Synthesis of 6-Oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone and Derivatives and a New, Convenient Preparation of *o*-Naphthazarin[1]

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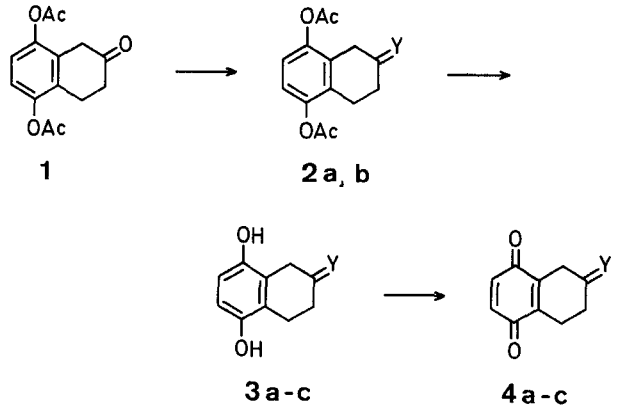
The anti-tumor anthracycline antibiotics daunomycin and adriamycin have attracted attention[2] and considerable efforts have been made to synthesise these molecules[3]. Recently[4], we reported a synthesis of tetracyclic compounds related to daunomycinone based on the Diels-Alder reaction between *o*-quinodimethanes and suitable tetrahydronaphthoquinones. In this connection, we have now developed a convenient preparation of the functionalised naphthoquinone derivatives **4a–c**, valuable intermediates in our synthetic approach[4,5] and in other related procedures[6,7]. The starting materials for the synthesis are the readily available 5,8-di-substituted 2-tetralones **1**, **3c**, and **5**[8].

The preparation of **4a** or **b** is achieved in good yield from 5,8-diacetoxy-2-tetralone (**1**) by conversion into dithioacetal **2a** or acetal **2b**, followed by methanolysis or alkaline hydrolysis, respectively, to give the hydroquinone **3a** or **b**, which is further oxidised with silver(I) oxide (Scheme **A**).



	Y
a	$-S-(CH_2)_3-S-$
b	$-O-(CH_2)_2-O-$
c	O

Scheme **A**

The parent compound, 6-oxo-5,6,7,8-tetrahydronaphthoquinone (**4c**), is obtained in 76% yield by silver(I) oxide oxidation of 5,8-dihydroxy-2-tetralone (**3c**). The quinone **4c** decomposes very easily, so that its structure was established by I.R. and ^{1}H-N.M.R. spectroscopy of the crude reaction product.

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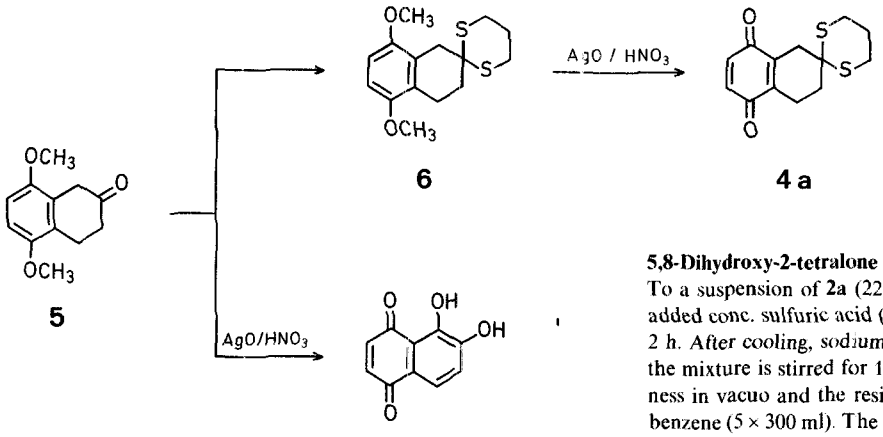
An alternative route for quinone **4a** is based on the oxidative demethylation with silver(II) oxide[9] in acidic media of the dimethyl ether **6** obtained from the tetralone **5**. However, under the reaction conditions, partial oxidative cleavage of the thioacetal group[10] takes also place, resulting in a low yield of **4a**.



Scheme **B**

Oxidative demethylation of **5** would be expected to yield 6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone (**4c**). However, we have found that the treatment of **5** with silver(II) oxide, in the presence of nitric acid, affords *o*-naphthazarin[11,12], 5,6-dihydroxy-1,4-naphthoquinone (**7**), in 62% yield. Formation of **7** may be assumed to proceed by oxidative demethylation, with simultaneous oxidation of the reactive benzyl position at C-1 of the tetralone[13], and subsequent aromatisation under the reaction conditions.

The reaction is a convenient preparation of *o*-naphthazarin in one step starting from the easily available 5,8-dimethoxy-2-tetralone (**5**). To our knowledge, **7** has been only prepared[12] in two steps starting from 3,5,6-trihydroxy-1,4-naphthoquinone, but the procedure is not satisfactory because of the difficult accessibility of the starting material[14], and the low overall yield attained (18%).

5,8-Diacetoxy-2-tetralone 1,3-Propanediyl *S,S*-Acetal (2a):
To a solution of 5,8-diacetoxy-2-tetralone[8] (**1**; 20.2 g, 0.077 mol) in chloroform (200 ml) is added propane-1,3-dithiol (8.6 g, 0.08 mol) and boron trifluoride etherate [20 ml (d: 1.13), 0.16 mol]. The reaction mixture is stirred at room temperature for 10 min and then worked up by successively washing with water, 15% aqueous sodium carbonate, and water, and drying with magnesium sulphate. The solvent is removed under reduced pressure to give **2a** as a colourless oil, which is induced to crystallise with ether. The product is recrystallised from ethanol; yield: 22.8 g (84%); m.p. 128 °C.

$C_{17}H_{20}O_4S_2$	calc.	C 57.94	H 5.72	S 18.16
(352.5)	found	57.82	5.70	18.05

M.S.: *m/e* (relative intensity) = 352 (92, M^+), 310 (72), 268 (88), 194 (64), 161 (100).

I.R. (nujol): ν = 1763, 1180 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 6.90 (s, 2 H_{arom}); 3.00 (s, 2H, CH_2-1); 3.0–2.6 (m, 6H, CH_2-4, 2SCH_2); 2.30, 2.28 (2s, 6H, 2$OCOCH_3$); 2.4–2.2 (m, 2H, CH_2-3); 2.2–1.9 ppm (m, 2H, $SCH_2CH_2CH_2S$).

5,8-Dimethoxy-2-tetralone 1,3-Propanediyl *S,S*-Acetal (6):
The same procedure is used as above starting from 5,8-dimethoxy-2-tetralone[8] (**5**; 10.8 g, 0.052 mol) in chloroform (160 ml), propane-1,3-dithiol (6.0 g, 0.055 mol) and boron trifluoride etherate [20 ml (d: 1.13), 0.16 mol]. The product is recrystallised from ethanol; yield: 13.5 g (87%); m.p. 116–117 °C.

$C_{15}H_{20}O_2S_2$	calc.	C 60.79	H 6.80	S 21.56
(296.5)	found	60.50	6.69	21.89

M.S.: *m/e* (relative intensity) = 296 (100, M^+), 222 (16), 189 (88), 164 (29).

I.R. (nujol): ν = 1605, 1255, 1096, 1080 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 6.57 (s, 2 H_{arom}); 3.71 (s, 6H, 2OCH_3); 3.14 (s, 2H, CH_2-1); 2.9–2.7 (m, 6H, CH_2-4, 2SCH_2); 2.22 (t, 2H, CH_2-3); 2.1–1.8 ppm (m, 2H, $SCH_2CH_2CH_2S$).

5,8-Dihydroxy-2-tetralone 1,3-Propanediyl *S,S*-Acetal (3a):
To a suspension of **2a** (22.0 g, 0.062 mol) in methanol (400 ml) is added conc. sulfuric acid (450 mg), and the mixture is refluxed for 2 h. After cooling, sodium hydrogen carbonate (1 g) is added and the mixture is stirred for 15 min. The solvent is evaporated to dryness in vacuo and the residue is extracted repeatedly with boiling benzene (5 × 300 ml). The extracts are cooled in an ice-bath and the deposited colourless crystalline pure product **3a** is collected by filtration; yield: 14.7 g (88%); colourless crystals; m.p. 163–164 °C (acetone/hexane).

$C_{13}H_{16}O_2S_2$	calc.	C 58.20	H 6.01	S 23.84
(268.4)	found	57.93	5.92	24.19

M.S.: *m/e* (relative intensity) = 268 (84, M^+), 194 (34), 161 (100).

I.R. (nujol): ν = 3426, 3228, 1620, 1280, 1250 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 8.49, 8.42 (2 br s, 2H, 2OH, removed by D_2O); 6.43 (s, 2 H_{arom}); 2.89 (s, 2H, CH_2-1); 3.0–2.5 (m, 6H, CH_2-4, 2SCH_2); 2.17 (t, 2H, CH_2-3); 2.1–1.7 ppm (m, 2H, $SCH_2CH_2CH_2S$).

6-Oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,3-Propanediyl *S,S*-Acetal (4a):
Method A: To a solution of **3a** (17.0 g, 0.063 mol) in anhydrous ether (1 l) are added anhydrous magnesium sulphate (17 g) and silver(I) oxide (30 g, 0.130 mol), and the mixture is magnetically stirred at room temperature for 45 min. The inorganic precipitate is filtered off and washed with chloroform (4 × 200 ml). Combined filtrate and washings are evaporated to dryness in vacuo and the residue recrystallised from ethanol; yield: 15.3 g (91%); orange crystals; m.p. 161–162.5 °C.

$C_{13}H_{14}O_2S_2$	calc.	C 58.64	H 5.30	S 24.06
(266.4)	found	58.89	5.34	23.98

M.S.: *m/e* (relative intensity) = 266 (100, M^+), 192 (29), 159 (26), 132 (58), 131 (19).

I.R. (nujol): ν = 1655, 1601, 1307 cm^{-1}.

U.V. (ethanol): λ_{max} = 250 ($\log \varepsilon$ = 4.1), 335 nm (2.8).

^{1}H-N.M.R. ($CDCl_3$): δ = 6.69 (s, 2 $H_{quinone}$); 3.0–2.8 (m, 6H, CH_2-5, CH_2-8, SCH_2); 2.7–2.5 (m, 2H, SCH_2); 2.16 (t, 2H, CH_2-7); 2.2–1.9 ppm (m, 2H, $SCH_2CH_2CH_2S$).

Method B: A solution of **6** (4.7 g, 0.016 mol) in dioxan (190 ml) is magnetically stirred and cooled at 5 °C in an ice-bath. To this solution are added 6 normal nitric acid (18 ml), and gradually silver(II) oxide (13 g, 0.105 mol) while the temperature is maintained below 15 °C. Stirring is continued at 5 °C for 20 min and then water (250 ml) is added. After extraction with chloroform (3 × 400 ml), washing with water, and drying with magnesium sulphate, the solvent is removed in vacuo to give a red residue. Recrystallisation from ethanol affords the quinone **4a**; yield: 950 mg (22%).

5,8-Diacetoxy-2-tetralone 1,2-Ethanediyl Acetal (2b):
A mixture of 5,8-diacetoxy-2-tetralone[8] (**1**; 2.62 g, 10 mmol), ethylene glycol (36 g), *p*-toluenesulphonic acid dihydrate (140 mg), and tetrahydrofuran (150 ml) is refluxed for 6 h and then water (500 ml) is added. The aqueous solution is extracted with chloroform (3 × 250 ml), the organic extract is washed with water, dried with magnesium sulphate, and the solvent removed to give an oil, which

is crystallised by cooling at −70 °C. The product is recrystallised from ethanol; yield: 2.39 g (78%); colourless crystals; m.p. 101.5 °C.

$C_{16}H_{18}O_6$	calc.	C 62.73	H 5.92
(306.3)	found	62.52	5.77

M.S.: *m/e* (relative intensity) = 306 (9, M^+), 264 (20), 222 (100), 178 (22), 136 (15), 87 (25).

I.R. (nujol): $\nu = 1754, 1200\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 6.85$ (s, $2H_{arom}$); 3.97 (s, 4H, $2OCH_2$); 2.9–2.6 (m, 4H, CH_2-1, CH_2-4); 2.27 (s, 6H, $OCOCH_3$); 1.87 ppm (t, 2H, CH_2-3).

5,8-Dihydroxy-2-tetralone 1,2-Ethanediyl Acetal (3b):

Aqueous sodium hydroxide (4%, 20 ml, 20 mmol) is added to a stirred solution of **2b** (1.87 g, 6.1 mmol) in tetrahydrofuran (20 ml) at room temperature under nitrogen. After 30 min the mixture is added to water (20 ml), neutralised with dilute hydrochloric acid, and extracted with ether (4 × 50 ml). The ether layer is dried with magnesium sulphate, the solvent evaporated, and the residue chromatographed on silica gel [benzene/ethyl acetate (1:1)], to give **3b**. The product is recrystallised from acetone/hexane or benzene; yield: 990 mg (73%); colourless crystals; m.p. 185–188 °C.

$C_{12}H_{14}O_4$	calc.	C 64.85	H 6.35
(222.2)	found	64.99	6.42

M.S.: *m/e* (relative intensity) = 222 (100, M^+), 178 (77), 136 (85), 87 (89).

I.R. (nujol): $\nu = 3360\ cm^{-1}$.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 8.34$ (br s, 2H, 2OH, removed by D_2O); 6.36 (s, $2H_{arom}$); 3.88 (s, 4H, $2OCH_2$); 2.7–2.5 (m, 4H, CH_2-1, CH_2-4); 1.73 ppm (t, 2H, CH_2-3).

6-Oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,2-Ethanediyl Acetal (4b):

The procedure described for the preparation of **4a** (Method A) is followed starting from **3b** (340 mg, 1.53 mmol), anhydrous magnesium sulphate (300 mg), and silver(I) oxide (1 g, 4.35 mmol) in ether (1 l), to give **4b**. The oily residue is purified by preparative T.L.C. on silica gel [benzene/ethyl acetate (1:1)] to give a yellow-orange oil; yield: 310 mg (92%) (Lit.[6], b.p. 150–160 °C/4 torr).

$C_{12}H_{12}O_4$	calc.	C 65.44	H 5.49
(220.2)	found	65.71	5.66

M.S.: *m/e* (relative intensity) = 220 (89, M^+), 148 (27), 147 (25), 146 (19), 86 (100).

I.R. (film): $\nu = 1656\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 6.70$ (s, $2H_{quinone}$); 4.02 (s, 4H, $2OCH_2$); 3.0–2.5 (m, 4H, CH_2-5, CH_2-8); 2.0–1.7 ppm (m, 2H, CH_2-7).

6-Oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone (4c):

The procedure described for the preparation of **4a** (Method A) is followed starting from 5,8-dihydroxy-2-tetralone (**3c**; 500 mg, 2.8 mmol), anhydrous magnesium sulphate (700 mg), and silver(I) oxide (2 g, 8.7 mmol) in ether (80 ml). In this case the reaction mixture is stirred for 2 h and the inorganic precipitate is washed repeatedly with ether instead of chloroform; yield (crude product): 380 mg (76%).

I.R. (nujol): $\nu = 1720, 1655\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 6.82$ (s, $2H_{quinone}$); 3.4–3.2 (m, 2H, CH_2-5); 3.2–2.3 ppm (m, 4H, CH_2-7, CH_2-8).

The quinone is thermally unstable; attempted recrystallisation from different solvents results in formation of dark coloured products which decompose at 160–190 °C.

5,6-Dihydroxy-1,4-naphthoquinone (7):

A powdered mixture of 5,8-dimethoxy-2-tetralone[8] (**5**; 2.5 g, 12 mmol) and silver(II) oxide (7 g, 57 mmol) is magnetically stirred and then dioxan (100 ml) and 6 normal nitric acid (10 ml) are added. At the beginning the reaction is strongly exothermic. Stirring is continued at room temperature for 15 min. Water (100 ml) is added to the resultant deep red solution which is then filtered. The aqueous solution is extracted repeatedly with ether, the organic extract is washed with water, dried with magnesium sulphate, and the solvent removed. The product is recrystallised from benzene or petroleum ether; yield: 1.43 g (62%); red needles; m.p. 178–182 °C (dec) [Lit.[12], m.p. 180–183 °C (dec)].

M.S.: *m/e* (relative intensity) = 190 (100, M^+), 162 (25), 134 (36), 108 (29).

I.R. (nujol): $\nu = 3300, 1643, 1590\ cm^{-1}$.

I.R. ($CHCl_3$): $\nu = 3535, 1666, 1645, 1594\ cm^{-1}$.

U.V. (ethanol): $\lambda_{max} = 224$ ($\log\varepsilon = 4.2$), 262 (4.0), 460 nm (3.5).

^{1}H-N.M.R. (DMSO-d_6): $\delta = 12.21$ (br s, 1H, disappears with D_2O, OH-5); 7.51, 7.22 (dd, $J = 8.4$ Hz, $2H_{arom}$); 7.05 ppm (s, $2H_{quinone}$).

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