Autoxidation of some tetralin and tetralone derivatives under basic conditions

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A number of tetralone derivatives have been subjected to a base-induced benzylic hydroxylation procedure. In cases where aromatization was possible it occurred whilst, in those cases where aromatization was prevented, hydroxylation appeared to have occurred. However, dehydroxylation or oxidation products were generally the only ones isolated. Where a successful hydroxylation product was indeed isolated, the yield proved to be poor.

In the hope of forming 1,3-cis-dihydroxy substitution similar to that in compound (9). While it was appreciated that an alternative position for benzylic hydroxylation was possible i.e. at C(1) to yield a trihydroxy derivative as in 10, it was considered to be acceptable since a similar substitution pattern also occurs in ring A of β-hydromycin.

Careful treatment of the alcohol (8), prepared from tetralone (11), with potassium tert-butoxide in dimethylformamide under aerobic conditions afforded the aromatized product.

The tetracyclic antibiotics daunomycin (1), adriamycin (2), and carminomycin (3) are of medicinal interest due to their very potent activity against various types of experimental tumours as well as a variety of human cancers. Of the more successful strategies employed in the synthesis of fully functionalized tetracyclic ring systems, those involving coupling of the AB to the CD moieties have shown the most promise. Consequently, many approaches towards the synthesis of the AB ring segment have been developed.

Coburn et al. have reported a successful hydroxylation procedure whereby the α-tetralone (4) was converted into the diol (5) having the correct C(7) and C(9) regio- and stereochemistry of daunomycin (1). No mention was made that the system (5) underwent dehydration or aromatization under the basic conditions that were used. In related studies by Hocquaux et al. and Lissel on the autoxidation of α- and β-tetralones with potassium superoxide, the major product isolated was 2-hydroxy-1,4-naphthoquinone (6). Similar autoxidations of the former tetralones with potassium tert-butoxide in dimethyl sulphoxide by Russell et al., afforded the same intermediate, viz. naphthalene 1,2,4-semiquinone (7) identified by its e.s.r. spectrum. Under similar conditions of base but different solvent, Giles et al. achieved benzylic hydroxylations of naphtho[2,3-c] pyrans. The latter investigations have now been extended to some tetralin derivatives, in order to determine the influence of functional groups, particularly the ring carbonyl, on the hydroxylation reaction.

Our first objective was to attempt a base-induced hydroxylation on 2-ethyl-2-hydroxytetralin (8) in the hope of forming 1,3-cis-dihydroxy substitution similar to that in compound (9). While it was appreciated that an alternative

* For clarity and consistency the numbering of all naphthalene derivatives in this paper is as drawn in structure (8), although strictly speaking the principal functional group should be assigned the lowest locant (e.g. 6-ethyl-6-hydroxy-1,4-dimethoxytetralin).
(17) in 78% yield, together with a more polar fraction in 9% yield, which was assigned structure (18) based on the following spectral data. A sharp strong band in the 3400 cm\(^{-1}\) region of the i.r. spectrum indicated the presence of an alcohol. In the \(^1\)H n.m.r. spectrum, the signal for 1-H appeared as a doublet at \(\delta\) 8.18 (J 2 Hz) while that of 4-H appeared as a doublet at \(\delta\) 8.22 (J 8 Hz). The 3-H signal was clearly identified as a doublet of doublets at \(\delta\) 7.55 (J 7 and 2 Hz). The methyl protons of the hydroxyethyl side chain appeared as a doublet at \(\delta\) 1.58 (J 7 Hz) while the corresponding methine 1'-H appeared as a downfield quartet at \(\delta\) 5.08 (J 7 Hz).

The origin of the hydroxyethyl naphthalene (18) was demonstrated in a separate experiment in which treatment of the ethyl naphthalene (17), under analogous conditions of base in dimethylformamide for 18 h, produced a 24% yield of the alcohol (18) with 74% of the starting material being recovered.

The ease of aromatization of the systems so far investigated, including the conversion of \(\beta\)-tetralone (11) into the \(\beta\)-napthol (15) [identified as the acetate (16)], did not establish whether the oxygen atom of the carbonyl group in compound (11) played any role during the hydroxylation procedure.

The next question that arose was the role of the carbonyl group at the 1-position, in the benzyl hydroxylation observed by Coburn et al. A convenient model for this purpose was the dimethyl tetralone (20), which was not expected to undergo aromatization under the reaction conditions employed.

Treatment of the \(\alpha\)-tetralone (20) under the usual conditions of hydroxylation yielded two products that were easily separated chromatographically into a less polar fraction (37%), assigned structure (24), and a more polar fraction (56%), assigned the diketone structure (22). Conditions of hydroxylation were varied over a range of temperature and time. In all cases, only compounds (22) and (24) were isolated, together with starting material. It would appear that the initially formed product at C(4), under the autoxidative conditions employed, was rather unstable and that either further oxidation or olefin formation occurred, to produce more stable end products.

When the solvent was changed from dimethylformamide to dimethyl sulphoxide, the autoxidation procedure was facilitated to a limited extent. Thus, when \(\alpha\)-tetralone (20) was treated under the usual conditions of hydroxylation in dimethyl sulphoxide, a very polar material was isolated (11%), assigned the structure (23), together with starting material (78%). The highly polar material proved to be rather unstable even upon attempted p.l.c. purification. However, it was fully characterized. The \(^1\)H n.m.r. spectrum showed the 4-H signal as the X part of an ABX system at \(\delta\) 5.20 (J 7.2 and 6.3 Hz); the coupling constants were confirmed by analysis of the signals observed for the AB protons attached to C(3). Each of these latter protons appeared as a doublet of doublets centred at \(\delta\) 2.02 and 2.27 with geminal coupling of 14.3 Hz. The first of these showed additional vicinal coupling to 4-H of 7.2 Hz while the second showed similar coupling of 6.3 Hz. The cyclohexenone ring has five of the six ring-carbons approximately coplanar, and the construction of a model demonstrates the relative conformational mobility of the ring system and that more than one conformation may be adopted by the molecule. It would therefore be premature to be specific about the configuration adopted by the hydroxy group without further study.

Finally, the tetramethyl \(\beta\)-tetralone (12) was prepared which could neither enolize nor aromatize, and which decomposed slowly under the usual conditions of hydroxylation.

In conclusion, it may be speculated that, in the case of \(\alpha\)-tetralone (20), the peroxide species (25) would be a feasible reaction intermediate which could form the observed products (22), (23), and (24), depending upon the solvent system. On the other hand, the non-aromatizable \(\beta\)-tetralone (12) did not produce isolable products, which would indicate that the carbonyl group in the 1-position favours the formation of the 4-peroxide species. In the cases of the \(\alpha\)-tetralone (11) and tetralin (9) where aromatization is possible, it occurs. This latter finding neither supports nor negates the initial formation of a similar benzylic peroxide intermediate as a precursor to the final aromatized products.
Experimental

Melting points are uncorrected. I.r. spectra were measured as Nujol mulls on a Pye-Unicam SP 300 spectrophotometer and 1H n.m.r. spectra were measured on a Varian EM 360 spectrometer at 60 MHz unless otherwise stated. Column chromatography was carried out on dry columns using silica gel (70—230 mesh). Light petroleum refers to that fraction of boiling range 60—80°C. The phrase ‘residue obtained upon work-up’ refers to the material remaining when the organic layer was separated, dried (MgSO4), and evaporated under reduced pressure.

2-Trimethylsilyloxy-1,3-butadiene

The method of House et al.15 was adapted as follows: To a mixture of triethylamine (60.6 g; 0.6 mol) (freshly distilled from lithium aluminium hydride), chlorotrimethylsilane (32.6 g; 0.3 mol), and dimethylformamide (100 ml), was added freshly distilled methyl vinyl ketone (17.5 g; 0.25 mol) and the whole was stirred and heated under reflux under N2 for 48 h. A voluminous precipitate of triethylammonium chloride formed during the reaction and thus a powerful stirrer is needed. The cooled mixture was diluted with pentane (300 ml) and filtered. The filtrate was washed with cold, saturated sodium hydrogen carbonate (3 x 100 ml), followed by cold saturated sodium hydrogen carbonate (100 ml). This was repeated twice more. The dried (MgSO4) pentane extract was filtered and concentrated to afford a residue which was distilled under water vacuum (24—28 mm Hg) to yield the product diene as a mobile oil (15 g; 42%); b.p. 32—34°C [lit.16 b.p. 25—28°C (12 mm Hg)], 8 0.2 (9H, s, SiMe3), 4.33 (2H, s, 1-H), 5.05 (1H, dd, J4',4 2 and J4',3 17 Hz, 4'-H), 5.43 (1H, dd, J4',2 and J4,3 17 Hz, 4-H), and 6.2 (1H, dd, J3',4 10 and J3,4 17 Hz, 3-H).

2-Trimethylsilyloxy-1,4,4a,5,8,8a-hexahydronaphthalene-5,8-dione (13)

A solution of 2-trimethylsilyloxy-1,3-butadiene (15 g; 105 mmol) and freshly recrystallized benzoquinone (8.1 g; 75 mmol) in dry benzene (80 ml) was stirred and heated at 60°C for 18 h under N2. Removal of the benzene at low temperature afforded a residue which was rapidly chromatographed using ethyl acetate—light petroleum (1:4) as eluent, to give the adduct (13) as a viscous, unstable light-brown oil (11.25 g; 60%). A small sample was purified by p.l.c. to afford a fairly colourless oil, vmax 1650 cm⁻¹; δ 0.28 (9H, s, SiMe3), 3.2 (6H, m, 1- and 4-H2, and 4a- and 8a-H2), 5.1 (1H, m, 3-H), and 6.9 (2H, s, 6- and 7-H) (Found: C, 62.2; H, 7.3). Calc. for C13H13O2Si: C, 62.4; H, 7.2%).

2,5,8-Trimethoxy-3,4-dihydronaphthalene (14) and 5,8-dimethoxy-2-tetralone (11)

The adduct (13) (8.6 g; 34.4 mmol) in dry acetone (150 ml) was treated with anhydrous potassium carbonate (23.74 g; 172 mmol) and dimethyl sulphate (21.67 g; 172 mmol) and heated under reflux with rapid stirring for 24 h. The cooled solution was filtered and the filtrate was evaporated to leave a residue which was taken up in ether (100 ml) and washed consecutively with concentrated ammonia (30 ml), water (50 ml), 0.5M-hydrochloric acid (50 ml), and brine (50 ml). The residue obtained upon work-up was chromatographed using ethyl acetate—light petroleum (1:5) as eluent. The first fraction eluted was the enol ether (14) as a viscous, light-brown semi-solid (972 mg; 13%); δ 2.38 (2H, t, J 7 Hz, 3-H), 2.94 (2H, t, J 7 Hz, 4-H), 3.8 (9H, s, 3 x OCH3), 5.94 (1H, s, 1-H), and 6.7 (2H, s, 7- and 8-H) (Found: C, 70.6; H, 7.0. Calc. for C13H16O4: C, 70.9; H, 7.3%). Further elution afforded the ß-tetralone (11) as a canary-yellow solid (5.39 g; 76%). It formed white plates from ethanol, m.p. 98—99°C (lit.,11 m.p. 99°C); vmax 1710 cm⁻¹; δ 5.25 (2H, t, J 7 Hz, 3-H), 3.13 (2H, t, J 7 Hz, 4-H), 3.53 (2H, s, 1-H), 3.8 and 3.83 (each 3H, s, OCH3), and 6.8 (2H, s, 6- and 7-H).

In a separate experiment it was shown that pure ß-tetra­lone (11) could be converted into a mixture of the enol ether (14) and ß-tetralone (11) under the above conditions.

5,8-Dimethoxy-1,1,3,3-tetramethyl-2-tetralone (12)

The ß-tetralone (11) (266 mg; 1.29 mmol) in dimethyl­formamide (4 ml) was treated with sodium hydride (200 mg of a 20% oil dispersion) and stirred under N2 at room temperature for 30 min, then methyl iodide (0.994 mg; 7 mmol) was added. Stirring was continued for 2 h after which the reaction mixture was poured into water (100 ml) and extracted with ether (3 x 60 ml). The residue obtained upon work-up was chromatographed using ethyl acetate—light petroleum (1:5) as eluent, to give the tetramethyl tetralone (12) (300 mg; 89%) as white waxy crystals from sublimation, m.p. 77—80°C; vmax 1704 cm⁻¹; δ 1.15 [6H, s, 1-(CH3)2], 1.52 [6H, s, 3-(CH3)2], 2.82 (2H, s, 4-H), 3.77 (6H, 2 x OCH3), and 6.72 (2H, s, 6- and 7-H) (Found: C, 73.4; H, 8.35. Calc. for C18H22O2: C, 73.3; H, 8.4%).

Treatment of this material with potassium t-butoxide in dimethylformamide led to decomposition products and recovery of starting material.

5,8-Dimethoxy-2-naphthol (15)

The ß-tetralone (11) (116 mg; 0.56 mmol) in dry dimethyl­formamide (15 ml) was treated all at once with potassium t-butoxide (250 mg; 2.25 mmol) and stirred in a dry (calcium chloride) aerobic atmosphere at 60°C for 1 h. The cooled solution was poured into aqueous ammonium chloride (50 ml) and extracted with ether (3 x 30 ml). The dried (MgSO4) ether extracts yielded a residue which was purified by chromatography using ethyl acetate—light petroleum (1:5) as eluent, to afford the ß-naphthol (15) (78 mg; 68%) as a colourless oil; vmax 3200—3500 cm⁻¹; δ 3.97 (6H, s, 2 x OCH3), 5.0 (1H, br. s, D2O exchangeable, 2-OH), 6.7 (2H, m, 6- and 7-H), 7.2 (1H, dd, J 8 and 2 Hz, 3-H), 7.61 (1H, d, J 2 Hz, 1-H), and 8.2 (1H, d, J 8 Hz, 4-H).
(16) (54 mg; 76%) as a thick colourless oil; $\nu_{\text{max}}$ (neat) 1760 cm$^{-1}$; δ 2.37 (3H, s, COCH$_3$), 3.97 (6H, s, 2 × OCH$_3$), 6.75 (2H, s, 6- and 7-H), 7.3 (1H, dd, J 6 and 2 Hz, 3-H), 7.98 (1H, d, J 2 Hz, 1-H), and 8.3 (1H, d, J 8 Hz, 4-H) (Found: C, 68.1; H, 5.5%; M$^+$, 246,093). Calc. for C$_{14}$H$_{16}$O$_3$: C, 72.4; H, 7.2%.

5,8-Dimethoxy-2,2-dimethyl-1-tetralone (22) (20) (183 mg; 78%) as white needles from cyclohexane, m.p. 84—85°C; $\nu_{\text{max}}$ 1680 cm$^{-1}$; δ 1.21 (6H, s, 2 × CH$_3$), 1.93 (2H, t, J 7 Hz, 3-H$_2$), 2.93 (2H, t, J 7 Hz, 4-H$_2$), 3.87 and 3.9 (each 3H, s, OCH$_3$), 6.85 (1H, d, J 9 Hz, 7-H), and 7.1 (1H, d, J 9 Hz, 6-H) (Found: C, 71.6; H, 7.6. Calc. for C$_{14}$H$_{16}$O$_3$: C, 71.8, H, 7.7%). The next fraction to be eluted was the methyl tetralone (21) (369 mg; 34%) as a yellow-light oil which solidified on standing. Sublimation yielded canary-yellow crystals, m.p. 64—65°C; $\nu_{\text{max}}$ 1684 cm$^{-1}$; δ 1,21 (3H, d, J 6 Hz, 2-CH$_3$), 1,5—1,3 (5H, br. m, 2-H, 3-, and 4-H$_2$), 3.83 and 3.87 (each 3H, s, OCH$_3$), 6.83 (1H, d, J 9 Hz, 7-H), and 7.07 (1H, d, J 9 Hz, 6-H) (Found: C, 70.85; H, 7.15. Calc. for C$_{13}$H$_{15}$O$_2$: C, 70.9; H, 7.3%).

2-Ethyl-2-hydroxy-1,2,3,4-tetrahydro-5,8-dimethoxy-naphthalene (8)
To a freshly prepared solution of ethylmagnesium bromide [from Mg (666 mg; 27.4 mmol) and ethyl bromide (4.14 g; 38 mmol)] in dry ether (60 ml) was added the β-tetralone (11) (290 mg; 1.41 mmol) in dry ether (15 ml) over a period of 10 min. After the initial exothermic reaction, the mixture was stirred for further 1 h at 35°C, then the magnesium salts were hydrolysed by the careful addition of aqueous 1M-hydrochloric acid (50 ml). The ethereal layer was dried (MgSO$_4$) and the residue obtained after work-up was chromatographed using ethyl acetate—light petroleum (9:40) as eluent for the starting material (11) (86 mg; 1,41 mmol) in dry ether (15 ml) over a period of time the reaction mixture assumed a reddish colour. The residue obtained upon work-up was chromatographed using ethyl acetate—light petroleum (3:10) followed by ethyl acetate as eluent. The first product isolated was the starting material (11) (86 mg; 78%) as a thick colourless oil; $\nu_{\text{max}}$ (film) 3440 cm$^{-1}$; δ 1.0 (3H, t, J 7 Hz, 2-CH$_3$CH$_2$$_2$), 1.67 (4H, m, 3-H$_2$ and 2-CH$_2$CH$_3$)$_2$, 2.1 (1H, br. s, D$_2$O exchangeable, 2-OH), 2.73 (4H, m, 1- and 4-H$_2$), 3.8 (6H, s, 2 × OCH$_3$), and 6.77 (2H, s, 6- and 7-H) (Found: C, 71.0; H, 8.3. Calc. for C$_{14}$H$_{16}$O$_2$: C, 71.2; H, 8.5%).

5,8-Dimethoxy-2,2-dimethyl-5$^{\alpha}$-1-tetralone (24) and 5,8-dimethoxy-2,2-dimethyl-1,4-tetralindione (22)
α-Tetralone (20) (287 mg; 1,65 mmol) in dimethylformamide (25 ml) at 60°C was treated with potassium t-butoxide (740 mg; 6.6 mmol) under dry aerobic conditions for 2 h. The reaction mixture was poured into aqueous ammonium chloride (100 ml) and the resulting solution was extracted with ether (3 × 80 ml). The residue obtained upon work-up was chromatographed using ethyl acetate—light petroleum (3:20) as eluent, to give the starting material (11) (86 mg; 30%), followed by the alcohol (8) (218 mg; 66%) as a light-yellow viscous oil; $\nu_{\text{max}}$ (film) 3440 cm$^{-1}$; δ 1.0 (3H, t, J 7 Hz, 2-CH$_3$CH$_2$$_2$), 1.67 (4H, m, 3-H$_2$ and 2-CH$_2$CH$_3$)$_2$, 2.1 (1H, br. s, D$_2$O exchangeable, 2-OH), 2.73 (4H, m, 1- and 4-H$_2$), 3.8 (6H, s, 2 × OCH$_3$), and 6.77 (2H, s, 6- and 7-H) (Found: C, 71.0; H, 8.3. Calc. for C$_{14}$H$_{16}$O$_2$: C, 71.2; H, 8.5%).

2-Ethyl-5,8-dimethoxynaphthalene (17) and 2-(1'-hydroxy-ethyl)-5,8-dimethoxynaphthalene (18)
The tertiary alcohol (8) (170 mg; 0.72 mmol) in dry dimethylformamide (18 ml) at 60°C was treated with potassium t-butoxide (323 mg; 2.88 mmol) all at once and stirred in a dry (CaCl$_2$) aerobic atmosphere for 1.5 h, during which time the reaction mixture assumed a reddish colour. The cooled reaction mixture was poured into saturated ammonium chloride (100 ml) and extracted with ether (3 × 80 ml). The residue obtained after work-up was chromatographed using ethyl acetate—light petroleum (1:5) as eluent. The first fractions yielded the ethylphenalene (17) (130 mg; 78%) as a colourless oil, δ 1.36 (3H, t, J 8 Hz, 2-CH$_3$CH$_2$$_2$), 2.90 (2H, q, J 8 Hz, 2-CH$_2$CH$_3$), 4.0 (6H, s, 2 × OCH$_3$), 6.77 (2H, s, 6- and 7-H), 7.53 (1H, dd, J 8 and 2 Hz, 3-H), 8.2 (1H, d, J 2 Hz, 1-H), and 8.32 (1H, d, J 8 Hz, 4-H) (Found: C, 77.85; H, 7.65. Calc. for C$_{14}$H$_{16}$O$_2$: C, 77.5; H, 7.45%). This was followed by starting material (11) (6%) and the hydroxyethylphenalene (18) (15 mg; 96%) as a viscous, colourless oil; $\nu_{\text{max}}$ (film) 3400 cm$^{-1}$; δ 1.58 (3H, d, J 7 Hz, 1'-CH$_3$), 1.9 (1H, br., D$_2$O exchangeable, 1'-OH), 3.96 (6H, s, 2 × OCH$_3$), 5.08 (1H, q, J 7 Hz, 1'-H), 6.69 (2H, s, 6- and 7-H), 7.55 (1H, dd, J 8 and 2 Hz, 3-H), 8.18 (1H, d, J 2 Hz, 1-H), and 8.22 (1H, d, J 8 Hz, 4-H) (Found: C, 72.4; H, 6.95. Calc. for C$_{14}$H$_{16}$O$_2$: C, 72.4, H, 7.2%).
(each 3H, s, OCH₃), 5,2 (1H, dd, J 7,2 and 6,3 Hz, 4-H), and 6,9 and 7,05 (each 1H, J 8 Hz, 7- and 6-H resp.) (Found: C, 67,35; H, 7,35; M⁺, 250,1223. Calc. for C₁₄H₁₈O₄: C, 67,2%; H, 7,2%; M, 250,1205).

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