

# A NOVEL QUINONE DIMETHIDE FORMED BY AERIAL OXIDATION OF 1,2,3,4,5,6,7,8- OCTAHYDRO-9, 10-DIHYDROXY-1,5 ANTHRACENEDIONE

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## Abstract

During the development of a new regiospecific synthetic methodology for 1,5-dihydroxy-9, 10-anthraquinone, it was observed that (anthrufin) preparative TLC of 1,2,3,4,5,6,7,8-octahydro-9, 10-dihydroxy-1,5-anthracenedione on silica gel produced a well-defined 1:1 complex of the dione and an aerial oxidation product of it, the quinone dimethide 1,2,3,4,5,6,7-hexahydro-9,10-dihydroxy-1,5-anthracenedione; both the complex and the quinone dimethide were characterised spectroscopically.

## Introduction

Anthraquinones occur naturally [1], are used as anti-cancer drugs [2,3], and form the basis of a wide range of dyestuffs [4]. During our synthetic studies on 1,5-dihydroxy-9,10-anthraquinone [5], we found a novel phenomenon involving equilibration between the hydroquinone (2) and the isomeric quinone dimethide (4) (Fig. 1). This paper describes our studies in this area.

## Results and Discussion

Demethylation of the hydroquinone dimethyl ether (1) [5] with boron tribromide in dichloromethane at 0°C gave a crude product from which the corresponding hydroquinone (2) was obtained in 78% yield by column chromatography. Separation of the crude product by

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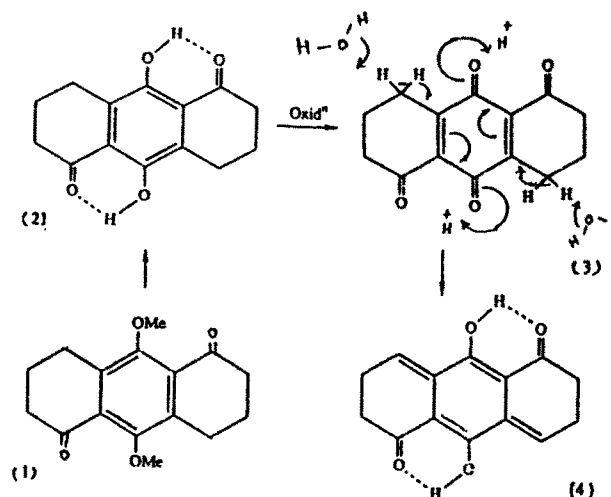


Figure 1.

preparative TLC on silica gel (Fig. 2) in air also gave the diketone (2) (band 4), but together with a range of

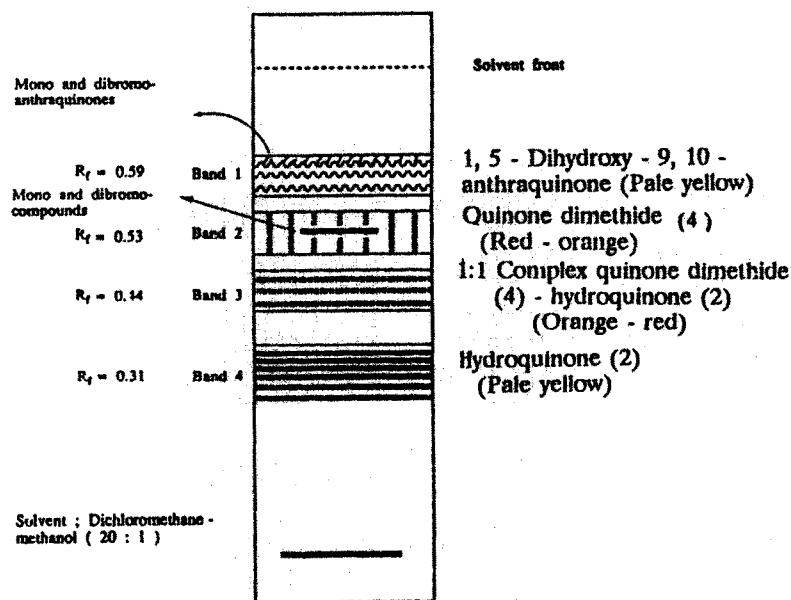


Figure 2.

oxidation products including 1,5-dihydroxy-9,10-anthraquinone [5] (band 1).

Particularly notable were band 2, which contained the quinone dimethide (4), and band 3 which contained a 1:1 complex of this quinone dimethide with the initial hydroquinone (2).

The quinone dimethide (4) was characterised by spectroscopic means (see experimental). Infrared spectroscopy indicated a strong and relatively low frequency absorption for the carbonyl group at  $1645\text{ cm}^{-1}$ , accounted for by intramolecular hydrogen bonding.

A very interesting point is that band 2 in TLC (Fig. 2) contains both the quinone dimethide (4) and the hydroquinone (2) in a 1:1 molar ratio exactly. The clearest spectroscopic characteristic of such a 1:1 complex is separate absorption by the two pairs of hydroxyl groups, at  $\delta 11.38$  and  $\delta 11.87$  respectively, with exactly equal intensity. Presumably, interaction occurs between these two components, perhaps involving a  $\pi$ -complex. The precise nature of the associative bonding in the 1:1 complex is unknown. Attempts to crystallise the complex were unsuccessful: it was only obtained as a red-brown viscous semi-solid, although this gave a  $^1\text{H}$  NMR spectrum in excellent accord with the 1:1 structure.

The quinone dimethide (4) is an oxidation product of the hydroquinone (2), probably formed by aerial oxidation on the silica TLC plate. Oxidation of (2) to the corresponding octahydro-1,5,9,10-anthracenedione (3) will result in repulsion [6] between the *peri*-carbonyl groups, which can be removed by bisenolisation to give (4), which is established by intramolecular hydrogen

bonding; enolisation may be either acid-driven [as indicated for (3)] or base induced [cf. (3)] and occur on the surface of the silica.

Monitoring of the demethylation reaction (1)  $\rightarrow$  (2) (Fig. 1) by TLC showed that it was complete in about ten minutes. However, scaling-up led to the formation of by-products, which are mainly brominated compounds. Thus, the presence of two molecular ion peaks at  $m/z$  324 and 326 of almost equal intensity in the mass spectrum may indicate that the quinone dimethide (4) is formed by aerial oxidation during the demethylation, or during aqueous work-up of the reaction mixture. These two peaks are attributed to a monobromo compound such as (5) formed via addition of hydrogen bromide (Fig. 4).

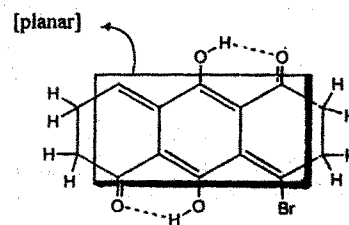


Figure 3.

### Conclusion

The central component of the novel compound (4) is a 1,4-benzoquinone dimethide moiety, established *inter*

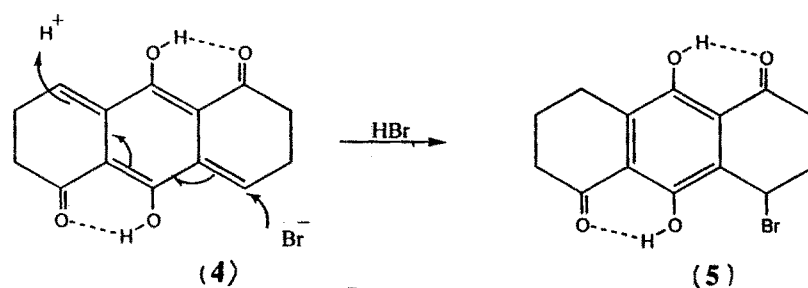


Figure 4.

alia by two electronic push (OH)-pull (C=O) systems, each giving rise to an intramolecularly hydrogen bonded six-membered quasiaromatic ring, and so resulting in a formal resemblance to 9,10-dihydro-9,10-bis(methylene)anthracene [7,8]. Further novelty is provided by the formation of a 1:1 complex between the quinone dimethide (4) and its dihydro compound (2).

### Experimental Section

Melting points (m.p.) were determined using a Kofler microscope and hot stage apparatus and are uncorrected. NMR spectra were recorded at 200 MHz using a Varian Gemini 200 spectrometer and at 300 MHz with a Bruker AC300 instrument. IR spectra were recorded on a Perkin-Elmer 1710 FT spectrometer. MS were measured using Kratos MS25 low resolution and Kratos Concept IS high resolution mass spectrometers. Spectra were determined under electron impact (EI) conditions at 70 eV, and under chemical ionisation (CI) conditions using ammonia as the reagent gas, as stated. The adsorbent for column chromatography was Merck silica 1 MFC 60-120 mesh. Preparative thin- and thick-layer chromatography were carried out using plates pre-coated with Merck silica gel 60 F254.

### 1,2,3,4,5,6,7,8-Octahydro-9,10-dihydroxy-1,5-anthracenedione (2)

A solution of (1) (10 mg, 0.0364 mmol) in dichloromethane (4 ml), at 0°C (ice-bath) was stirred magnetically and boron tribromide (0.7 ml, 0.0262 g/ml in dichloromethane, 0.0728 mol) was added. After the mixture was stirred for 13 min, it became deep red. Then 5 mL of 15% HCl solution was added and the mixture was diluted with water (to 30 ml) and extracted with ether (3×10 ml). The combined extracts were washed with water (3×10 ml), dried with sodium sulphate, and then evaporated. The crude product (0.0075 g, 85%) was solid.

Column chromatography (20:1 dichloromethane-methanol), on silica gel (C60-40/60) gave the relatively

pure product as yellowish flat beads (0.007 g, 78%), m.p. 188-195°C. This compound was also isolated by preparative TLC (Fig. 2). It had  $\nu_{\max}$  (film) 2950 m, 1640 (s), 1413, 1362 (m), 1337 (m), 1245 (s)  $\text{cm}^{-1}$ ;  $\delta$  (300 MHz,  $\text{CDCl}_3$ ) 2.12 (quintet,  $J$  6 Hz, 4H, 2 x  $\text{CH}_2$ , collapsed to triplet by irradiation at either 2.75 or 2.94), 2.75 (t,  $J$  6 Hz, 4H, 2 x  $\text{CH}_2$ , collapsed to singlet by irradiation at 2.12), 2.94 (t,  $J$  6 Hz, 4H, 2 x  $\text{CH}_2$ ), 11.88 (s, 2H, 2 x OH);  $m/z$  (EI) 248 [2.3 ( $\text{M}+2$ )<sup>+</sup>], 247 (18.8 ( $\text{M}+1$ )<sup>+</sup>), 246 [100.0 ( $\text{M}^*$ )], 218 [5.5, ( $\text{OH}$ )<sub>2</sub> C<sub>6</sub> ( $\text{CH}_2$ )<sub>3</sub> CH<sub>2</sub><sup>+</sup>], 204 [3.5, ( $\text{OH}$ )<sub>2</sub> C<sub>6</sub> ( $\text{CH}_2$ )<sub>3</sub> COCH<sub>2</sub>CH<sub>2</sub><sup>+</sup>], 190 [20.4, ( $\text{OH}$ )<sub>2</sub> C<sub>6</sub> ( $\text{CH}_2$ )<sub>3</sub> COCH<sub>2</sub><sup>+</sup>];  $m/z$  (CI/ $\text{NH}_3$ ) 264 [0.6 ( $\text{M}+\text{NH}_4$ )<sup>+</sup>], 248 [39.8 ( $\text{M}+1+\text{H}$ )<sup>+</sup>], 247 [100.0 ( $\text{M}+\text{H}$ )<sup>+</sup>], 246 [40.9 ( $\text{M}$ )<sup>+</sup>], 218 (2.2), 204 (0.6), 190 (2.9).

### 1,2,3,5,6,7-Hexahydro-9,10-dihydroxyanthracene-1,5-dione (4)

This quinone dimethide was found during work-up of the demethylation product (2), and was isolated in 6% yield by preparative TLC using 20:1 dichloromethane-methanol. (Note: this material was also present in another band, but as a 1:1 complex with the hydroquinone (2), as shown in Fig. 2). The quinone dimethide (4), a red-orange semi-solid, had  $\nu_{\max}$  (film) 3437 (s), 2917 (s), 1645 (s), 1414 (w), 1365 (m), 1328 (m)  $\text{cm}^{-1}$ ;  $\delta$  (300 MHz,  $\text{CDCl}_3$ ) 2.47 (m,  $J_1$  6 Hz,  $J_2$  3.74 Hz, 4H, 2 x  $\text{CH}_2$ , changed to a triplet + quartet by irradiation at 3.12, 3.08, 3.06, 3.01 and 2.98), 2.95-3.20 (relatively symmetrical complex multiplet, 4H, 2 x  $\text{CH}_2$ , collapsed to a quartet with further fine coupling by irradiation at 2.47), 4.75, (t,  $J$  3.95, 2H, collapsed to a singlet by irradiation at 2.47), 11.38 ('singlet', shown by expansion to be two singlets, separated by 0.6 Hz, at 20°C, 2 x OH, unchanged by irradiation elsewhere). These two singlets persisted at -50°C and +50°C, but were broader at -50°C, probably due to the greater viscosity of the solution. The position of these peaks also changed, from 11.52 (-50°C) to 11.38 (+20°C) and 11.35 (+50°C), which may be due to changes in the strength of intramolecular hydrogen bonding. At -50°C, the splitting pattern in the 2.95-3.20 region became simpler, showing a 'dd' ( $J_1$  14,  $J_2$  3.1, centred at 3.18) and a 'dt' ( $J_1$  14,  $J_2$  3.1, centred at 3.0). This compound

showed  $m/z$  (EI) 244 [3.6, (M<sup>+</sup>) C<sub>14</sub>H<sub>12</sub>O<sub>4</sub>], 245 [58.2, (M+1)<sup>+</sup>];  $m/z$  (CI/NH<sub>3</sub>) 245 [7.2, (M+H)<sup>+</sup>], 262 [3.3, (M+NH<sub>3</sub>)<sup>+</sup>], 218 (0.7), 190 (0.5). Reduction on the probe resulted in the hydroquinone (2)  $m/z$  246 [100.0, (M<sup>+</sup>), 247 [13.5, (M+1)<sup>+</sup>], 218 [5.7, (HO)<sub>2</sub>C<sub>6</sub>CO(CH<sub>2</sub>)<sub>3</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub><sup>+</sup>], 190 [17.5, (HO)<sub>2</sub>C<sub>6</sub>CO(CH<sub>2</sub>)<sub>3</sub>CH<sub>2</sub><sup>+</sup>], and  $m/z$  (CI/NH<sub>3</sub>) 246, 247, 248 (16.7, 100.0, 14.9).

#### 1:1 Complex between quinone dimethide (4) and hydroquinone (2)

This complex was isolated in about 5% yield from another band (Fig. 2) during preparative thin-layer chromatography of the crude diketone (2). It formed an orange-red semi-solid, the solid portion of which melted over the range 185-195°C. It had  $\nu_{\max}$  (film) 2955 (s), 1646 (s), 1414 (s), 1366 (m), 1333 (m), 1247 (s) cm<sup>-1</sup>;  $\delta$  (300 MHz, CDCl<sub>3</sub>) 2.1 [m,  $J$  6.5 Hz, 2 x CH<sub>2</sub>, collapsed to a triplet ( $J$  6.5 Hz) by irradiation at 2.95, and collapsed to a triplet ( $J$  5.6 Hz) by irradiation at 2.71], 2.45 (complex m, 2 x CH<sub>2</sub>, changed to simpler multiplet by irradiation at 4.75, and with other changes in the multiplet resulting from irradiation at 3.18), 2.71 (t,  $J$  6.5 Hz, 2 x CH<sub>2</sub>, collapsed to a singlet by irradiation at 2.1), 2.95 (t,  $J$  6.5 Hz, 2 x CH<sub>2</sub>, collapsed to a singlet irradiation at 2.1), 3.01 (m, 2H, collapsed to an indistinct doublet ( $J$  0.95 Hz) by irradiation at 2.45 and altered to another multiplet by irradiation at 3.18), 3.15 (t,  $J$  4.75 Hz, 1H collapsed to a singlet by irradiation at 2.45 and changed to an indistinct doublet ( $J$  1.5 Hz) by irradiation at 3.18),

3.18 (t,  $J$  4.75 Hz, 1H, collapsed to a singlet by irradiation at 2.45), 4.75 (t,  $J$  3.95 Hz, 2H collapsed to a singlet by irradiation at 2.45), 11.38 (s, 1H, unchanged by irradiation at any of the above positions);  $m/z$  (EI) reduction of the quinone dimethide part of the complex took place on the probe giving only a spectrum of the hydroquinone (2). viz 247 [5.7, (M+1)<sup>+</sup>], 246 [10.3, (M<sup>+</sup>)] 205, 204 [63.2, 35.5 (M-COCH<sub>2</sub>)<sup>+</sup>];  $m/z$  (CI/NH<sub>3</sub>) 248 [11.1, (M+1+H)<sup>+</sup>], 247 [3.0, (M+H)<sup>+</sup>]; 206 [100.0, [(M-CH<sub>2</sub>CO)+H]<sup>+</sup>].

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