gently stirred slurry was maintained at reflux for 36 h under a nitrogen atmosphere. The modified silica was collected by filtration and washed thoroughly with benzene, ethyl acetate, methanol, acetone, ether, and pentane. After vacuum drying, elemental analysis of the CSPs afforded the following.

CSP 2 Anal. Found: C, 7.33; H, 1.00; N, 0.24; Si, 42.62. Calcd: 0.17 mmol of amide/g (based on N); 0.21 mmol of amide/g (based on C).

CSP 3 Anal. Found: C, 8.27; H, 1.07; N, 0.42; Si, 42.08. Calcd: 0.30 mmol/g (based on N); 0.28 mmol/g (based on C).

Acknowledgment. This work has been supported by a grant from the National Science Foundation.

Registry No. (±)-I (X = NH, R_1 = CH_3, R_2 = $COOCH_3$), 74928-18-0; (±)-I (X = NH, R_1 = *i*-C_3H_7, R_2 = $COOCH_3$), 74928-20-4; (±)-I (X = NH, R_1 = *i*-C_4H_9, R_2 = $COOCH_3$), 74928-21-5; (±)-I (X = NH, R_1 = *t*-C_7H_9, R_2 = $COOCH_3$), 90696-95-0; (±)-I (X = NH, R_1 = phenyl, R_2 = $COOCH_3$), 74928-23-7; (±)-I (X = NH, R_1 = benzyl, R_2 = $COOCH_3$), 74928-24-8; (±)-I (X = NH, R_1 = 4-F-benzyl, R_2 = $COOCH_3$), 90696-96-1; (±)-I (X = NH, R_1 = α-naphthyl, R_2 = $COOCH_3$), 90696-97-2; (±)-I (X = NH, R_1 = CH_3, R_2 = CONH-*n*-Bu), 74928-25-9; (±)-I (X = NH, R_1 = *i*-C_3H_7, R_2 = CONH-*n*-Bu), 74928-26-0; (±)-I (X = NH, R_1 = *i*-C_4H_9, R_2 = CONH-*n*-Bu), 74928-27-1; (±)-I (X = NH, R_1 = phenyl, R_2 = CONH-*n*-Bu), 74928-29-3; (±)-I (X = NH, R_1 = benzyl, R_2 = CONH-*n*-Bu), 74928-30-6; (±)-I (X = NH, R_1 = C_2H_5, R_2 = CH_2OH), 90696-98-3; (±)-I (X = NH, R_1 = C_2H_5, R_2 = CH_2OMe), 90696-99-4; (±)-I (X = NH, R_1 = *i*-C_3H_7, R_2 = CH_2OH), 74928-36-2; (±)-I (X = NH, R_1 = phenyl, R_2 = CH_3), 14402-00-7; (±)-I (X = NH, R_1 = phenyl, R_2 = *i*-C_3H_7), 74927-94-9; (±)-I (X = NH, R_1 = benzyl, R_2 = CH_3), 14402-01-8; (±)-I (X = NH, R_1 = *n*-C_4H_9, R_2 = CH_3), 90697-00-0; (±)-I (X = NH, R_1 =*n*-C_5H_{11}, R_2 = CH_3), 90697-01-1; (±)-I (X = O, R_1 = phenyl, R_2 = CH_3), 21286-22-6; (±)-I (X = O, R_1 = phenyl, R_2 = *t*-C_4H_9), 74928-02-2; (±)-I (X = O, R_1 = phenyl, R_2 = *n*-C_4H_9), 90697-02-2; (±)-I (X = O, R_1 = phenyl, R_2 = cyclopropyl), 74928-01-1; (±)-I (X = O, R_1 = 4-Cl-phenyl, R_2 = CH_3), 74928-07-7; (±)-I (X = O, R_1 = 9-anthryl, R_2 = CH_3), 74928-10-2; (*R*)-I (X = NH, R_1 = CH_3, R_2 = $COOCH_3$), 69632-41-3; (*R*)-I (X = NH, R_1 = *i*-C_3H_7, R_2 = $COOCH_3$), 69632-45-7; (*R*)-I (X = NH, R_1 = *i*-C_4H_9, R_2 = $COOCH_3$), 90697-03-3; (*R*)-I (X = NH, R_1 = *t*-C_4H_9, R_2 = $COOCH_3$), 90761-56-1; (*R*)-I (X = NH, R_1 = phenyl, R_2 = $COOCH_3$), 69632-50-4; (*R*)-I (X = NH, R_1 = benzyl, R_2 = $COOCH_3$), 69632-43-5; (*R*)-I (X = NH, R_1 = CH_3, R_2 = CONH-*n*-Bu), 69632-52-6; (*R*)-I (X = NH, R_1 = *i*-C_3H_7, R_2 = CONH-*n*-Bu), 69632-54-8; (*R*)-I (X = NH, R_1 = *i*-C_4H_9, R_2 = CONH-*n*-Bu), 90761-57-2; (*S*)-I (X = NH, R_1 = phenyl, R_2 = CONH-*n*-Bu), 69632-59-3; (*R*)-I (X = NH, R_1 = benzyl, R_2 = CONH-*n*-Bu), 69632-56-0; (*R*)-I (X = NH, R_1 = C_2H_5, R_2 = CH_2OH), 90761-58-3; (*R*)-I (X = NH, R_1 = C_2H_5, R_2 = CH_2OCH_3), 90761-59-4; (*R*)-I (X = NH, R_1 = *i*-C_3H_7, R_2 = CH_2OH), 90761-60-7; (*R*)-I (X = NH, R_1 = phenyl, R_2 = CH_3), 69632-32-2; (*R*)-I (X = NH, R_1 = phenyl, R_2 = *i*-C_3H_7), 69632-36-6; (*S*)-I (X = NH, R_1 = benzyl, R_2 = CH_3), 15719-22-9; (*R*)-I (X = NH, R_1 = benzyl, R_2 = CH_3), 86118-08-3; (*S*)-*N*-(3,5-dinitrobenzoyl)leucine, 7495-01-4; (*S*)-leucine, 61-90-5; 3,5-dinitrobenzoyl chloride, 99-33-2; (*R*)-*N*-(11-(triethoxysilyl)undecanoyl)-α-(6,7-dimethyl-1-naphthyl)isobutylamine, 90697-04-4; (*R*)-*N*-(10-undecenoyl)-α-(6,7-dimethyl-1-naphthyl)isobutylamine, 90761-61-8; triethoxysilane, 998-30-1; (*R*)-*N*-(11-(triethoxysilyl)undecanoyl)-α-(1-naphthyl)ethylamine, 90718-44-8; *N*-(3,5-dinitrobenzoyl)-DL-alanine, 74928-52-2; *N*-(3,5-dinitrobenzoyl)-DL-valine, 74928-53-3; *N*-(3,5-dinitrobenzoyl)-DL-leucine, 74928-54-4; *N*-(3,5-dinitrobenzoyl)-DL-isoleucine, 74928-60-2; *N*-(3,5-dinitrobenzoyl)-DL-*n*-leucine, 90697-05-5; *N*-(3,5-dinitrobenzoyl)-DL-phenylglycine, 74958-71-7; *N*-(3,5-dinitrobenzoyl)-DL-4-OH-phenylglycine, 90697-06-6; *N*-(3,5-dinitrobenzoyl)-DL-methionine, 74928-56-6; *N*-(3,5-dinitrobenzoyl)-(*S*)-alanine, 58248-10-5; *N*-(3,5-dinitrobenzoyl)-(*S*)-valine, 77495-25-1; *N*-(3,5-dinitrobenzoyl)-(*S*)-isoleucine, 90697-07-7; *N*-(3,5-dinitrobenzoyl)-(*S*)-*n*-leucine, 90697-08-8; *N*-(3,5-dinitrobenzoyl)-(*S*)-phenylglycine, 90761-62-9; *N*-(3,5-dinitrobenzoyl)-(*S*)-4-OH-phenylglycine, 90761-63-0; *N*-(3,5-dinitrobenzoyl)-(*S*)-methionine, 58248-12-7.

Oxidation of Phenols with Iodine in Alkaline Methanol

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Received January 24, 1984

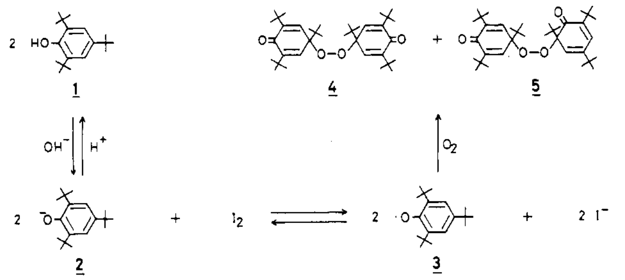
The use of iodine as an oxidizing agent for phenolic compounds has been explored. The reaction has been conducted in methanol containing such alkali as potassium hydroxide and, depending on the nature of the substituents and on the amount of iodine employed, leads to iodination, oxidation to give a stable phenoxy radical, oxidative dimerization, or benzylic oxidation. In general the reaction proceeds smoothly at room temperature, and under appropriate conditions yields of products are good to excellent. Oxidative dimerization of 2,4- and 2,6-di-*tert*-butylphenols involves iodination followed by iodine-catalyzed dimerization. The oxidation of 4-methylphenols with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in methanol has been carried out for comparison.

Iodine under basic condition is a known reagent for iodination of phenols. The reagent has occasionally been reported to bring about oxidative coupling of certain phenolic substances under appropriate conditions,[1,2] but a systematic study on the use of iodine as an oxidizing agent for phenols has not appeared. I have investigated the oxidation of phenols with iodine in alkaline methanol, and this paper reports the results.

Results and Discussion

2,4,6-Tri-*tert*-butylphenol (1). Addition of a methanolic iodine (0.5 molar equiv) solution to a solution of 1 in methanol containing excess potassium hydroxide (KOH) immediately afforded blue 2,4,6-tri-*tert*-butylphenoxy radical 3. Introduction of oxygen into the blue solution gave quinolide peroxides 4 (47%) and 5 (41%) as the al-

Scheme I



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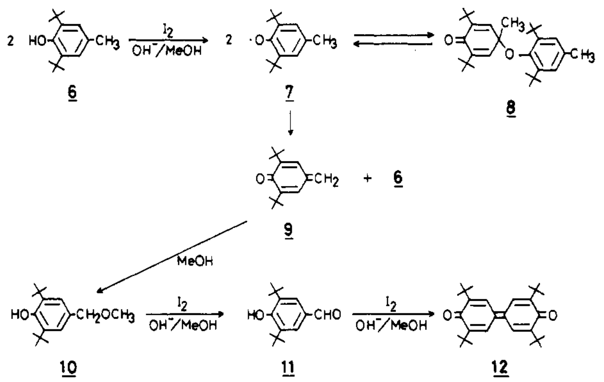
[1] Musso, H. In "Oxidative Coupling of Phenols"; Taylor, W. I., Battersby, A. R., Eds.; Marcel Dekker: New York, 1967; p 1.

[2] Bowman, D. F.; Hewgill, F. R. *J. Chem. Soc. C* 1971, 1777.

0022-3263/84/1949-3046$01.50/0

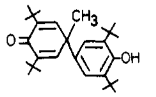
Scheme II



most exclusive products. The reaction of phenolate anion 2 with iodine to produce 3 (and iodide ion) may be reversible, as sodium iodide in acetic acid is known to reduce 3, liberating free 1 and iodine (Scheme I).[3] The unsymmetric peroxide 5 has been recently found by Russian workers in the reaction of 3 with oxygen in benzene.[4] They have obtained 4 and 5 in a ratio of 3:1. The product from the reaction between 1 and bromine in alkaline methanol is 2,4,6-tri-*tert*-butyl-4-methoxy-2,5-cyclohexadien-1-one.[5]

2,6-Di-*tert*-butyl-4-methylphenol (6). Upon dropwise addition of a methanolic iodine (0.5 molar equiv) solution to a solution of 6 in methanol containing KOH, the reaction mixture exhibited a transitory light blue-greenish color, indicative of formation of the corresponding phenoxy radcal 7, which soon disappeared and an almost colorless substance began to precipitate. The precipitate, isolated in 93% yield by filtration, was 4-phenoxy-2,5-cyclohexadien-1-one 8, a product of dimerization of 7 by C–O coupling. Dimer 8 had been prepared earlier by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[6] or by copper–amine-catalyzed autoxidation[7] of 6. It is notable that these reactions are conducted in methanol in which 8, unstable in solution, is poorly soluble. If filtration was omitted in the above experiment and the reaction mixture containing the precipitate of 8 was continuously stirred, it gradually disappeared until a homogeneous solution was obtained. From the ether extract of the solution poured into water, 6 (41%) and 2,6-di-*tert*-butyl-4-(methoxymethyl)phenol (10) (44%) were isolated. This is interpreted in terms of dissociation of 8 into 7 by equilibrium, which disproportionates into equimolar amounts of 6 and quinone methide 9 that adds the solvent to form 10 (Scheme II).[6] The oxidation of ether 10 with iodine (1 molar equiv) under the basic condition gave 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (11) quantitatively. As expected from these results, 11 was obtained in high yield (83%) if 6 was oxidized with 2 molar equiv of iodine. In this case the primary product 8 was found to disintegrate very rapidly; the precipitate of 8 in the reaction mixture had for the most part disappeared when dropwise addition of iodine to the phenol 6 solution was complete. This indicates that iodine can not only oxidize 6 to 7 which dimerizes to 8, but also accelerate the collapse of 8. It is assumed that iodine either catalyzes dissociation of 8 to 7 or interrupt the reverse reaction, thus shifting the equilibrium between the two in favor of 7, or that it oxidizes 7 to give 10 possibly via 9. Aldehyde 11 was obtained also in high yield (85%) when anhydrous potassium carbonate (K_2CO_3) was used as alkali in place of KOH in the reaction of 6 with iodine (2 molar equiv). Use of excess iodine, however, ought to be avoided for the preparation of 11 from 6 or 10, since 11 was found to react with iodine in alkaline (KOH) methanol to yield 3,5,3′,5′-tetra-*tert*-butyl-4,4′-diphenoquinone (12) by a slow but quantitative process. The oxidation of 6 with bromine gives 11 in *tert*-butyl alcohol or in acetic acid–water but affords 2,6-di-*tert*-butyl-4-methoxy-4-methyl-2,5-cyclohexadien-1-one in methanol.[8]

Dimer 8 could also be prepared in high yield (over 90%) by oxidation of 6 with aqueous iodine (0.5 molar equiv to excess) and potassium iodide (KI) in a solvent mixture of methanol and ethylenediamine (EDA) as base. It is noteworthy that addition of ether (or benzene) to a reaction mixture containing a precipitate of 8, thus prepared in situ by employing excess iodine, led to rapid degradation of 8 and gave 2,6-di-*tert*-butyl-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-methyl-2,5-cyclohexadien-1-one (13) (40%) and 4,4′-dihydroxy-3,5,3′,5′-tetra-*tert*-butylbiphenyl (14) and 2,6-di-*tert*-butyl-1,4-benzoquinone (15) as the minor products. Without addition of ether, 8 survived for a relatively long time under these conditions. Decomposition of pure 8 by dissolution in ether in the presence or absence of iodine or oxygen afforded none of these demethylated products but gave a mixture of products including 1,2-bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethane (16) and 3,5,3′,5′-tetra-*tert*-butylstilbene-4,4′-quinone (17) as well as 6. Demethylated dimer 13 has been only a minor product from oxidation with a metal peroxide[9] or autoxidations[10-12] of 6, although Hewitt has reported that high-yield conversion of 6 to 13 can be achieved by the autoxidation using a copper–amine catalyst under appropriate conditions.[7]



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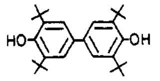

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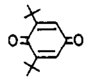

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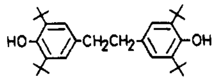

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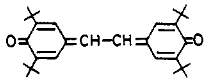

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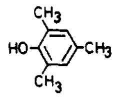
2,4,6-Trimethylphenol (18). The reaction of 18 with iodine (1 molar equiv) and KOH was rapid and gave 2,6-dimethyl-4-(methoxymethyl)phenol (19) in excellent yield (84%) as well as 3,5-dimethyl-4-hydroxybenzaldehyde (20) (5%) and recovered 18 (2%). Methyl ether 19 has been



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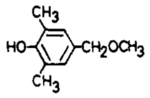

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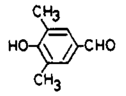

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(3) (a) Cook, C. D. *J. Org. Chem.* **1953**, *18*, 261. (b) Müller, E.; Ley, K. *Chem. Ber.* **1954**, *87*, 922.

(4) (a) Roginskii, V. A.; Plekhanova, L. G.; Dubinskii, V. Z.; Nikiforov, G. A.; Miller, V. B.; Ershov, V. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 1327. (b) Batanov, I. A.; Nikiforov, G. A.; Ershov, V. V. *Ibid.* **1982**, 359.

(5) Laufer, R. J. DOS Patent 2116904, 1970; *Chem. Abstr.* **1972**, *76*, 33866. Cf. also: Müller, E.; Ley, K.; Kiedaisch, W. *Chem. Ber.* **1954**, *87*, 1605.

(6) Becker, H.-D. *J. Org. Chem.* **1965**, *30*, 982.

(7) Hewitt, D. G. *J. Chem. Soc. C* **1971**, 2967.

(8) Coppinger, G. M.; Campbell, T. W. *J. Am. Chem. Soc.* **1953**, *75*, 734.

(9) Sugita, J. *Nippon Kagaku Zasshi* **1966**, *87*, 1082; *Chem. Abstr.* **1967**, *66*, 94777.

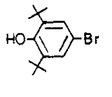
(10) Kharasch, M. S.; Joshi, B. S. *J. Org. Chem.* **1957**, *22*, 1439.

(11) Benjamin, B. M.; Raaen, V. F.; Hagaman, E. W.; Brown, L. L. *J. Org. Chem.* **1978**, *43*, 2986.

(12) Orlando, C. M., Jr. *J. Org. Chem.* **1968**, *33*, 2516.

prepared only in fair yield by pernitrous acid oxidation of **18** in methanol.[13] As an alternative method for preparing **19**, the DDQ (1 molar equiv) oxidation of **18** in methanol[6] was attempted, affording **19** (62%), **20** (19%), and **18** (10% recovery). The reaction of **18** with 2 molar equiv of iodine yielded **20** (83%). Phenol **18** can be transformed into **20** by various oxidants,[6,14] but the iodine method appears to be most preferable on the basis of yield, ease of manipulation, and cost per equivalent. Bromine in acetic acid–water is a poor reagent for conversion of **18** into **20**.[14e]

2,6-Di-*tert*-butylphenol (21). It was found that **21** is first iodinated to yield 2,6-di-*tert*-butyl-4-iodophenol (**22**), which then is rapidly converted into diphenoquinone **12** by an iodine-catalyzed process. Slightly more than 1 molar equiv of iodine, therefore, was required in order to covert all of **21** into **12**. The catalytic reaction possibly proceeds via the intermediacy of bi(iodocyclohexadienone) **23** which has been believed to be extremely labile at least near room temperature and spontaneously deiodinated to generate **12** (Scheme III).[15] 2,6-Di-*tert*-butyl-4-bromophenol (**24**) was also catalytically and exclusively converted to **12** by iodine in methanol containing excess KOH. Bi(bromocyclohexadienone) **25**,[6,15] structurally analogous to **23** but relatively stable in neutral solution, was sensitive to base and prone to spontaneously decompose into **12**. Under a carefully controlled condition with a limited amount of EDA as base, however, **25** was isolated as a mixture with **12** from the reaction of **24** and aqueous iodine–KI in methanol (see Experimental Section). This fact implies that the transformation of **24** into **12** indeed proceeds by way of **25**. Polymerization of some 4-halogenophenolates to yield poly(1,4-phenylene oxides) can be catalyzed by iodine.[16]



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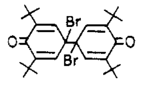

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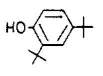
2,4-Di-*tert*-butylphenol (26). If phenol **26** was allowed to react, for example, with 0.995 molar equiv of iodine, the reaction terminated after rapidly affording 2,4-di-*tert*-butyl-6-iodophenol (**27**) in 90% yield. A similar reaction of **26** for 1 h using 1.06 molar equiv of iodine, on the other hand, gave **27** (30%) and oxepinobenzofuran **28** (61%). The reaction was faster with 1.4 molar equiv of iodine, and **28** was isolated in high yield (83%). The reaction of the primary product **27** to yield **28** is also an iodine-initiated process which, however, is relatively slow. Oxepinobenzofuran **28** has been assumed to arise from 2,2′-diphenoquinone **29** by spontaneous valence isomerization,[17] and it has lately been argued that **28** is in equilibrium with other forms of valence isomers.[18]



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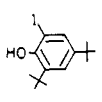

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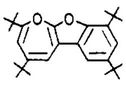

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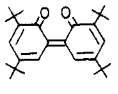

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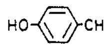
***p*-Cresol (30).** With 4 molar equiv of iodine, the reactioin of **30** in methanol containing KOH gave 2,6-diiodo-4-(methoxymethyl)phenol (**32**) (12%), but the major product was 2,6-diiodo-4-methylphenol (**31**) (74%). The first 2 mol of iodine were rapidly consumed for the ortho iodination of **30**, but the consumption became slow thereafter. The persistant brown color of the reaction mixture, indicative of the existence of iodine, disappeared in 2 h, when the reaction was interrupted. A large part of the last 2 mol of iodine was thus used for other iodine-consuming reactions than the oxidation of the methyl group of diiodophenol **31** to give **32**. Yield of **32** was improved (34%) at the expense of **31** (14%) by conducting the reaction of **30** for 1.5 h using a large excess (ca. 14 molar equiv) of iodine. The use of K_2CO_3 as base in place of KOH did not lead to the substantial improvement of the reaction. Methyl ether **32** was obtained finally in good yield (62%) by employing sodium methoxide (MeONa) as base in the reaction using the large excess of iodine. In none of the experiments was 3,5-diiodo-4-hydroxybenzaldehyde (**33**) obtained. The DDQ (1 molar equiv) oxidation of **31** in methanol gave a complex mixture of products, from which **32** (29%) was isolated but no **33** was found. As a synthetic tool for **32**, the iodine method is more convenient than the DDQ method, as it can be prepared in one flask directly from **30** and in higher yield.



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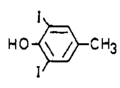

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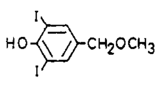

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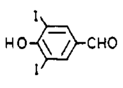
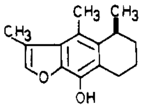
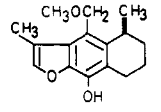


33

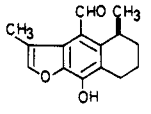
Cacalol (34). Finally the iodine oxidation was applied to cacalol (**34**), the major sesquiterpenic constituent of *Cacalia delfiniifolia* Sieb. et Zucc., which contains a *p*-cresol moiety.[19] The reaction of **34** with iodine (1 molar equiv) in methanol containing MeONa as base was rapid and afforded 11-methoxycacalol (**35**) in 62% yield. Methyl ether **35** was obtained in lower yield (28%) if K_2CO_3 was employed in place of MeONa. With 2 molar equiv of iodine, a similar oxidation of **34** using MeONa yielded cacalal (**36**), another sesquiterpene isolated from the same plant,[20] albeit in poor yield (0.8%). The reaction of **34** and DDQ (1 molar equiv) in methanol was fast but complex and gave **35** in low yield (15%) and 2,3-dichloro-5,6-dicyanohydroquinone (DDQH$_2$) (97%). With 2 molar equiv of DDQ, a similar reaction of **34** afforded no **36** while DDQ was recovered as DDQH$_2$ (98%).



34



35



36

The results presented in this paper would suffice to prove that iodine in methanol containing such alkali as KOH or MeONa is useful not only for oxidative coupling of phenolic substances but also for benzylic oxidation of 4-alkylphenols. As typically shown in the reaction of **30** to yield **32** via **31**, the oxidation of the alkyl group of an ortho-unsubstituted 4-alkylphenol is preceded by the faster ortho iodination, and an excess of iodine will be required

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[13] Ershov, V. V.; Zlobina, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1965**, 1675. Cf. also: McNelis, E. *J. Am. Chem. Soc.* **1966**, *88*, 1074.

[14] (a) Itahara, T.; Sakakibara, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 631. (b) Nishinaga, A.; Itahara, T.; Matsuura, T. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 356. (c) Kon, E.; McNelis, E. *J. Org. Chem.* **1975**, *40*, 1515. (d) Ershov, V. V.; Zlobina, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, 2235. (e) Ershov, V. V.; Volod'kin, A. A.; Nikiforov, G. A.; Dyumaev, K. M. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1962**, 1839.

[15] Ley, K.; Müller, E.; Mayer, R.; Scheffler, K. *Chem. Ber.* **1958**, *91*, 2670.

[16] (a) Hunter, W. H.; Seyfried, L. M. *J. Am. Chem. Soc.* **1921**, *43*, 151. (b) Staffin, G. D.; Price, C. C. *Ibid.* **1960**, *82*, 3632.

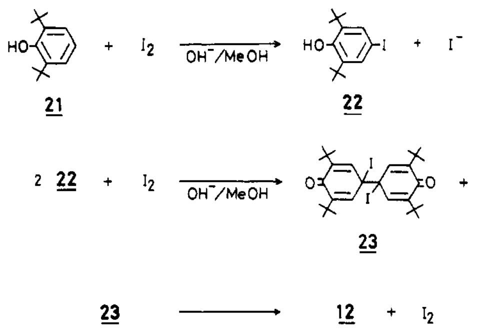
[17] Meyer, H.; Schneider, H.-P.; Rieker, A.; Hitchcock, P. B. *Angew. Chem.* **1978**, *90*, 128.

[18] Becker, H.-D.; Gustafsson, K.; Raston, C. L.; White, A. H. *Aust. J. Chem.* **1979**, *32*, 1931. Cf. also: Becker, H.-D.; Lingert, H. *J. Org. Chem.* **1982**, *47*, 1095.

[19] Naya, K.; Miyoshi, Y.; Mōri, H.; Takai, K.; Nakanishi, M. *Chem. Lett.* **1976**, 73.

[20] Naya, K.; Takai, K.; Nakanishi, M.; Omura, K. *Chem. Lett.* **1977**, 1179.

Scheme III



when the rate of oxidation of a phenol is low since other slow processes become competitive that consume iodine. The iodination in the reactive ortho position, however, may contribute to supress side reactions which otherwise accompany and complicate the oxidation reaction of the 4-alkyl group. The ortho iodine may, if necessary, be easily removed by the conventional method. The iodine oxidation of the alkyl group of *o*-alkylphenols is presumably slow, if at all, as only the *p*-methyl group of 18 is oxidized. The reaction of 18 with many other oxidants also results in the exclusive para oxidation.[6,14] As far as the nature of the products is concerned, the iodine oxidation of phenols in alkaline methanol is often comparable with the DDQ oxidation in methanol, but it often gives the products of benzylic oxidation in higher yield. In addition, iodine is inexpensive. The iodine method, however, will be disfavored particularly when the desired product is unstable under the basic condition, as illustrated in the attempted preparation of 25 from 24. The iodine oxidation of phenols was studied under other basic conditions as well, but it was in general less effective and appeared to be less attractive than that in alkaline methanol (see Experimental Section). Evidence for the phenoxy radical formation was obtained in some cases, but it remained uncertain whether it is involved in all of the iodine oxidation of phenols investigated.

Experimental Section

All melting points are uncorrected. IR spectra were taken with a Hitachi EPI-G3 spectrophotometer. ^{1}H NMR spectra were obtained on a Hitachi R-20B spectrometer operating at 60 MHz. Column chromatography was conducted by using Merck silica gel 60. TLC was run on silica gel.

Materials. Methanol and EDA were distilled and the heart cuts were stored in sealed bottles. Other reagents were used as purchased unless otherwise described.

General Procedure. To a stirred solution of a phenol (2 mmol) in methanol (10–15 mL) containing alkali (ca. 15 mmol), was dropwise added a solution of iodine (1–4 mmol) in methanol (5–10 mL) under nitrogen over a period of ca. 10 min. The mixture was stirred for an appropriate time under nitrogen. The reaction mixture was poured into water, made weakly acid with dilute HCl, and extracted with ether. In case residual iodine was taken up into the ether extract, it was treated with an aqueous $NaHSO_3$ solution. The extract was washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to leave a residual mixture of products.

Oxidation of 2,4,6-Tri-*tert*-butylphenol (1). A reaction of 1 (524 mg, 2 mmol) was conducted for 10 min by using iodine (256 mg, 1 mmol) and KOH (0.82 g) in methanol (20 mL in total). Upon dropwise addition of the deep brown iodine solution, the initially colorless alkaline solution containing 1 immediately turned blue. Oxygen was bubbled through the reaction mixture for 10 min, when the deep blue color of phenoxy radical 3 was discharged and a crystalline mixture of quinolide peroxides 4 and 5 was precipitated. The whole reaction mixture was poured into water and extracted with ether. The extract was washed with water, dried, and evaporated to leave a crystalline residue (559 mg) which consisted of 4 and 5 almost exclusively (TLC). An aliquot (203 mg) of the residue was chromatographed on a silica gel plate developed with petroleum ether–benzene (10:3) to give yellow crystals of 4 (94 mg, 47%), identical with an authentic sample[21] (mp, IR, ^{1}H NMR, and TLC), mp 139–140.5 °C dec (after recrystallization from ethanol) as well as yellow crystals of 5 (83 mg, 41%), mp 131–132 °C dec (ethanol) (lit.[4a] mp 129–129.5 °C dec).

Oxidation of 2,6-Di-*tert*-butyl-4-methylphenol (6). A reaction of 6 (440 mg, 2 mmol) was carried out by using iodine (254 mg, 1 mmol), KOH (0.91 g), and methanol (20 mL). Upon dropwise addition of the iodine solution, the alkaline solution containing 6 produced a transient light green color which soon disappeared, and an almost colorless substance began to precipitate. After addition of iodine, the precipitate was collected by means of filtration and washed quickly with a little water and methanol to give colorless crystals of dimer 8 (408 mg, 93%), identical with an authentic sample[6] (mp and IR), mp 87–89 °C dec.

The reaction was repeated. Isolation of 8 by filtration was omitted and the mixture was stirred for 2 h under nitrogen until the precipitate of 8 disappeared. The reaction mixture was worked up according to the general procedure to leave a residue, which was chromatographed on a column containing silica gel (15 g). Elution with petroleum ether afforded 6 (179 mg, 41% recovery) followed by methyl ether 10 (218 mg, 44%): mp 100–101 °C (diisopropyl ether) (lit.[22] mp 99.5 °C).

A reaction of 6 (443 mg, 2 mmol) was carried out by using iodine (1.02 g, 4 mmol), KOH (0.89 g), and methanol (25 mL). A precipitate of 8, formed during addition of iodine, had for the most part disappeared when the addition was complete. The nearly homogeneous mixture was stirred for 25 min. A crystalline residue was recrystallized from ethyl acetate to afford colorless crystals of 11 (325 mg, 69%): mp 185–187 °C (lit.[8] mp 189 °C). The filtrate was evaporated to leave a residue, which was chromatographed on a column containing silica gel (15 g) with petroleum ether–ether (25:1) to yield additional 11 (66 mg, 14%).

2,6-Di-*tert*-butyl-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-methyl-2,5-cyclohexadien-1-one (13). To a stirred solution of 6 (440 mg, 2 mmol) in a solvent mixture of methanol (5 mL) and EDA (5 mL) was added dropwise under nitrogen a solution of iodine (1.27 g, 5 mmol) and KI (2.62 g) in water (7 mL) over a 10-min period. Precipitation of 8 was rapid. After addition of iodine, ether (25 mL) was added to the mixture containing 8.[23] The mixture was vigorously stirred for 40 min under nitrogen. The ethereal layer was separated, washed with an aqueous $NaHSO_3$ solution followed by water, dried, and evaporated to leave an oily residue, crystallization of which from diisopropyl ether gave colorless crystals of 13 (82 mg, 19%): mp 154–156.5 °C (lit.[12] mp 154–156 °C). The structure was ascertained by elemental analysis (Calcd for $C_{29}H_{44}O_2$: C, 82.02; H, 10.44. Found: C, 82.04; H, 10.44) and mass spectrum [*m/e* 424 (M^+)] as well as by the ^{1}H NMR and IR spectra. The filtrate obtained after isolation of 13 was evaporated to leave an oily residue, which was chromatographed on a column containing silica gel (40 g). Elution with petroleum ether gave additional 13 (89 mg, 21%). Other products isolated in smaller quantities by the chromatography are 4,4′-dihydroxybiphenyl 14, identical with an authentic sample[10] (mp, IR, ^{1}H NMR, and TLC), mp 181–182 °C, and *p*-benzoquinone 15, mp 66–68 °C (lit.[24] mp 67–68 °C). Decomposition of pure 8 (0.94 mmol) in ether (10 mL) for 40 min under nitrogen afforded 6 (27%), 1,2-bis(4-hydroxyphenyl)ethane 16 (42%), mp 167–168 °C (lit.[25] mp 169–170 °C), and 4,4′-stilbenequinone 17 (19%), mp 307–308 °C (lit.[25] mp 315–316 °C).

Oxidation of 2,4,6-Trimethylphenol (18). A reaction of 18 (272 mg, 2 mmol) was conducted for 10 min by using iodine (514 mg, 2 mmol), KOH (0.87 g), and methanol (20 mL). An oily

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[21] Cook, C. D.; Woodworth, R. C. *J. Am. Chem. Soc.* **1953**, *75*, 6242.

[22] Kharasch, M. S.; Joshi, B. S. *J. Org. Chem.* **1957**, *22*, 1435.

[23] Unless ether was added, 8, virtually insoluble in the solvent mixture, was stable in the presence of excess iodine under the condition and collected in high yield (over 90%) by filtration even after the reaction mixture was stirred for 8 h.

[24] Müller, E.; Ley, K. *Chem. Ber.* **1955**, *88*, 601.

[25] Cook, C. D.; Nash, N. G.; Flanagan, H. R. *J. Am. Chem. Soc.* **1955**, *77*, 1783.

residue was chromatographed on a column containing silica gel (20 g) with petroleum ether–ether (20:1), giving **18** (4 mg, 2% recovery) and colorless crystals of methyl ether **19** (279 mg, 84%): mp 57–59 °C (petroleum ether–diisopropyl ether) (lit.[13] mp 56–58 °C); ^{1}H NMR (CDCl$_3$) δ 2.18 (s, 6 H), 3.32 (s, 2 H), 4.29 (s, 3 H), 5.20 (br s, 1H), 6.89 (s, 2 H); IR (CHCl$_3$) 3580, 3380, 1488, 1197, 1154, 1095, 870 cm^{-1}. Further elution afforded colorless crystals of 4-hydroxybenzaldehyde **20** (14 mg, 5%): mp 114–116 °C (benzene) (lit.[6] mp 114–115 °C). A similar reaction of **18** (273 mg, 2 mmol) for 2 h using iodine (1.04 g, 4.1 mmol), KOH (0.87 g), and methanol (20 mL) gave **20** (246 mg, 83%).

With DDQ in Methanol. A reaction of **18** (136 mg, 1 mmol) and DDQ (227 mg, 1 mmol) in methanol (6 mL) was conducted for 13 h according to the procedure described by Becker for the oxidation of **18** with 2 molar equiv of DDQ in methanol.[6] An oily residue obtained after removal of DDQH$_2$ (230 mg, quantitative) was chromatographed on a silica gel plate developed with petroleum ether–ether (1:1), giving **18** (13 mg, 10% recovery), **19** (103 mg, 62%), and **20** (28 mg, 19%).

Reactions of 2,6-Di-*tert*-butylphenol (21) and 2,6-Di-*tert*-butyl-4-halophenols (22 and 24). A reaction of **21** (413 mg, 2.00 mmol) was conducted for 15 min by using iodine (512 mg, 2.02 mmol), KOH (0.87 g), and methanol (21 mL). The reaction mixture was filtered to give reddish brown crystals of 4,4′-diphenoquinone (407 mg, quantitative): mp 240–241 °C (benzene) (lit.[10] mp 246 °C). A similar reaction of **21** employing 0.97 molar equiv of iodine terminated rapidly after yielding **21** (2% recovery), 4-iodophenol **22** (28%), and **12** (70%).

A reaction of **22**[15,26] (332 mg, 1 mmol) was conducted for 5 min by using iodine (16 mg, 0.06 mmol), KOH (0.65 g), and methanol (17 mL). The reaction mixture was filtered to give **12** (204 mg, quantitative).

To a stirred solution of 4-bromophenol **24**[15] (157 mg, 0.55 mmol) in methanol (5 mL) was added at one time a solution of iodine (68 mg, 0.27 mmol) and KI (0.16 g) in water (3 mL) under nitrogen. To the mixture was added dropwise a solution of EDA (15 mg, 0.25 mmol) in methanol (5 mL) over a 2-min period. After the mixture was stirred for 20 min under nitrogen, it was filtered to give **12** (60 mg, 54%). The filtrate was poured into water and extracted with ether. The extract was washed with an aqueous NaHSO$_3$ solution and water, dried, and evaporated to leave a semisolid, which was treated with a little methanol. The insoluble crystals (40 mg), isolated by filtration, were a mixture of bi(bromocyclohexadienone) **25** and **12** (TLC), the former being the major component as shown by comparing the IR spectrum with that of an authentic mixture of **25**[6] and **12**.

Reaction of 2,4-Di-*tert*-butylphenol (26). A reaction of **26** (413 mg, 2.00 mmol) was conducted for 1 h by using iodine (538 mg, 2.12 mmol), KOH (0.83 g), and methanol (20 mL). The reaction mixture was filtered to give yellow crystals of oxepinobenzofuran **28** (155 mg, 38%), identical with an authentic sample[27] (mp, IR, and ^{1}H NMR), mp 150–154 °C dec (dioxane). The filtrate was poured into water and extracted with ether. The extract was washed with an aqueous NaHSO$_3$ solution and water, dried, and evaporated to leave an oily residue, which was crystallized with a little methanol. Filtration afforded additional **28** (94 mg, 23%). The methanol filtrate was evaporated to leave an oily residue, from which 6-iodophenol **27** (202 mg, 30%) was isolated by column chromatography, mp 76–78 °C (ethanol) (lit.[27] mp 76–78 °C). A similar reaction of **26** (413 mg, 2 mmol) for 25 min using iodine (714 mg, 2.8 mmol), KOH (0.83 g), and methanol (23 mL) gave **28** (340 mg in total, 83%). Phenol **27** was hardly obtained.

Reaction of *p*-Cresol (30). To a solution of **30** (219 mg, 2 mmol) in methanol (20 mL) containing MeONa (4.23 g) was added portionwise iodine (7.28 g, 29 mmol) over a 5-min period. The brown solution (due to iodine) was stirred for 1.5 h until it became pale yellow. A crystalline residue was chromatographed on a column containing silica gel (25 g) with petroleum ether–ether (20:1), affording colorless crystals of 2,6-diiodo-4-methylphenol (**31**) (157 mg, 22%), mp 60–62 °C (petroleum ether) (lit.[28] mp 59–59.5 °C). Further elution gave colorless crystals of 2,6-diiodo-4-(methoxymethyl)phenol (**32**) (488 mg, 62%): mp 97–99 °C (diisopropyl ether); ^{1}H NMR (CDCl$_3$) δ 3.36 (s, 3 H), 4.30 (s, 2 H), 5.71 (br s, 1 H), 7.65 (s, 2 H); IR (CHCl$_3$) 3480, 1465, 1195, 1162, 1100 cm^{-1}; mass spectrum, *m/e* 390 (M$^+$). Anal. Calcd for $C_8H_8I_2O_2$: C, 24.64; H, 2.07. Found: C, 24.62; H, 2.08. Aldehyde **33** was not found.

Oxidation of Cacalol (34). A reaction of **34**[29] (460 mg, 2 mmol) was conducted for 5 min with iodine (511 mg, 2 mmol), MeONa (1.17 g), and methanol (25 mL). An oily residue was chromatographed on a column containing silica gel (30 g) with petroleum ether–ether (20:1) to give an oily mixture (19 mg) containing **34**. Further elution afforded 11-methoxycacalol (**35**) (321 mg, 62%) as a nearly colorless liquid, identical with an authentic sample[29] (IR, ^{1}H NMR, and TLC).

A reaction of **34** (460 mg, 2 mmol) was conducted for 50 min with iodine (1.02 g, 4 mmol), MeONa (1.17 g), and methanol (25 mL). A residue was chromatographed to give **35** (49 mg, 9%) and an oily mixture (31 mg) containing cacalal (**36**). The oil was chromatographed on a silica gel plate developed with petroleum ether–ether (1:1) to give colorless crystals of **36** (4 mg, 0.8%), identical with a natural specimen[29] (admixture mp, IR, and TLC), mp 154–157 °C (diisopropyl ether).

Reactions of Phenols with Iodine under Other Basic Conditions. To a stirred solution of a phenol (2 mmol) in a solvent mixture of methanol (5–10 mL) and EDA (5 mL) was added dropwise a solution of iodine (1–4 mmol) and KI (ca. 3 molar equiv with respect to iodine) in water (5–10 mL) over a ca. 10-min period. The mixture was stirred for an appropriate time under nitrogen. By this standard procedure,[30] **1** was converted to **3** almost quantitatively only by employing excess iodine (1.5 molar equiv). Dimer **8** was obtained in high yield from the reaction of **6** with iodine (0.5 molar equiv). Phenol **21** was led to **12** via **22**, but a relatively large quantity of iodine was required to complete the latter catalytic process. The reaction of **26** with iodine (1.5 molar equiv) only gave apparently intractable material except **27** (26%), and that of **18** with 2 molar equiv of iodine resulted in the formation of a complex reaction mixture containing a trace amount of **20**.

To a stirred mixture of ether (10 mL) and water (10 mL) containing a phenol (2 mmol) and KOH (ca. 15 mmol), was added dropwise a solution of iodine (4 mmol) in ether (15 mL) over a ca. 15-min period, and the heterogeneous mixture was stirred vigorously for an appropriate time under nitrogen. By this standard procedure,[31] **6** was recovered intact after reaction for 15 h, and **18** was led to a complicated mixture of products from which **20** was isolated in 9% yield.

Acknowledgment. This work was generally supported by Professor Keizo Naya of the Department of Chemistry, Faculty of Science, Kwansei Gakuin University, to whom I expresses my gratitude. I am indebted to the Analytical Centers of Toyo Jozo & Co., Ltd., and of Faculty of Science, Osaka City University, for elemental analyses and mass spectral determinations.

Registry No. **1**, 732-26-3; **2**, 18995-30-7; **3**, 2525-39-5; **4**, 1975-14-0; **5**, 56501-19-0; **6**, 128-37-0; **7**, 6858-01-1; **8**, 2179-51-3; **9**, 2607-52-5; **10**, 87-97-8; **11**, 1620-98-0; **12**, 2455-14-3; **13**, 14387-13-4; **14**, 128-38-1; **15**, 719-22-2; **16**, 1516-94-5; **17**, 809-73-4; **18**, 527-60-6; **19**, 5048-02-2; **20**, 2233-18-3; **21**, 128-39-2; **22**, 40084-31-9; **23**, 91084-20-7; **24**, 1139-52-2; **25**, 2179-38-6; **26**, 96-76-4; **27**, 89209-02-9; **28**, 65355-46-6; **29**, 91084-21-8; **30**, 106-44-5; **31**, 2432-18-0; **32**, 91084-22-9; **34**, 24393-79-1; **35**, 24393-79-1; **36**, 65080-19-5; I$_2$, 7553-56-2.

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(26) The melting point (88–90 °C) was considerably higher than that reported (76.5–78.5 °C[15]) for **22**. The pure sample was obtained after repeated recrystallization. The structure for **22** was substantiated by elemental analysis (Calcd for $C_{14}H_{21}OI$: C, 50.61; H, 6.37. Found: C, 50.55; H. 6.48) and mass spectrum [*m/e* 332 (M$^+$)], as well as by the ^{1}H NMR and IR spectra.

(27) Müller, E.; Mayer, R.; Narr,;B. Rieker, A.; Scheffler, K. *Liebigs Ann. Chem.* **1961**, *645*, 25. Cf. ref 17.

(28) Cambie, R. C. Rutledge, P. S.; Smith-Palmer, T.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1161.

(29) The samples of cacalol (**34**), 11-methoxycacalol (**35**), and cacalal (**36**) were generously provided by Professor Naya. Compound **35** has been prepared in his laboratory by transformation of **36** (unpublished work).

(30) Cf.: Potts, K. T. *J. Chem. Soc.* **1953**, 3711, and ref 2.

(31) Cf. ref 2.