Quinones. Part VII.[1] New Routes to 2-Hydroxy-1,4-naphthaquinones

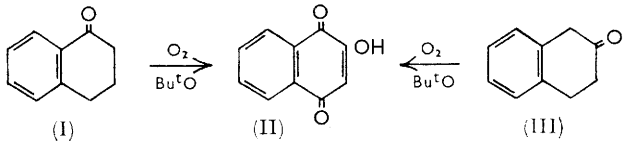
By A. C. Baillie and R. H. Thomson

Both α- and β-tetralones can be converted into 2-hydroxy-1,4-naphthaquinones by autoxidation in the presence of potassium t-butoxide. 1,2-Dihydroxynaphthalenes, which are likely intermediates, are rapidly autoxidised under the same conditions to give the same products and the method can be used for converting 1,2-naphthaquinones into 2-hydroxy-1,4-naphthaquinones.

Autoxidation of 5,7,8-trimethoxy-1-tetralone, followed by demethylation, gave 2,5,7,8-tetrahydroxy-1,4-naphthaquinone identical with mompain, a metabolite of *Helicobasidium mompa* Tanaka.

AUTOXIDATION of ketones in basic solution usually results in cleavage of the carbon chain *via* decomposition of the intermediate α-hydroperoxide.[2] The latter may also collapse to an α-diketone which normally undergoes benzilic acid rearrangement in strongly basic solution, but α-diketones which are highly enolised are stable under these conditions and can be isolated. It is therefore possible, in suitable cases, to use the reaction preparatively to introduce an oxygen function adjacent to a ketonic group, and this has formed the basis of a number of elegant triterpenoid,[3] steroid,[4] and carotenoid[5] syntheses.

In applying this autoxidation reaction to tetralones we had in mind the possibility that oxygenation might also occur at the benzylic [C(4)] carbon atom leading to the formation of 2-hydroxy-1,4-naphthaquinones. This is so. The method was first used for the synthesis of the polyhydroxynaphthaquinone, spinochrome D,[6] and is now shown to be a general procedure.* When shaken in t-butyl alcohol containing excess of potassium t-butoxide both α- (I) and β- (III)-tetralone absorb



(I) (II) (III)

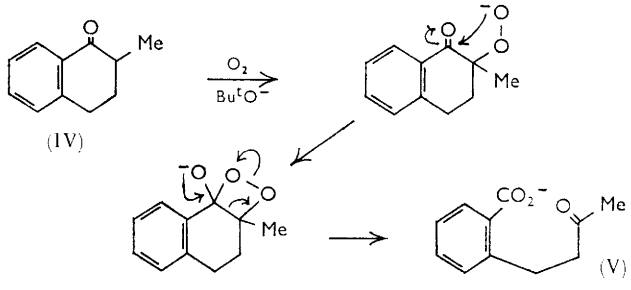
2 mol. of oxygen to form the hydroxyquinone (II), the faster reaction of the β-isomers reflecting the enhanced activity of the benzyl position at C(1) (see Table 1). Yields are moderate but with highly substituted α-tetralones are usually better than those obtained by the conventional condensation with 2 mol. of *p*-nitrosodimethylaniline, followed by acid hydrolysis, and the procedure is much quicker. Autoxidation of 5,7,8-trimethoxy-1-tetralone gave (with some difficulty) the corresponding hydroxytrimethoxynaphthaquinone, demethylation of which afforded 2,5,7,8-tetrahydroxy-1,4-naphthaquinone identical with mompain, a metabolic product of *Helicobasidium mompa* Tanaka.[7]

Autoxidation of 2-methyl-1-tetralone (IV) gave the keto-acid (V) (Scheme 1). In this case formation of an α-diketone is not possible and the usual cleavage product is formed. Evidently tetralones autoxidise normally and since both α- and β-tetralone give the same product the common intermediate must be the α-diketone (VI). The latter would enolise in strongly basic solution giving (VII) which is the di-anion of an *ortho*-quinol and therefore, in the presence of oxygen,

TABLE 1

Formation of 2-hydroxy-1,4-naphthaquinones by autoxidation of tetralones

α-Tetralone	1,4-Naphthaquinone	Yield (%)
Parent compound	2-Hydroxy-	72
6-Methoxy-	2-Hydroxy-6-methoxy-	68
7-Methoxy-	2-Hydroxy-7-methoxy-	69
5,6,7-Trimethoxy-	2-Hydroxy-5,6,7-trimethoxy-	46
5,6,8-Trimethoxy-	2-Hydroxy-5,6,8-trimethoxy-	16
5,6,7,8-Tetramethoxy-	2-Hydroxy-5,6,7,8-tetramethoxy-[6]	28
β-Tetralone		
Parent compound	2-Hydroxy-	55
6-Methoxy-	2-Hydroxy-6-methoxy-	50
7-Methoxy-	2-Hydroxy-7-methoxy-	60
8-Methoxy-	2-Hydroxy-8-methoxy-	60



Scheme 1

would form the semiquinone anion (VIII). Further autoxidation may then proceed (Scheme 2) by the capture of a molecule of oxygen to give the hydroperoxy-radical (IX), and hence the hydroxyquinone (II). The later stages may be regarded as the autoxidation of a vinylogous ketone. In support, we find that 1,2-dihydroxynaphthalene is very rapidly autoxidised under the same conditions to form 2-hydroxy-1,4-naphtha-

* Dr. Kasturi has informed us that he has independently discovered the reaction with α-tetralones (T. R. Kasturi and T. Arunachalam), *Canad. J. Chem.*, 1966, **44**, 1086.

[1] Part VI, J. F. Garden and R. H. Thomson, *J. Chem. Soc.*, 1957, 2483.

[2] W. von E. Doering and R. M. Haines, *J. Amer. Chem. Soc.*, 1954, **76**, 482; E. Elkik, *Bull. Soc. chim. France*, 1959, 933.

[3] R. Hanna and G. Ourisson, *Bull. Soc. chim. France*, 1961, 1945.

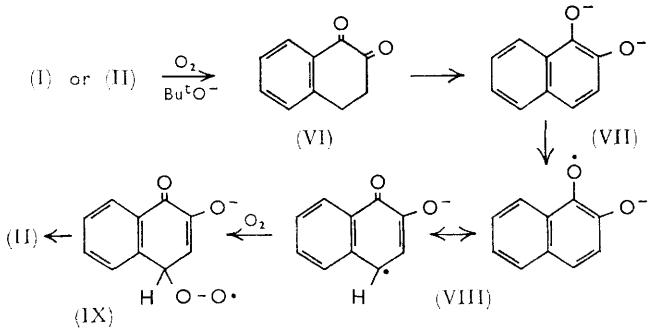
[4] E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1962, 1578.

[5] J. B. Davis and B. C. L. Weedon, *Proc. Chem. Soc.*, 1960, 182.

[6] H. A. Anderson, J. Smith, and R. H. Thomson, *J. Chem. Soc.*, 1965, 2141.

[7] S. Natori, Y. Kumada, and H. Nishikawa, *Chem. Pharm. Bull.*, 1965, **13**, 633.

quinone (67%) with absorption of 1 mol. of oxygen. This is also a general oxidative reaction and provides a quick method for converting 1,2-naphthaquinones into



Scheme 2

2-hydroxy-1,4-naphthaquinones (Table 2). Alkaline solutions of 1,3-dihydroxynaphthalenes autoxidise [8] in air to 2-hydroxy-1,4-naphthaquinones but under similar conditions 1,2-dihydroxynaphthalenes behave more as catechols and form dimers which give dark products on

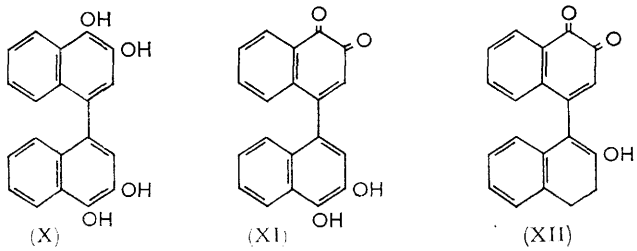
TABLE 2

Formation of 2-hydroxy-1,4-naphthaquinones by autoxidation of 1,2-dihydroxynaphthalenes

1,2-Dihydroxynaphthalene	1,4-Naphthaquinone	Yield (%)
Parent compound	2-Hydroxy-	67
6-Methoxy-	2-Hydroxy-6-methoxy-	51
7-Methoxy-	2-Hydroxy-7-methoxy-	56
6-Bromo-	6-Bromo-2-hydroxy-	53

further oxidation. Oxygen capture (VIII ⟶ IX) predominates when the solutions are shaken in oxygen but better yields are obtained by starting from the corresponding tetralones.

Scheme 2 is in general accord with earlier results. [9] Straus *et al.*[9a] obtained several products by shaking aqueous methanolic potassium hydroxide solutions of 1,2-dihydroxynaphthalene in air; absorption of 0·5 mol. of oxygen gave the dimer (X) which was converted into the quinhydrone (XI) on further oxygenation, while



uptake of 1·5 mol. of oxygen gave 2-hydroxy-1,4-naphthaquinone (50—55%, crude). This implies that at least part of the latter was derived from the dimeric products; this was confirmed by further autoxidation of (X) and (XI), in separate experiments, both of which gave small yields of 2-hydroxy-1,4-naphthaquinone after absorption of "excess of oxygen." Formation of dimers (from VIII) is readily understood and the subsequent breakdown probably proceeds by addition of water to the quinhydrone (XI) (or the diquinone [10]) and a reverse aldol reaction. The small yield (5%) of 2-hydroxy-1,4-naphthaquinone obtained by autoxidation of 2-benzylidene-1-tetralone probably arises in the same way.

In the autoxidation of β-tetralones the solution is initially blue but quickly changes to red. Wanzlick and his co-workers [11] have shown that the anions of hydroxyquinones of type (XII) are responsible for the blue colour (a diagnostic test for β-tetralones). These compounds, they suggested, are produced by oxidation of the ketone to β-naphthaquinone [*via* (VI) and (VII)], followed by Michael addition of the enolate anion of the β-tetralone, although other modes of formation are possible. They further pointed out that the blue solutions would absorb oxygen, turning brown, and this side reaction may account for the diminished yield of hydroxyquinones (II) obtained from β-tetralones.

EXPERIMENTAL

Tetralones were made by standard procedures. Reduction of 2,3-dimethoxynaphthalene with sodium and ethanol [12] gave only β-tetralone, presumably *via* elimination of methanol from 1,2-dihydro-2,3-dimethoxynaphthalene and further reduction (cf. ref. 13).

Autoxidation of Tetralones.—General procedure. The α- or β-tetralone (0·5 g.) in t-butyl alcohol (5 ml.) was added to a solution of potassium t-butoxide in t-butyl alcohol (20 ml., N) saturated with oxygen. The solution, which became red immediately (blue with β-tetralones), was shaken in oxygen until 2 mol. had been absorbed (*ca.* 15 min. for β-tetralones, 30 min. for α-tetralones), acidified with dilute hydrochloric acid, and extracted with chloroform. The hydroxyquinone was isolated by shaking the extract with aqueous sodium hydrogen carbonate, followed by acidification.

In the oxidation of α-tetralone itself, the residual chloroform solution yielded a dark oil (*ca.* 50 mg.) on evaporation which was shown, by thin-layer chromatography, to be chiefly starting material with traces of other compounds. Using 20 ml. of 0·2N-potassium t-butoxide solution the yield of 2-hydroxy-1,4-naphthaquinone fell to 60% (reaction time 100 min.) and with 20 ml. of 0·1N basic solution virtually no oxygen was taken up. When oxygen uptake was restricted to 1 mol., under the usual conditions, the yield dropped to 35% (from 70—75%) and unchanged tetralone was recovered (*ca.* 50%).

2-Hydroxy-6,7-dimethoxy-3-methyl-1,4-naphthaquinone.—This gave orange-red *plates*, m. p. 231—233° (from light petroleum, b. p. 100—120°) (Found: C, 62·6; H, 4·8. $C_{13}H_{12}O_5$ requires C, 62·8; H, 4·8%).

2-Hydroxy-5,7,8-trimethoxy-1,4-naphthaquinone.—This

[8] R. Meyer and K. Wolfsleben, *Ber.*, 1911, **44**, 1958; G. Soliman and A. Latif, *J. Chem. Soc.*, 1944, 55.

[9] (*a*) F. Straus, O. Bernoully, and P. Mautner, *Annalen*, 1925, **444**, 165; (*b*) A. Weissberger and W. Scharze, *Annalen*, 1931, **487**, 53.

[10] S. C. Hooker and J. G. Walsh, *J. Chem. Soc.*, 1894, **65**, 321.

[11] H.-W. Wanzlick, M. Lehmann-Horchler, and S. Mohrmann, *Chem. Ber.*, 1957, **90**, 2521.

[12] J. W. Cornforth, R. H. Cornforth, and R. Robinson, *J. Chem. Soc.*, 1944, 689.

[13] B. Weinstein and A. H. Fenselau, *J. Org. Chem.*, 1964, **29**, 2102.

was obtained by autoxidation of 5,7,8-trimethoxy-1-tetralone as usual but the reaction was terminated after uptake of 1 mol. oxygen. The crude *product*, isolated in the normal manner, was chromatographed on a column of silicic acid in benzene–chloroform (1 : 1) and crystallised from aqueous methanol in bronze needles, m. p. 174°; yield (allowing for recovered tetralone) (16%) (Found: C, 58·8; H, 5·0. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·55%).

2,5,7,8-*Tetrahydroxy*-1,4-*naphthaquinone*.—The above quinone (100 mg.) was refluxed with 48% hydrobromic acid (15 ml.) for 45 min., cooled, and poured into water. The brown precipitate (40 mg.) sublimed at 150°/0·1 mm. to give red *needles*, decomp. >300° (Found: C, 53·5; H, 2·6. $C_{10}H_{10}O_6$ requires C, 54·05; H, 2·7%); $\lambda_{max.}$ (EtOH) 228, 272, 319, 486, 518, 554 mμ (log ε 4·43, 4·06, 3·93, 3·75, 3·80, 3·63); $\nu_{max.}$ (KBr) 3155, 1600, 1473, 1433, 1410, 1364, 1314, 1218, 1178, 1105, 1092, 939, 861, 816, 802, 677 cm.$^{-1}$. The ultraviolet and infrared spectra were identical with those of mompain and the natural and synthetic quinones were indistinguishable when run on MN 300 cellulose in 90% formic acid.

Autoxidation of 1,2-*Dihydroxynaphthalene*.—The diol (0·5 g.) in t-butyl alcohol (10 ml.) was autoxidised as described above, 1 mol. of oxygen being absorbed within 1 min. Isolation of the material soluble in aqueous sodium hydrogen carbonate gave 2-hydroxy-1,4-naphthaquinone (67%).

Formation of 2-*Hydroxy*-1,4-*naphthaquinones from* 1,2-*Naphthaquinones*.—*General procedure*. The 1,2-naphthaquinone (0·5 g.) was dissolved in hot benzene, cooled, and shaken with saturated aqueous sodium dithionite until the benzene layer was colourless. The organic phase was washed with water, dried ($MgSO_4$), filtered, and reduced *in vacuo* to *ca.* 20 ml. This solution was then added to an oxygen-saturated solution of potassium t-butoxide in t-butyl alcohol as above, and shaken until 1 mol. of oxygen was absorbed (<1 min.), followed by the usual isolation procedure.

Autoxidation of 2-*Methyl*-1-*tetralone*.—The ketone (0·5 g.) was autoxidised as usual. After 1 mol. of oxygen had been absorbed uptake became very slow and was terminated. The solution was acidified and extracted with ether which was shaken with aqueous sodium hydroxide. The alkaline solution was made acid and the product taken into ether. Evaporation and crystallisation of the residue from aqueous methanol, and then from benzene–light petroleum (b. p. 60—80°) gave 4-(o-*carboxyphenyl*)*butan*-2-*one* as colourless needles, m. p. 115—116° (0·27 g.) (Found: C, 68·4; H, 6·3. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·25%); $\nu_{max.}$ (KBr) 1690, 1704 cm.$^{-1}$; the n.m.r. spectrum measured at 60 Mc./sec. (in $CDCl_3$) showed peaks at τ 7·83 (CH_3 singlet; 3 protons), *ca.* 7·17 and 6·68 ($-CH_2-CH_2-$, 2 multiplets; 4 protons) together with signals for 1 carboxyl and 4 aromatic protons. The compound dissolved in aqueous sodium hydrogen carbonate and gave a positive iodoform test.

Autoxidation of 2-*Benzylidene*-1-*tetralone*.—Under the usual conditions only 0·2 mol. of oxygen was absorbed in 2 hr. Working-up gave a fraction soluble in aqueous sodium hydrogen carbonate which gave a yellow precipitate on acidification identified as 2-hydroxy-1,4-naphthaquinone (5%). Concentration of the filtrate yielded benzoic acid (3%).

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