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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Use of 1-Halo Derivatives of the 2,2,6,6-Tetramethylpiperidine Series as Oxidants and Halogenating Agents

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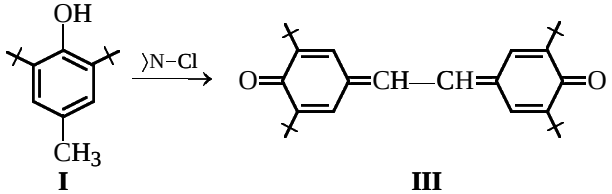
Abstract—1-Halo derivatives of the 2,2,6,6-tetramethylpiperidine series oxidize sterically hindered phenols to form dimers and *p*-quinones.

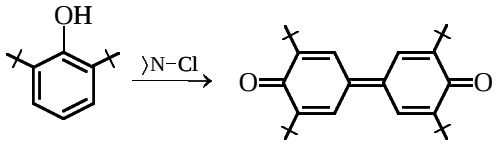
The capability of sterically shielded phenols to undergo oxidation is well known [1] and is one of the main characteristic properties of this class of compounds, allowing their use as effective antioxidants [2]. Diverse oxidation products are formed (phenoxyl radicals, quinoid compounds, quinones), depending on the structure of the phenols being oxidized and on the oxidant chosen. For example, oxidation of 2,4,6-tri-*tert*-butylphenol with PbO_2 or MnO_2 yields a stable phenoxyl radical, whereas oxidation with $NaNO_2$ yields quinones [1].

In this context, it seemed of interest to study the oxidation of shielded phenols with 1-halo derivatives of the 2,2,6,6-tetramethylpiperidine (TMP) series. These agents have apparent advantages over other *N*-haloalkylamines in that they show relatively high stability and low nucleophilicity; these compounds can be prepared in high yield from the available 2,2,6,6-TMP derivatives [3–5].

The oxidation of sterically hindered phenols with halo derivatives of the 2,2,6,6-TMP series is usually performed in an organic solvent, e.g., benzene or methylene chloride. 2,6-di-*tert*-butyl-4-methylphenol **I** and 2,6-di-*tert*-butylphenol **II** are oxidized with 1-halo derivatives of the 2,2,6,6-TMP series to form dimers: 3,3',5,5'-tetra-*tert*-butylstilbenoquinone **III** and 3,3',5,5'-tetra-*tert*-butyldiphenoquinone **IV**, respectively:

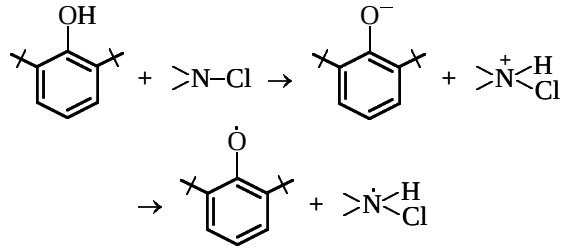


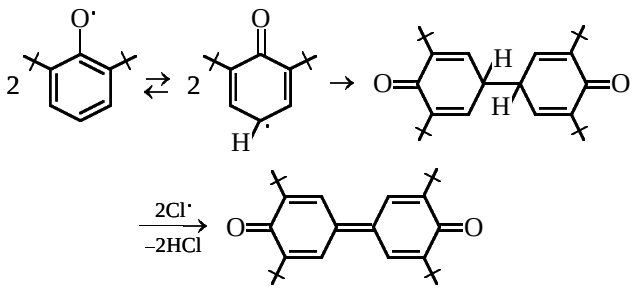
I **III**



II **IV**

In an organic solvent, the dimerization apparently occurs by the radical mechanism [1]. The reaction rate depends on the rate of protonation of the 1-halo derivative. The possible pathway of dimer formation in the oxidation of phenols with chloramines of the 2,2,6,6-TMP series is shown in the scheme:





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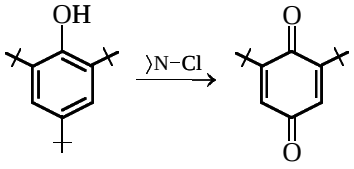
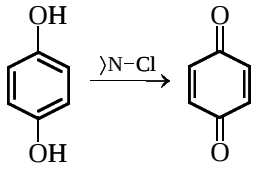
The stability of the forming phenoxyl radical is determined by the structural features of the initial phenol molecule. For example, in oxidation of 2,4,6-tri-*tert*-butylphenol **V**, we obtained 2,6-di-*tert*-butylbenzoquinone **VI**. 2,4,6-Tri-*tert*-butylphenol does not undergo noticeable dimerization because of the high stability of the forming 2,4,6-tri-*tert*-butylphenoxyl radical [6]:



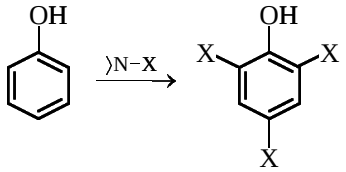
V **VI**

1-Chloro-2,2,6,6-TMP oxidizes hydroquinone **VII** in an organic solvent to *p*-benzoquinone **VIII** in quantitative yield:



VII **VIII**

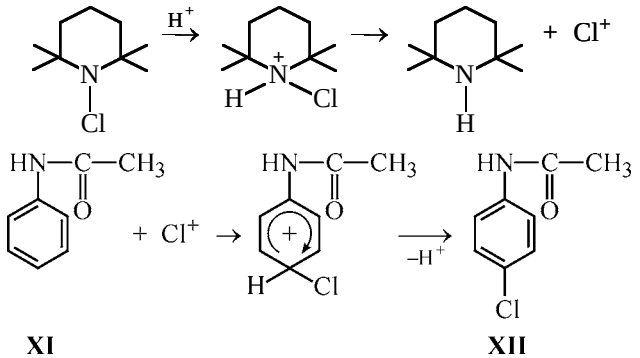
Phenol **IX** in organic solvent reacts with 1-chloro derivatives of the 2,2,6,6-TMP series to form 2,4,6-trichlorophenol **Xa** and with 1-bromo derivatives to form 2,4,6-tribromophenol **Xb**:



IX **Xa**, **Xb**

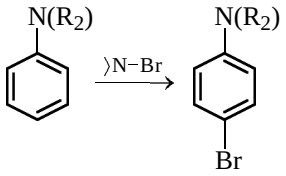
where X = Cl (**Xa**), Br (**Xb**).

In acidic solutions, the reactions apparently occur by the electrophilic mechanism, which is confirmed by the formation of *p*-chloroacetanilide **XII** as the only product in the reaction of acetanilide **XI** with 1-chloro-2,2,6,6-TMP:



XI **XII**

1-Bromo-4-hydroxy-2,2,6,6-TMP reacts with dimethylphenylamine and diethylphenylamine in a weakly acidic solution (pH 4–5) also to form the corresponding *p*-bromo derivatives **XIIIa** and **XIIIb**:



XIIIa, **XIIIb**

where R = CH_3 (**XIIIa**), C_2H_5 (**XIIIb**).

EXPERIMENTAL

3,3',5,5'-Tetra-*tert*-butylstilbenoquinone III. 2,6-Di-*tert*-butyl-4-methylphenol (Ionol), 4.4 g (0.02 mol), and 1-bromo-4-hydroxy-2,2,6,6-tetramethylpiperidine, 9.2 g (0.04 mol), were dissolved in 50 ml of benzene, and the mixture was allowed to stand at 25°C for 4–5 days. After the disappearance of the starting Ionol (TLC monitoring), the precipitate of 4-hydroxy-2,2,6,6-tetramethylpiperidinium bromide was separated. The solvent was distilled off under reduced pressure; 3.9 g (90%) of 3,3',5,5'-tetra-*tert*-butylstilbenoquinone was obtained; mp 304–305°C (from benzene).

The reaction with 1-chloro-4-hydroxy-2,2,6,6-tetramethylpiperidine was performed similarly. The reaction was slower, being complete in 6–7 days. Yield of **III** 3.6 g (85%).

3, 3', 5, 5'-Tetra-*tert*-butyldiphenoquinone IV. A mixture of 1 g (0.005 mol) of 2,6-di-*tert*-butylphenol and 1.7 g (0.01 mol) of 1-chloro-4-hydroxy-2,2,6,6-tetramethylpiperidine in 50 ml of benzene was allowed to stand for 2 days. After the disappearance of the starting phenol (TLC monitoring), the precipitate of 4-hydroxy-2,2,6,6-tetramethylpiperidinium chloride was separated. The solvent was distilled off under reduced pressure; 0.9 g (90%) of 3',3,5',5-tetra-*tert*-butyldiphenoquinone was obtained; mp 240–242°C. The isolated product was identified by comparison with an authentic sample [5].

2,6-Di-*tert*-butyl-*p*-benzoquinone VI. A mixture of 2.6 g (0.01 mol) of 2,4,6-tri-*tert*-butylphenol and 3.4 g (0.02 mol) of 1-chloro-2,2,6,6-tetramethylpiperidine in 50 ml of benzene was placed in a flask equipped with a reflux condenser and heated for 20 h on a water bath kept at 60°C. The mixture was cooled, the precipitated crystals of 2,2,6,6-tetramethylpiperi-

dinium chloride were filtered off, the solvent was evaporated, and the residue was chromatographed on a column (Al_2O_3, Brockmann grade II l = 20 cm, d = 3 cm, eluent hexane). The yellow fraction was collected. The solvent was removed under reduced pressure; 1.15 g (55%) of 2,6-di-*tert*-butyl-*p*-benzoquinone **VI** was obtained; mp 78–79°C (from hexane); published data [6]: mp 78–80°C.

***p*-Benzoquinone VIII.** A mixture of 2.2 g (0.02 mol) of hydroquinone and 3.6 g (0.02 mol) of 1-chloro-2,2,6,6-tetramethylpiperidine in 20 ml of methylene chloride was allowed to stand for 12 h. The precipitate of 2,2,6,6-tetramethylpiperidinium ch loride (3.5 g) was filtered off, and the solvent was distilled off on a rotary evaporator; 1.72 g (80%) of *p*-benzoquinone **VIII** was obtained, mp 116°C (from water). The product was identified by comparison with an authentic sample [7].

2,4,6-Trichlorophenol Xa. A mixture of 0.94 g (0.01 mol) of phenol and 5.66 g (0.03 mol) of 1-chloro-4-hydroxy-2,2,6,6-tetramethylpiperidine in 50 ml of benzene was allowed to stand for 24 h at room temperature. The benzene solution was extracted with 10% NaOH, the organic layer was separated, and the aqueous layer was acidified with HCl to pH 1. 2,4,6-Trichlorophenol precipitated from the aqueous phase; it was separated, washed with water, and dried in air. Yield 1.78 g (91%); mp 63–65°C (from ethanol–water, 1 : 1); published data [8]: mp 64–65°C. 4-Hydroxy-2,2,6,6-tetramethylpiperidine was isolated from the benzene layer; yield 4.2 g (90%), mp 130–132—C (from ethyl acetate) [9].

2,4,6-Tribromophenol Xb was prepared similarly, by the reaction of phenol with 1-bromo-4-hydroxy-2,2,6,6-tetramethylpiperidine. Yield 82%, mp 96–98°C (from ethanol–water, 1 : 1). Mixing with an authentic sample gave no depression of the melting point [8].

***p*-Chloroacetanilide XII.** Acetanilide, 2.7 g (0.02 mol), and 1-chloro-2,2,6,6-tetramethylpiperidine, 3.7 g (0.021 mol), were dissolved in 30 ml of benzene, and 25 ml of 1 M HCl was added. The mixture was stirred and heated on a water bath at 50–60°C for 15–20 min. The reaction progress was monitored by TLC. After the reaction was complete, the mixture was cooled, the organic layer was separated, and the solvent was evaporated under reduced pressure. The crystals of 4-chloroacetanilide were filtered off. Yield of **XII** 3.2 g (92%); rhombic needles, mp 175–177°C; published data [10]: mp 177–178°C.

***p*-Bromoacetanilide** was prepared similarly by the reaction with 1-bromo-2,2,6,6-tetramethylpiperidine; mp 167–168°C (from ethanol–water, 1 : 1). The product was identified by comparison with an authentic sample [10].

***p*-Bromo-*N*,*N*-diethylaniline XIIIb**. *N*,*N*-Diethylaniline, 1.49 g (0.01 mol), was dissolved in 20 ml of benzene, and a solution of 2.5 g (0.01 mol) of 1-bromo-4-hydroxy-2,2,6,6-tetramethylpiperidine in 20 ml of benzene was gradually added. The mixture was heated on a water bath at 60°C for 40–45 min. Then the mixture was cooled, and white crystals of 4-hydroxy-2,2,6,6-tetramethylpiperidine were filtered off. The solvent was evaporated, and 2.1 g (90%) of *p*-bromo-*N*,*N*-diethylaniline (white oily crystals) was obtained; mp 31–33°C (from ethanol–water, 1 : 1). Mixing with an authentic sample gave no depression of the melting point [10].

***p*-Bromo-*N*,*N*-dimethylaniline XIIIa** was prepared similarly. Yield 85%; mp 54–56°C (from ethanol–water, 1 : 1); published data [10]: mp 55–56°C.

CONCLUSIONS

(1) 2,6-Di-*tert*-butyl-4-methylphenol and 2,6-di-*tert*-butylphenol in an organic solvent are oxidized by 1-halo derivatives of 2,2,6,6-tetramethylpiperidine to form dimers.

(2) 1-Chloro-2,2,6,6-tetramethylpiperidine oxidizes in an organic solvent 2,4,6-tri-*tert*-butylphenol and hydroquinone to 2,6-di-*tert*-butylbenzoquinone and *p*-benzoquinone, respectively.

(2) Phenol in an organic solvent and aromatic amines in an acidic solution in the presence of 1-halo derivatives of the 2,2,6,6-tetramethylpiperidine series undergo halogenation.

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