 $[M]^+$, 1035.67 $[M + Na]^+$, 1052.28 $[M + K]^+$.

2,5-Bis[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(diphenoxyphosphoryl)methyl]hydroquinone (6) was synthesized similarly from methylidene quinone (1 g, 2.2 mmol) and hydroquinone (0.12 g, 1.1 mmol) in a yield of 0.96 g (95%), m.p. 152—154 °C (from pentane). Found (%): C, 68.92; H, 7.02; P, 7.16. $C_{60}H_{68}O_{10}P_2$. Calculated (%): C, 71.27; H, 6.78; P, 6.13. ^{1}H NMR, δ: 1.22, 1.29 (both s, 18 H each, $C(CH_3)_3$); 5.06, 5.25 (both d, 1 H each, PCH, $J_{P,H}$ = 27.00 Hz); 5.95 (s, 2 H, OH); 6.56 (s, 1 H, H(3)); 6.77 (d, 2 H, H(9′), J = 8.00 Hz); 6.88, 6.99 (both d, 2 H each, H(9′), J = 8.30 Hz); 7.04 (d, 2 H, H(9′), J = 8.00 Hz); 7.07—7.17 (m, 8 H, H(10′)); 7.22 (t, 4 H, H(11′), J = 8.50 Hz); 7.34 (s, 4 H, H(2′), H(6′)); 7.58 (s, 1 H, H(6)); 8.25 (s, 2 H, OH). ^{31}P NMR (C_6H_6), δ: 21.32, 22.18. IR, ν/cm^{-1}: 3637 (OH); 3162 (OH); 1617, 1535 (arom.); 1206 (P=O); 1057 (POC). MS (MALDI), *m/z*: 1010.45 $[M]^+$, 1034.45 $[M + Na]^+$, 1051.43 $[M + K]^+$.

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