A reaction of 6-bromo-1,2-naphthoquinone with tri(*n*-butyl)phosphine: a convenient route to phosphorus-containing 1,2-naphthoquinones and 1,2-dihydroxynaphthalenes

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A reaction of 6-bromo-1,2-naphthoquinone with tri(*n*-butyl)phosphine gave 2-hydroxy-4-tri(*n*-butyl)phosphonionaphth-1-olate (betaine with the P—C bond). When treated with bromine, this betaine changed into (6-bromo-1,2-dihydroxy-4-naphthyl)tri(*n*-butyl)phosphonium bromide and (6-bromo-1,2-dioxo-1,2-dihydro-4-naphthyl)tri(*n*-butyl)phosphonium bromide in the ratio ~1 : 1.

Key words: 1,2-naphthoquinones, tri(*n*-butyl)phosphine, phosphobetaines, phosphonium salts, phosphorylation, bromination, naphthalene-1,2-diols.

In recent years, the chemistry of *o*-quinones, quinone methides, and masked quinones has received much attention because these compounds are naturally abundant, exhibit a variety of biological activities, and find use in the synthesis of metal complexes and N- and O-containing heterocycles and in enantioselective synthesis.[1—7]

Compounds of tervalent phosphorus are employed in the chemistry of quinones mainly for the preparation of phosphoranes or quasiphosphonium salts of the betaine structure with the P^+—OC bond, which are further used in organic synthesis.[8,9] In the 1,2-naphthoquinone series, reactions with P^{III} derivatives have been least studied. In particular, it has been demonstrated that they react with phosphites to give phosphoranes.[8] At the same time, many 1,2-naphthoquinone derivatives, especially 4-substituted 1,2-naphthoquinones, are known to exhibit various biological activities: they are metabolites in the biodegradation of polycyclic aromatic hydrocarbons[10] and can serve as models of their binding by amino acids.[11] For this reason, development of methods for the synthesis of phosphorus-containing derivatives of 1,2-naphthoquinones is of current interest, because introduction of phosphorus-containing substituents often imparts new biological properties to the resulting compounds.

Earlier,[12] we have found that a reaction of 6-bromo-1,2-naphthoquinone (**1**) with tris(diethylamino)phosphine followed by treatment of intermediate 6-bromo-4-[tris(diethylamino)phosphonio]-2-hydroxynaphth-1-olate with bromine unexpectedly gives phosphorus-containing 1,2-naphthoquinone: (6-bromo-1,2-dioxo-1,2-dihydro-4-naphtyl)tris(diethylamino)phosphonium bromide. In the present work, we tried to extend this approach to other P^{III} derivatives, specifically to trialkylphosphines. For instance, a reaction of naphthoquinone **1** (a medicinal substance of the system-acting drug "bonafton") with tri(*n*-butyl)phosphine afforded phosphobetaine (**2**) with the P—C bond (δ_P 22.6) in high yield (Scheme 1).

The position of the phosphonium substituent in compound **2** was located from NMR data. For instance, the ^{13}C NMR spectrum of compound **2** contains a doublet at δ 95.34 for the C(4) atom ($^1J_{PC(4)}$ = 88.9 Hz). The signal multiplicity for the C(3), C(4a), and C(8a) nuclei unambiguously indicates that the phosphonium group is localized in position 4 of the naphthalene system: the $^{13}C—\{^1H\}$ NMR spectrum shows doublets for the C(3) and C(4a) nuclei with $^2J_{PCC}$ = 10.2 and 8.7 Hz, respectively, and a doublet for C(8a) with a larger coupling constant ($^3J_{PCCC(8a)}$ = 12.7 Hz).

The plausible mechanism of the reaction is shown in Scheme 2. Apparently, the first step involves one-electron transfer from the P atom to the quinone molecule to give ion—radical pair (**3**), which is in equilibrium with resonance structures **4** and **5**. Localization of the unpaired electron in position 4 of the naphthalene system (structure **5**) seems to be thermodynamically more favorable because of conjugation with the benzene ring. Then, recombination of the radicals in this ion—radical pair (**5**) gives rise to a P—C bond and hence structure **6**. Subsequent proton transfer followed by electron density redistribution yield the final phosphobetaine **2**.

Treatment of compound **2** with bromine under mild conditions gave a mixture of phosphonium salts **7** and **8** (Scheme 2). Apparently, the initial step is the oxidation of

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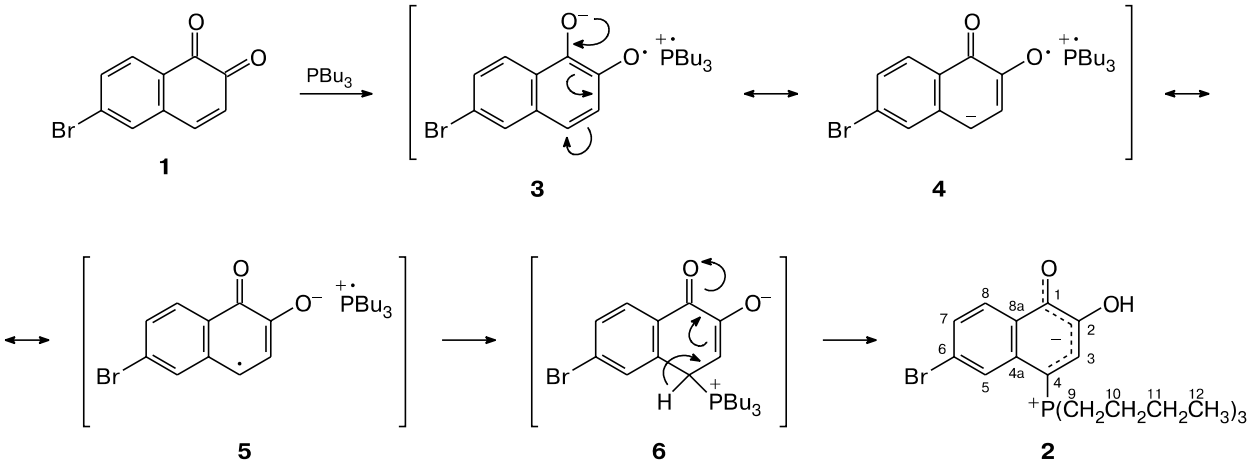
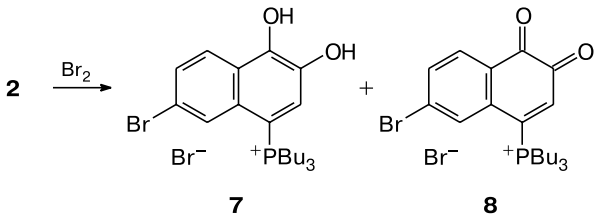
Scheme 1



betaine **2** by bromine into quinone **8**. The evolved HBr adds to the starting phosphobetaine **2** to give the corresponding dihydroxynaphthalene **7**. This mechanism is confirmed by the ratio of products **7** and **8** (1 : 1).

Scheme 2



The structures of compounds **7** and **8** were proven by ^{31}P, ^{1}H, and ^{13}C NMR spectroscopy. In the $^{31}P—\{^{1}H\}$ NMR spectrum, they produce singlets at δ_P 29.6 and 35.5, respectively. The $^{13}C—\{^{1}H\}$ NMR spectrum of compound **7** shows low-field signals (δ_C 144.99 and 139.90) for the C(1) and C(2) atoms, which is characteristic of a dihydroxybenzene fragment. In addition, the IR spectrum of compound **7** contains an intense absorption band at 3126 cm^{-1} due to the stretching vibrations of phenolic OH groups. Substantially lower-field signals (δ_C 180.81 and 181.34) for the C(1) and C(2) atoms are characteristic of compound **8**. They were assigned with consideration to the multiplicity in the ^{13}C NMR spectra. The IR spectrum of compound **8** shows an intense absorption band due to the C=O group (1672 cm^{-1}).

In summary, the sequence of the reactions of naphthoquinone **1** with tri(*n*-butyl)phosphine and of the resulting betaine **2** with bromine is a convenient synthetic route to 4-phosphorus-containing 1,2-dihydroxynaphthalenes or 1,2-naphthoquinones of the types **7** and **8**, respectively.

Experimental

^{1}H, ^{13}C, $^{13}C—\{^{1}H\}$, ^{31}P, and $^{31}P—\{^{1}H\}$ NMR spectra were recorded on Bruker Avance 600 (600 (^{1}H) and 150.9 MHz (^{13}C)), Bruker MSL-400 (100.6 MHz (^{13}C)), and Bruker CXP-100 instruments (36.48 MHz (^{31}P)) (20 °C, δ scale with reference to Me_4Si) with signals for the residual protons of the deuterated solvent or the carbon nuclei as the internal standards (^{1}H and ^{13}C) and with H_3PO_4 as the external standard (^{31}P). IR spectra were recorded on a Bruker Vector-22 FTIR spectrometer in Nujol.

6-Bromo-2-hydroxy-4-tri(*n*-butyl)phosphonionaphth-1-olate (2). A solution of tri(*n*-butyl)phosphine (1.05 mL, 4.22 mmol) in CH_2Cl_2 (10 mL) was added dropwise with constant bubbling of argon to a stirred suspension of quinone **1** (1 g, 4.22 mmol) in CH_2Cl_2 (10 mL). The reaction mixture turned black, producing a strong exothermic effect. After 10 min, the solution acquired a green tinge and gradually produced a yellow green precipitate, which was filtered off and dried *in vacuo* (12 Torr). The yield was 1.37 g (77%), m.p. 172—175 °C. Found (%): C, 60.01; H, 7.05; P, 7.02. $C_{22}H_{32}BrO_2P$. Calculated (%): C, 60.14; H, 7.29; P, 7.06. IR, ν/cm^{-1}: 3478 (OH); 2724; 1596, 1532 (C=C arom., C=C); 1347, 1309, 1268, 1209, 1158, 1111, 1068, 989, 968, 911, 826, 772, 723, 663, 426. $^{31}P—\{^{1}H\}$ NMR ($CDCl_3$), δ_P: 22.6 (s). ^{1}H NMR ($CDCl_3$), δ: 0.91 (t, H(12), $^{3}J_{H(11)CCH(12)}$ = 6.6 Hz); 1.47—1.50 (m, H(10), overlap with the signal for H(11)); 2.60 (dt, H(9), $^{3}J_{H(10)CCH(9)}$ = 8.1 Hz, $^{2}J_{PCH(9)}$ = 11.7 Hz); 7.54 (d, H(8), $^{3}J_{H(7)CCH(8)}$ = 8.9 Hz); 7.71 (s, H(5)); 7.80 (d, H(3), $^{3}J_{PCCH(3)}$ = 15.2 Hz); 8.31 (dd, H(7), $^{4}J_{H(5)CCCH(7)}$ = 1.0 Hz, $^{3}J_{H(8)CCH(7)}$ = 8.9 Hz). ^{13}C NMR (150.9 MHz, $CDCl_3$), δ_C, *J*/Hz)*: 13.28 (qt (s), C(12), $^{1}J_{HC(12)}$ = 125.3 Hz, $^{3}J_{HC(10)CC(12)}$ = 4.2 Hz); 21.22 (dt (d), C(9), $^{1}J_{PC(9)}$ = 49.8 Hz, $^{1}J_{HC(9)}$ = 130.7 Hz, $^{3}J_{HC(11)CC(9)}$ = 3.6 Hz); 23.69 (m (d), C(11), $^{3}J_{PCCC(11)}$ = 15.3 Hz, overlap with the signal for C(10)); 23.96 (m (d), C(10), $^{2}J_{PCC(10)}$ = 4.1 Hz, overlap with the signal for C(11)); 95.34 (dd (d), C(4), $^{1}J_{PC(4)}$ = 88.9 Hz, $^{3}J_{HC(5)CC(4)}$ = 4.8 Hz); 120.54 (ddd (s), C(6), $^{3}J_{HC(8)CC(6)}$ = 8.4 Hz, $^{2}J_{HC(5)C(6)}$ = 4.8 Hz, $^{2}J_{HC(7)C(6)}$ = 4.8 Hz); 123.66 (ddd (d),

* Hereafter, the signal shape in the $^{13}C—\{^{1}H\}$ NMR spectrum is enclosed in parentheses.

C(5), $^1J_{HC(5)}$ = 158.0 Hz, $^3J_{PCCC(5)}$ = 5.1 Hz, $^3J_{HC(7)CC(5)}$ = 4.8 Hz); 126.01 (ddd (d), C(8a), $^3J_{PCCC(8a)}$ = 12.7 Hz, $^3J_{HC(7)CC(8a)}$ = 6.6—7.2 Hz, $^3J_{HC(5)CC(8a)}$ = 6.6—7.2 Hz); 126.71 (d (s), C(8), $^1J_{HC(8)}$ = 167.0 Hz); 128.61 (dd (d), C(3), $^1J_{HC(3)}$ = 159.2 Hz, $^2J_{PCC(3)}$ = 10.2 Hz); 128.69 (dd (s), C(7), $^1J_{HC(7)}$ = 169.4 Hz, $^3J_{HC(5)CC(7)}$ = 4.8 Hz); 129.79 (ddt (d), C(4a), $^2J_{PCC(4a)}$ = 8.7 Hz, $^3J_{HC(3)CC(4a)}$ = 6.0 Hz, $^2J_{HC(5)C(4a)}$ = 1.8 Hz); 141.28 (dd (d), C(2), $^3J_{PC(4)CC(2)}$ = 16.8 Hz, $^2J_{HC(3)C(2)}$ = 4.2—5.4 Hz); 147.83 (d (s), C(1), $^3J_{HC(3)CC(1)}$ = 5.4 Hz).

(6-Bromo-1,2-dioxo-1,2-dihydro-4-naphthyl)tri(*n*-butyl)phosphonium bromide (8). Bromine (0.06 mL, 1.3 mmol) was added dropwise to a solution of compound **2** (0.56 g, 1.3 mmol) in CH_2Cl_2 (10 mL). The reaction mixture turned red. The orange precipitate that formed was filtered off and dried in air. The yield of compound **8** was 0.25 g (37%), m.p. 145—150 °C. IR, ν/cm^{-1}: 1672 (C=O); 1573 (C=C arom., C=C); 1313, 1274, 1233, 1159, 1088, 966, 832, 723. $^{31}P—\{^1H\}$ NMR ($CDCl_3$—DMSO-d_6 (1 : 3)), δ_P: 35.5 (s). ^1H NMR ($CDCl_3$—DMSO-d_6 (1 : 3)), δ: 0.89 (t, H(12), $^3J_{H(11)CCH(12)}$ = 7.2 Hz); 1.45 (qt, H(11), $^3J_{H(12)CCH(11)}$ = 7.2 Hz, $^3J_{H(10)CCH(11)}$ = 7.8 Hz); 1.51 (tt, H(10), $^3J_{H(9)CCH(10)}$ = 8.1 Hz, $^3J_{H(11)CCH(10)}$ = 7.8 Hz); 2.74 (dt, H(9), $^3J_{H(10)CCH(9)}$ = 8.1 Hz, $^2J_{PCH(9)}$ = 12.1 Hz); 7.03 (d, H(3), $^3J_{PCCH(3)}$ = 18.5 Hz); 7.63 (br.s, H(5)); 7.82 (d, H(8), $^3J_{H(7)CCH(8)}$ = 8.9 Hz); 8.06 (dd, H(7), $^3J_{H(8)CCH(7)}$ = 8.2 Hz, $^4J_{H(5)CCCH(7)}$ = 0.8—1.0 Hz). ^{13}C NMR (100.9 MHz, $CDCl_3$—DMSO-d_6 (1 : 3)), δ_C: 18.36 (qt (s), C(12), $^1J_{HC(12)}$ = 125.0 Hz, $^3J_{HC(10)CC(12)}$ = 2.4—3.9 Hz); 24.33 (dtd (d), C(9), $^1J_{PC(9)}$ = 46.5 Hz, $^1J_{HC(9)}$ = 133.3 Hz, $^3J_{HC(11)CC(9)}$ = 3.8—4.9 Hz, $^2J_{HC(10)C(9)}$ = 2.0—2.3 Hz); 28.26 (m (d), C(10), $^2J_{PCC(10)}$ = 10.3 Hz, overlap with the signal for C(11)); 28.36 (tm (d), C(11), $^3J_{PCCC(11)}$ = 1.6 Hz, $^1J_{HC(11)}$ = 129.8 Hz); 133.23 (ddd (d), C(5), $^1J_{HC(5)}$ = 164.9 Hz, $^3J_{PCCC(5)}$ = 1.6 Hz, $^3J_{HC(7)CC(5)}$ = 4.2 Hz); 134.23 (ddd (s), C(6), $^3J_{HC(8)CC(6)}$ = 9.0—10.0 Hz, $^2J_{HCC(6)}$ = 2.2—2.8 Hz, $^2J_{HCC(6)}$ = 1.7 Hz); 134.95 (ddd (d), C(4), $^1J_{PC(4)}$ = 63.1 Hz, $^3J_{HC(5)CC(4)}$ = 5.5—6.3 Hz, $^2J_{HC(3)C(4)}$ = 3.4—4.1 Hz); 136.63 (d (s), C(3), $^1J_{HC(3)}$ = 168.1 Hz); 137.23 (dt (d), C(8a), $^3J_{PCCC(8a)}$ = 10.9 Hz, $^3J_{HC(5)CC(8a)}$ = 6.8 Hz, $^3J_{HC(7)CC(8a)}$ = 6.8 Hz); 137.88 (m (d), C(4a), $^2J_{PCC(4a)}$ = 8.0 Hz); 139.43 (dd (s), C(7), $^1J_{HC(7)}$ = 173.2 Hz, $^3J_{HC(5)CC(7)}$ = 4.9—5.5 Hz); 147.73 (dd (s), C(8), $^1J_{HC(8)}$ = 170.7 Hz, $^2J_{HCC(8)}$ = 2.6—3.5 Hz); 180.81 (dd (s), C(1), $^3J_{HC(3)CC(1)}$ = 4.6 Hz, $^3J_{HC(8)CC(1)}$ = 1.7 Hz); 181.34 (br.d (d), C(2), $^3J_{PCCC(2)}$ = 15.9 Hz).

(6-Bromo-1,2-dihydroxy-4-naphthyl)tri(*n*-butyl)phosphonium bromide (7). The filtrate obtained in the synthesis of compound **8** was concentrated in water aspirator vacuum to a brown glassy mass, which was treated with Et_2O—CH_2Cl_2 (2 : 1, 12 mL). The yellow precipitate that formed was filtered off and dried in air. The yield of compound **7** was 0.24 g (37%), m.p. 195—198 °C. IR, ν/cm^{-1}: 3126 (OH); 1591, 1570, 1495 (C=C arom., C=C); 1403, 1323, 1277, 1221, 1208, 1164, 1061, 980, 962, 902, 758, 721, 648, 408. $^{31}P—\{^1H\}$ NMR ($CDCl_3$—DMSO-d_6 (1 : 3)), δ_P: 29.6 (s). ^1H NMR ($CDCl_3$—DMSO-d_6 (1 : 3)), δ: 0.86 (t, H(12), $^3J_{H(11)CCH(12)}$ = 6.5 Hz); 1.41—1.42 (m, H(10), overlap with the signal for H(11)); 2.74 (dt, H(9), $^3J_{H(10)CCH(9)}$ = 7.2 Hz, $^2J_{PCH(9)}$ = 11.5 Hz); 7.64 (d, H(8), $^3J_{H(7)CCH(8)}$ = 9.1 Hz); 7.86 (d, H(3), $^3J_{PCCH(3)}$ = 14.9 Hz); 8.07 (br.s, H(5)); 8.19 (dd, H(7), $^3J_{H(8)CCH(7)}$ = 9.1 Hz, $^4J_{H(5)CCCH(7)}$ = 1.3 Hz). ^{13}C NMR (100.9 MHz, $CDCl_3$—DMSO-d_6 (1 : 3)), δ_C: 12.95 (qt (s), C(12), $^1J_{HC(12)}$ = 124.9 Hz, $^3J_{HC(10)CC(12)}$ = 4.1 Hz); 20.00 (ddt (d), C(9), $^1J_{PC(9)}$ = 48.9 Hz, $^1J_{HC(9)}$ = 131.9 Hz, $^3J_{HC(11)CC(9)}$ = 4.2 Hz); 22.94 (m (d), C(11), $^3J_{PCCC(11)}$ = 15.9 Hz, overlap with the signal for C(10)); 23.23 (m (d), C(10), $^2J_{PCC(10)}$ = 3.8 Hz, overlap with the signal for C(11)); 99.77 (dd (d), C(4), $^1J_{PC(4)}$ = 81.0 Hz, $^3J_{HC(5)CC(4)}$ = 4.3 Hz); 119.69 (d (s), C(6), $^3J_{HC(8)CC(6)}$ = 6.1 Hz); 124.51 (dd (s), C(7), $^1J_{HC(7)}$ = 162.8 Hz, $^3J_{HC(5)CC(7)}$ = 5.9 Hz); 124.88 (dd (d), C(8a), $^3J_{PCCC(8a)}$ = 11.5 Hz, $^3J_{HCCC(8a)}$ = 4.6—5.7 Hz); 125.13 (d (s), C(8), $^1J_{HC(8)}$ = 165.6 Hz); 127.89 (dd (d), C(3), $^1J_{HC(3)}$ = 159.6 Hz, $^2J_{PCC(3)}$ = 8.3 Hz); 128.77 (dd (s), C(5), $^1J_{HC(5)}$ = 168.7 Hz, $^3J_{HC(7)CC(5)}$ = 5.5 Hz); 129.35 (br.d (d), C(4a), $^2J_{PCC(4a)}$ = 8.5 Hz); 139.90 (d (d), C(2), $^3J_{PCCC(2)}$ = 16.7 Hz); 144.99 (br.m (s), C(1)).

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