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Oxidation of Substituted Phenols with Chlorine Dioxide

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Abstract—Chlorine dioxide was used to oxidize sterically hindered phenols and their derivatives (2,6-di-*tert*-butylphenol, 2,6-diisobornylphenol, 2,6-di-*tert*-butyl-4-methylphenol, 2,6-diisobornyl-4-methylphenol, and 3,5-diisobornyl-4-hydroxybenzaldehyde) in organic solvent.

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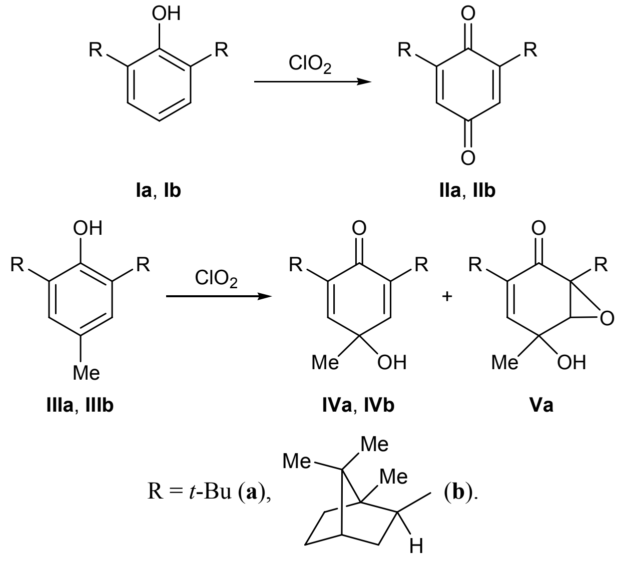
Quinone derivatives constitute important groups of natural compounds such as dyes, pigments, antibiotics, vitamins, etc. Plastoquinones and ubiquinones play an important role in photosynthesis and electron transfer precesses due to their ability to absorb visible light [1]. Formerly, quinones were used in the manufacture of dyes. In recent time, the scope of application of quinone derivatives rapidly extends. They are used as reagents in synthesis, polymer modifiers and stabilizers, and catalysts of chemical reactions. Development of procedures for the synthesis of quinones from sterically hindered phenols attracts interest from the practical viewpoint.

Oxidation of phenols with various oxidants was studied in sufficient detail [2–7]. Oxidation of phenols with chlorine dioxide (ClO_2) was studied in [8–10]; it was shown that 2,6-disubstituted phenols are thus oxidized to the corresponding 1,4-quinones (yield 67–95%) or diphenoquinones; 2,4-disubstituted phenols react with ClO_2 to form 4-alkyl-*p*-quinols.

In the present work we examined oxidation of sterically hindered phenols **Ia**, **Ib**, **IIIa**, and **IIIb** with chlorine dioxide in pyridine on cooling or in dimethylformamide at 20°C (Scheme 1). The oxidation of 2,6-di-*tert*-butylphenol (**Ia**) gave 2,6-di-*tert*-butylbenzoquinone (**IIa**) [8]. By oxidation of 2,6-diisobornylphenol (**Ib**) we obtained previously unknown 2,6-diisobornyl-1,4-benzoquinone (**IIb**). Its structure was confirmed by IR and NMR spectroscopy. The IR spectrum of **IIb** contained an absorption band at 1653 cm^{-1}, which is typical of carbonyl stretching vibrations in quinones. In the ^{1}H NMR spectrum of **IIb** we observed signals from protons in two bicyclic substituents and two protons in the quinone ring (δ 6.62 ppm). Compound **IIb** displayed in the ^{13}C NMR spectrum signals from carbon atoms in the isobornyl groups, C=C carbon atoms in the quinone ring resonated at δ_C 132.39 and 153.34 ppm, and signals from carbonyl carbon atoms were located at δ_C 187.88 and 188.59 ppm.

Oxidation of 4-methyl-substituted phenols **IIIa** and **IIIb** with ClO_2 afforded 2,6-dialkyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-ones **IVa** and **IVb**. No chlorination products were detected in the reaction mixtures. The spectral parameters of compound **IVa** were consistent with those reported in [11]. When phenol **IIIa** was oxidized in pyridine on cooling, the substrate-to-oxidant molar ratio being 1 : 3, a mixture

Scheme 1.

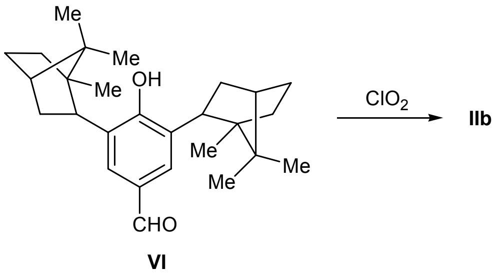


of products was formed. It was separated by column chromatography to isolate major product **IVa** and 1.5% of 1,3-di-*tert*-butyl-5-hydroxy-5-methyl-7-oxabicyclo-[4.1.0]hept-3-en-2-one (**Va**). The latter was identified by comparing its melting point and ^{1}H NMR and IR spectra with the corresponding published data [6].

The IR spectrum of newly synthesized 2,6-diisobornyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one (**IVb**) contained absorption bands at 3423 (OH) and 1666 cm^{-1} (C=O). Protons in the cyclohexadiene ring of **IVb** resonated in the ^{1}H NMR spectrum at δ 6.64 ppm, and the carbonyl carbon signal appeared in the ^{13}C NMR spectrum at δ_C 185.82 ppm; the C–OH signal was observed at δ_C 62.23 ppm.

Quinone **IIb** was also obtained instead of the expected carboxy derivative in the oxidation of 3,5-diisobornyl-4-hydroxybenzaldehyde (**VI**) with chlorine dioxide (Scheme 2). The yield of **IIb** was 80% when the reaction was carried out in dimethylformamide at 20°C. Presumably, the reaction is accompanied by oxidative decarboxylation. Chlorine dioxide is a fairly potent oxidant, reactions with its participation occur at a high rate, and we failed to isolate hydroxybenzoic acid. Quinone **IIb** was formed in 36% yield by oxidation of **VI** in pyridine on cooling with the use of 3 equiv of ClO_2; the product was isolated after prolonged keeping of the reaction mixture.

Scheme 2.



Thus oxidation with chlorine dioxide of sterically hindered phenols having a methyl group in the *para* position with respect to the OH group yields 4-hydroxy-4-methyl-2,5-cyclohexadien-1-ones. Phenols having no substituent in the *para* position with respect to the hydroxy group, as well as 4-hydroxybenzaldehyde derivative, are converted into the corresponding 1,4-benzoquinones.

EXPERIMENTAL

The IR spectra were recorded from solutions in carbon tetrachloride on a Shimadzu IR Prestige 21 spectrometer with Fourier transform. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-II-300 spectrometer at 300.17 and 75.5 MHz, respectively, using $CDCl_3$ as solvent. The elemental compositions were determined on an EA1110 automatic CHNS-O analyzer. Thin-layer chromatography was performed on Sorbfil plates using benzene–petroleum ether (1 : 1) as eluent; spots were made visible by treatment with a 5% solution of potassium permanganate.

A solution of chlorine dioxide in methylene chloride was prepared by extraction of ClO_2 from an aqueous solution with a concentration *c* of 8–9 g/l, followed by drying over $MgSO_4$.

2,6-Di-*tert*-butylcyclohexa-2,5-diene-1,4-dione (IIa). *a*. 2,6-Di-*tert*-butylphenol, 0.2563 g (1.24 mmol), was dissolved in 2 ml of pyridine, and 48 ml (3.72 mmol) of a solution of ClO_2 in methylene chloride was added under stirring at 6–10°C over a period of 60 min. The solvent was evaporated, and the residue was subjected to column chromatography on silica gel using chloroform as eluent. Yield 0.1353 g (51%), orange crystals, mp 64–65°C; published data [8]: mp 65–66°C. IR spectrum: ν 1654 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 1.31 s (18H, *t*-Bu), 6.53 s (2H, CH). ^{13}C NMR spectrum, δ_C, ppm: 29.38 (CH_3), 35.89 [**C**(CH_3)$_3$], 130.15 (CH), 158.04 (C^2, C^6), 188.44 (C=O), 189.31 (C=O).

b. A mixture of atmospheric air and ClO_2 (from an aqueous solution containing 3.45 mmol of ClO_2) was bubbled over a period of 60 min through a solution of 0.237 g (1.15 mmol) of 2,6-di-*tert*-butylphenol in 10 ml of dimethylformamide at 20°C. The mixture was then treated with an ice water acidified with hydrochloric acid, and the precipitate was filtered off, washed with water, and dried. Yield 0.2187 g (86%).

Compounds **IIb**, **IVa**, **IVb**, and **Va** were synthesized in a similar way.

2,6-Bis(1,7,7-trimethylbicyclo[2.2.1]heptane-2-yl)cyclohexa-2,5-diene-1,4-dione (IIb). Yield 56 (*a*), 74% (*b*); yellow crystals, mp 223–225°C. IR spectrum: ν 1653 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 0.77 s (6H, CH_3), 0.85 s and 0.86 s (12H, CH_3); 1.84–1.93 m, 1.63–1.52 m, and 1.39–1.34 m (12H, CH_2); 1.90–1.84 m (2H) and 3.17 t (2H, *J* = 9 Hz) (2′-H, 4′-H), 6.62 s (2H, 3-H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 14.45 (CH_3), 19.88 (CH_3), 20.05 (CH_3), 27.32 (CH_2), 33.42 (CH_2), 39.61 (CH_2), 45.09 (CH), 45.31 (CH), 45.52 (C), 51.10 (C), 132.39 (C^3, C^5), 153.34 (C^2, C^6), 187.88 (C=O), 188.59 (C=O). Found, %: C 82.02: H 9.52; O 8.46. $C_{26}H_{36}O_2$. Calculated, %: C 82.10; H 9.47; O 8.43.

2,6-Di-*tert*-butyl-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (IVa). Yield 60–63%, light yellow powder, mp 111–113°C; published data [5]: mp 111–112°C. IR spectrum, ν, cm^{-1}: 3273 (OH), 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.27 s (18H, *t*-Bu), 1.82 s (3H, CH_3), 6.67 d (2H, CH, *J* = 3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 29.32 [C(**C**H_3)$_3$], 31.28 (CH_3), 34.69 [**C**(CH_3)$_3$], 62.69 (C), 141.62 (CH), 145.13 (C^2, C^6), 184.98 (C=O).

4-Hydroxy-4-methyl-2,6-bis(1,7,7-trimethylbicyclo[2.2.1]heptane-2-yl)cyclohexa-2,5-dien-1-one (IVb). Yield 62–78%, light yellow powder, mp 127°C. IR spectrum, ν, cm^{-1}: 3423 (OH), 1666 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.67 s (3H, CH_3), 0.69 s (3H, CH_3), 078 s (6H, CH_3), 0.82 s (6H, CH_3), 1.24–1.30 m (4H, CH_2), 1.35–1.41 m (2H, CH), 1.48–1.51 m (4H, CH_2), 1.73 s (3H, CH_3), 1.78–1.86 m (4H, CH_2), 3.05 t (2H, CH, *J* = 9 Hz), 6.64 d (2H, 3-H, 5-H, *J* = 6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.79 (CH_3), 19.51 (CH_3), 21.30 (CH_3), 27.40 (CH_2), 30.82 (CH_3), 33.10 (CH_2), 39.27 (CH_2), 43.68 (CH), 45.38 (CH), 48.23 (C), 49.73 (C), 62.23 (COH), 138.52 (C^2, C^6), 143.46 (C^3, C^5), 185.82 (C=O). Found, %: C 81.73; H 10.12; O 8.15. $C_{27}H_{40}O_2$. Calculated, %: C 81.82; H 10.10; O 8.08.

1,3-Di-*tert*-butyl-5-hydroxy-5-methyl-7-oxabicyclo[4.1.0]hept-3-en-2-one (Va). Yield 1.5%, yellow powder, mp 103°C; published data [6]: mp 102–103°C. ^{1}H NMR spectrum, δ, ppm: 1.15 s and 1.19 s (9H each, *t*-Bu), 1.34 s (3H, CH_3), 2.48 s (1H, OH), 3.56 d (1H, CH, *J* = 3 Hz), 6.09 d (1H, CH, *J* = 3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 25.98 (CH_3), 26.12 [C(**C**H_3)$_3$], 29.28 [C(**C**H_3)$_3$], 32.31 [**C**(CH_3)$_3$], 34.63 [**C**(CH_3)$_3$], 61.65 (C–O), 64.50 (C^1), 68.97 (C^5) 139.10 (C), 143.10 (C^3), 191.04 (C=O).

Oxidation of 4-hydroxy-3,5-bis(1,7,7-trimethylbicyclo[2.2.1]heptane-2-yl)benzaldehyde (VI). *a.* A solution of 0.0997 g (0.25 mmol) of 4-hydroxy-3,5-bis(1,7,7-trimethylbicyclo[2.2.1]heptane-2-yl)benzaldehyde (**VI**) in 5 ml of pyridine was cooled to 6–10°C, and 10 ml (0.5 mmol) of a solution of ClO_2 in methylene chloride was added under stirring over a period of 60 min. When the reaction was complete, the mixture was washed with cold water and dried over Na_2SO_4, the solvent was evaporated under reduced pressure, and the crystalline residue was washed with ethanol. Yield of **IIb** 0.0184 g (36%).

b. A mixture of air and ClO_2 (from an aqueous solution containing 0.78 mmol of ClO_2) was bubbled over a period of 60 min through a solution of 0.1046 g (0.26 mmol) of compound **VI** in 10 ml of dimethylformamide maintained at 20°C. The mixture was treated with ice water acidified with hydrochloric acid, and the precipitate was filtered off, washed with water, and dried. Yield of **IIb** 0.0801 g (80%).

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