Reaction of Spiroanthracenones with DDQ: a One-pot Synthesis of Benz[*a*]anthraquinones

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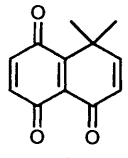
The dihydroxyspiroanthracenones **7–10** have been prepared from the spironaphthalenetrione **2** and treated with DDQ to afford the corresponding angular quinones **12–15**.

A growing group of benz[*a*]anthraquinones, named the angucyclines, have attracted much interest in recent years due to their inherent biological activity.[1–4] The synthetic effort in this field has been directed toward the preparation of some members of the angucyclinone subclass and related compounds.[5–13] Recently, we have reported the cycloaddition of the quinone **1** with various 1,3-dienes[14] as a model study for the preparation of analogues of angucyclinone **3**, starting from the spironaphthalenetrione **2**.[15] We now report results on the synthesis of various spirodihydroxyanthracenones obtained from compound **2** and their subsequent reaction with DDQ to provide access to the benz[*a*]anthraquinones in a one-pot sequence.



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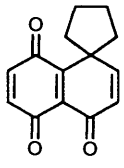

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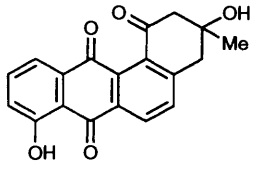

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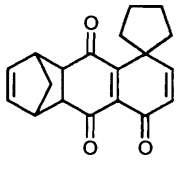

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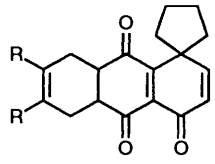
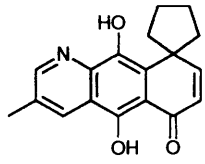
Based on the cycloaddition of compound **1** with various 1,3-dienes, which took place across the unsubstituted quinone double bond,[14] we decided to obtain the related 1,2,3,4-tetrahydrobenz[*a*]anthraquinones by a Diels–Alder reaction of the quinone **2** with 1,3-dienes, followed by aromatisation and a dienone–phenol rearrangement.

The cycloaddition of compound **2** with cyclopentadiene, buta-1,3-diene, 2,3-dimethylbuta-1,3-diene and 1-(dimethylamino)-3-methyl-1-azabuta-1,3-diene[16] afforded compounds **4**, **5**, **6** and **7**,† respectively in high yields. Adduct **4** was easily purified by column chromatography on silica gel, however compounds **5** and **6** undergo a facile enolisation on silica gel to give the hydroquinones **8** and **9**. Adduct **4** was converted into the hydroquinone **10** by reaction with a solution of hydrobromic acid in acetic acid.



5 R = H
6 R = Me



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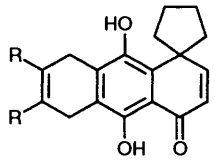
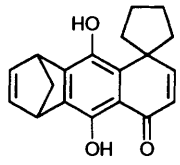


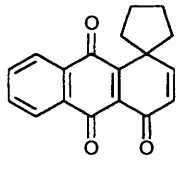
8 R = H
9 R = Me



10

We attempted to obtain the quinone **11** by reaction of the spiroanthracenone **8** with 7.5 mol equiv. of DDQ in benzene solution, under reflux, for 10 h. Surprisingly, the treatment afforded an orange solid substance (m.p. 202–204 °C) which was characterised as 6-hydroxybenz[*a*]anthracene-7,12-quinone **12**. The structure of this angular quinone **12** was deduced primarily from its ^{1}H NMR spectrum.

In order to understand the scope of this useful transformation, we treated compounds **7**, **9** and **10** with DDQ under the above conditions. In all cases the respective angular quinone **14**, **13** and **15** were isolated‡ in 53, 60 and 57% yields, respectively.



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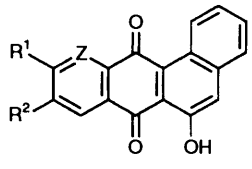
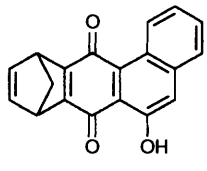


12 $R^1 = R^2 = H$, Z = CH
13 $R^1 = R^2 = Me$, Z = CH
14 $R^1 = H$, $R^2 = Me$, Z = N



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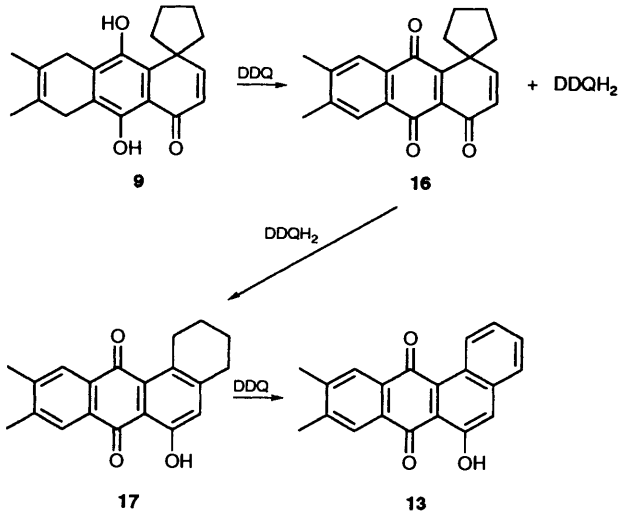
† The structure of compound **7** is proposed on the basis of the analysis of the HOMO–LUMO interactions of quinone **2** with 1-(dimethylamino)-3-methyl-1-azabuta-1,3-diene by using the AM1 semiempirical method.

‡ The structure of all new compounds were assigned on the basis of 200 MHz ^{1}H NMR, 50 MHz ^{13}C NMR, and IR spectral data. All new compounds gave satisfactory elemental analyses.

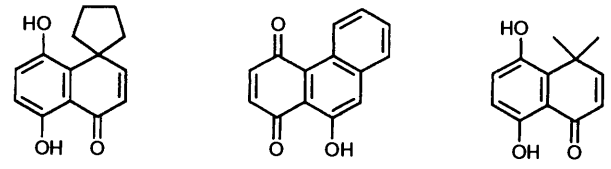
All these results indicate that the conversion of compound **9** into the angular quinone **13** probably proceeds *via* an initial hydrogen transfer reaction to provide the quinone **16**. The strong acid 2,3-dichloro-5,6-dicyano-1,4-dihydroxybenzene ($DDQH_2$) generated *in situ* in these redox reactions, induces the dienone–phenol rearrangement of compound **16** to afford the tetrahydrobenz[*a*]anthraquinone intermediate **17** which, by a subsequent dehydrogenation, leads to the angular quinone **13**. This reaction sequence, outlined in Scheme 1, is probably also operative for the conversion of compounds **7**, **8** and **10** into the angular quinones **12**, **14** and **15**.

The reaction sequence of Scheme 1 was supported on the



9 **16** **17** **13**

Scheme 1



18 **19** **20**

basis of two additional experiments. When the reaction of compound **9** with DDQ was performed for 4 h in a benzene solution, the quinone **16** was detected (^1H NMR) and isolated from the reaction mixture. Furthermore, the reaction of compound **16** with 2 mol equiv. of $DDQH_2$ in benzene solution at reflux for 16 h, afforded a 60:40 mixture of compounds **16** and **17** (evaluated by ^1H NMR); the tetrahydrobenz[*a*]-anthraquinone **17** was readily isolated by column chromatography.

It is noteworthy that the reaction of spironaphthalenone **18** with DDQ provides the 6-hydroxyphenanthrenequinone **19** in 67% yield. However, when compound **20** was submitted to the same treatment, only the quinone **1** was generated. The ability of compounds **7**, **8**, **9**, **10** and **18** to rearrange, in contrast with the inertness of **20**, may be attributed to the strain imposed by the spiro substituents, which is alleviated by ring expansion.

In summary, we have developed an efficient method[17] to obtain the benz[*a*]anthraquinones from the naphthalenetrione **2** through a three steps sequence. The dienone–phenol rearrangement involved in this new method represents the first example of this type of rearrangement induced by an organic acid generated *in situ* in a non-aqueous medium.

Experimental

Preparation of 9,10-*Hydroxyspiro*[5,8-*hydroanthracene*-1,1′-*cyclopentan*]-4-*one* **8**.—Buta-1,4-diene was bubbled for 3 min through a solution of the quinone **2** (150 mg, 0.66 mmol) in dichloromethane (20 cm^3), and then the mixture was left in a sealed flask at room temperature for 3 days. The volatile components were evaporated and the resultant pale yellow residue was dissolved in benzene (10 cm^3) and stirred overnight with silica gel (0.5 g). Filtration, followed by evaporation of the solvent gave the anthracenone **8** (150 mg, 82%) as a yellow solid, m.p. 231–232 °C (cyclohexane) (Found: C, 76.5; H, 6.6. $C_{18}H_{18}O_3$ requires: C, 76.6; H, 6.4%); ν_{max}/cm^{-1} 3200 and 1620; $\delta_H(CDCl_3$; 200 MHz) 1.60–2.80 (8 H, m, 4 × CH_2), 3.20 (4 H, br s, 5-CH_2 and 8-CH_2), 5.80–5.60 (2 H, m, 6- and 7-H), 6.15 (1 H, d, $J_{2,3}$ 10, 2-H), 7.14 (1 H, s, OH), 7.16 (1 H, d, $J_{3,2}$ 10, 3-H) and 13.16 (1 H, s, OH).

One-pot Synthesis of 6-*Hydroxybenz*[a]*anthracene*-7,12-*quinone* **12**.—A mixture of the spiroanthracenone **8** (100 mg, 0.355 mmol) and DDQ (600 mg, 2.64 mmol) in benzene (30 cm^3) was heated under reflux for 10 h. The reaction mixture was poured into chloroform (30 cm^3) and then washed with 10% aq. sodium hydrogen carbonate (2 × 20 cm^3). The organic layer was washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to afford the crude quinone **12**. Preparative TLC using dichloromethane as the eluent gave pure quinone **12** (61 mg, 63%), as an orange solid, m.p. 202–204 °C (ethanol) (Found: C, 78.6; H, 3.8. $C_{18}H_{12}O_3$ requires C, 78.8; H, 3.7%); ν_{max} KBr/cm^{-1} 1630 and 1600; $\delta_H(CDCl_3)$ 7.50 and 7.65 (3 H, 2 m, 2-, 3- and 4-H), 7.62 (1 H, s, 5-H), 7.79 (2 H, m, B_2 of A_2B_2, 9- and 10-H), 8.25 (2 H, m, A_2 of A_2B_2, 8- and 11-H), 9.41 (1 H, m, 1-H) and 12.41 (1 H, s, OH); $\delta_C(CDCl_3)$ 119.5, 121.1, 126.2, 126.4, 127.2, 127.3, 127.9, 128.5, 128.8, 129.5, 129.9, 132.0, 133.6, 135.0, 139.2, 156.8, 185.4 and 190.1.

Acknowledgements

Support provided by the Fondo Nacional de Ciencia y Tecnologia de Chile (FONDECYT, Grant No. 92-0603 and 92-055) is gratefully acknowledged. Thanks are also due to FONDECYT for a fellowship to C. D. P.-M.

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Paper 4/06553K
Received 26*th October* 1994
Accepted 26*th October* 1994