Reactions of Heterocyclic Quinone Methides: 1-Methyl-3-methylene-2,4(1*H*,3*H*)-quinolinedione

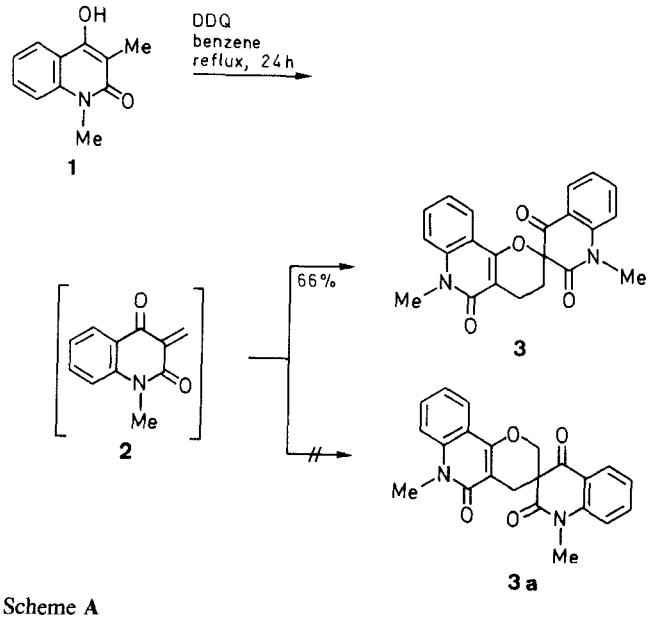
M. A. Chauncey,*[1] M. F. Grundon[2]

Department of Chemistry, University of Ulster, Coleraine, Northern Ireland

1-Methyl-3-methylene-2,4(1*H*,3*H*)-quinolinedione (**2**), prepared from 4-hydroxy-1,3-dimethyl-2(1*H*)-quinolinone (**1**) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gives the dimer **3**. Compound **2** also reacts *in situ* with 2,2-dimethyl-2*H*-1-benzopyran and with isopropenyl acetate to give Diels–Alder cycloaddition products.

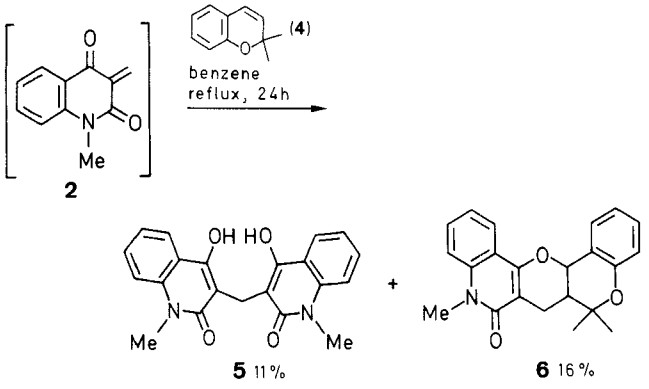
Methylene-substituted quinones constitute a group of reactive organic compounds involved as intermediates in many chemical and biochemical processes. They are comparable with α,β-unsaturated ketones but are more reactive due to the additional driving force of aromatisation after conjugative addition. In our studies to synthesise biologically active molecules, it was felt appropriate to explore the reactivity of *in situ* generated methylene substituted quinones in cycloaddition reactions.

Of particular interest was the dimer formation of 4-hydroxy-1,3-dimethyl-2(1*H*)-quinolinone (**1**). Preparation of the required 1-methyl-3-methylene-2,4(1*H*,3*H*)-quinolinedione (**2**) was carried out by refluxing a solution of the quinolinone **1** in benzene in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme A). In the absence of any other substrate, dimerisation of the resultant methylenequinone **2** occurred to give compound **3** in 66% yield. The structure was distinguished from the alternative **3a** by the presence of two-proton multiplets in the ^{1}H-NMR spectrum at $\delta = 2.61$ and 2.34 which were attributed to adjacent methylene groups. This dimerisation is analogous to that of 2,6-dibenzylidenecyclohexanone[3] and of methylene-substituted quinones derived from *o*-alkylphenols.[4]



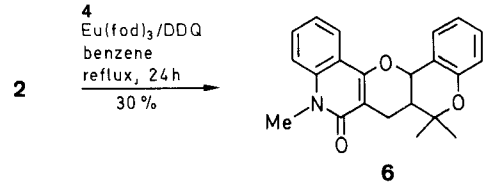
Scheme A

The compound 2,2-dimethyl-2*H*-1-benzopyran (**4**) is a moiety which occurs in many natural products and biologically active molecules.[5] We wished to form a molecule containing the quinolone **1** and the benzopyran **4**. An efficient synthesis of **4** was performed by dehydrogenation of 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran[6] using DDQ, the product being obtained in 77% yield. On generation of the methylenequinone **2** in the presence of **4**, two products were isolated, these being the known bis-quinolone **5** (11%)[11] and the cycloaddition product **6** (16%). Spectroscopic evidence for **6** was provided by a low-field doublet in the ^{1}H-NMR spectrum at $\delta = 5.68$ with a coupling constant of 4.4 Hz indicating a *cis*-configuration as expected from a Diels–Alder reaction. This can be attributed to the proton at the ring junction adjacent to oxygen and the benzene ring. Mass analysis gave a molecular ion at $m/z = 347$ as expected and fragments at $m/z = 188$ attributable to the protonated methylenequinone and $m/z = 160$ corresponding to the benzopyran moiety.



Scheme **B**

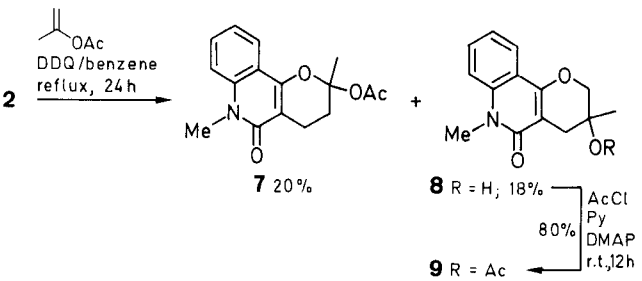
Diels–Alder reactions are often catalysed by Lewis acids; recently the catalytic effect of such Lewis acids as lanthanide complexes has been reported.[7] This prompted us to use the shift reagent Eu(fod)$_3$ (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-4,6-dionato) as the catalyst in this reaction with the result that the yield of **6** was increased to 30% and the formation of **5** was completely eliminated.



Scheme **C**

Further examination of the reaction gave no trace of the dimer **3** indicating that **4** was not in direct competition with the methylenequinone **2** as the dienophilic species. The methylene quinone **2** can be regarded as an electron-deficient enone and in the presence of the electron-rich benzopyran **4** it preferentially undergoes an inverse electron demand cycloaddition reaction.[8]

A similar situation was observed in the presence of the electron-rich olefin, isopropenyl acetate. No dimer **3** was detected and two products were isolated which were shown to be regioiosmeric Diels–Alder cycloadducts (Scheme **D**). As expected the first product isolated **7** possessed an acetate moiety as shown by a ^{1}H-NMR singlet at $\delta = 1.99$. The two methylene signals appear as multiplets between $\delta = 2$ and 3 thus proving them to be adjacent. Mass analysis gave the anticipated molecular ion at $m/z = 287$ and the methylenequinone fragment at $m/z = 188$. The second product **8** gave a molecular ion at $m/z = 245$ with the ^{1}H-NMR showing two singlets at $\delta = 2.1$ and 3.43 for the methylene protons.



Scheme **D**

In both cases, angular annulation has been indicated by the presence of a 2-quinolinone carbonyl signal in the IR spectrum at $\nu = 1640\ cm^{-1}$. Had a linear structure been present, the compound would be a 4-quinolinone with an IR signal at $\nu \sim 1615\ cm^{-1}$, this is also the case for the pyran dimer **6**. IR-data also indicated the presence of an OH group with a signal at $\nu = 3300\ cm^{-1}$ further confirming the hemiacetal structure. The fact that regioisomeric compounds have been produced strongly suggests *in situ* hydrolysis of the corresponding acetate to give compound **8**; particularly as no trace of the respective hemiacetal and acetate was found in the reaction.

Acetylation of the alcohol function proved to be more difficult than expected but treatment with acetyl chloride in pyridine gave the desired acetate moiety **9** which was readily hydrolysed. Mass spectrometry gave no molecular ion but a mass of $m/z = 228$ was observed which corresponds to the loss of the acetoxy group; the IR spectrum showed a strong carbonyl signal at $\nu = 1690\ cm^{-1}$ and ^{1}H-NMR indicated an acetyl group with a singlet at $\delta = 2.15$. The fact that no molecular ion was observed tends to indicate the instability of the proposed acetate in the reaction.

Attempts to synthesize linearly annulated compounds via the methylenequinone route were unsuccessful. Protection of the 4-hydroxy function and treatment with DDQ gave no product; this may be due to the possible disruption of the benzenoid system in the formation of the desired methylene compound which is an unfavourable situation. *N*-Demethylated quinolones were also found to be unreactive with this method.

All reagents were freshly obtained, of commercial quality grade. Eu(fod)$_3$ was purchased from Aldrich Chemical Co. Solvents were purified and dried before use according to standard procedures. Melting points were obtained using a Kofler Micro Hot stage and

are uncorrected. Microanalyses were obtained from the Butterworth Microanalytical Consultancy Ltd. Mass spectra were obtained using an AEI MS9 instrument. IR spectra were recorded on a Perkin-Elmer 457 instrument. ^{1}H-NMR spectra were obtained using a Perkin-Elmer R32 90 MHz instrument and a Bruker 360 MHz spectrometer.

4-Hydroxy-1,3-dimethyl-2(1*H*)quinolinone (1):
Freshly distilled *N*-methylaniline (20 g, 20.2 mL, 0.18 mol) and diethyl malonate (39 g, 38.5 mL, 0.22 mol) are refluxed, using a short air condenser, under a N_2 atmosphere for 3 h. The solution is allowed to cool to ~100 °C and is stirred into cold MeOH. A colourless precipitate is formed which is recrystallised from EtOH to give **1** as a colourless crystalline solid; yield: 25 g (71%); mp 222–223 °C (Lit.[9] mp 221–222 °C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.15 (s, 3H, CH_3), 4.65 (s, 1H, OH), 7.10–7.50 (m, 3 H_{arom}), 8.10 (d, 1H, H-5$_{arom}$).

1,6′-Dimethyl-3′,4′-dihydrospiro[quinoline-3,2′-2′*H*-pyrano[3,2-*c*]quinoline]-2,4,5′(1*H*,3*H*,6′*H*)-trione (3):
A solution of **1** (1 g, 5.3 mmol) and DDQ (1.79 g, 7.9 mmol) in dry benzene (200 mL) is stirred under reflux for 24 h. The solution is cooled and filtered. The filtrate is washed with 3 N NaOH (2 × 100 mL) and H_2O (200 mL), dried (Na_2SO_4) and evaporated. The residue is crystallised from MeOH to give **3** as a colourless crystalline solid; yield: 650 mg (66%); mp 240–242 °C.

$C_{22}H_{18}N_2O_4$	calc.	C 70.58	H 4.81	N 7.48
(374.4)	found	68.81	4.59	7.14

IR (KBr): ν = 1645 (2-quinolinone), 1675 (ArC=O), 1720 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.34 (d, 2H, CH_2), 2.60 (d, 2H, $ArCH_2$), 3.50 (s, 3H, N-CH_3), 3.70 (s, 3H, N-CH_3), 7.13–8.20 (m, 8 H_{arom}).

MS (DEI): m/z = 374 (M^+).

2,2-Dimethyl-2*H*-1-benzopyran (4):
To a solution of 2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran[6] (5 g, 0.03 mol) in dry benzene (200 mL) is added DDQ (13.6 g, 0.06 mol) and the mixture is stirred under reflux for 48 h. The mixture is filtered and the filtrate is evaporated to give an oily residue which is triturated with hexane. After filtration the solvent is evaporated and the residual oil is distilled under reduced pressure to give **4** as a yellow oil; yield: 3.8 g (77%); bp 104–108 °C/4 Torr (Lit.[10] bp 79–80 °C/2.5 Torr).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.40 (s, 6H, 2 × CH_3), 5.55 (d, 1H, J = 9 Hz, CH), 6.27 (d, 1H, J = 9 Hz, ArCH), 6.60–7.10 (m, 4 H_{arom}).

6,6,9-Trimethyl-8-oxo-6,8,9,14a-tetrahydro-6*H*,7*H*-[1]benzopyrano[3′,4′:5,6]pyrano[3,2-*c*]quinoline (6):
To a solution of **1** (1 g, 5.3 mmol) and **4** (846 mg, 5.3 mmol) in dry benzene (200 mL) is added DDQ (1.20 g, 0.53 mmol) and Eu(fod)$_3$ (5%mol, 274 mg) and the solution is stirred under reflux for 24 h. The mixture is cooled and filtered and the filtrate is washed with 2 M NaOH (2 × 50 mL), H_2O (100 mL), dried and evaporated. The residue is triturated with petroleum ether and the solid is recrystallised from EtOH to give **6** as a colourless solid; yield: 549 mg (30%); mp 239–240 °C.

$C_{22}H_{21}NO_3$	calc.	C 76.05	H 6.05	N 4.03
(347.1)	found	76.20	6.08	4.01

IR (KBr): ν = 1640 cm^{-1} (2-quinolinone).

^{1}H-NMR (360 MHz, $CDCl_3$/TMS): δ = 1.47 (s, 3H, CH_3), 1.50 (s, 3H,CH_3), 2.29–2.33 (m, 1H, CH), 2.35–2.42 (m, 1H, CH_2), 2.83–2.89 (m, 1H, CH_2), 3.64 (s, 3H, N-CH_3), 5.68 (d, 1H, J = 4.4 Hz, CH), 6.77–8.18 (m, 8 H_{arom}).

MS (DEI): m/z = 347 (M^+).

Byproduct N,N-Dimethyl-3,3′-methylene-bis(4-hydroxy-2(1H)-quinolinone) **(5)**: yield: 210 mg (11%); mp 306–310 °C (Lit.[11] mp 301–308 °C).

IR (KBr): ν = 3200 (OH), 1640 cm^{-1} (2-quinolinone).

2-Acetoxy-2,6-dimethyl-5-oxo-3,4,5,6-tetrahyro-2*H*-pyrano[3,2-*c*]quinoline (7):
To a solution of **1** (1 g, 5.3 mmol) and freshly distilled isopropenyl acetate (529 mg, 5.3 mmol) in dry benzene (200 mL) is added DDQ (1.68 g, 7.4 mmol) and the solution is stirred under reflux for 24 h. The mixture is cooled, filtered and the filtrate is evaporated. The residual gum is triturated with petroleum ether and the solid is recrystallized from Et_2O to give **7** as a colourless crystalline solid; yield: 300 mg (20%); mp 135 °C.

$C_{16}H_{17}NO_4$	calc.	C 66.87	H 5.92	N 4.87
(287.1)	found	66.27	5.92	4.74

IR (KBr): ν = 1640 (2-quinolinone), 1680 cm^{-1} ($COCH_3$).

^{1}H-NMR (360 MHz, $CDCl_3$/TMS): δ = 1.76–1.88 (m, 1H, CH_2), 1.94 (s, 3H, CH_3), 1.99 (s, 3H, $COCH_3$), 2.42–2.53 (m, 1H, CH_2), 2.72–2.80 (m, 2H, $ArCH_2$), 3.69 (s, 3H, N-CH_3), 7.20–7.99 (m, 4 H_{arom}).

MS (DEI): m/z = 287 (M^+).

3-Hydroxy-3,6-dimethyl-5-oxo-3,4,5,6-tetrahydro-2H-pyrano[3,2-c]quinoline **(8)**:
Concentration of the mother liquor gives **8** as a colourless crystalline solid; yield: 237 mg (18%); mp 192–194 °C.

$C_{14}H_{15}NO_3$	calc.	C 68.64	H 6.11	N 5.71
(245.1)	found	67.82	6.03	5.36

IR (KBr): ν = 1645 (2-quinolinone), 3300 cm^{-1} (OH).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.30 (s, 3H, CH_3), 2.10 (s, 2H, $ArCH_2$), 3.43 (s, 2H, OCH_2), 3.48 (s, 3H, N-CH_3), 7.10–8.0 (m, 5 H_{arom}, OH).

MS (DEI): m/z = 245 (M^+).

3-Acetoxy-3,6-dimethyl-5-oxo-3,4,5,6-tetrahydro-2*H*-pyrano[3,2-*c*]quinoline (9):
The alcohol **8** (200 mg, 0.8 mmol) in dry pyridine (3 mL) is stirred with AcCl (0.07 mL, 0.99 mmol) and DMAP (20 mg) for 12 h at r.t. H_2O (10 mL) is added and the mixture is extracted with Et_2O (3 × 30 mL) and the organic layer is dried (Na_2SO_4) and evaporated to give **9** as a colourless solid; yield 187 mg (80%); mp 212–214 °C.

$C_{16}H_{17}NO_4$	calc.	C 66.87	H 5.92	N 4.87
(287.1)	found	66.52	5.47	4.73

IR (KBr): ν = 1640 (2-quinolinone), 1690 cm^{-1} ($COCH_3$).

^{1}H-NMR ($CDCl_3$): δ = 1.35 (s, 3H, CH_3), 2.10 (s, 2H, $ArCH_2$), 2.15 (s, 3H, $COCH_3$), 3.43 (s, 2H, OCH_2), 3.50 (s, 3H, N-CH_3), 7.10–8.0 (m, 4 H_{arom}).

MS (DEI): m/z = 228 ($M^+ - C_2H_3O_2$).

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(1) Current address: Daiichi Pure Chemicals Co. Ltd., 2117 Muramatsu, Tokai-mura, Ibaraki-ken, 319-11, Japan.
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