Metacyclophanes and Related Compounds. XXV. Generation of Bis (o-quinone methide) from [2.2] Metacyclophane Having Spiro Skeleton and Its Reactions with Alcohols, Acetic Acid, and Ethenes

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Metacyclophanes and Related Compounds. XXV.[1] Generation of Bis (o-quinone methide) from [2.2]Metacyclophane Having Spiro Skeleton and Its Reactions with Alcohols, Acetic Acid, and Ethenes[2]

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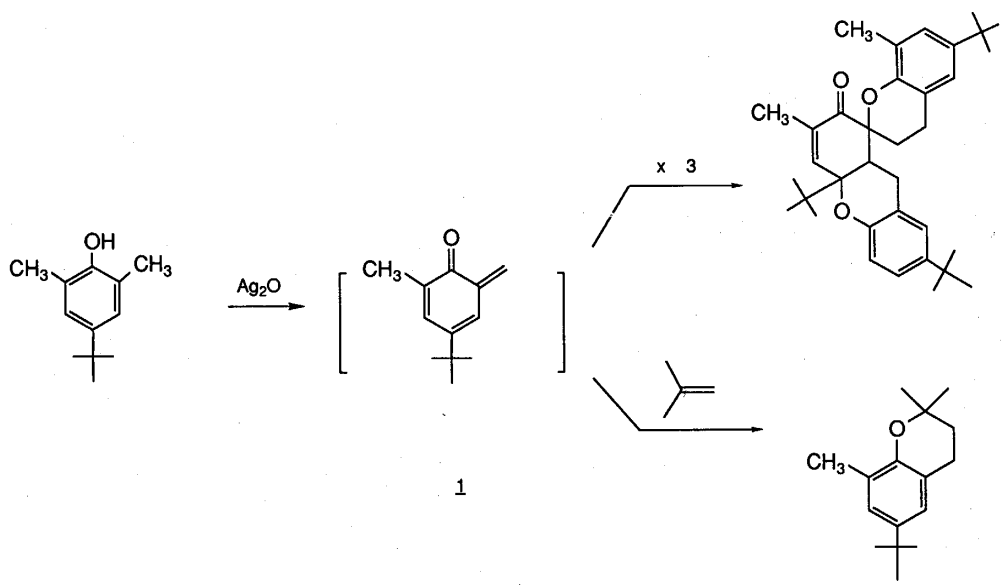
Spiro compound **3** obtained in the oxidation of 8,16-dihydroxy[2.2]metacyclophane **2** with Ag_2O, readily generated bis(o-quinone methide) **4** on mild heating, which was trapped with methanol, ethanol, acetic acid to give diarylethane **5**. [4+2]Cycloadduct **9** of **4** and ethene **8** was obtained when **3** was thermolyzed in the presence of **8** in refluxing benzene.

Previously, it was reported that the oxidation of 2,6-dimethyl-4-t-butylphenol with Ag_2O afforded the trimer of o-quinone methide **1**.[3] Intermediate formation of **1** was subsequently confirmed by the formation of [4+2]cycloadduct with dienophiles (Scheme I).[4]

We recently found that the oxidation of 8,16-dihydroxy[2.2]metacyclophane **2** with



Scheme I

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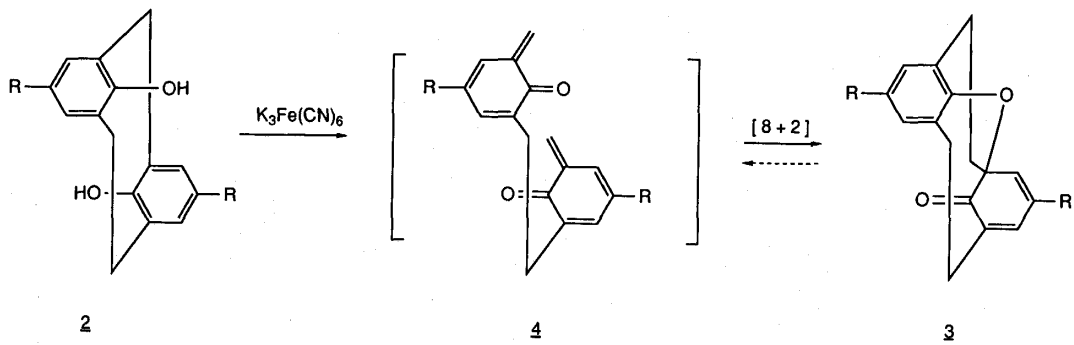
$K_3Fe(CN)_6$ afforded the intramolecular O–C coupling product **3** having spiro skeleton (Scheme II).[2)5)] Compound **3** corresponds to the intramolecular [4+2]cycloadduct of bis(o-quinone methide) **4**.



2 4 3

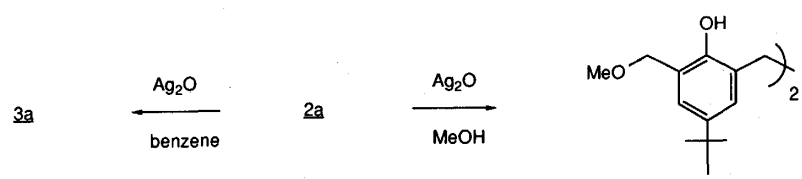
a : R = t-Bu, b : R = H

Scheme II

The present paper deals with the cycloreversion of **3** on mild heating to generate **4** and the reaction of **4** with alcohols, acetic acid, and ethenes.

Results and Discussion

The oxidation of 5,13-di-t-butyl derivative **2a** in benzene by Ag_2O as well as aqueous $K_3Fe(CN)_6$[5)] afforded intramolecular O–C coupling product **3a** in 70% yield. When methanol was employed in place of benzene as a solvent, unexpected product **5a**, which corresponds to an 1:1-adduct of **3a** and methanol, was obtained (Scheme III).



5a

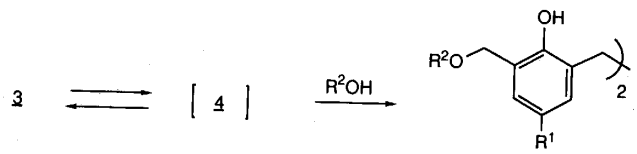
Scheme III

The formation of **5a** suggests that spiro compound **3a** produced in the oxidation of **2a** by Ag_2O reacted with methanol to afford **5a**. Therefore, **3a** and **3b** were treated with methanol, ethanol, and acetic acid (Table 1 and Scheme IV).

Table 1 Reaction of **3** with methanol, ethanol and acetic acid.

Run	Substrate	Reagents	Time (h)	Product (%)[a]
1[b]	**3a**	Methanol	3	**5a** (76)
2[b]	**3a**	Ethanol	2	**5b** (96)
3[b]	**3b**	Ethanol	2	**5c** (84)
4[c]	**3a**	Acetic Acid	2	**5d** (82)

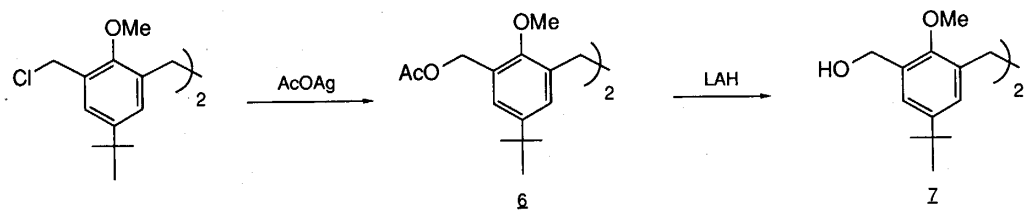
a) Isolated yields are shown. b) Under reflux. c) Temperature : 100-105°C.



a : R^1 = t-Bu, R^2 = Me, b : R^1 = t-Bu, R^2 = Et
c : R^1 = H, R^2 = Et, d : R^1 = t-Bu, R^2 = Ac

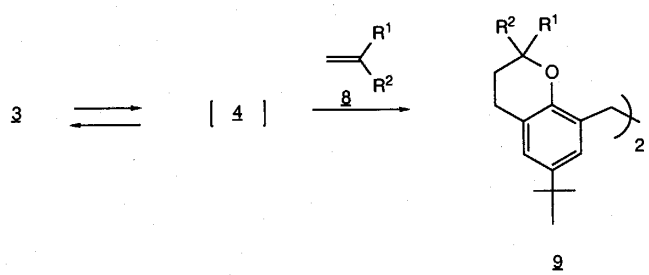
Scheme IV

When **3a** was treated with boiling methanol, the expected **5a,** whose structure was determined by comparison of its spectral data with those of isomeric **7** prepared via **6** (Scheme V), was obtained in 76% yield. Ethanol similarly reacted with **3a** and **3b** to give the corresponding **5b** and **5c** in good yield, respectively. Compound **3a** reacted with acetic acid to give diester **5d** in good yield.



Scheme V

The above results suggest the intermediate formation of bis(o-quinone methide) **4** from spiro metacyclophane **3.** In order to confirm this, reactions of **3a** with electron-rich dienophiles [4] such as ethyl vinyl ether **(8a)** and *α*-methystyrene **(8b)** were investigated in benzene under reflux. The expected [4+2]cycloadducts, **9a** and **9b,** were obtained in 96 and 99% yield, respectively (Scheme VI).



a : R^1 = H, R^2 = OEt, b : R^1 = Me, R^2 = Ph

Scheme VI

The reaction of **3a** with electron-deficient dimethyl acetylenedicarboxylate did not give the expected cycloadduct and a complex mixture of unidentified products was obtained.

In conclusion, spiro compound **3** is a convenient precursor of bis(o-quinone methide) **4** to generate on mild heating.

Experimental Section

All melting points are uncorrected. NMR spectra were recorded at 100MHz with JEOL FX-100 NMR spectrometer in $CDCl_3$ with Me_4Si as an internal reference. IR spectra were measured on KBr pellets or a liquid film on NaCl plates in a Nippon Bunko IR-A-102 spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-01 SG-2 spectrometer at 75 eV using a direct inlet system. Column chromatography was carried out on silica gel.

Oxidation of 2a with $K_3Fe(CN)_6$. To a solution of 511 mg (1.45 mmol) of **2b** in 10 mL of benzene was gradually added at room temperature a solution of 2.40 g of $K_3Fe(CN)_6$ and 1.74 g of KOH in 50 mL of water over a period of 15 min. After the reaction mixture was stirred at room temperature for 30 min, the organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated in vacuo to leave a residue which was triturated with a small amount of hexane to give 50 mg (98%) of 5,6′-di-tert-butyl-3,8′-ethanospiro[cyclohexa-3,5-dien-2-one-1,2′-chroman] **(3a)**[5] as pale yellow prisms (hexane: benzene=2:1), mp $>$ 280°C (dec.).

Anal. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found: C, 82.27; H, 8.57.

Oxidation of 2b with $K_3Fe(CN)_6$. A solution of 348 mg (1.45 mmol) of **2b** in 10 mL of benzene was treated with a solution of 2.40 g of $K_3Fe(CN)_6$ and 1.74 g of potassium hydroxide in 50 mL of water and worked up as described above to give 120 mg (35%) of 3,8′-ethanospiro [cyclohexa-3,5-dien-2-one-1,2′-chroman] **(3b)** as pale yellow prisms (hexane), mp 96-98°C; IR (KBr) ν(C=O) 1718 cm^{-1}; NMR δ 2.56 (8H, broad s) and 6.54 (6H, broad s); mass spectrum, m/e 283 (M^+).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.63; H, 6.01.

Oxidation of 2a with Ag_2O in benzene. After a mixture of 150 mg (0.426 mmol) of **2a**, 148 mg (0.64 mmol) of Ag_2O, and 4 mL of benzene was refluxed for 3h, the precipitated solid was filtered and washed with dichloromethane. The filtrate and the washings were combined and concentrated in vacuo to leave a residue which, on chromatography with a 1:1-mixture of hexane and benzene as an eluent, gave 104 mg (70%) of **3a**.

Oxidation of 2a with Ag_2O in methanol. A mixture of 150 mg (0.426 mmol) of **2a**, 148 mg (0.64 mmol) of Ag_2O, and 4 mL of methanol was refluxed for 3 h. It was worked up as

described above and the crude product was purified by chromatography with a 1:1-mixture of hexane and ethyl acetate, giving 1,2-di(5-tert-butyl-2-hydroxy-3-methoxymethyl)phenylethane **(5a)** as pale yellow oil; IR (KBr) ν(OH) 3400 cm^{-1}; NMR δ 1.27 (18H, s), 2.87 (4H, s), 3.44 (6H, s), 4.62 (4H, s), 6.96 (2H, d, J=3Hz), 7.07 (2H, d, J=3Hz), and 7.60 (2H, s, exchanged by D_2O); mass spectrum, m/e 414 (M^+).

Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 75.35; H, 8.96.

Reaction of 3a with methanol. After a solution of 50 mg (0.14 mmol) of **3a** in 7 mL of methanol was refluxed for 3h, it was evaporated in vacuo to leave a residue which, on chromatography with a 1:1-mixture of hexane of and ethyl acetate as an eluent, gave 45 mg (76%) of **5a.**

Reaction of 3a with ethanol. After a solution of 150 mg (0.43 mmol) of **2b** in 20 mL of ethanol was refluxed for 2h, it was treated as described above to give 182 mg (96%) of 1,2-di-(5-tert-butyl-2-hydroxy-3-ethoxymethyl)phenylethane **(5b)** as pale yellow oil; IR (NaCl) ν (OH) 3260 cm^{-1}; NMR δ 1.25 (18H, s), 1.26 (6H, t, J=7 Hz), 2.88 (4H, q, J=7 Hz), 3.58 (4H, s), 4.64 (4H, s), 6.87 (2H, d, J=3 Hz), and 7.05 (2H, d, J=3 Hz); mass spectrum, m/e 442 (M^+).

Anal. Calcd for $C_{28}H_{42}O_4$: C, 75.98; H, 9.56. Found: C, 75.79; H, 9.37.

Reaction of 3b with ethanol. After a solution of 30 mg (0.126 mmol) of **3b** in 5 mL of ethanol was refluxed for 2 h, it was treated as described above to give 35 mg (84%) of 1,2-di-(2-hydroxy-3-ethoxymethyl)phenylethane **5c** as pale yellow prisms (hexane), mp 86–87°C; IR (KBr) ν (OH) 3350 cm^{-1}; NMR δ 1.28 (6H, t, J=7 Hz), 2.88 (4H, s), 3.58 (4H, q, J=7 Hz), 4.67 (4H, s), 6.76 (2H, dd, J=7 and 7Hz), 6.90 (2H, dd, J=2 and 7 Hz), and 7.07 (2H, dd, J=2 and 7 Hz); mass spectrum, m/e 330 (M^+).

Anal. Calcd for $C_{20}H_{26}H_4$: C, 72.70; H, 7.93. Found: C, 72.26; H, 7.98.

Reaction of 3a with acetic acid. After a solution of 100 mg (0.285 mmol) of **3a** in 15 mL of acetic acid was heated at 100–105°C for 2h, it was concentrated in vacuo to leave a residue which, on chromatography using a 1:1-mixture of hexane and ethyl acetate as an eluent, gave colorless solid. Recrystallization from hexane afforded 110 mg (82%) of 1,2-di(5-tert-butyl-2-hydroxy-3-acethoxymethyl)phenylethane **(5d)** as colorless prisms, mp 106–107°C; IR (KBr) ν (OH) 3430 and 3350, and ν(C=O) 1740 and 1720 cm^{-1}; NMR δ 1.26 (18H, s), 2.08 (6H, s), 2.84 (4H, s), 5.12 (4H, s), 7.11 (4H, s), and 7.85 (2H, broad s); mass spectrum, m/e 470 (M^+).

Anal. Calcd for $C_{28}H_{38}O_6$: C, 71.46; H, 8.14. Found: C, 71.31; H, 8.05.

Preparation of 1,2-di(3-acetoxymethyl-5-tert-butyl-2-methoxy)phenylethane (6). After a solution of 902 mg (2 mmol) of 1,2-di(5-tert-butyl-3-chloromethyl-2-methoxy)phenylethane [6] in

50 mL of glacial acetic acid containing 4.20 g (25 mmol) of AgOAc was heated at 85–90°C for 4h, the solvent was evaporated in vacuo and the residue was extracted with dichloromethane. The extract was washed successively with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated in vacuo to leave a residue which, on recrystallization from hexane, gave 800 mg (80%) of **6** as colorless needles, mp 129–130°C; IR (KBr) ν (C=O) 1740 cm^{-1}; NMR δ 1.25 (18H, s), 2.08 (6H, s), 2.93 (4H, s), 3.74 (6H, s), 5.12 (4H, s), 7.11 (2H, d, J=3 Hz), and 7.17 (2H, d, J=3 Hz); mass spectrum, m/e 498 (M^+).

Anal. Calcd for $C_{30}H_{42}O_6$: C, 72.26; H, 8.49. Found: C, 72.45; H, 8.54.

Preparation of 1,2-di(5-tert-butyl-3-hydroxy-2-methoxy)phenylethane (7). An ether solution (10 mL) of 498 mg (1.0 mmol) of **6** was added to a gently refluxing suspension of 190 mg (5.0 mmol) of $LiAlH_4$ in dry ether (10 mL). After the reaction mixture was refluxed for 1h, it was quenched with ethyl acetate and 10% sulfuric acid under external ice-cooling, extracted with ether, dried over Na_2SO_4, and evaporated in vacuo to leave a residue which, on recrystallization from a 2:1-mixture of hexane and benzene, gave 400 mg (97%) of **7** as colorless prisms, mp 159–160°C; IR (KBr) ν (OH) 3320 cm^{-1}; NMR δ 1.28 (18H, s), 2.30 (2H, broad s), 2.92 (4H, s), 3.75 (6H, s), 4.78 (4H, s), 7.10 (2H, d, J=3 Hz), and 7.17 (2H, d, J=3 Hz); mass spectrum, m/e 414 (M^+).

Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 75.40; H, 9.24.

Reaction of 3a with 8a. After a solution of 100 mg (0.285 mmol) of **3a** and 2 mL of **8a** in 2 mL of benzene was refluxed for 24h, it was concentrated in vacuo to leave a residue which, on chromatography with a 1:1-mixture of hexane and ethyl acetate as an eluent, gave 135 mg (96%) of pale yellow oil. Recrystallization of this oil from ethanol gave 1,2-di[(2-ethoxy-6-tert-butyl)chroman-8-yl]ethane **(9a)** as colorless prisms, mp 97–98°C; NMR δ 1.20 (6H, t, J=7 Hz), 1.24 (18H, s), 1.88–2.06 (4H, m), 2.46–2.95 (4H, m), 2.86 (4H, s), 3.06–4.12 (4H, m), 5.24 (2H, t, J=3 Hz), 6.85 (2H, d, J=2.5 Hz), and 6.94 (2H, d, J=2.5 Hz); mass spectrum, m/e 494 (M^+).

Anal. Calcd for $C_{32}H_{46}O_4$: C,77.69; H, 9.37. Found: C, 77.34; H, 9.32.

Reaction of 3a with 8b. A solution of 100 mg (0.285 mmol) of **3a** and 2 mL of **8b** in 2 mL of benzene was treated as described above to give 165 mg (99%) of 1,2-di[(6-tert-butyl-2-methyl-2-phenyl)chroman-8-yl]ethane **(9b)** as colorless prisms (ethanol), mp 64–65°C; NMR δ 1.22 (18H, s), 1.60 (6H, d, J=2 Hz), 2.00–2.78 (8H, m), 3.10 (4H, broad s), 6.78 (2H, d, J=2.5 Hz), 7.02 (2H, d, J=2.5 Hz), and 7.08–7.44 (10H, m); mass spectrum, m/e 586 (M^+).

Anal. Calcd for $C_{42}H_{50}O_2$: C, 85.96; H, 8.59. Found: C, 85.45; H, 8.66.

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