

Synthesis of the Fungal Pigment 2,7-Dihydroxy-5-methyl-1,4-naphthoquinone

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Abstract

The title compound has been synthesized and shown to be identical with material derived from the fungus *Verticillium lamellicola* by comparison of their respective dimethyl ethers.

This paper describes a synthesis of the naphthoquinone (1). This structure was assigned in 1973 to a product isolated from broth extracts of the fungus *Verticillium lamellicola* (F. E. V. Smith). The same compound was obtained following treatment of the major metabolite lamellicolic anhydride (2) with alkali in air.¹

Natural naphthoquinones incorporating an α -methyl substituent are exceedingly rare² but compound (1) seemed accessible from intermediates employed in our earlier syntheses of natural α -methylantraquinones.^{3,4} Thus autoxidation of the tetralone (3)^{3,5} in potassium *t*-butoxide solution according to the procedure of Baillie and Thomson⁶ gave the new naphthoquinone (4) in 60% yield. Such reactions are known to proceed by introduction of an oxygen substituent adjacent to the carbonyl group followed by conversion into the 1,4-quinone system. The ¹H n.m.r. spectrum of the product (4) contained a singlet quinonoid resonance (δ 6.22) in addition to signals consistent with the substituted benzenoid ring.

Brief treatment of (4) with ethereal diazomethane gave the dimethyl ether (5). This was identical with an authentic sample of (5) derived from *V. lamellicola*.¹ The same quinone (5) was also obtained in low yield by treatment of the synthetic bromo quinone (6)³ with sodium methoxide in benzene.⁷

These comparisons confirm structure (1) for the natural quinone from *V. lamellicola*.¹ The compound itself was synthesized by brief treatment of synthetic methyl ether (4) in an aluminium chloride/sodium chloride melt.

¹ McCorkindale, N. J., McRitchie, A., and Hutchinson, S. A., *J. Chem. Soc., Chem. Commun.*, 1973, 108.

² Thomson, R. H., 'Naturally Occurring Quinones' 2nd Edn (Academic Press: London 1971).

³ Cameron, D. W., Crossley, M. J., Feutrill, G. I., and Griffiths, P. G., *Aust. J. Chem.*, 1978, **31**, 1363.

⁴ Cameron, D. W., Feutrill, G. I., Griffiths, P. G., and Hodder, D. J., *J. Chem. Soc., Chem. Commun.*, 1978, 688.

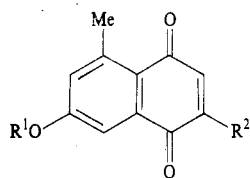
⁵ Dreiding, A. S., and Pummer, W. J., *J. Am. Chem. Soc.*, 1953, **75**, 3162.

⁶ Baillie, A. C., and Thomson, R. H., *J. Chem. Soc. C*, 1966, 2184.

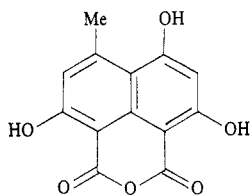
⁷ Castonguay, A., and Brassard, P., *Synth. Commun.*, 1975, **5**, 377.

Experimental

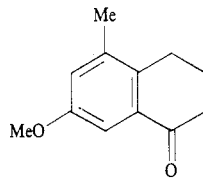
Unless otherwise stated infrared spectra were measured as KBr discs, electronic spectra in ethanol (95%) and ^1H n.m.r. spectra in CDCl_3 . Chemical shifts are quoted on the δ scale from SiMe_4 as internal reference. Thin-layer chromatography (t.l.c.) was carried out on Merck silica gel GF.



	R ¹	R ²
(1)	H	OH
(4)	Me	OH
(5)	Me	OMe
(6)	Me	Br



(2)



(3)

2-Hydroxy-7-methoxy-5-methyl-1,4-naphthoquinone (4)

A solution of the tetralone (3)^{3,5} (200 mg) in *t*-butyl alcohol (2 cm³) was added to a solution of potassium (312 mg) in *t*-butyl alcohol (8 cm³) under oxygen.⁶ The solution rapidly turned red and was shaken for 20 min. The solution was brought to pH 1 with dilute hydrochloric acid and then extracted with chloroform (2 × 25 cm³). The organic liquors were extracted with 10% aq. sodium bicarbonate (3 × 25 cm³), this extract acidified and re-extracted into chloroform (2 × 25 cm³). The chloroform solution was dried and evaporated to give 2-hydroxy-7-methoxy-5-methyl-1,4-naphthoquinone (4) (160 mg) as a yellow solid which formed red needles from ethyl acetate/light petroleum, m.p. 180–182.5° (Found: C, 66.1; H, 4.5. C₁₂H₁₀O₄ requires C, 66.1; H, 4.6%). λ_{max} (log ϵ) (in ethanol containing 1% formic acid) 264, 298, 346, 408sh nm (4.36, 4.08, 3.51, 3.14). ν_{max} 3000br, 1685, 1625, 1590, 1550 cm⁻¹. δ 2.72, s, ArCH₃; 3.93, s, OCH₃; 6.22, s, H 3; 7.02, d, *J* 2.5 Hz, H 6; 7.52, d, *J* 2.5 Hz, H 8. *m/e* 218 (M, 42%).

2,7-Dimethoxy-5-methyl-1,4-naphthoquinone (5)

(i) A solution of the foregoing compound (4) (30 mg) in ice-cold ether (10 cm³) was treated with an excess of ethereal diazomethane over 1 h. A few drops of acetic acid were added and the solution was evaporated to a yellow solid which was subjected to preparative t.l.c. in toluene/ethyl acetate (19:1). The major yellow band gave a solid which was sublimed (160°, 0.1 Pa) and recrystallized from ethyl acetate to give 2,7-dimethoxy-5-methyl-1,4-naphthoquinone (5) (12 mg), yellow needles, m.p. 172–173.5° (lit.¹ 172–173°). The melting point was undepressed in admixture with authentic material¹ and the two samples had identical i.r. absorption, R_F value and fluorescence under long wavelength u.v. light. λ_{max} (log ϵ) 263, 292, 345, 400br nm (4.31, 4.06, 3.35, 3.23). ν_{max} (in CHCl₃) 1685, 1645, 1630, 1595, 1569 cm⁻¹. δ 2.72, s, ArCH₃; 3.87, 3.93, s, s, 2 × OCH₃; 6.04, s, H 3; 6.99, d, *J* 2.5 Hz, H 6; 7.54, d, *J* 2.5 Hz, H 8. *m/e* 232 (M, 100%).

(ii) A mixture of 2-bromo-7-methoxy-5-methyl-1,4-naphthoquinone (6)³ (20 mg) and sodium methoxide (13 mg) in anhydrous benzene (4 cm³) was stirred for 72 h at room temperature. A further quantity of sodium methoxide (10 mg) was added and stirring was continued for another 24 h. The brown solution was acidified with acetic acid, filtered and the filtrate evaporated to an orange solid. Preparative t.l.c. in toluene/ethyl acetate (4:1) and recovery of the yellow band, R_F 0.26, gave compound (5) (4 mg), m.m.p. with material from (i) 172–172.5°. It was identical with this material in i.r. absorption, n.m.r. spectrum and chromatographic behaviour.

2,7-Dihydroxy-5-methyl-1,4-naphthoquinone (1)

The methyl ether (4) (20 mg) was added to a melt of anhydrous aluminium chloride (2 g) and sodium chloride (0.5 g) at 140°. The mixture was quickly heated to 180°, stirred for 2 min, air cooled for 1 min, then poured into ice (100 g) containing concentrated hydrochloric acid (10 cm³). The yellow suspension was extracted into ethyl acetate (2 × 25 cm³) and the extracts washed, dried

and evaporated to give an orange solid. This was sublimed (240°, 0.1 Pa) to give 2,7-dihydroxy-5-methyl-1,4-naphthoquinone (1) (10 mg), orange platelets, m.p. >260° (dec.) (lit.¹ 250° dec.). An authentic sample of this material from *V. lamellicola* was no longer available but the i.r. and ¹H n.m.r. spectra of synthetic (1) were in agreement with those of the natural compound.

Acknowledgments

We are grateful to Dr N. J. McCorkindale for a sample and spectra of (5) and for spectra of (1). We acknowledge an Australian Postgraduate Research Award (to P.G.G.).

Manuscript received 5 August 1980

Corrigendum

Volume 33, Number 8

Page 1733: Equation (13) should read

$$\alpha_{\alpha\beta} = \alpha_{\alpha\beta}^0 + \beta_{\alpha\beta\gamma} F_{\gamma} \quad (13)$$

Corrigendum

The Crystal and Molecular Structure of Metachloral, 2(e),4(e),6(e),8(e)-Tetrakis-(trichloromethyl)-1,3,5,7-tetraoxocan

David G. Hay and Maureen F. Mackay. *Aust. J. Chem.*, 1980, **33**, 2249–53.

Since completing the study of metachloral reported in the above paper we have discovered errors in the text and in Fig. 1. The revisions are presented here.

Page 2251, Fig. 1: for O(2), O(2'), C(1), C(2), C(3), C(4), Cl(1), Cl(2), Cl(3), Cl(4), Cl(5), Cl(6) read O(2'), O(2), C(2), C(1), C(4), C(3), Cl(5), Cl(6), Cl(4), Cl(2), Cl(1), Cl(3) respectively

Page 2252, line 3: for C(1), O(1), C(2), O(2) read C(2), O(1), C(1), O(2')

Page 2252, lines 7–9: for Atoms C(1), O(2), C(1') and O(2') describe only an approximate plane (atoms coplanar within ± 0.3 Å), and the dihedral angle between it and the plane defined above is 146°. read The dihedral angle between this plane and the plane of the four atoms C(2), O(2), C(2') and O(2') is 115°.

Page 2252, lines 9–11: The torsion angles around the tetraoxocan ring should read: O(2')–C(1)–O(1)–C(2), +12.8°; C(1)–O(1)–C(2)–O(2), –83.5°; O(1)–C(2)–O(2)–C(1'), +125.2°; C(2)–O(2)–C(1')–O(1'), –74.6°.

Page 2252, 3rd and 4th last lines: for C(1) read C(2') and for C(2) read C(1)