A Convenient Synthesis of Benzo[*g*]pyrrolo[3,2-*c*]quinoline-6,11-diones

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Abstract: The synthesis of a new class of angular tetracyclic quinones is described. Our strategy involves Diels–Alder reaction of pyrroloquinolinequinone **9**, generated in situ from pyrroloquinoline **8**, and dienes. The required pyrroloquinoline **8** was prepared in four steps from commercially available compounds. All compounds were tested for trypanocidal activity in vitro against *Trypanosoma cruzi* epimastigotes.

Key words: benzo[*g*]pyrrolo[3,2-*c*]quinoline, heterocyclic quinones, pyrroloquinoline, Diels–Alder reaction, heterocycles

Phenanthroviridin (**1**) and its aglycon **2** are the only examples of naturally occurring benzo[*b*]phenanthridines (Figure 1). These compounds were isolated from *Streptomyces viridiochromogenes* DSM3972, and both are active against lung carcinoma in mice.[1] The unique structural pattern and the potential pharmacological interest of phenanthroviridins **1** and **2**, have stimulated the total synthesis of these compounds.[2] However, analogues of these molecules with heterocyclic rings replacing the phenyl moieties have not been reported.

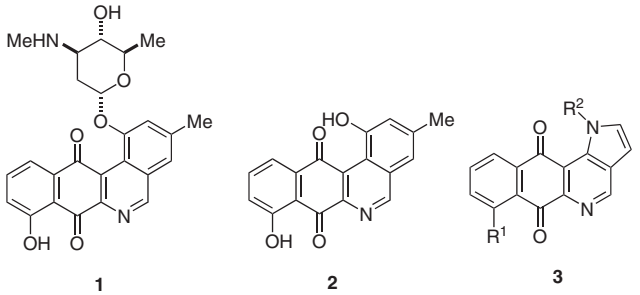
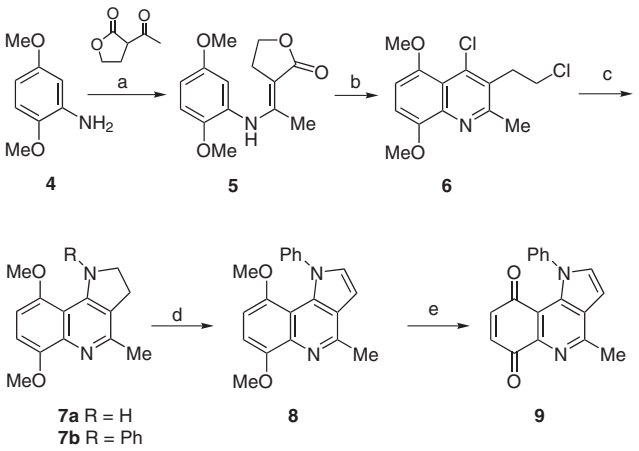


Figure 1 Phenanthroviridin (**1**), its aglycon **2** and the hetero analogue **3**

In our continuing search for new heterocyclic quinones with useful biological activity,[3] we wished to develop a method for the synthesis of hetero analogs of phenanthroviridin such as **3** (Figure 1). We assumed that these compounds would be accessible through pyrroloquinoline **7** as key intermediate. It is interesting to note that compound **7** has an angular tricyclic ring system which is the core structure unit of some natural alkaloids with unique biological activity.[4] Their unusual structure have stimulated intense synthetic studies,[5] however, the search for simple and suitable methods that incorporate the quinone moiety is always necessary. We describe here our approach to obtain benzo[*g*]pyrrolo[3,2-*c*]quinolines from readily available compounds. Retrosynthetic considerations suggested that a useful precursor for our purpose was dichloroquinoline **6**, which could be obtained from 2,5-dimethoxyaniline (**4**) (Scheme 1). The reaction of anilines with 2-acetylbutyrolactone, described first by Ozawa et al.,[6] is emerging as a helpful method for the synthesis of pyrroloquinolines.[7]



Scheme 1 *Reagents and conditions*: (a) 2-acetylbutyrolactone, toluene, reflux, 24 h, 83%; (b) $POCl_3$, reflux, 4 h, 63%; (c) aniline, EtOH, reflux, 2 h, 70%; (d) Pd/C, mesitylene, reflux, 24 h, 57%; (e) AgO, HNO_3, THF, 5 min.

Reaction of aniline **4** with acetylbutyrolactone in toluene at 110 °C gave furanone **5** in good yield, which underwent cyclization upon treatment with phosphorus oxychloride at 80–90 °C to give dichloroquinoline **6**. Attempt to obtain N-unsubstituted pyrrolo[3,2-*c*]quinoline **7a** by reaction of **6** with sodium azide and triphenylphosphine failed; nevertheless *N*-phenylpyrrolo[3,2-*c*]quinoline **7b** was obtained in 70% yield by treatment of compound **6** with aniline in ethanol at reflux. The next step was the aromatization of the five-membered ring using 10% Pd/C in boiling mesitylene, to afford compound **8**. The shielding effect of the *N*-phenyl ring accounts for the unusual chemical shift of the methoxy group at C-6 in compounds **7b** and **8** (δ = 2.64 and 3.00, respectively). Then the oxidative demethylation of hydroquinone dimethyl ether **8** was studied. Initially, we attempted oxidation with ceric ammonium nitrate (CAN),[8] but after 6 hours at room temper-

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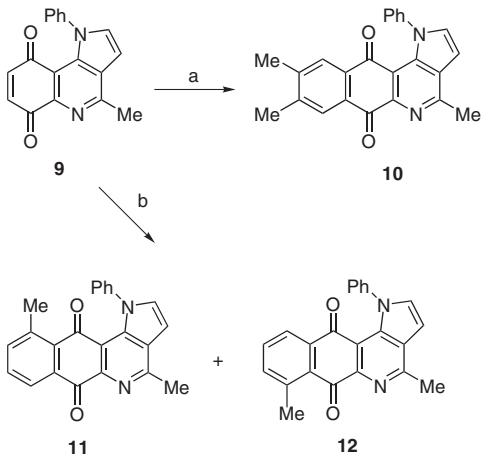
ature the starting material was recovered. However, using silver(II) oxide and nitric acid[9] quinone **9** could be observed by TLC, but decomposed during chromatographic purification. To overcome this problem, quinone **9** generated in situ, was trapped with 2,3-dimethylbuta-1,3-diene followed by the addition of DBU to give tetracyclic quinone **10** in 81% yield.

Similarly, quinone **9** was reacted with penta-1,3-diene to afford a mixture of regioisomers **11** and **12** in a 1:2.4 ratio (Scheme 2). Although in this case the regioselectivity was not high, it is interesting to note that the reaction of quinoline-5,8-dione with penta-1,3-diene gave almost a 1:1 mixture of regioisomers.[10]



Scheme 2 *Reagents and conditions*: (a) i. 2,3-dimethylbuta-1,3-diene, $CHCl_3$, 120 °C, 18 h, ii. DBU, r.t., 24 h, 81%; (b) i. penta-1,3-diene, $CHCl_3$, 120 °C, 18 h, ii. DBU, r.t., 24 h, 64%.

The structural assignment was made by 2D ^1H-^{13}C HMBC correlations performed on the major regioisomer **12**. Interestingly, the chemical shift of the methyl protons at C-10 in compound **11** ($\delta = 2.31$) is shielded compared to that of the methyl protons at C-7 in **12** ($\delta = 2.87$), probably due to the anisotropic shielding effect of the N-aromatic ring.

Encouraged by the interesting antiprotozoal activity exhibited by many heterocyclic quinones,[3,11] we next examined the in vitro trypanocidal activity of the synthesized compounds against Tulahuén strain at 50, 20, 10 and 5 μM concentrations as described earlier.[12] The IC_{KC50} at 5 μM concentration for all compounds was then determined in order to establish their relative efficacy in vitro, compared to the standard drug benznidazole. Compounds **6** and **11** are more active than the standard drug benznidazole. The most active compound is the one not possessing the quinone moiety **6**, probably because it is a better electrophile than quinone **11** (Table 1).

In summary, the synthesis of the phenanthroviridin hetero analogues of **3** has been successfully accomplished through a simple method. This strategy should enable access to other hetero analogues of phenanthroviridin.

Table 1 Effect of Compounds upon Culture Growth of *T. cruzi* Epimastigotes

Compound	IC_{kc50} (μM)
5	>100
6	6.0 ± 0.2
7b	21.2 ± 2.8
8	19.1 ± 1.2
10	13.2 ± 2.7
11	10.4 ± 0.1
12	17.1 ± 0.4
benznidazole	11.4 ± 1.5

Melting points were determined with a Meltemp apparatus and are not corrected. IR spectra were obtained on a Bruker Model Vector 22 spectrophotometer. NMR spectra (^1H and ^{13}C) were recorded on a Bruker AM-200 spectrometer 200 (200 MHz and 50 MHz), using TMS as internal reference. Column chromatography was performed on silica gel Merck 60 (70–230 mesh). Elemental analyses were performed on a Fison EA 1108 CHNS-O analyzer. Accurate MS measurements were determined at the SERC Mass Spectrometry Centre, Leicester University.

3-[1-(2,5-Dimethoxyphenylamino)ethylidene]dihydrofuran-2(3*H*)-one (5)

A solution of 2,5-dimethoxyaniline **4** (7.66 g, 50 mmol) and 2-acetylbutyrolactone (6.41 g, 50 mmol) in toluene (25 mL) was refluxed for 24 h. Evaporation of the solvent gave a solid, which was washed with cold Et_2O and recrystallized from EtOH to afford furanone **5** (10.9 g, 83%); mp 108.5–110 °C.

IR (KBr): 3280, 3205, 1690, 1640, 1610, 1255, 1220 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.03$ (s, 3 H, CH_3), 2.90 (t, 2 H, CH_2C=, $J = 7.9$ Hz), 3.75 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.34 (t, 2 H, CH_2O, $J = 7.9$ Hz), 6.60 (m, 2 H), 6.82 (d, 1 H, $J = 8.6$ Hz), 9.91 (s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 17.8$ (q), 26.6 (t), 55.8 (q), 56.38 (q), 65.3 (t), 89.8 (s), 109.0 (d), 111.2 (d), 111.3 (s), 112.0 (d), 129.3 (s), 147.0 (s), 153.4 (s), 173.8 (s).

Anal. Calcd for $C_{14}H_{17}NO_4$ (263.30): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.90; H, 6.64; N, 5.34.

4-Chloro-3-(2-chloroethyl)-5,8-dimethoxy-2-methylquinoline (6)

A solution of furanone **5** (2.63 g, 10.0 mmol) in $POCl_3$ (15 mL) was refluxed for 4 h, and then the excess $POCl_3$ was removed in vacuo. The residue was poured onto iced water, neutralized with Na_2CO_3 and stirred overnight. The solid was filtered, dried and recrystallized from EtOH to give quinoline **6** (1.90 g, 63%); mp 156–158 °C

IR (KBr): 1612, 1475, 1315, 1270 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.85$ (s, 3 H, CH_3), 3.49 (m, 2 H, CH_2CH_2Cl), 3.75 (m, 2 H, CH_2CH_2Cl), 3.91 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 6.85 (d, 1 H, ArH, $J = 8.9$ Hz), 6.95 (d, 1 H, ArH, $J = 8.9$ Hz).

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 25.0$ (q), 33.7 (t), 41.3 (t), 56.2 (q), 56.8 (q), 107.6 (2 d), 118.5 (s), 129.5 (s), 140.4 (s), 140.6 (s), 149.1 (s), 149.2 (s), 157.5 (s).

Anal. Calcd for $C_{14}H_{15}Cl_2NO_2$ (300.19): C, 56.02; H, 5.04; N, 4.67. Found: C, 56.20; H, 5.10; N, 4.65.

2,3-Dihydro-6,9-dimethoxy-4-methyl-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinoline (7b)

A solution of **6** (300 mg, 1.0 mmol) and aniline (190 mg, 2.0 mmol) in EtOH (30 mL) was refluxed for 2 h, and the solvent was removed in vacuo. The residue was taken up in aq $NaHCO_3$, and the crude product was extracted with $CHCl_3$. The organic solution was washed with H_2O, dried, and evaporated. Recrystallization from EtOH gave **7b** (225 mg, 70%); mp 188–190 °C.

IR (KBr): 1262, 1065, 1090 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.64 (s, 3 H, OCH_3), 3.06 (s, 3 H, CH_3), 3.20 (t, *J* = 9.0 Hz, 2 H, NCH_2CH_2), 4.00 (s, 3 H, OCH_3), 4.23 (t, *J* = 9.0 Hz, 2 H, NCH_2CH_2), 6.41 (d, *J* = 8.7 Hz, 1 H, 7-H or 8-H), 6.80 (d, *J* = 8.7 Hz, 1 H, 8-H or 7-H), 6.95 (m, 3 H), 7.20 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.1 (q), 27.0 (t), 54.4 (q), 56.0 (q), 57.7 (t), 102.6 (d), 106.1 (d), 111.4 (s), 120.0 (2 d), 123.0 (d), 123.6 (s), 128.6 (2 d), 142.0 (s), 147.9 (s), 149.2 (s), 150.5 (s), 150.8 (s), 154.4 (s).

Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.40): C, 74.98; H, 6.29; N, 8.74. Found: C, 75.10; H, 6.32; N, 9.04.

6,9-Dimethoxy-4-methyl-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinoline (8)

A mixture of **7b** (150 mg, 0.47 mmol), 10% Pd/C (30 mg) and mesitylene (25 mL) was heated at 200 °C in an autoclave for 24 h. After removal of the catalyst on Celite, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using EtOAc–CH_2Cl_2 (1:1) as eluent to afford pyrroloquinoline **8** (85 mg, 57%); mp 155–157 °C.

IR (KBr): 1615, 1510, 1493, 1260 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.00 (s, 3 H, OCH_3), 3.01 (s, 3 H, CH_3), 4.06 (s, 3 H, OCH_3), 6.58 (d, *J* = 8.6 Hz, 1 H, 7-H or 8-H), 6.88 (d, *J* = 8.6 Hz, 1 H, 8-H or 7-H), 6.89 (d, *J* = 3.3 Hz, 1 H, 6-H or 7-H), 7.28 (m, 2 H, ArH), 7.40 (m, 3 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.1 (q), 54.0 (q), 56.2 (q), 103.2 (d), 103.5 (d), 105.0 (d), 110.6 (s), 123.9 (s), 124.4 (2 d), 126.5 (d), 128.7 (2 d), 131.7 (d), 134.2 (s), 137.0 (s), 144.9 (s), 147.0 (s), 149.5 (s), 153.9 (s).

Anal. Calcd for $C_{20}H_{18}N_2O_2$ (318.38): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.15; H, 5.95; N, 8.60.

4,8,9-Trimethyl-1-phenyl-1*H*-benzo[*g*]pyrrolo[3,2-*c*]quinoline-6,11-dione (10)

To a solution of pyrroloquinoline **8** (70 mg, 0.22 mmol) in MeCN (5 mL), were added AgO (150 mg, 1.2 mmol) and 6 N HNO_3 (0.4 mL). The suspension was stirred for 5 min at r.t., and H_2O (10 mL) was added. The mixture was extracted with $CHCl_3$ (2 × 15 mL), the combined organic extracts were dried ($MgSO_4$) and filtered. To the solution was added 2,3-dimethylbuta-1,3-diene (25 μL, 0.22 mmol) and the mixture was heated at 120 °C in a sealed tube for 18 h. After cooling to r.t., the cycloadduct was aromatized by stirring 24 h in the presence of DBU (100 μL). The residue obtained after evaporation of the solvent was purified by flash column chromatography on silica gel (CH_2Cl_2) to give compound 10 (65 mg, 81%); mp 233–235 °C.

IR (KBr): 1670 cm^{-1} (C=O).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 3.02 (s, 3 H, CH_3), 6.92 (d, *J* = 3.3 Hz, 1 H), 7.28 (m, 2 H, ArH), 7.50 (m, 3 H, ArH), 7.52 (d, *J* = 3.3 Hz, 1 H), 7.63 (s, 1 H, ArH), 8.08 (m, 1 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.1 (2 q), 22.7 (q), 103.7 (d), 118.1 (s), 124.6 (2 d), 127.4 (d), 127.6 (d), 128.2 (d), 128.9 (2 d), 129.8 (s), 130.6 (s), 131.7 (s), 135.3 (s), 136.5 (d), 142.1 (s), 143.5 (s), 143.7 (s), 144.0 (s), 158.0(s), 182.6 (s), 182.9 (s).

HRMS: *m/z* calcd for $C_{24}H_{19}N_2O_2$: 367.14464 (MH^+); found 367.14466.

4,8,9-Trimethyl-1-phenyl-1*H*-benzo[*g*]pyrrolo[3,2-*c*]quinoline-6,11-dione (11) and 4,8,9-Trimethyl-1-phenyl-1*H*-benzo[*g*]pyrrolo[3,2-*c*]quinoline-6,11-dione (12)

To a solution of quinone **9** obtained from pyrroloquinoline **8** (70 mg, 0.20 mmol) as above, was added penta-1,3-diene (25 μL, 0.25 mmol) and the mixture was heated at 120 °C in a sealed tube for 18 h. After cooling to r.t., the cycloadduct was aromatized by stirring 24 h in the presence of DBU (100 μL). Column chromatography of the residue, obtained after evaporation of the solvent, on silica gel (CH_2Cl_2) gave the aromatized adducts **11** and **12** (50 mg, 64%).

HRMS: *m/z* calcd for $C_{23}H_{17}N_2O_2$: 353.12899 (MH^+); found: 353.12907.

The mixture of aromatized adducts **11** and **12** was purified by two consecutive flash chromatography on silica gel (CH_2Cl_2) to afford **11** and **12**.

11

Yield: 9.0 mg (11%); mp 220–222 °C.

IR (KBr): 1675 cm^{-1} (C=O).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 3.00 (s, 3 H, CH_3), 6.93 (d, *J* = 3.3 Hz, 1 H, 3-H), 7.32 (m, 2 H, ArH), 7.52 (m, 5 H, ArH), 7.54 (d, *J* = 3.3 Hz, 1 H, 2-H), 8.21 (d, *J* = 7.3 Hz,1 H, 7-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (q), 23.1 (q), 103.9 (d), 120.6 (s), 125.0 (2 d), 126.3 (d), 128.1 (d), 129.6 (2 d), 130.0 (s), 132.8 (s), 132.9 (d), 134.5 (s), 135.4 (s), 136.1 (d), 137.6 (d), 139.9 (s), 141.8 (s), 143.0 (s), 158.2 (s), 183.5 (s), 185.8 (s).

12

Yield: 21 mg (26%); mp 228–230 °C.

IR (KBr): 1670 cm^{-1} (C=O).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.87 (s, 3 H, CH_3), 3.00 (s, 3 H, CH_3), 6.91 (d, *J* = 3.3 Hz, 1 H, 3-H), 7.24 (m, 2 H, ArH), 7.48 (m, 5 H, ArH), 7.51 (d, *J* = 3.3 Hz, 1 H, 2-H), 7.75 (m, 1 H, 7-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.2 (q), 23.8 (q), 104.2 (d), 117.5 (s), 125.1 (2 d), 125.4 (d), 128.1 (d), 129.3 (2 d), 129.8 (s), 131.0 (s), 133.2 (d), 135.3 (s), 135.8 (s), 136.5 (d), 137.9 (d), 142.2 (s), 142.3 (s), 144.9 (s), 158.7 (s), 183.5 (s), 184.6 (s).

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