Synthesis of 1*H*-2-Benzopyran-5,8-dione Derivatives from 2-(1-Hydroxyalkyl)-1,4-benzoquinones and Enamines

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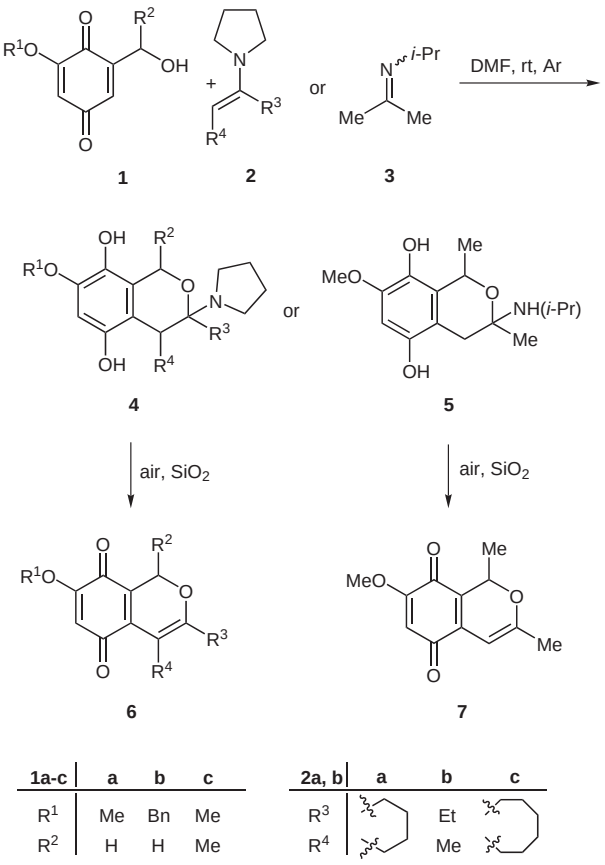
Abstract: An efficient synthesis of the title benzopyranodione derivatives based on a Michael addition/cyclization sequence between 2-(1-hydroxyalkyl)-1,4-benzoquinones and enamines (or an imine) is described.

Key words: enamines, heterocycles, benzoquinones

Current efforts in our laboratory focus on the development of convenient methods for the synthesis of heterocyclic-fused quinone derivatives.[1,2] We have recently demonstrated a novel method for the construction of 1*H*-naphtho[2,3-*c*]pyran-5,10-dione system via the Michael addition/cyclization sequence between 2-(1-hydroxyalkyl)-1,4-naphthoquinones and enamines (or imines) and its application to facile total syntheses of antibiotics, such as pentalongin, (±)-eleutherin, and (±)-isoeleutherin.[1] In studies designed to further explore the utility of this new annelation in the synthesis of pyran-fused quinone derivatives we examined reactions of 2-(1-hydroxyalkyl)-1,4-benzoquinones, which has been little used in synthesis,[3,4] with enamines. The purpose of this paper is to disclose the results of these reactions affording 1*H*-2-benzopyran-5,8-dione derivatives **6**, **7**, and **9**.[5] Some of this class of benzopyrandione derivatives exhibit biological activities[5c,d,g,i] and are useful intermediates for the synthesis of biologically important products.[6]

We began this study with the reaction between 2-hydroxymethyl-1,4-naphthoquinone and 1-(1-pyrrolidinyl)cyclohexene (**2a**) in toluene or DMF at room temperature. It, however, resulted in the formation of numerous unidentifiable products. We next selected 2-alkoxy-6-(1-hydroxyalkyl)-1,4-benzoquinones **1** as substrates in order to suppress the attack of enamines at the 2- and 4- positions of the quinones and allowed to react them with pyrrolidine enamines **2**. Addition of enamines **2** to quinones **1** in a Michael addition manner at the 3-position of the quinones, followed by cyclization of the resulting iminium ion intermediates, proceeded smoothly in DMF[7] (within 10 min) to afford 3-(1-pyrrolidinyl-1*H*-3,4-dihydro-2-benzopyran-5,8-diols **4**. Oxidation and elimination of pyrrolidine from these hydroquinone intermediates during workup and purification procedures using preparative TLC on silica gel gave rise to 1*H*-2-benzopyran-5,8-diones **6**, as illustrated in Scheme 1. The results are summarized in Table 1, which indicates that fair to good yields were obtained, in general. An imine **3** was shown to be effective in the reaction with a 2-hydroxymethyl-1,4-benzoquinone **1c** under similar conditions and the expected 1*H*-2-benzopyran-5,8-dione derivative **7** was obtained via **5**, but in somewhat lower yield (Entry 5).



Scheme 1

After treatment of 6-alkoxy-2-hydroxymethyl-1,4-benzoquinones **1a** and **1b** with enamines **2** and **8**, oxidation of the hydroquinone intermediates (type **4**) was effected by treating with silver oxide to give 3-(1-pyrrolidinyl)(or-morpholino)-3,4-dihydro-1*H*-2-benzopyran-5,8-diones **9**, as a single diastereoisomer in each case (Scheme 2). Each of these products is thought to be thermodynamically more stable than the corresponding diastereoisomer. The results are summarized in Table 2, which indicates that the yields of the desired products are good, in general.

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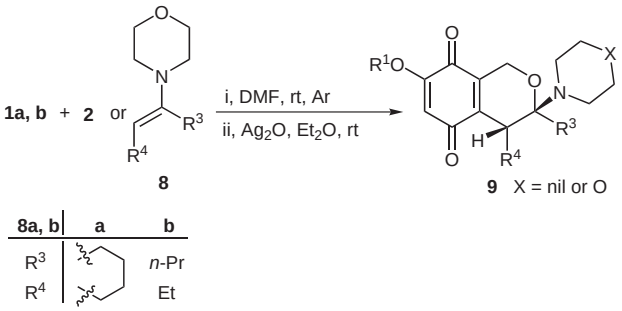
Table 1 Preparation of 1*H*-2-Benzopyran-5,8-dione Derivatives **6** and **7**

Entry	Quinone **1**	Enamine **2** or Imine **3**	Product **6**/**7** (Yield, %)[a]
1	**1a**	**2a**	**6a** (73)
2	**1a**	**2b**[b]	**6b** (63)
3	**1b**	**2a**	**6c** (80)
4	**1c**	**2a**	**6d** (64)
5	**1c**	**3**	**7** (46)

[a] All yields are based on products isolated by preparative TLC on silica gel.
[b] A mixture of stereoisomers was used.



Scheme 2

NOE experiments were useful in determining the relative stereochemistry of these products unambiguously. Thus, for example, irradiation of the signal at δ = 2.8–2.9 due to the methylene protons adjacent to the nitrogen of pyrrolidine ring of compound **9c** resulted in an enhancement of the signal at δ = 3.05–3.15 due to the conjunctive proton (6.3%). For compound **9d**, an 8.2% enhancement of the signal at δ = 3.16 due to the 4-H was observed on irradiation of the signal at δ = 2.75–2.85 due to the methylene protons adjacent to nitrogen of the morpholine ring.

Table 2 Preparation of 3-Amino-3,4-dihydro-1*H*-2-benzopyran-5,8-dione Derivatives **9**

Entry	Quinone **1**	Enamine **2** or **8**	Product **9** (Yield, %)[a]
1	**1a**	**2a**	**9a** (90)
2	**1a**	**8a**	**9b** (82)
3	**1a**	**2c**	**9c** (94)
4	**1a**	**8b**[b]	**9d** (66)
5	**1b**	**2a**	**9e** (84)

[a] All yields are based on products isolated by preparative TLC on silica gel.
[b] A mixture of stereoisomers was used.

In conclusion, we have demonstrated a convenient synthesis of 1*H*-benzo[2]pyran-5,8-dione derivatives from readily available starting materials. Since the method is experimentally simple, it may be of value in heterocyclic quinone synthesis.

The melting points were determined on a Laboratory Devices MEL-TEMP II melting point apparatus and are uncorrected. The IR spectra were recorded using KBr disks (unless stated otherwise) on a Perkin-Elmer 1600 Series FT IR spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz in $CDCl_3$. Low-resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use.

Enamines **2b**, **2c**, and **8b** were prepared by the Stork's method.[8] Imine **3** was prepared by the Bunnelle's method.[9]

Quinones 1b and 1c

3-Benzyloxy-2-hydroxybenzaldehyde[10] was reduced with $NaBH_4$ in THF to give 3-benzyloxy-2-hydroxybenzyl alcohol in 90% yield.

Mp 52–53 °C (hexane–Et_2O).

IR: 3576, 1614 cm^{-1}.

^{1}H NMR: δ = 2.26 (1 H, t, *J* = 6.6 Hz), 4.74 (2 H, d, *J* = 6.6 Hz), 5.11 (2 H, s), 6.03 (1 H, s), 6.75–6.95 (3 H, m), 7.3–7.45 (5 H, m).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.02; H, 6.20.

Oxidation of this benzyl alcohol according to the procedure reported by Stevens[4] gave 2-benzyloxy-6-(hydroxymethyl)-1,4-benzoquinone (**1b**) in 35% yield.

Mp 111–113 °C (hexane–$CHCl_3$).

IR: 3389, 1682, 1659, 1614, 1600 cm^{-1}.

^{1}H NMR: δ = 2.06 (1 H, br s), 4.55 (2 H, s), 5.04 (2 H, s), 5.97 (1 H, d, *J* = 2.3 Hz), 6.71 (1 H, d, *J* = 2.3 Hz), 7.35–7.4 (5 H, m).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 69.03; H, 4.95. 2-Hydroxy-3-methoxybenzaldehyde was treated with an excess of methylmagnesium bromide in THF at 0 °C to give 1-(2-hydroxy-3-methoxyphenyl)ethanol in 74% yield.

R_f 0.27 (EtOAc–hexane, 1:2).

IR (neat): 3384, 1614 cm^{-1}.

^{1}H NMR: δ = 1.54 (3 H, d, *J* = 6.7 Hz), 2.56 (1 H, br s), 3.88 (3 H, s), 5.05–5.2 (1 H, m), 6.26 (1 H, br s), 6.75–6.9 (3 H, m).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.35; H, 7.30.

This alcohol was oxidized as described for the preparation of **1b** to give 2-(1-hydroxyethyl)-6-methoxy-1,4-benzoquinone (**1c**) in 35% yield.

Mp 102–103 °C (hexane–$CHCl_3$).

IR: 3481, 1678, 1654, 1622, 1602 cm^{-1}.

^{1}H NMR: δ = 1.45 (3 H, d, *J* = 6.6 Hz), 2.21 (1 H, d, *J* = 5.0 Hz), 3.83 (3 H, s), 4.8–495 (1 H, m), 5.91 (1 H, d, *J* = 2.6 Hz), 6.72 (1 H, q, *J* = 1.3 Hz).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.60; H, 5.54.

All other chemicals used in this study including **1a** were commercially available.

1*H*-2-Benzopyran-5,8-dione Derivatives 6; Typical Procedure
8-Methoxy-1,2,3,4-tetrahydro-6*H*-dibenzo[*b,d*]pyran-7,10-dione (6a)
To a soln of 2-hydroxymethyl-6-methoxy-1,4-benzoquinone (**1a**) (50 mg, 0.30 mmol) in DMF (3 mL) at 0 °C under argon was added 1-(1-pyrrolidinyl)cyclohexene (**2a**) (45 mg, 0.30 mmol). The mixture was stirred at the same temperature for 10 min before it was treated with sat. aq NH_4Cl. The resulting mixture was extracted with Et_2O (3 × 10 mL) and the combined extracts were washed with brine. After drying and evaporation of the solvent the residue was separated by preparative TLC on SiO_2 (EtOAc-hexane, 1:1) to give **6a** (54 mg, 73) as purple needles.

Mp 150–152 °C (hexane).

IR: 1645, 1618, 1601 cm^{-1}.

^1H NMR: δ = 1.65–1.7 (4 H, m), 2.2–2.3 (2 H, m), 2.6–2.7 (2 H, m), 3.80 (3 H, s), 4.87 (2 H, s), 5.76 (1 H, s).

MS: *m*/*z* (%) = 246 (62) [M^+], 231 (100).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.36; H, 5.58.

3-Ethyl-7-methoxy-4-methyl-1*H*-2-benzopyran-5,8-dione (6b)
Purple needles; mp 89–91 °C (hexane–Et_2O).

IR: 1650, 1619, 1603 cm^{-1}.

^1H NMR: δ = 1.14 (3 H, t, *J* = 7.3 Hz), 2.09 (3 H, s), 2.36 (2 H, q, *J* = 7.3 Hz), 3.80 (3 H, s), 4.82 (2 H, s), 5.76 (1 H, s).

MS: *m*/*z* (%) = 234 [M^+] (61) , 219 (100).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.44; H, 6.03.

8-Benzyloxy-1,2,3,4-tetrahydro-6*H*-dibenzo[*b,d*]pyran-7,10-dione (6c)
Purple needles, mp 153–155 °C (hexane–Et_2O).

IR: 1649, 1620, 1602 cm^{-1}.

^1H NMR: δ = 1.65–1.7 (4 H, m), 2.2–2.3 (2 H, m), 2.5–2.6 (2 H, m), 4.87 (2 H, s), 5.03 (2 H, m), 5.80 (1 H, s), 7.35–7.4 (5 H, m).

MS: *m*/*z* (%) = 322 (100) [M^+].

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.74; H, 5.59.

8-Methoxy-6-methyl-1,2,3,4-tetrahydro-6*H*-dibenzo[*b,d*]pyran-7,10-dione (6d)
Purple needles, mp 113–115 °C (hexane–Et_2O).

IR: 1651, 1620, 1602 cm^{-1}.

^1H NMR: δ = 1.28 (3 H, d, *J* = 6.6 Hz), 1.8–1.95 (2 H, m), 2.15–2.25 (2 H, m), 2.45–2.55 (2 H, m), 2.65–2.8 (2 H, m), 3.80 (3 H, s), 5.47 (1 H, q, *J* = 6.6 Hz), 5.74 (1 H, s).

MS: *m*/*z* (%) = 260 (100) [M^+].

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.22; H, 6.20.

7-Methoxy-1,3-dimethyl-1*H*-2-benzopyran-5,8-dione (7)
Purple needles, mp 142–144 °C (hexane–Et_2O).

IR: 1651, 1627, 1599 cm^{-1}.

^1H NMR: δ = 1.34 (3 H, d, *J* = 6.5 Hz), 1.98 (3 H, s), 3.81 (3 H, s), 5.54 (1 H, q, *J* = 6.5 Hz), 5.71 (1 H, s), 5.79 (1 H, s).

MS: *m*/*z* (%) = 220 (53) [M^+], 205 (100).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.27; H, 5.52.

3,4-Dihydro-1*H*-2-benzopyran-5,8-diones 9; Typical Procedure
***cis*-8-Methoxy-4a-(1-pyrrolidinyl)-1,2,3,4,4a,10b-hexahydro-6*H*-dibenzo[*bd*]pyran-7,10-dione (9a)**
To a soln of 2-hydroxymethyl-6-methoxy-1,4-benzoquinone (**1a**) (50 mg, 0.30 mmol) in DMF (3 mL) at 0 °C under argon was added 1-(1-pyrrolidinyl)cyclohexene (**2a**) (45 mg, 0.30 mmol). After 10 min the mixture was worked up in a similar manner as described for the preparation of **6a**. The ethereal soln was added to a stirred suspension of Ag_2O [prepared from 0.25 g (1.5 mmol) of $AgNO_3$ by the literature method[11]] in Et_2O (3 mL) in the presence of anhyd Na_2SO_4 (1.7 g). After stirring for 1 h, the solids were filtered off and the filtrate was concentrated. The residual solid was recrystallized from hexane–Et_2O to give pure **9a** (86 mg, 90%, as dark-orange plates: mp 138–140 °C).

IR: 1673, 1656, 1636, 1604 cm^{-1}.

^1H NMR: δ = 1.15–1.85 (11 H, m), 1.95–2.0 (1 H, m), 2.5–2.6 (4 H, m), 2.75–2.85 (1 H, m), 3.78 (3 H, s), 4.42 (1 H, dd, *J* = 18.5, 1.3 Hz), 4.47 (1 H, d, *J* = 18.5 Hz), 5.85 (1 H, s).

MS: *m*/*z* (%) = 317 (71) [M^+], 247 (100).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.16; H, 7.18; N, 4.39.

***cis*-8-Methoxy-4a-morpholino-1,2,3,4,4a,10b-hexahydro-6*H*-dibenzo[*b,d*]pyran-7,10-dione (9b)**
Dark-orange plates; mp 170–171 °C (hexane–Et_2O).

IR: 1676, 1659, 1631, 1604 cm^{-1}.

^1H NMR: δ = 1.25–2.05 (8 H, m), 2.4–2.45 (2 H, m), 2.55–2.6 (2 H, m), 2.85–2.95 (1 H, m), 3.45–3.55 (4 H, m), 3.81 (3 H, s), 4.39 (1 H, d, *J* = 18.8 Hz), 4.47 (1 H, d, *J* = 18.8 Hz), 5.86 (1 H, s).

MS: *m*/*z* (%) = 333 (29) [M^+], 247 (100).

Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.88; H, 6.97; N, 4.41.

***cis*-3-Methoxy-6a-(1-pyrrolidinyl)-6a,7,8,9,10,11,12,12a-octahydro-5*H*-cycloocta[*c*][2]benzopyran-1,4-dione (9c)**
Dark-orange plates; mp 120–121 °C (hexane–Et_2O).

IR: 1673, 1656, 1636, and 1604 cm^{-1}.

^1H NMR: δ = 1.35–1.85 (14 H, m), 1.95–2.05 (2 H, m), 2.65–2.75 (2 H, m), 2.8–2.9 (2 H, m), 3.05-3.15 (1 H, m), 3.80 (3 H, s), 4.15 (1 H, dd, *J* = 18.5, 2.3 Hz), 4.33 (1 H, d, *J* = 18.5 Hz), 5.87 (1 H, s).

MS: *m*/*z* (%) = 345 (97) [M^+], 274 (100).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.46; H, 7.76; N, 3.98.

(3*RS*,4*RS*)-4-Ethyl-7-methoxy-3-morpholino-3-propyl-3,4-dihydro-1*H*-[2]benzopyran-5,8-dione (9d)
Dark-orange plates; mp 140–141 °C (hexane–Et_2O).

IR: 1672, 1655, 1630, 1615 cm^{-1}.

^1H NMR: δ = 0.81 (3 H, t, *J* = 7.6 Hz), 0.94 (3 H, t, *J* = 7.3 Hz), 1.25–2.0 (6 H, m), 2.45–2.55 (2 H, m), 2.75–2.85 (2 H, m), 3.19 (1 H, dd, *J* = 6.6, 5.3 Hz), 3.4–3.5 (4 H, m), 3.83 (3 H, s), 4.30 (1 H, dd, *J* = 18.9, 1.6 Hz), 4.39 (1 H, d, *J* = 18.9 Hz), 5.89 (1 H, s).

MS: *m*/*z* (%) = 49 (6.1) [M^+], 263 (44), 193 (100).

Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.33; H, 7.53; N, 3.88.

***cis*-8-Benzyloxy-4a-(1-pyrrolidinyl)-2,3,4,4a,6,10b-hexahydro-1*H*-dibenzo[*b,d*]pyran-7,10-dione (9e)**

Dark-orange plates; mp 132–135 °C (hexane–Et_2O).

IR: 1669, 1654, 1635, 1610 cm^{-1}.

^1H NMR: δ = 1.2–1.3 (2 H, m), 1.4–1.8 (9 H, m), 1.9–2.0 (1 H, m), 2.5–2.6 (4 H, m), 2.75–2.85 (1 H, m), 4.41 (1 H, dd, *J* = 18.5, 1.3 Hz), 4.47 (1 H, d, *J* = 18.5 Hz), 5.01 (2 H, s), 5.91 (1 H, s), 7.35–7.45 (5 H, m).

MS: *m*/*z* (%) = 393 (45) [M^+], 302 (63), 91 (100).

Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.16; H, 6.91; N, 3.60.

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