Ortho Oxidation of 2,6-Dimethylphenol with Trifluoroperoxyacetic Acid

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Slow addition of hydrogen peroxide to a solution of 2,6-dimethylphenol and trifluoroacetic acid in methylene chloride affords primarily a product of ortho oxidation, the dimer (III) of 2,6-dimethyl-*o*-quinol (II). When the reagents are mixed together all at once, however, 2,6-dimethylbenzoquinone is the overwhelmingly predominant product. A cyclic hydrogen-bonded transition state is suggested to account for the ortho hydroxylation of 2,6-dimethylphenol with trifluoroperoxyacetic acid formed *in situ* from hydrogen peroxide and trifluoroacetic acid.

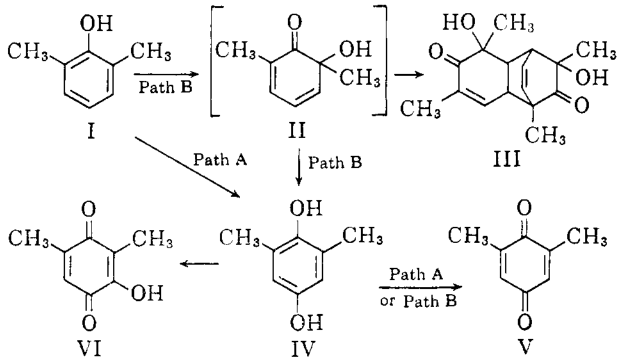
Recently, Musgrave and co-workers[1] have found that oxidation of 2,6-dimethylphenol with trifluoroperoxyacetic acid affords only one isolable product, 2,6-dimethylbenzoquinone, in 77% yield. We now wish to report that under certain conditions a different major product, resulting from ortho oxidation of the phenol, is obtained. The relative amounts of this product and 2,6-dimethylbenzoquinone formed are strongly dependent upon the concentration of oxidant.

When three molar equivalents of 50–85% hydrogen peroxide are added very slowly to a solution of 2,6-dimethylphenol (I) and one half of a molar equivalent of trifluoroacetic acid in methylene chloride solution, the major product is the compound $C_{16}H_{20}O_4$, isolated in 42% yield. 2,6-Dimethylbenzoquinone (V) is also obtained in 27% yield. When the hydrogen peroxide is added all at once, however, $C_{16}H_{20}O_4$ is obtained in 10% yield and 2,6-dimethylbenzoquinone in 60% yield. 2,6-Dimethyl-3-hydroxybenzoquinone (VI) is isolated as a minor product (3–7% yield) using either procedure.

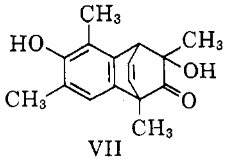
The physical and spectral properties of the compound $C_{16}H_{20}O_4$ (see Experimental) are in agreement with those reported[2] recently for the Diels–Alder dimer[3] (III) of 6-hydroxy-2,6-dimethyl-2,4-cyclohexadienone (II). Mixed melting point determination with an authentic specimen of III prepared by sodium periodate oxidation[2] of I confirms the identity of this product.

That acidic hydrogen peroxide is not an effective oxidant under these conditions was shown by the failure of 2,6-dimethylphenol to react with hydrogen peroxide in the presence of *p*-toluenesulfonic acid in either methylene chloride (heterogeneous) or ether (homogeneous) diluent. Slow addition of preformed trifluoroperoxyacetic acid (no free hydrogen peroxide present) to I in methylene chloride in the presence of disodium hydrogen phosphate acid scavenger affords products III, V, and VI in 40, 20, and 7% yields, respectively. Accordingly, then, trifluoroperoxyacetic acid is the active oxidizing agent involved in the formation of all three products.

In the absence of a complete kinetic study, these results are subject to several interpretations. Any effort to explain them, however, must be consistent with the following additional observations. 2,6-Dimethylhydroquinone (IV) has been shown to be a precursor to both products V (72% yield) and VI (10% yield). The dimer (III) is not transformed to V on further treatment with hydrogen peroxide and trifluoroacetic acid. The hydroxyquinone (VI) is not formed from V under the conditions of the reaction.



It appears that product V could arise from I by either of two possible paths. The first (path A) is a direct oxidative route involving the hydroquinone (IV) as a primary intermediate. The second (path B) would involve initial formation of unstable 2,6-dimethyl-*o*-quinol (II) followed by acid-catalyzed allylic rearrangement of II to IV. This 1,3-migration of hydroxyl, rendered irreversible by the driving force of aromatization, is analogous to a similar migration of fluorine encountered recently.[4] There the Diels–Alder dimer of 6-fluoro-2,6-dimethyl-2,4-cyclohexadienone was found to undergo reversal to monomer at 140° followed by hydrogen fluoride-catalyzed rearrangement to 4-fluoro-2,6-dimethylphenol. Our own efforts to carry out a similar reaction with the dimer (III) of 6-hydroxy-2,6-dimethyl-2,4-cyclohexadienone (II) at 145° in the presence of trifluoroacetic acid have been thwarted by the tendency of III to undergo irreversible acid-catalyzed dehydration to VII[2] (23% yield) prior to conversion to monomer.[5] 2,6-Dimethylhydroquinone (IV) could not be isolated from the complex mixture of products obtained under these conditions.



VII

Regardless of the principal path to V, the experimental results indicate that the rate equation for the

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[1] R. D. Chambers, P. Goggin, and W. K. R. Musgrave, *J. Chem. Soc.* 1804 (1959).

[2] E. Adler, J. Dahlen, and G. Westin, *Acta Chem. Scand.*, **14**, 1580 (1960).

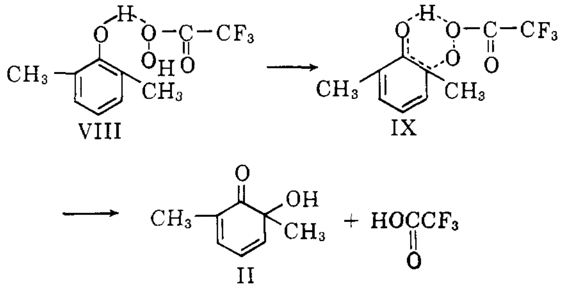
[3] A. S. Kende and P. MacGregor, *J. Am. Chem. Soc.*, **83**, 4197 (1961), have reported that this product is also formed in 22% yield when sodium 2,6-dimethylphenoxide reacts with perchloryl fluoride in dimethylformamide solution.

[4] A. S. Kende and P. MacGregor, *Chem. Ind.* (London), 460 (1962)

[5] The dimer (III) has been reported (ref. 2) to form the stable acetate of 2,6-dimethyl-*o*-quinol on refluxing (140°) with acetic anhydride and sodium acetate.

formation of V contains at least one term having a higher order in oxidizing agent than the corresponding term in the rate equation for the formation of III. Then, in the presence of a high concentration of trifluoroperoxyacetic acid, V would be expected to be the predominant product. When the concentration of oxidizing agent is very low, however, the rate of formation of V would be reduced significantly more than the rate of formation of III so that the latter becomes the major product.

It is our view that the 2,6-dimethyl-*o*-quinol (II) arises from an intermediate (VIII) in which hydrogen bonding anchors the peroxy acid in a position favorable for attack on the ortho carbon atom by the electrophilic peracid oxygen. The hydrogen bonded complex may then proceed *via* cyclic transition state IX to give product II. Analogy for IX exists in the cyclic hydrogen bonded transition state proposed by Henbest[6] to account for the selective *cis* epoxidation of 2-cyclohexenol with perbenzoic acid.



Consistent with this theory is the observation that 2,6-di-*t*-butylphenol fails to yield any 2,6-di-*t*-butyl-*o*-quinol dimer on oxidation with trifluoroperoxyacetic acid under conditions wherein III is obtained from I in moderate yield. Here, the steric requirements of the *t*-butyl groups are too great to permit hydrogen bonding[7,8] between the phenol and trifluoroperoxy acetic acid. Consequently, 2,6-di-*t*-butylbenzoquinone (70% yield) is the only product[9] isolated.

Experimental

Oxidation of 2,6-Dimethylphenol with Hydrogen Peroxide–Trifluoroacetic Acid.—Hydrogen peroxide (0.2 mole of 50–85%) was added in small portions over a 20-hr. period to a stirred solution of 2,6-dimethylphenol (12.2 g., 0.1 mole) and trifluoroacetic acid (4.0 g., 0.035 mole) in 50 ml. of methylene chloride at 25–30°. Stirring was continued at 25° for 8 hr. Then, trifluoroacetic acid (4.0 g., 0.035 mole) was added followed by hydrogen peroxide (0.1 mole of 50–85%) in small portions over a 5-hr. period. The mixture was stirred at 25° for 8 hr. and at 42° for 2–4 hr.

After dilution with methylene chloride the mixture was washed with water and extracted thrice with a 10% sodium bicarbonate solution. The wine-colored alkaline extract was washed twice with methylene chloride and the washings added to the organic solution. Drying and removal of the solvent under vacuum left 8.9–9.4 g. of yellow solid which was leeched with three 20-ml. portions of hot *n*-hexane. The pale yellow, insoluble material (5.3–5.8 g., 39–42% yield) melted at 187–190° and was recrystallized from chloroform to give white plates, m.p. 193–195° (lit., m.p. 194–196°). The melting point of an admixture with 2,6-dimethyl-*o*-quinol dimer (III), prepared by sodium periodate oxidation,[2] was undepressed; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2.88, 5.80, and 5.95 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 242 mμ (ϵ 6990).

Anal. Calcd. for $C_{16}H_{20}O_4$: 69.5; H, 7.30; hydroxyl value, 0.72 $\frac{\text{eg.}}{100\text{ g.}}$; mol. wt., 276. Found: C, 69.8; H, 7.35; hydroxyl value, 0.73 $\frac{\text{eg.}}{100\text{ g.}}$; mol. wt., 278 (ebullioscopic).

The hexane-soluble portion was concentrated to 10 ml. and crystallized to give 3.6 g. (27% yield) of 2,6-dimethylbenzoquinone[1] (V), m.p. 70–71°.

The sodium bicarbonate extract was acidified with 20% sulfuric acid and extracted twice with methylene chloride. After drying and removal of methylene chloride the residue was sublimed to give orange crystals (0.5–1.0 g., 3–7% yield) of 2,6-dimethyl-3-hydroxybenzoquinone (VI) which melted at 101–102° (lit.[10], m.p. 103°) on recrystallization from *n*-hexane.

Anal. Calcd. for $C_8H_8O_3$: C, 63.2; H, 5.30; neut. equiv., 152. Found: C, 63.6; H, 5.45; neut. equiv., 151.

Oxidation of 2,6-Di-t-butylphenol with Hydrogen Peroxide–Trifluoroacetic Acid.—The reaction was carried out and processed in the same manner as that described for 2,6-dimethylphenol with the exception that an additional 0.035 mole of trifluoroacetic acid was added to the reaction mixture when hydrogen peroxide addition was complete. From 20.6 g. (0.1 mole) of 2,6-di-*t*-butylphenol there was obtained, after washing with sodium bicarbonate, 19 g. of a red liquid which crystallized on cooling. Recrystallization from 90% ethanol afforded 15.3 g. (70% yield) of yellow prisms, m.p. 62–63°. After sublimation and recrystallization from ethanol the 2,6-di *t*-butylbenzoquinone melted at 65–66° (lit.,[11] m.p. 65–66°).

Anal. Calcd. for $C_{14}H_{21}O_2$: C, 76.4; H, 9.10. Found: C, 76.8; H, 9.10.

Oxidation of 2,6-Dimethylhydroquinone with Hydrogen Peroxide–Trifluoroacetic Acid.—Hydrogen peroxide (0.2 mole of 85%) was added all at once to a stirred mixture of 2,6-dimethylhydroquinone (13.8 g., 0.1 mole), trifluoroacetic acid (8 g., 0.07 mole), and methylene chloride (200 ml.) at 25°. Stirring was continued at 25° for 24 hr. at which time the mixture was filtered to remove a small amount of intractable solid (m.p. >300°).

The filtrate was washed with water and extracted three times with 10% sodium bicarbonate solution. The wine-colored alkaline extract was washed twice with methylene chloride and the washings added to the organic solution. Drying and removal of the solvent under reduced pressure gave 9.8 g. (72% yield) of V, m.p. 65–68°. Recrystallization from *n*-hexane afforded yellow needles, m.p. 71–72°.

The sodium bicarbonate extract was processed in the same manner as that described for 2,6-dimethylphenol to give 1.5 g. (10% yield) of VI, m.p. 97–100°, after sublimation.

Oxidation of 2,6-Dimethylphenol with Trifluoroperoxyacetic Acid.—A solution of trifluoroperoxyacetic acid[12] (110 ml., 2.1 *M*) in methylene chloride was added dropwise over an 8-hr. period to a stirred mixture of I (12.2 g., 0.1 mole), disodium hydrogen phosphate (120 g., 0.85 mole), and methylene chloride (100 ml.) at 15–20°. Stirring was continued at 20–25° for 2 hr. at which time 98% of the peroxy acid had been consumed. Solids were collected and exhaustively washed with hot methylene chloride.

The methylene chloride solution was processed in the usual manner to afford 5.0 g. (40% yield) of crude III, m.p. 187–190°. Distillation of the hexane soluble portion gave 3.5 g., b.p. 65–80° (3 mm.), which melted at 40–55°. Analysis of the distillate by gas-liquid chromatography at 200° on a column packed with Carbowax 20 M on Fluoropak showed the presence of 2.4 g. (20% yield) of V and 1.1 g. of I.

The solids were dissolved in the sodium bicarbonate extract and the solution acidified with 20% sulfuric acid. Extraction with methylene chloride followed by sublimation afforded 1.0 g (7% yield) of VI, purified by recrystallization from hexane.

Dehydration of Dimer of 2,6-Dimethyl-*o*-quinol (III).—A solution of III (2.76 g., 0.01 mole) and trifluoroacetic acid (0.2 g.) in 60 ml. of toluene in a glass-lined sealed reactor under nitrogen was maintained at 145° for 6 hr. The mixture was

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[6] H. A. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

[7] L. J. Bellamy and R. L. Williams, *Proc. Roy. Soc.*, *A*, **254**, 119 (1960).

[8] G. A. Harlow and D. B. Bruss, *Anal. Chem.*, **30**, 1833 (1958).

[9] This failure to observe dimer is also consistent with another interpretation whereby the initially formed oxidation product, 2,6-di-*t*-butyl-*o*-quinol, might be expected to dimerize much less readily than 2,6-dimethyl-*o*-quinol because of the steric strain introduced into the dimer by the presence of the *t*-butyl groups; see D. Y. Curtin and D. H. Dybvig, *J. Am. Chem. Soc.*, **84**, 225 (1962).

[10] J. D. McClure and P. H. Williams, *J. Org. Chem.*, **27**, 24 (1962).

[11] S. J. Metro, *J. Am. Chem. Soc.*, **77**, 2901 (1955).

[12] W. D. Emmons and G. B. Lucas, *ibid.*, **77**, 2287 (1955).

diluted with ether, washed with 10% sodium bicarbonate, and dried. Solvent was removed on a rotary evaporator under reduced pressure to give 2.3 g. of partially crystalline residue. Crystallization from toluene afforded 1.2 g. of product melting at 130–150°. Recrystallization from chloroform followed by recrystallization from ethanol gave 0.59 g. (23% yield) of VII as white plates, m.p. 170–172° (lit.,[2] m.p. 172–174°); $\lambda_{\max}^{\text{KBr}}$ 2.92, 5.90, 6.21, and 6.33 μ.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.01; mol. wt., 258. Found: C, 73.9; H, 6.91; mol. wt. (mass spectroscopy), 258.

The Preparation of Carbodiimides, Isocyanates, and Isothiocyanates by Metal Ion-assisted Elimination of Mercaptan[1,2]

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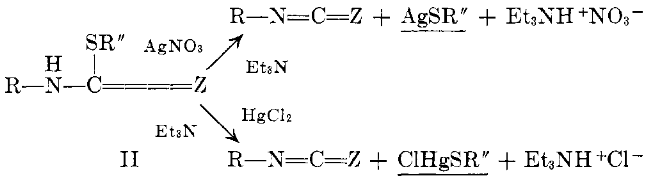
Solutions of reactive intermediates of structure I (carbodiimides, isocyanates, and isothiocyanates) which may be used for subsequent reaction without further treatment may be prepared conveniently by treating compounds of structure II with solutions of silver nitrate or mercuric chloride. An alkyl mercaptan is eliminated in the reaction as an insoluble metal mercaptide. In typical experiments, products of condensation of the intermediates with amines or alcohols were obtained in 50–100% yield.

Compounds of the general structure I, namely the carbodiimides (Z = NR′), the isocyanates (Z = O),

$$R{-}N{=}C{=}Z \qquad Z = NR', \text{O, or S}$$

and the isothiocyanates (Z = S) are widely useful as intermediates,[3] but frequently high reactivity, instability, and/or lachrymatory properties make them difficult to handle in the isolated state.

In the present study it has been found that solutions of intermediates of type I may be prepared by heavy metal ion-assisted elimination of mercaptan from molecules of type II. The elimination is effected by treating a solution of a compound of type II with a solution of silver nitrate or mercuric chloride in the presence of an acid acceptor. The heavy metal mercaptide is formed rapidly under mild conditions and precipitates, leaving a solution of the reactive intermediate which may be used directly for subsequent reaction. The elimination reaction is not without precedent, since strong heating is known to eliminate mercaptan from N,S-disubstituted dithiocarbamates,[4] and elimination of heavy metal sulfides from 1,3-disubstituted thioureas[3b] and dithiocarbamate salts[5] is well known. For small scale synthetic work, however, it is apparent that the new technique offers considerable convenience, since it obviates the necessity for isolating and purifying the reactive intermediate and provides optimum conditions for rapid reaction and high yields. In the discussion which follows, the elimination reaction will be considered primarily in terms of its utility as a synthetic method.



II

Starting materials for the synthesis of the carbodiimides are the 1,2,3-trisubstituted thiopseudoureas[6]; for the isocyanates, the N,S-disubstituted thiolcarbamates[7]; and for the isothiocyanates, the N,S-disubstituted dithiocarbamates.[8] All are prepared by well known methods. The only metal salts which have been found useful for mercaptan elimination are silver nitrate and mercuric chloride. Both are soluble in a fair number of organic solvents, react rapidly with compounds of type II, and given mercaptides insoluble in most organic solvents as long as the alkyl group which is eliminated (R″ in II) is small. Zinc chloride is also soluble in many organic solvents, but usually does not assist the elimination reaction. Acetonitrile and dimethylformamide are the best solvents for the silver nitrate reaction, and acetone, methanol, ethanol, and dimethylformamide for the mercuric chloride reaction. Though dimethyl sulfoxide is a good solvent for both metal salts, large amounts of tarry by-products are formed when it is used. As a matter of convenience, triethylamine has been used most commonly as the acid acceptor.

The elimination reaction is carried out by adding a solution of the metal salt to a solution of the substrate (II) and the acid acceptor at room temperature or below. The reaction is exothermic and sometimes requires cooling. The silver mercaptides precipitate instantly, frequently in very finely divided form. A small amount of diatomaceous earth added to the reaction mixture *before* precipitation of the silver mercaptide gives a more easily filtered solid. Formation of the mercury mercaptides is usually complete in half an hour, and they precipitate in granular form. The alkylmercaptomercuric chloride (RSHgCl) is formed, not the dimercaptide (RSHgSR).[9] When the elimination reaction is complete, carbodiimide and isothiocyanate solutions may be filtered and used directly for

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[1] This work was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Contract no. DA-49-193-MD-2174.

[2] Presented in part at the Thirteenth Annual Kansas City Chemistry Conference, November 17, 1961.

[3] See, for example: (a) I. D. Morton and E. Hoggarth, "Chemistry of Carbon Compounds," Vol. IB, E. H. Rodd, ed., Elsevier Publishing Co., Amsterdam, 1952, pp. 939 and 945; (b) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953); (c) J. R. Schaeffer, *Org. Chem. Bull.*, **33**, No. 2 (1961).

[4] E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1962, p. 239.

[5] Ref. 4, p. 215.

[6] Ref. 4, Vol. I, p. 32.

[7] W. H. Schuller and C. Niemann, *J. Am. Chem. Soc.*, **75**, 3425 (1953).

[8] Ref. 4, Vol. I, p. 923.

[9] The nature of the mercury mercaptide was established by treating 1,3 diphenyl-2-*n*-propyl-2-thiopseudourea with mercuric chloride in acetone. *n*-Propylmercaptomercuric chloride, a compound of known[10] melting point, was obtained in 84% yield.

[10] Ref. 4, Vol. I, p. 145.