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Studies on quinones. Part 34: The reaction of styrene with activated 1,4-benzoquinones: access to potential antiprotozoal pyranobenzoquinones☆

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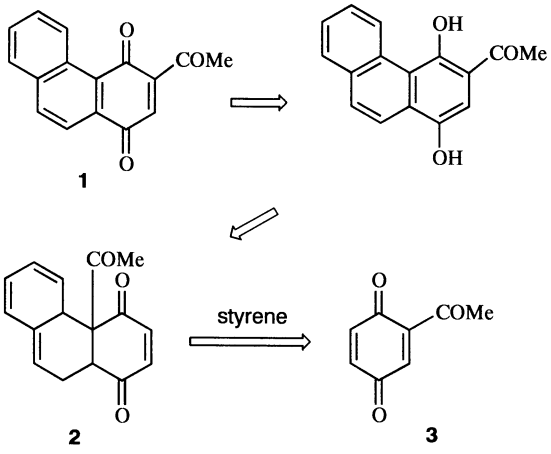
Abstract—Styrene reacts with highly electrophilic monosubstituted 1,4-benzoquinones to provide pyranobenzoquinone and phenanthrene derivatives, depending on the nature of the quinone substituent. The participation of transient Diels–Alder adduct intermediates in these reactions and their thermal-induced rearrangements are discussed. The in vitro antiparasital effects of the pyranobenzoquinones against *Trypanosoma cruzi* and *Leishmania* spp. are reported. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The Diels–Alder reaction of 1,3-dienes and monosubstituted 1,4-benzoquinones containing electron-withdrawing groups (activated quinones) occurs across the substituted quinone double bond providing angular cycloadducts.[1–10] A noteworthy feature of these Diels–Alder adducts is that they undergo thermal[2–4,6–8] and acid-induced rearrangements[9,10] to afford a variety of carbo- and heterocyclic compounds. Our interest in the synthesis and biological evaluation of angular quinones related to antibiotic angucyclinones[11,12] and heterocyclic analogues[13,14] led us to explore the preparation of 2-acetylphenanthrene-1,4-quinone (**1**), a potentially useful precursor of carbo- and heterocyclic angular quinones. Based on the aforementioned behaviour of activated 1,4-benzoquinones and on the cycloaddition reactions of styrene with quinones,[15–19] we envisaged a retrosynthetic approach to **1** via a Diels–Alder reaction of styrene and 2-acetyl-1,4-benzoquinone (**3**) followed by a [1,5] acetyl migration in adduct **2** (Scheme 1).

The regiochemistry of adduct **2** was assumed by considering the primary HOMO and LUMO coefficients of the diene (styrene) and quinone **3**, respectively.[20]



Scheme 1. Strategy for angular quinone **1** synthesis.

2. Results and discussion

The reaction of styrene with 2 equiv. of quinone **3** was firstly examined in benzene at room temperature. Under these conditions no reaction was observed. Nevertheless, when the reaction was carried in benzene at reflux for 7 h, a complex reaction mixture was obtained. Flash chromatography provided pyranobenzoquinone **4** (67%) together with trace amounts of benzopyran **5**. Along with these products 2,5-dihydroxyacetophenone (**6**) was detected (^{1}H NMR) in the reaction mixture.

☆ For Part 33 of this series see ref. 29.

Keywords: Diels–Alder adduct rearrangements; pyranobenzoquinones; antiparasital activity.

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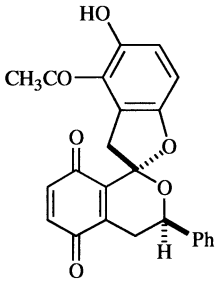

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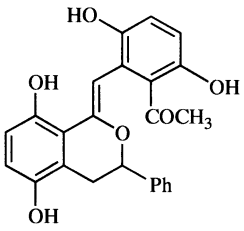

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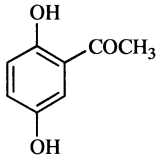

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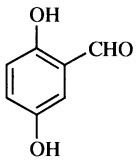
The structure of compound **4** was supported by spectral data and elemental analysis. The ^{1}H and ^{13}C NMR spectra revealed the presence of a quinone nucleus [δ_H 6.86 (d) and 6.74 (d); δ_C 186.0 and 187.4] fused to a pyran ring [δ 5.19 (dd, 1H), 3.07 (dd, 1H), and 2.63 (dd, 1H)]. The spiro-fused benzo[*b*]furan fragment in **4** was deduced from the signals of two coupled methylene protons at δ 4.11 and 3.60 (J=16.6 Hz), an acetyl group (δ 2.55) and a strong hydrogen bonded hydroxyl proton (δ 12.27). The orientation of the phenyl group on the pyran ring was found to be pseudoequatorial on the basis of the values of the vicinal coupling constant between the methine and methylene protons (J=3.1 and 11.5 Hz). The relative configuration of compound **4** was established by NOE-difference spectrum. Irradiation of the proton at δ 5.19 ppm results in no nuclear Overhauser enhancement of the protons at δ 4.11 and 3.60 ppm. Hence, the pseudoaxial methine proton on the pyran ring, and the methylene protons on the furan ring, were on opposite faces of the molecule **4**.

The structure of compound **5** was mainly assigned by the ^{1}H NMR spectrum which displays hydroxyl protons (δ 12.31, 8.47 and 2.49 ppm), the protons of a phenyl group (δ 7.27), four aromatic protons of two AB systems [δ 7.03 and 6.92 (2d, 2H, J=9 Hz); 6.70 and 6.49 (2d, 2H; J=8.5 Hz)], an olefinic proton (δ 6.23), three mutually coupled protons [δ 5.74 (dd, J=5.9 and 9.5 Hz); δ 3.22 (dd, 1H, J=6 and 17.7 Hz], 2.84 (d, 1H, J=17.9 Hz)] and the protons of an acetyl group at δ 2.74 ppm.

Although the reaction of **3** with styrene did not yield the desired compound **2**, it did reveal a new access to the pyranobenzoquinone system, which is present in a variety of biological relevant naturally occurring pyranonaphthoquinones.[21] In view of this interesting formation of the pyranobenzoquinone system we investigated the scope of the reaction of styrene with the activated benzoquinones **8** and **11**.

The reaction of **8** and 1.1 equiv. of styrene was performed by in situ generation of **8** from 2,5-dihydroxybenzaldehyde (**7**) and silver(I) oxide in benzene solution, under reflux, for 4 h. The treatment afforded a reaction mixture from which pyranobenzoquinone **9** (66%) was isolated by chromatography. The structure of **9** was established by its ^{1}H and ^{13}C NMR spectra, and by comparison with the spectral properties of pyranobenzoquinone **10**, which was prepared as previously reported.[22] The relative *trans* configuration between the aryl substituents in **9** was deduced by comparison of the ^{1}H NMR spectral properties with those of structurally related 1,3-disubstituted benzo- and naphtopyrans with known stereochemistry.[23,24]



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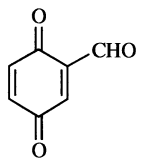

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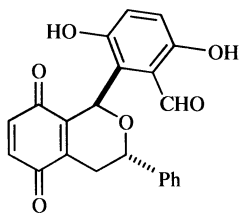

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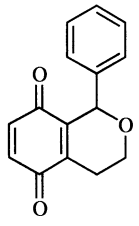

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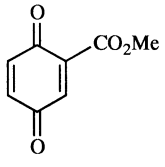
The reaction of styrene with 2-methoxycarbonyl-1,4-benzoquinone (**11**) was carried out in refluxing benzene for 24 h. In this case the result was different; in fact, when **11**, prepared from methyl 2,5-dihydroxybenzoate,[25] was reacted with styrene, compounds **12** (10%) and trace amounts of quinone **13** were isolated from the complex reaction mixture. Location of the methoxycarbonyl group in **12** was assigned on the basis of the HMBC spectrum. The quaternary carbon at δ 159,8 ppm (C-4) showed ^{2}J-HMBC and ^{3}J-HMBC correlations with the proton of the hydrogen bonded OH group at δ 11.07 ppm, and the proton at δ 7.60 ppm (C-5), respectively.



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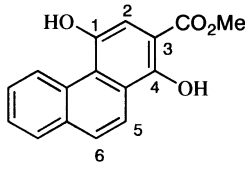

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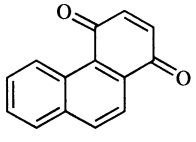

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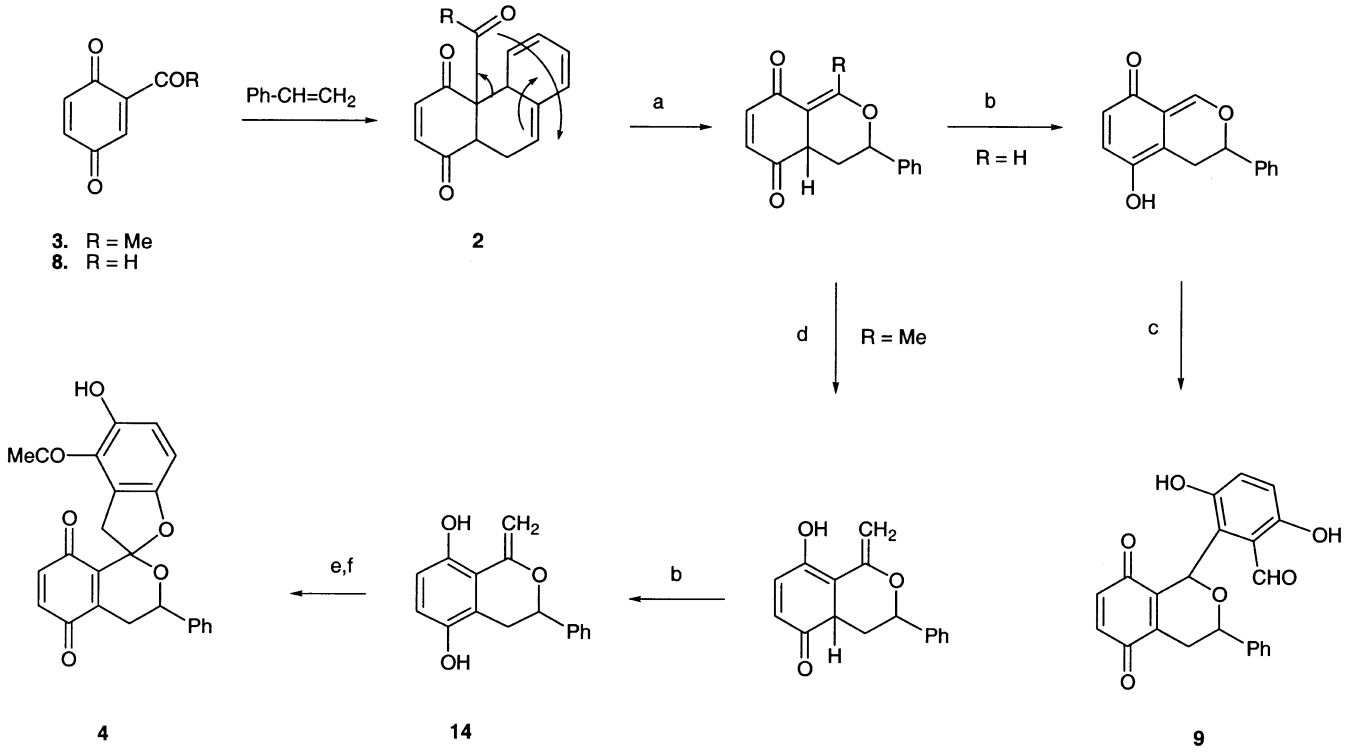
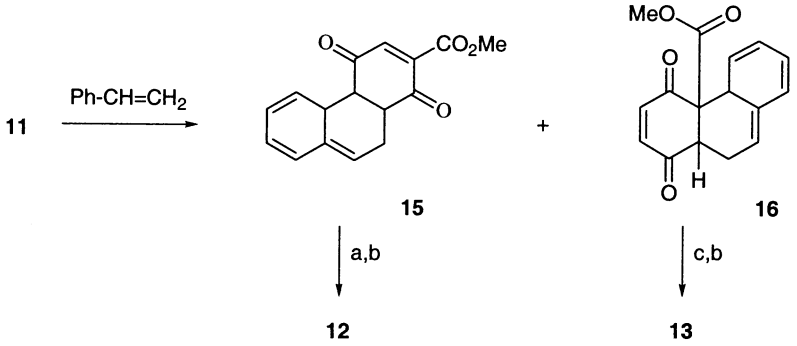


Scheme 2. Probable mechanism formation of pyranobenzoquinones **4** and **9**. *Reactions* (a) [3,3] sigmatropic rearrangement; (b) enolisation; (c) Michael reaction with **8**, (d) [1,5] sigmatropic hydrogen shift; (e) [3+2] process with **3**, (f) redox reaction with **3**.

Concerning the mechanism of the reactions studied, it is reasonable to assume that the products were formed via Diels–Alder adduct intermediates. In the case of the reaction of styrene with 2-acetyl-1,4-benzoquinone (**3**) we found a similar reaction reported by Bruce et al.[26] On the basis of this precedent and the relatively low polarity of the reaction medium (benzene) compounds **4** and **5** were probably formed through a [3,3] sigmatropic shift in Diels–Alder adduct **2** as shown in Scheme 2. Compound **5**, which was not included in Scheme 2, presumably was produced by Michael addition of adduct **14** to **3** followed by deprotonation–enolisation reactions in the respective intermediate. It is reasonable to assume that formation of quinone **9** also proceeds via a [3,3] sigmatropic shift in the angular Diels–Alder adduct resulting from the cycloaddition between **8** and styrene (Scheme 2).

The different behaviour of quinone **11** with respect to quinones **3** and **8** may be explained by considering that the addition of diene across the 5,6-double bond of quinone **11** is more favourable than across the 2,3-double bond (Scheme 3). This may be due to steric interaction between the substituents that inhibit the approach of the reacting components. A similar result has previously been reported by Sammes et al, in which 2-benzoyl-1,4-benzoquinone reacts with 1,3-dienes to yield 5,6- or 2,3-cycloadducts depending on the diene.[4]

Our interest to evaluate the antiprotozoal efficacy of heterocyclic quinones led us to test the in vitro capability of pyranobenzoquinones **4**, **9** and **10** against *Trypanosoma cruzi* and *Leishmania* spp. The bioassays against *T. cruzi* were carried out using the trypomastigotes (blood) forms of the parasite obtained from mice inoculated intraperitoneally, as was described in detail in a previous work.[27] Quinones **4** and **10** display 98 and 73% reduction in parasite



Scheme 3. Probable course formation of compounds **12** and **13**. *Reactions*: (a) enolisation, (b) aromatisation, (c) *cis* elimination.

Table 1. In vitro activity of quinones **4** and **9** against macrophages and amastigotes forms of *L. amazonensis*

Concentration ($\mu g\ mL^{-1}$)	Compound **4**				Compound **9**			
	Macrophages		Amastigotes		Macrophages		Amastigotes	
	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive
Control	12	88	22	78	29	71	22	78
100	6	94	74	26	29	71	28	72
50	6	94	46	54	23	77	78	22
25	8	92	46	54	22	78	77	23

number at 250 $\mu g\ mL^{-1}$ using gentian violet as the reference drug.

Quinones **4**, **9** and **10** were also cytotoxic at 10 $\mu g\ mL^{-1}$ against *L. brasilensis*, *L. donovani* and *L. amazonensis*. Compounds **4** and **9** were evaluated in vitro against intracellular *L. amazonensis* amastigotes in mouse peritoneal macrophages (Table 1). A moderate activity for **4** was observed in these assays since a 46% of lysis was counted at low concentration (25 $\mu g\ mL^{-1}$) while a 74% of lysis was observed at 100 $\mu g\ mL^{-1}$. Quinone **9** displays a better activity since a 77% of lysis was observed at 25 $\mu g\ mL^{-1}$. The results obtained in these trials confirm the leishmanicidal effect of pyranoquinones **4** and **9** at non cytotoxic concentration against macrophages.

In conclusion, our study provides evidence of the thermal rearrangement of transient Diels–Alder adducts of styrene and activated benzoquinones. The reactions of styrene with quinones **3** and **8** offers interesting possibilities to prepare 1,3-substituted pyranobenzo- and pyranonaphthoquinones from acyl-1,4-quinones. Further studies on the synthesis of new members of pyranoquinones and their biological evaluation are underway.

3. Experimental

3.1. General methods

All reagents were of commercial quality, reagent grade, and were used without further purification. Mps were determined on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were recorded on FT Bruker spectrophotometer for KBr disc and the wave numbers (ν) are given in cm^{-1}. The ^1H, ^{13}C NMR, and NOE difference spectra were acquired on a Bruker AM-200 spectrometer. HMBC spectra were recorded on a Bruker AM-300 spectrometer. The NMR spectra were determined in $CDCl_3$ solutions using TMS as an internal reference. Chemical shifts are reported in δ ppm downfield and J values are given in Hertz. Silica gel Merck 60 (70–230 mesh), and DC-Alufolien $60F_{254}$ were used for preparative column and analytical TLC, respectively.

3.1.1. Reaction of styrene with 2-acetyl-1,4-benzoquinone (3). A solution of quinone **3** (0.76 g, 7.45 mmol), freshly distilled styrene (0.39 g, 3.73 mmol) and benzene (75 mL) was refluxed for 7 h. The solvent was removed in vacuo and the residue was flash chromatographed on silica gel (dichloromethane) to give 4′-acetyl-5,8-dioxo-2′,3,3′,4,5,8-hexahydro-5′-hydroxy-3-phenyl-spiro{1*H*-benzo[*c*]pyran-1,2′-benzo-[*b*]furan} (**4**) (1.12 g; 67%) as yellow crystals (ethyl alcohol) mp 130–131°C (Found: C, 71.82; H, 4.55. $C_{24}H_{18}0_6$ requires: C, 71.64; H, 4.51%); IR: ν 3180 br (O–H), 1675, 1670, and 1640 (C=O); ^1H NMR: δ 2.55 (s, 3H, COMe), 2.63 (dd, 1H, J=19.5 and 11.5 Hz, 4-H),); 3.07 (dd, 1H, J=19.5 and 3.1 Hz, 4-H′), 3.60 (d, 1H, J=16.5 Hz, 2′-H), 4.11 (d, 1H, J=16.5 Hz, 2′-H′), 5.19 (dd, 1H, J=11.5 and 3.1 Hz, 3-H), 6.78 (d, 1H, J=10.2 Hz, 6- or 7-H), 6.84 (d, 1H, J=8.9 Hz, 5′-H), 6.87 (d, 1H, J=10.2 Hz, 7- or 6-H), 6.99 (d, 1H, J=8.9 Hz, 6′-H), 7.27–7.43 (m, 5H, Ar–H), 12.27 (s, 1H, OH); ^{13}C NMR:δ 32.0, 46.5, 55.3, 71.8, 107.2, 118.2, 118.7, 119.2, 127.4, 128.1, 129.1, 129.6, 137.2, 138.0, 138.6, 141.7, 144.0, 152.0, 158.6, 186.0, 187.4, 205.5.

Further elution with dichloromethane provided trace amounts of 1(2-acetyl-3,6-dihydroxybenzylidene)-5,8-dihydroxy-3-phenyl-3,4-dihydro-1*H*-benzo[*c*]pyran (**5**); ^1H NMR:δ 12.31 (s, 1H, exchangeable with D_2O, OH), 8.47 (s, 1H, exchangeable with D_2O, OH), 7.27 (m, 5H, Ar–H), 7.03 (d, 1H, part A of AB system, J=9 Hz, Ar–H), 6.92 (d, 1H, part A of AB system, J=9 Hz, Ar–H), 6.70 (d, 1H, part A of AB system, J=8.5 Hz, Ar–H), 6.49 (d, 1H, part A of AB system, J=8.5 Hz, Ar–H), 6.23 (s, 1H, olefinic), 5.74 (dd, 1H, J=5.9 and 9.5 Hz, methine), 3.22 (dd, 1H, J=6 and 17.7 Hz, C*H*H], 2.84 (d, 1H, J=17.9 Hz, CH*H*), 2.74 (s, 3H, $COCH_3$), 2.49 (s, 1H, exchangeable with D_2O, OH); ^{13}C NMR: δ 29.6, 30.5, 75.7, 108.5, 115.1, 117.8, 119.5, 119.7, 119.9, 122.2, 122.3, 126.1, 126.6, 128.0, 128.5, 141.1, 147.7, 149.1, 152.6, 153.9, 158.1, 203.8.

3.1.2. Reaction of styrene with in situ generated 2-formyl-1,4-benzoquinone (8). A stirred suspension of 2,5-dihydroxybenzaldehyde (**7**) (0.50 g, 2.62 mmol), freshly distilled styrene (0.22 g, 4.04 mmol), silver(I) oxide (1.34 g, 2.62 mmol), dry magnesium sulfate (500 mg) and benzene (50 mL) was heated to reflux for 5 h. The reaction mixture was filtered, the filtrate was evaporated under reduced pressure and the excess of styrene was removed by maintaining the residue under vacuo for 2 h at 70–80°C. Flash chromatography of the residue on silica gel (dicloromethane) provided *trans*-1(2-formyl-3,6-dihydroxyphenyl)-3-phenyl-3,4-dihydro-1*H*-benzo[*c*]-pyran-5,8-dione (**9**) (0.45 g; 66%) as a red solid (chloroform) mp 174.5–175.4°C (Found: C, 70.32; H, 4.75. $C_{22}H_{16}O_6$ requires: C, 70.21; H, 4.29%); IR: ν 3284 (OH), 1658 and 1625 (C=O); ^1H NMR: δ 2.54 (dd, 1H, J=17.5 and 9.0 Hz, 4-H), 2.95 (d, 1H, J=17.5 Hz, 4-H′), 5.27 (d with fine coupling, 1H, J=9.0 Hz, 3-H), 6.10 (s, 1H, 1-H), 6.70–7.00 (m, 4H, 6-, 7-, 4′- and 5′-H), 7.37 (m, 5H, Ar–H),

9.74 (s, 1H, CHO), 10.75 (s, 1H, OH); ^{13}C NMR: δ 28.6, 29.7, 53.5, 68.8, 93.8, 118.8, 120.3, 122.0, 126.1, 128.4, 126.8, 128.9, 136.3, 136.4, 136.58,139.7, 141.6, 150.4, 157.8, 184.6, 186.3, 196.2.

3.1.3. 3,4-Dihydro-1*H*-benzo[*c*]pyran-5,8-quinone (10). Quinone **10** was prepared via a previously reported procedure;[22] ^{1}H NMR: δ 2.65 (m, 2H, 4-H), 3.80 (m, 2H, 3-H), 5.67 (dd, 1H, J=2 and 2 Hz, 1-H), 6.66 (d, 1H, J=10 Hz, 6- or 7-H), 6.80 (d, 1H, J=10 Hz, 7- or 6-H), 7.33 (m, 5H, Ar–H); ^{13}C NMR:δ 22.4, 59.4, 72.8, 128.5, 128.5, 128.57, 136.1, 136.6, 139.0, 141.0, 142.0, 185.3, 186.1.

3.1.4. Reaction of styrene with 2-methoxycarbonyl-1,4-benzoquinone (11). A solution of quinone **11** (1.00 g, 6.02 mmol), freshly distilled styrene (0.62 g, 5.96 mmol) and benzene (50 mL) was heated to reflux for 24 h. The solvent was removed in vacuo and the residue was flash chromatographed on silica gel (dichloromethane–light petroleum 1:1) to afford methyl 1,4-dihydroxyphenantrene-3-carboxylic acid (**12**) (0.16 g; 10%) as yellow crystals (ethyl alcohol) mp 118–120°C. (Found: C, 71.65; H, 4.21. $C_{16}H_{12}O_4$ requires: C, 71.64; H, 4.51%); IR: ν 3400 br (O–H), and 1665 (C=O); ^{1}H NMR:δ 4.09 (s, 3H, OMe), 6.91 (d, 1H, J=9 Hz, 6-H), 7.36–7.51 (m, 4H, 4-, 7-, 8-, and 9-H), 7.60 (d, 1H, J=9 Hz, 5-H), 7.89 (dd, 1H, J=8 Hz, 2, 10-H), 11.07 (s, 1H, OH); ^{13}C NMR:δ 52.3, 103.3, 103.5, 114.1, 116.4, 125.1, 128.7, 128.9, 129.0, 130.1, 148.7, 158.0, 159.8, 171.3. Further elution provided trace amounts of phenanthrene-1,4-dione (**13**) as red crystals 150–151.5°C (lit.28 148–150°C).

3.2. In vitro leishmanicidal activity

Promastigotes inhibition studies were performed on *L. amazonensis* (IFLA/BR/67/PH8), *L. brasiliensis* (MHOM/BR/75/M2903) and *L. donovani*(MHOM/BR/74/PP75) grown at 22°C in Schneider's *Drosophila* medium containing 20% foetal bovine serum. Promastigotes cultures in the logarithmic phase were transferred at a concentration of 10^6 cell per mL. Compounds (1 mg) were dissolved in 40 μL DMSO and diluted with the medium to reach compound concentrations of 100 μg mL^{-1}. The solution was placed in microtitre plates. All assays were carried out in triplicate. The activity of the compounds was evaluated after 72 h by optical observation of a drop of each culture with a microscope and compared with control cells. Assays to assess the drug concentration required to inhibit parasite growth were performed in triplicate.

3.3. Activity on *Leishmania* spp. amastigotes

Resident macrophages were harvested from the peritoneal cavities of normal BALB/c mice in ice-cold phosphate-buffered saline (PBS). The cells were plated at 2×106 per mL (0.1 mL per well) in Lab-Tek 24-chamber slides (Nunc, Naperville, I11) and incubated at 37°C under an atmosphere of 4% CO_2 for 1 h. *L. amazonensis* amastigotes were isolated from mice granuloma and were added at 5:1 parasite/macrophage ratio, and the cultures were incubated for a further 4 h. Then, 0.5 mL of product in RPMI 1640 medium (Gibco France) at different concentrations in triplicate was added for a further 48 h. The cultures were examined under light microscopy. The number of dead intracellular amastigotes was determined by counting at least 100 macrophages, previously stained with Trypan blue. The results were expressed as percentage of dead amastigotes in relation to infected controls without the product.

A similar procedure was carried out to test cytotoxicity. Non infected macrophages were stained with Trypan Blue and the results are expressed as percentage of dead macrophages in relation with controls without the product.

Acknowledgements

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