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Phosphonium salts with a dihydroxynaphthyl substituent: versatile synthesis and evaluation of antimicrobial activity

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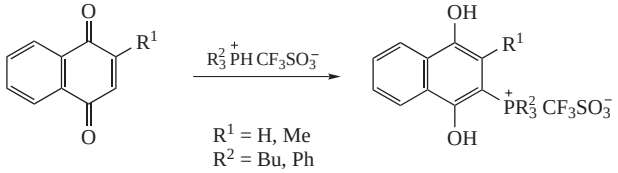
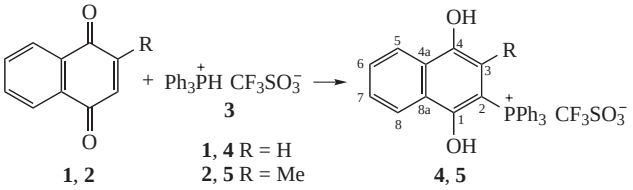
(1,4-Dihydroxynaphthalen-2-yl)phosphonium salts were obtained by reaction of P–H phosphonium salts with substituted 1,4-naphthoquinones. Some representatives of this series possess high activity against Gram-positive bacteria (*Staphylococcus aureus* ATCC 209p, *Bacillus cereus* ATCC 8035).



New means to obtain functionally substituted phosphonium salts are topical due to their high practical importance for the creation of materials with valuable optical properties,[1] catalysts[2] and ionic liquids.[3] Recently, much attention was focused on the biological properties of phosphonium salts which manifest antioxidant[4] and antimicrobial activities[5] and are tumor growth inhibitors (owing to the capability to selectively penetrate through cell membranes and be accumulated in the mitochondria of tumor cells, thus suppressing their functions).[6] Analysis of literature shows that simple or general catalytic methods for the synthesis of functionalized arylphosphonium salts are lacking. The known methods[7] mainly include treatment of triphenylphosphine with various alkyl and aryl halides, catalytic cross-coupling reactions,[8] as well as other less common approaches (for a review, see ref. 8).

We have recently found that 1,2-naphthoquinones react with tertiary and secondary phosphines to give phosphobetaines containing a P–C bond, which can be precursors of phosphonium salts.[9] In this study we attempted to apply this method to 1,4-naphthoquinone derivatives. However, the reaction of 2-methyl-1,4-naphthoquinone **2** with triphenylphosphine did not provide a new P–C bond formation but instead resulted in slow oxidation of phosphine to phosphine oxide (^{31}P NMR). In view of this, we modified the procedure, *viz.*, 1,4-naphthoquinones **1** and **2** were coupled with phosphonium salts containing a reactive P–H bond,† obtained *in situ* from trialkyl(aryl)phosphines and trifluoromethanesulfonic acid using the known technique.[10] This approach really proved to be efficient in the case of triphenylphosphonium salt **3** and afforded phosphonium salts **4** and **5** in nearly quantitative yields (Scheme 1).‡ The reaction occurs under mild conditions (CH_2Cl_2, 20 °C, 15 min). The formation of 1,4-dihydroxynaphthylphosphonium moiety and a P–C bond follows from the changes in the chemical shift and multiplicity of the phosphorus atom signal in the ^{31}P NMR spectra of the reaction products. Unlike the starting P–H phosphonium salt **3**, the final tetraarylphosphonium salts **4** and **5** do not have a direct coupling constant from the proton and



Scheme 1

† *Triphenylphosphonium trifluoromethylsulfonate* **3**. Trifluoromethanesulfonic acid (0.16 ml, 1.89 mmol) was added dropwise with stirring to a solution of triphenylphosphine (0.5 g, 1.89 mmol) in CH_2Cl_2 (5.5 ml). The mixture was stirred for 1 h. The resulting salt was further used without isolation.

Tributylphosphonium trifluoromethylsulfonate **6**. A solution of CF_3SO_3H (0.32 ml, 3.63 mmol) was added dropwise to a solution of Bu_3P (0.73 g, 3.63 mmol) in CH_2Cl_2 (8 ml) with stirring, cooling in a water bath and intense bubbling of dry argon. The mixture was stirred for 30 min. The resulting salt was further used without isolation. $^{31}P/^{31}P\{^1H\}$ NMR (242.9 MHz, CH_2Cl_2) δ: 13.8 [dm (s), $^1J_{PH}$ 477.0 Hz].

‡ *(1,4-Dihydroxynaphthalen-2-yl)triphenylphosphonium trifluoromethylsulfonate* **4**. A solution of 1,4-naphthoquinone (0.30 g, 1.89 mmol) in CH_2Cl_2 (7 ml) was added dropwise to a solution of triphenylphosphonium triflate **3** (0.78 g, 1.89 mmol) in CH_2Cl_2 (5.5 ml) with constant stirring and intense bubbling of dry argon. After 24 h of standing the dark-brown solution was evaporated under reduced pressure (14 Torr) to give a brown precipitate of **4**, which was washed with 15 ml of hexane. Yield 1.02 g (95%), mp 89–93 °C (decomp.).

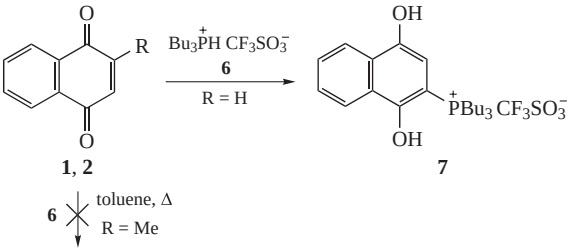
(1,4-Dihydroxy-3-methylnaphthalen-2-yl)triphenylphosphonium trifluoromethylsulfonate **5**. A solution of 2-methyl-1,4-naphthoquinone (0.28 g, 1.66 mmol) in CH_2Cl_2 (7 ml) was added dropwise to a solution of triphenylphosphonium triflate **3** (0.68 g, 1.66 mmol) in CH_2Cl_2 (5 ml) with intense bubbling of dry argon. After 24 h of standing the orange reaction mixture was evaporated under reduced pressure (14 Torr) to give a pink precipitate of **5**, which was purified by recrystallization from the mixture of acetone–diethyl ether–light petroleum (1 : 2 : 3). Yield 0.75 g (78%), mp 174–176 °C.

(1,4-Dihydroxynaphthalen-2-yl)tributylphosphonium trifluoromethylsulfonate **7**. A solution of 1,4-naphthoquinone (0.30 g, 1.90 mmol) in CH_2Cl_2 (8 ml) was added dropwise to a solution of tributylphosphonium triflate **6** (0.67 g, 1.90 mmol) in CH_2Cl_2 (4 ml) with stirring and intense bubbling of dry argon. After 24 h of standing the dark-brown reaction mixture was evaporated under reduced pressure (12 Torr) to give dark-green oil, which was crystallized during the storage under diethyl ether–hexane (15 ml, 1 : 2). The crystalline precipitate of **7** was filtered and dried *in vacuo* (14 Torr). Yield 0.92 g (96%), mp 128 °C.

For spectral characteristics of compounds **4**, **5** and **7**, see Online Supplementary Materials.

manifest themselves as a multiplet in the ^{31}P NMR spectrum. The formation of a P–C bond in compound **4** unambiguously follows from the presence of a doublet at δ 96.79 (C^2) with direct constant $^1J_{PC}$ 95.1 Hz in the ^{13}C-{^1H} NMR spectrum. The carbon atoms bound to oxygen are shifted downfield to δ 152.80 (C^1) and 148.21 (C^4, $^3J_{PCCC}$ 16.3 Hz); only one of them has a coupling constant with phosphorus through three bonds. The presence of hydroxy groups is confirmed by the presence of a broad absorption band around 3250 cm^{-1} in the IR spectrum. The multiplicity of the signals and the number of carbon atoms totally agree with the suggested structures.

Under similar conditions, the reaction of P–H salt **6** obtained from tributylphosphine requires essentially more time, namely 3 days (Scheme 2). Figure S2 (see Online Supplementary Materials) demonstrates the ^{31}P and ^{31}P-{^1H} NMR spectra of the reaction mixture 48 h after the reaction start. The process occurs in 90–94% during this time (the reaction mixture demonstrates a signal of the P–H phosphonium salt **6** around δ 13.8, $^1J_{PH}$ 477.0 Hz). This is apparently due to a higher nucleophilicity of tributylphosphine and, hence, a lower acidity of the tributylphosphonium triflate compared to triphenylphosphonium one.



Scheme 2

Phosphonium salt **7** was isolated as yellow crystals in nearly quantitative yield (96%). Its ^{13}C NMR spectrum contains a doublet of C^2 at δ 97.38 ($^1J_{PC}$ 83.7 Hz). The multiplicity of the C^{8a}, C^4 and C^3 signals unambiguously indicates the presence of a phosphonium group in the dihydroxyphenylene moiety of the naphthalene ring. The resonances of the C^{8a} and C^4 nuclei manifest themselves as doublets with $^3J_{PCCC}$ 9.4 and 8.7 Hz, respectively, whereas the resonance of C^3 is observed as a doublet with a smaller constant as $^2J_{PCC}$ 7.2 Hz. The carbon atoms of butyl groups bound to phosphorus resonate in the ^{13}C-{^1H} spectrum as a doublet at δ 19.52 ($^1J_{PC}$ 50.6 Hz). The C^{13} carbon in the triflate anion resonates at δ 120.95 (q, $^1J_{FC}$ 321.2–321.5 Hz). The IR spectrum of compound **7** contains an intense broad band around 3285 cm^{-1} corresponding to the stretching vibrations of phenolic groups.

The structure of phosphonium salt **7** was ultimately confirmed by XRD[§] (Figure 1). Its bond lengths, valence and torsion angles in the molecules in a crystal are within the standard values for each type of chemical bond.[11] Apart from the electrostatic interaction, the anion and the cation are held together by hydrogen bonds between the hydroxyl hydrogen atoms of the cation and the oxygen atoms of two anions. In addition to the strong H-bonds, a lot of CH···O interactions occur in the crystal, which result in crystal packing consisting of alternating layers of cations and anions, parallel to the *ab* plane (see Figure S1, Table S2, Online Supplementary Materials).

An attempt to extend the reaction of salt **6** onto 2-methyl-1,4-naphthoquinone **2** failed, and the expected product did not form even on prolonged heating in toluene (see Scheme 2).

We have evaluated the *in vitro* antimicrobial activity (bacteriostatic, fungistatic, antibacterial and antifungal) of compounds **4**, **5** and **7** in the concentration range of 15.6–500 μg ml^{-1} (Table 1).[¶] The obtained data have demonstrated that any significant activity of compounds **4**, **5** and **7** is restricted to the test strains of the Gram-positive bacteria *Sa* and *Bc* with **5** showing the best activity (in the case of *Sa*). The observed bacteriostatic activity of **5** towards *Sa* was fourfold higher than that of the reference compound chloramphenicol. Compound **5** also revealed limited fungistatic activity. None of the compounds prepared showed antimicrobial properties with the Gram-negative bacteria tested within the concentration range studied.

Compound **5**, the most active of compounds examined, was also tested for hemolytic activity at its minimum inhibitory concentration (MIC). However, it exhibited only very low activity[12] (see Table 1).

In conclusion, we have developed a new efficient synthesis of phosphonium salts bearing a dihydroxynaphthyl moiety, based

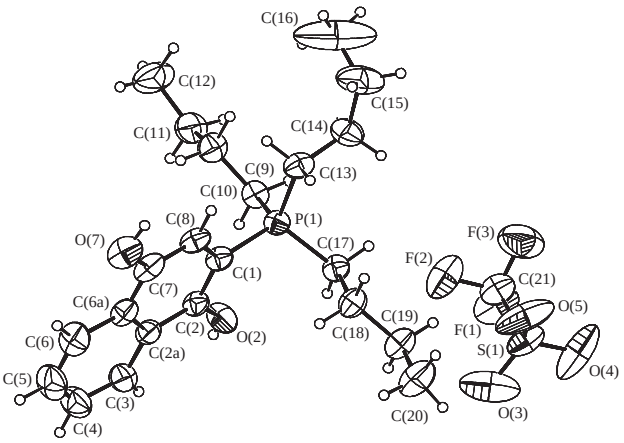


Figure 1 Geometry of phosphonium salt **7** in crystal. Selected bond lengths (Å), bond and torsion angles (°): P(1)–C(1) 1.778(4), P(1)–C(9) 1.799(4), P(1)–C(13) 1.796(4), P(1)–C(17) 1.787(4), O(2)–C(2) 1.364(5), O(7)–C(7) 1.370(5); C(1)–P(1)–C(17) 110.9(2), C(1)–P(1)–C(13) 110.0(2), C(17)–P(1)–C(13) 108.7(2), C(1)–P(1)–C(9) 109.8(2), C(17)–P(1)–C(9) 109.3(2), C(13)–P(1)–C(9) 108.1(2); C(9)–P(1)–C(1)–C(2) 60.8(4), C(1)–P(1)–C(9)–C(10) 68.3(4), C(1)–P(1)–C(13)–C(14) –179.3(3), C(1)–P(1)–C(17)–C(18) –48.6(4).

§ *Crystallographic data for* **7**: crystals of $C_{23}H_{34}F_3O_5PS$ (M = 510.53) are monoclinic, space group $P2_1/n$, at 296(2) K: a = 10.340(3), b = = 14.387(4) and c = 17.856(5) Å, β = 102.409(4)°, V = 2594.3(13) $Å^3$, Z = 4, d_{calc} = 1.307 g cm^{-3}, μ(MoKα) = 0.238 mm^{-1}, F(000) = 1080. Total of 19988 reflections were measured and 5079 independent reflections (R_{int} = 0.0544) were used in a further refinement. The refinement converged to wR_2 = 0.2729 and GOF = 1.034 for all independent reflections [R_1 = 0.0777 was calculated for 2616 observed reflections with $I > 2\sigma(I)$]. The measurements were made on a Bruker SMART Apex II diffractometer with graphite-monochromated MoKα radiation (λ = = 0.71073 Å). The structure was solved by direct methods, and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with SHELXL-14 program[14] using a full-matrix least-squares procedure. The hydrogen atom positions were fixed geometrically at calculated distances and allowed them to ride on the parent atoms. All calculations were performed using the WinGX[15] and APEX2[16] programs. The figures were made using the PLATON[17] and MERCURY programs.[18]

CCDC 1497454 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

¶ Bacteriostatic and fungistatic properties were studied by the method of serial dilutions in liquid media,[19] in order to determine the MIC for the inhibition of the growth and multiplication of the test organism. Bactericidal and fungicidal activities were determined for the complete destruction of the microbial cells using the described method.[20] The activity of compounds **4**, **5** and **7** was evaluated against cultures of Gram-positive bacteria: *Staphylococcus aureus* ATCC 209p (*Sa*), *Bacillus cereus* ATCC 8035 (*Bc*); Gram-negative bacteria: *Escherichia coli* CDC F-50 (*Ec*), *Pseudomonas aeruginosa* ATCC 9027 (*Pa*); and fungi: *Aspergillus niger* BKMF-1119 (*An*), *Trichophyton mentagrophytes var. gypseum* 1773 (*Tm*), *Candida albicans* 855-653 (*Ca*).

Table 1 Antimicrobial and hemolytic activity of compounds **4**, **5** and **7**.

Compound	Minimum inhibitory concentration / μg ml^{-1}														Hemolytic activity	
	Bacteriostatic and fungistatic activity							Bactericidal and fungicidal activity							Concentration / μg ml^{-1}	Hemolysis (%)
	Sa	*Bc*	*Ec*	*Pa*	*An*	*Tm*	*Ca*	*Sa*	*Bc*	*Ec*	*Pa*	*An*	*Tm*	*Ca*		
4	125	125	>500	>500	>500	>500	>500	125	>500	>500	>500	>500	>500	>500		
5	15.6	500	500	500	500	125	250	15.6	>500	>500	>500	>500	125	>500	15.6	0.1
7	250	62.5	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500		
Chloramphenicol	62.5	2.5	25													
Ketoconazole						3.9	3.9									

on the reaction of 1,4-naphthoquinones with P–H phosphonium salts. The reaction occurs under mild conditions and provides high yields of the target compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2017.03.008.

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