Some Oxidations of 3-t-Butyl-4-dimethylaminophenol

By **D. F. Bowman** and **F. R. Hewgill,*** Department of Organic Chemistry, University of Western Australia, Nedlands, Western Australia, 6009

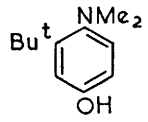
Chemical evidence is presented for the formation of an intermediate quinoneimonium cation on oxidation of 3-t-butyl-4-dimethylaminophenol by silver oxide in ether or by bromine in aqueous acetic acid. In the former case subsequent reaction leads to an aminoquinoneimonium salt, in the latter to 2-bromo-5-t-butyl-1,4-benzoquinone. The mechanisms of these reactions are discussed.

SINCE the discovery by Willstätter and Pfannenstiel [1] of the formation of easily hydrolysed quinoneimines on oxidation of 4-aminophenol and 4-methylaminophenol, a number of studies [2] of the behaviour of *p*-aminophenol at various electrodes indicate that its oxidation in acid or alkaline solution involves a reversible two-electron transfer, followed by a rate-controlling hydrolysis of the quinoneimine to *b*-benzoquinone. Comparable studies appear not to have been made for 4-dimethylaminophenol. The marked effect of a *p*-methoxy-group [3] on the oxidative behaviour of phenols has led us to examine the more strongly electron-donating dimethylamino-group. 3-t-Butyl-4-dimethylaminophenol (I) appeared particularly suitable for study, as oxidation of its methoxy-analogue gave high yields of the quinone in acid solution [4] and of the trimeric spiroketal in basic solution.[5]

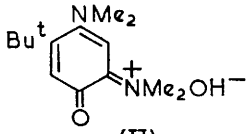
Preferential *N*-methylation of 4-amino-3-t-butylphenol, which usually produces the quaternary ammonium salt,[6] gave the dimethylamino-compound (I) directly. Oxidation of phenol (I) by alkaline ferricyanide gave t-butyl-1,4-benzoquinone (12%) and an intractable red gum which could not be purified. The same quinone was the product (87%) of oxidation with acidified ceric sulphate. Oxidation with silver oxide in ether also gave

[1] R. Willstätter and A. Pfannenstiel, *Ber.*, 1904, **37**, 4605; 1905, **38**, 2244.
[2] J. B. Conant and M. F. Pratt, *J. Amer. Chem. Soc.*, 1926, **48**, 3178; I. E. Knoblock, *Coll. Czech. Chem. Comm.*, 1949, **14**, 508; W. K. Snead and A. E. Remick, *J. Amer. Chem. Soc.*, 1957, **79**, 6121; and J. D. Voorhies and S. M. Davis, *J. Phys. Chem.*, 1963, **67**, 332.
[3] D. F. Bowman, F. R. Hewgill, and B. R. Kennedy, *J. Chem. Soc.* (*C*), 1966, 2274.
[4] F. R. Hewgill, B. R. Kennedy, and D. Kilpin, *J. Chem. Soc.*, 1965, 2904.
[5] F. R. Hewgill, *J. Chem. Soc.*, 1962, 4987.
[6] S. Hünig, *Chem. Ber.*, 1952, **85**, 1056.

this quinone and a hygroscopic bright red gum (7%) to which we assign the quinoneimonium hydroxide structure (II). The yield of the latter was increased to 12% when the oxidation was carried out with added dimethylammonium chloride.

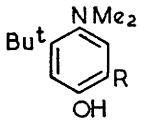


(I)

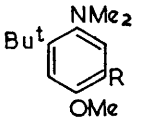


(II)

The ionic character of product (II) was indicated by its solubility in water. In the n.m.r. spectrum resonances at τ 3·53 and 3·96 were consistent with two uncoupled cyclohexadienone protons, while resonances at τ 6·32 (3H) and 6·49 (9H) were ascribed to one and three *N*-methyl groups respectively, the former being assigned to the *N*-methyl group adjacent to and coplanar with the carbonyl function. The marked shift to lower field of the *N*-methyl resonances is consistent with the presence of a conjugated quaternary nitrogen system.[7] Bands at 1660 and 1615 cm.$^{-1}$ in the i.r. spectrum are typical of the 2,4-cyclohexadienone structure.[8] The u.v. and visible spectra, and the solubility, of compound (II) resemble those reported for the aminochrome obtained on oxidation of 2-methyladrenaline with silver oxide.[9] Reduction of the salt (II) gave the diaminophenol (III), the n.m.r. spectrum of which was consistent with this formulation, further (III) could be reoxidised with silver oxide in chloroform to the salt (II).



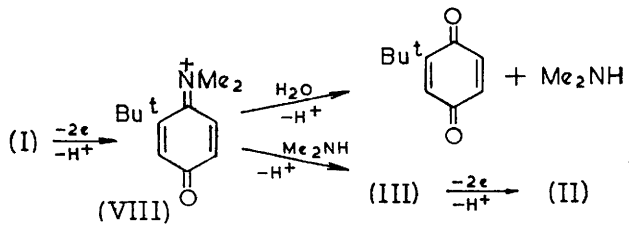
(III) R = NMe_2
(IV) R = NO_2
(V) R = NH_2
(XI) R = Br



(VI) R = $\overset{+}{N}Me_3I^-$
(VII) R = NMe_2

Though a projected synthesis of the diaminophenol (III) was unsuccessful, the corresponding anisole (VII) was prepared as follows. Nitrosation of phenol (I) gave, instead of the expected nitroso-compound, the nitrophenol (IV), together with unchanged phenol. Reduction of (IV) to the aminophenol (V), followed by methylation to (VI) and treatment with ethanolamine, gave the anisole (VII), which proved identical with material obtained from the bisdimethylaminophenol (III).

To explain the formation of the diaminophenol (III) the mechanism shown in Scheme 1 is suggested, in which the intermediate quinoneimonium ion (VIII) is attacked by dimethylamine liberated on its hydrolysis to the major product, t-butyl-1,4-benzoquinone. It is likely that the intermediate ion (VIII) would be a species of very limited stability, as coplanarity of the dimethylamino-group with the ring would introduce strain comparable to that found in *o*-di-t-butylbenzene, a factor that may materially assist subsequent nucleophilic substitution. As dimethylamine is known to be an excellent nucleophile for



SCHEME 1

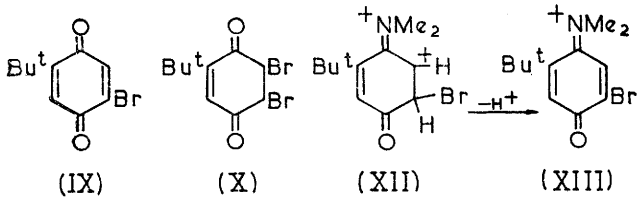
quinones,[10] the absence of t-butyldimethylamino-1,4-benzoquinone among the products is further evidence for the intermediacy of an ion such as (VIII). The anomalous nitrosation of phenol (I) may also involve ion (VIII), and proceed by oxidation to this, followed by nucleophilic substitution by nitrite. Unlike the diaminophenol (III), the nitrophenol (IV) is not likely to be further oxidised.

Bromine has been used to oxidise hydroquinones to bromo-1,4-benzoquinones,[11] and to seek additional evidence for the ion (VIII) the reaction of this reagent with phenol (I) was examined. The addition of 1 mol. of bromine to a solution of the phenol in acetic acid at room temperature produced a precipitate of the hydrobromide. The filtrate on dilution with water gave 2-bromo-5-t-butyl-1,4-benzoquinone (IX). When the experiment was repeated at 5° in acetic acid containing 5% (v/v) of water, a medium in which the hydrobromide is soluble, the unhalogenated quinone was formed in quantitative yield. With 2 mol. of bromine in the same solvent, the bromo-quinone (IX) was isolated in 30% yield, as well as the unhalogenated quinone.

At first sight the mechanism of bromination appears to involve initial formation of t-butyl-1,4-benzoquinone and bromination of this. However, treatment of this quinone with bromine in aqueous acetic acid gave 2-t-butyl-5,6-dibromocyclohex-2-ene-1,4-dione (X), in which addition rather than substitution had occurred. The intermediate is therefore not t-butyl-1,4-benzoquinone but a species which can give rise to this by hydrolysis, and which can be brominated and hydrolysed to the bromo-quinone (IX). Furthermore, reduction of the orange reaction mixture containing the phenol (I) and bromine (1 mol.) in aqueous acetic acid with bisulphite gave a quantitative recovery of phenol (I). Similar reduction of the reaction mixture containing 2 mol. of bromine gave 2-bromo-5-t-butyl-4-dimethylaminophenol (XI) as well as phenol (I). The position of the bromine

[7] L. M. Jackman, ' Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, London, 1959, p. 56.
[8] K. Dimroth, H. Perst, K. Schlömer, K. Worschech, and K.-H. Müller, *Chem. Ber.*, 1967, **100**, 629.
[9] R. A. Heacock and O. Hutzinger, *Canad. J. Chem.*, 1965, **43**, 2535.
[10] W. K. Anslow and H. Raistrick, *J. Chem. Soc.*, 1939, 1446.
[11] S. R. Chechik, *J. Amer. Pharm. Assoc.*, 1933, **22**, 506, *Chem. Abs.*, 1933, **27**, 5316.

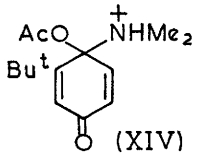
substituent in compound (XI) was confirmed by the result of a Sandmeyer reaction on the diazotised amine (V).



(IX) (X) (XII) (XIII)

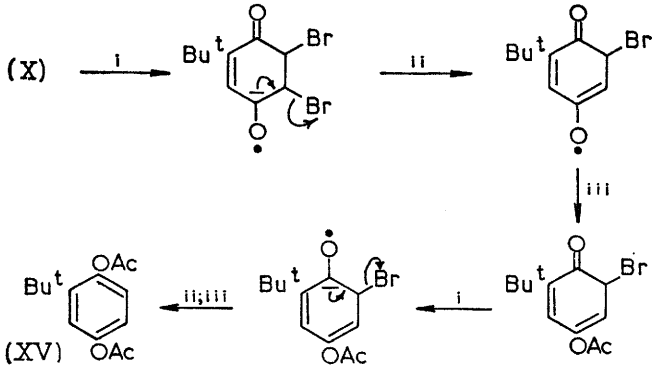
The evidence provided by these reactions favours the initial oxidation of phenol (I) to a species such as the ion (VIII) which may be brominated, hydrolysed to the quinone, or reduced to the starting material. Bromination of ion (VIII) does not apparently involve nucleophilic addition of bromide ion, and subsequent oxidation and hydrolysis of the resulting bromophenol. This was confirmed by the failure of high concentrations of bromide to effect bromination of solutions containing (VIII). We therefore conclude that bromination of (VIII) is by electrophilic addition of bromonium ion to give the carbonium ion (XII), which by loss of a proton leads to the ion (XIII). This can be hydrolysed or reduced to the observed products (IX) and (XI).

The inconsistency inherent in this mechanism is that the same position in the nucleus of (VIII) is involved in both nucleophilic and electrophilic attack. Furthermore, some means of stabilising the sterically crowded ion (VIII) and of reducing the electrophilic character of the 2-position would be necessary before bromination could occur. Addition of a solvent molecule as in (XIV) would achieve both these ends.



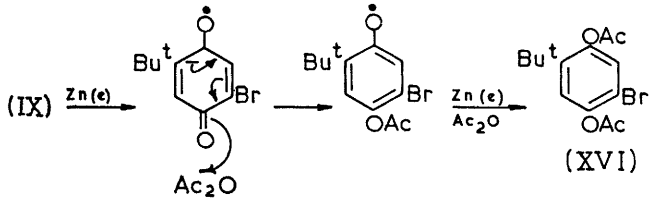
(XIV)

Treatment of the dibromo-compound (X) with sodium acetate gave the bromo-quinone (IX). A comparison of the reductive acetylation of these two compounds is interesting in that the former gave t-butylhydroquinone diacetate (XV) and the latter 2-bromo-5-t-butylhydroquinone diacetate (XVI): a difference that is consistent with the mechanisms of Schemes 2 and 3, and with previous reports of the loss of α-substituents in this type of reaction.[12]



Scheme 2

Reagents: i, Zn(e); ii, $-Br^-$; iii, Zn(e)–Ac_2O



Scheme 3

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. spectra were obtained with a Varian A60 spectrometer at 60 Mc./sec. and i.r. and u.v. spectra with Perkin-Elmer 137G and 137UV instruments.

3-t-Butyl-4-dimethylaminophenol (I).—Sulphanilic acid (65 g.) in water (300 ml.) was treated with sodium carbonate (18 g.) and warmed. The cooled solution was treated with sodium nitrite (24 g.) in water (70 ml.) and poured onto ice (400 g.) and hydrochloric acid (50 ml.). This suspension of the diazonium salt was added slowly at 5° with vigorous stirring to 3-t-butylphenol (44 g.) in aqueous sodium hydroxide (230 ml. of 20%) and the deep-red solution was set aside overnight. The semicrystalline mass was then heated to 60° and stirred during the addition of sodium dithionite (150 g.) in small portions. The mixture was cooled and the fawn precipitate was filtered off and dissolved in chloroform. This solution was washed with aqueous sodium carbonate (5%) and water, and evaporated under reduced pressure. The residue crystallised from benzene–light petroleum to give *4-amino-3-t-butylphenol* (46 g.) as prisms (changing to cubes at 130°), m.p. 158—158·5° (Found: C, 72·6; H, 9·0; N, 8·4. $C_{10}H_{15}NO$ requires C, 72·7; H, 9·2; N, 8·5%). τ ($CDCl_3$) 6·89 (NH_2) and 8·58 (Bu^t).

The aminophenol (33 g.) and sodium hydrogen carbonate (68 g.) were stirred overnight in water (150 ml.) with dimethyl sulphate (68 ml.) at 30°. The mixture was heated briefly with concentrated ammonia solution, and was then cooled; the precipitated *3-t-butyl-4-dimethylaminophenol* (I) (32 g.) was dried *in vacuo* over phosphorus pentoxide, and crystallised from light petroleum as prisms (changing to needles at 85°), m.p. 98—100° (Found: C, 74·3; H, 9·9; N, 7·6. $C_{12}H_{19}NO$ requires C, 74·6; H, 9·9; N, 7·25%), τ (CCl_4) 2·75 (OH), 7·45 (2 NCH_3) and 8·67 (Bu^t); $\lambda_{max.}$ (MeOH) 230 and 277 mμ (log ε 3·52 and 3·10). No trimethiodide formed when (I) was treated with iodomethane in dry methanol.

Oxidation of 3-t-Butyl-4-dimethylaminophenol (I).—(a) *By potassium ferricyanide.* A solution of potassium ferricyanide (5·8 g.) in aqueous sodium hydroxide (180 ml. of 3%) was added dropwise to a stirred solution of the phenol (2·0 g.) in ether (50 ml.) under nitrogen. The ether layer was separated, the acidified (HOAc) aqueous layer was extracted with ether, and the combined extracts were washed with water, dried, and evaporated to leave a red gum. Chrom-

[12] H. O. House, 'Modern Synthetic Reactions,' W. A. Benjamin, New York, 1965, p. 56.

[13] C. J. R. Adderley and F. R. Hewgill, *J. Chem. Soc.* (*C*), 1968, 2770.

atography on alumina and elution with light petroleum gave t-butyl-1,4-benzoquinone (0·2 g.), m.p. and mixed m.p. 57—58°. Elution with more polar solvents gave dark red, non-crystalline material.

(b) *By ceric sulphate.* The phenol (1·9 g.) in acetone (100 ml.) was stirred during the addition of ceric sulphate (450 ml., 0·05M) in aqueous sulphuric acid (5%) during 1·5 hr. The mixture was filtered and the dried precipitate crystallised from light petroleum to give t-butyl-1,4-benzoquinone (1·4 g.), m.p. and mixed m.p. 57—58°.

(c) *By silver oxide.* The phenol (2·5 g.) in ether (80 ml.) was shaken with silver oxide (6 g.) for 20 min. The brown solution was filtered and the silver residue was extracted with chloroform. Evaporation of the magenta coloured extract gave *5-t-butyl-4-dimethylamino-NN-dimethyl-1,2-quinoneimonium hydroxide* (II) (180 mg.) as a red gum too hygroscopic for analysis; τ ($CDCl_3$) 3·53, 3·96 (2 vinylic H), 6·32 (NMe), 6·49 (3 NMe), and 8·60 (Bu^t); $\nu_{max.}$ ($CHCl_3$) 1670 and 1620 $cm.^{-1}$; $\lambda_{max.}$ (H_2O) 212, 266, 310sh and 514 mμ (log ε 3·78, 3·67, 3·19, and 3·02). The yield of this material was increased to *ca.* 12% by the addition of dimethylammonium chloride to the reaction mixture. Steam distillation of the brown gum obtained from the ethereal filtrate gave t-butyl-1,4-benzoquinone, m.p. and mixed m.p. 57—58°.

Reactions of the Quinoneimonium Hydroxide (II).—Reduction of compound (II) with aqueous sodium dithionite or hydrogen (1 mol.) over palladium–charcoal gave *5-t-butyl-2,4-bisdimethylaminophenol* (III) as prisms, m.p. 82—84° from light petroleum (Found: C, 70·9; H, 9·7; N, 11·9. $C_{14}H_{24}N_2O$ requires C, 71·1; H, 10·2; N, 11·9%), τ (CCl_4) 2·97, 3·24 (2 ArH), 7·37, 7·45 (2 NMe_2) and 8·62 (Bu^t); $\nu_{max.}$ (CS_2) 3360 $cm.^{-1}$; $\lambda_{max.}$ (MeOH) 232 and 288 mμ (log ε, 3·84 and 3·50).

This phenol (III) (0·2 g.), dimethyl sulphate (1 ml.), and sodium hydrogen carbonate (3 g.) were shaken in water (10 ml.) at 10° for 3 hr. The solution was treated with an excess of ammonia solution heated to 50°, saturated with potassium iodide, and allowed to cool. The precipitate was crystallised from aqueous acetone to give *4-t-butyl-5-dimethylamino-2-methoxyphenyltrimethylammonium iodide* (VI) (0·2 g.) as prisms, m.p. 234° (sealed tube) (Found: C, 48·9; H, 7·4; I, 31·8; N, 7·0. $C_{16}H_{29}IN_2O$ requires C, 49·0; H, 7·5; I, 32·4; N, 7·1%).

The iodide (VI) (130 mg.) was heated under reflux in ethanolamine for 10 min. The mixture was poured into water, extracted with benzene, and the extract was washed with water, dried, and evaporated. The residue, *5-t-butyl-2,4-bisdimethylaminoanisole* (VII) crystallised as needles, m.p. 45—46° (from aqueous acetone) (Found: C, 71·8; H, 10·6; N, 11·2. $C_{15}H_{26}N_2O$ requires C, 72·0; H, 10·5; N, 11·2%); τ (CCl_4) 3·26, 3·30 (2 ArH), 6·21 (OMe), 7·28, 7·43 (2 NMe_2) and 8·62 (Bu^t).

Synthesis of 5-t-Butyl-2,4-bisdimethylaminoanisole (VII).—3-t-Butyl-4-dimethylaminophenol (5·7 g.) in acetic acid (60 ml.) was treated dropwise with sodium nitrite (2·2 g.) in water (10 ml.) during 1 hr. Water (60 ml.) was added and the precipitate was filtered off and crystallised from methanol to give *5-t-butyl-4-dimethylamino-2-nitrophenol* (IV) (3·4 g.) as yellows plates, m.p. 80—81° (Found: C, 60·3; H, 7·7; N, 11·7. $C_{12}H_{18}N_2O_3$ requires C, 60·5; H, 7·6; N, 11·8%), τ (CCl_4) −0·35 (OH), 2·02, 2·88 (2 ArH), 7·39 (NMe_2), and 8·57 (Bu^t); $\nu_{max.}$ (CS_2) 3250 $cm.^{-1}$; $\lambda_{max.}$ (MeOH) 222, 286, and 368 mμ (log ε 3·78, 3·77, and 3·44).

Hydrogenation of the nitrophenol (IV) in ethanol over palladium–charcoal required 3 mol. of hydrogen and gave *2-amino-5-t-butyl-4-dimethylaminophenol* (V) as needles, m.p. 214—216° (sealed tube), from chloroform (Found: C, 69·0; H, 10·1; N, 13·2. $C_{12}H_{20}N_2O$ requires C, 69·2; H, 9·7; N, 13·5%); $\lambda_{max.}$ (MeOH) 231 and 293 mμ (log ε 3·83 and 3·51). Methylation as described for phenol (III) gave the quaternary iodide (VI), m.p. and mixed m.p. 234°, and demethylation of this with ethanolamine gave the anisole (VII), m.p. and mixed m.p. 45—46°.

Bromination of 3-t-Butyl-4-dimethylaminophenol (I).—(a) *In acetic acid.* Bromine (3·2 g., 1 mol.) in acetic acid was added dropwise during 30 min. to a stirred solution of the phenol (3·9 g.) in acetic acid (60 ml.). The precipitate was filtered off and the filtrate was poured into water and extracted with ether. The residue from evaporation of the washed and dried ether extract crystallised from light petroleum to give 2-bromo-5-t-butyl-1,4-benzoquinone (IX) (2·5 g.), m.p. 110—112°.(lit.,[13] 110—112°). Addition of aqueous sodium hydrogen carbonate to the original precipitate and extraction with ether gave 3-t-butyl-4-dimethylaminophenol, m.p. and mixed m.p. 98—100°.

(b) *In aqueous acetic acid with 1 mol. of bromine.* Reaction (a) was repeated at 5° in acetic acid (80 ml.) containing water (4 ml.). The orange mixture was poured into water and extracted with ether. Evaporation of the washed and dried extract gave t-butyl-1,4-benzoquinone (3·1 g.), m.p. and mixed m.p. 57—58°.

In a further experiment the orange mixture was immediately added to sodium metabisulphite (15 g.) in water (60 ml.) at 5°. The colourless solution was neutralised with sodium hydrogen carbonate and extracted with ether. Evaporation of the washed and dried solvent gave 3-t-butyl-4-dimethylaminophenol, m.p. and mixed m.p. 98—100°.

(c) *In aqueous acetic acid with 2 mol. of bromine.* The phenol (3·9 g.) in acetic acid (80 ml.) containing water (4 ml.) was treated dropwise with bromine (6·4 g.) in acetic acid during 3 hr. at 5°. The red solution was poured into water and extracted with ether. The residue, after removal of the dried solvent, was chromatographed on alumina. Elution with light petroleum first gave 2-bromo-5-t-butyl-1,4-benzoquinone (IX) (3·2 g.), m.p. and mixed m.p. 110—112°, then t-butyl-1,4-benzoquinone (0·8 g.), m.p. and mixed m.p. 57—58°.

When the red solution was added to sodium metabisulphite as in (b), and the extracted material was chromatographed on alumina, light petroleum eluted *2-bromo-5-t-butyl-4-dimethylaminophenol* (XI) (1·2 g.) as prisms, m.p. 38—39° (from light petroleum) (Found: C, 53·2; H, 6·4; N, 4·8; Br, 29·5. $C_{12}H_{18}BrNO$ requires C, 53·0; H, 6·7; N, 5·1; Br, 29·4%); τ (CCl_4) 2·70, 3·04 (2 ArH), 4·81 (OH), 7·43 (NMe_2), and 8·62 (Bu^t). Elution with benzene–light petroleum (1 : 4) gave 3-t-butyl-4-dimethylaminophenol (2·2 g.) m.p. and mixed m.p. 98—100°.

Bromination of t-Butyl-1,4-benzoquinone.—Bromine (3·2 g.) in acetic acid was added dropwise to a stirred solution of the quinone (3·3 g.) in acetic acid (50 ml.) during 20 min. The solution was poured into ice–water, the precipitate was filtered off, taken up in ether, washed, and dried. Evaporation of the ether gave *2-t-butyl-5,6-dibromocyclohex-2-ene-1,4-dione* (X) (6·1 g.) as pale yellow cubes, m.p. 109—110° (from light petroleum) (Found: C, 37·1; H, 4·0; Br, 49·4. $C_{10}H_{12}Br_2O_2$ requires C, 37·1; H, 3·7; Br, 49·3%); τ (CCl_4) 3·55 (broad, vinylic H), 5·30 (2H), and 8·70 (Bu^t);

$\nu_{max.}$ (CS_2, Perkin-Elmer 521 Grating Spectrometer) 1702 $cm.^{-1}$ with a shoulder at 1695 $cm.^{-1}$; $\lambda_{max.}$ (MeOH) 269 and 370 mμ (log ε 4·07 and 2·16). On admixture with 2-bromo-5-t-butyl-1,4-benzoquinone the m.p. was depressed to 91°.

The enedione (X) when shaken overnight with sodium acetate in acetic acid gave 2-bromo-5-t-butyl-1,4-benzoquinone, m.p. and mixed m.p. 110—112°.

Reductive Acetylations.—The enedione (X) (1·0 g.) was heated under reflux with sodium acetate (0·5 g.) and zinc dust (0·2 g.) in acetic anhydride (20 ml.) for 30 min. After addition of dilute sulphuric acid, the product was extracted with ether. Evaporation of the washed and dried extract gave t-butylhydroquinone diacetate, m.p. and mixed m.p. 64—65°.

Similar treatment of the bromo-quinone (IX) gave 2-bromo-5-t-butylhydroquinone diacetate as plates, m.p. 75—77° (from light petroleum) (Found: C, 51·5; H, 5·4; Br, 24·5. $C_{14}H_{17}BrO_4$ requires C, 51·1; H, 5·2; Br, 24·3%), τ (CCl_4) 2·75; 2·93 (2 ArH) 7·75, 7·79 (2 OAc), and 8·70 (Bu^t).

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