Medium-sized Cyclophanes. Part 40.[1] Generation of a Bis(*o*-quinone methide) from [*n*.2]Cyclophanes having a Spiro Skeleton and their Trapping Reaction with Nucleophiles and Dienophiles

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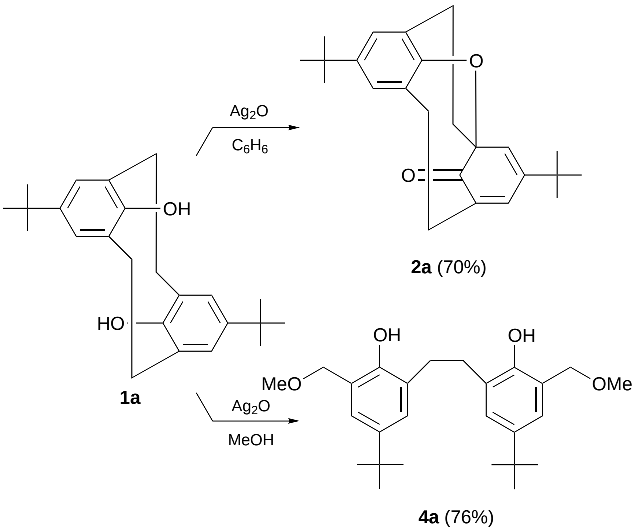
Spiro compounds **2**, obtained from the oxidation of dihydroxy[*n*.2]metacyclophanes **1** with $K_3Fe(CN)_6$, readily generate a bis(*o*-quinone methide) **3** with mild heating which is trapped with nucleophiles and dienophiles to give diarylalkanes **4–6** and [4+2] cycloadducts **8**, respectively.

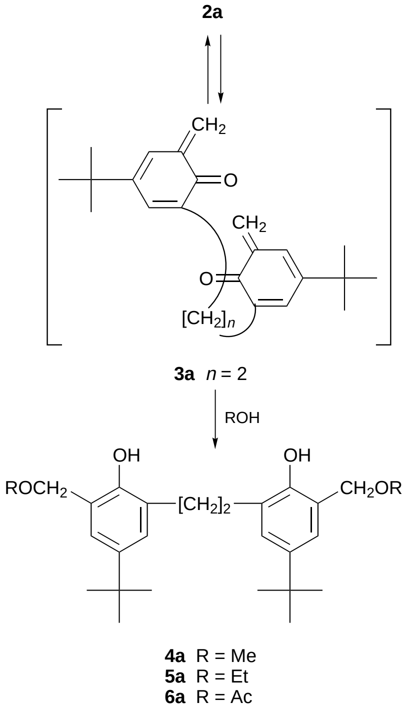
Quinone methides have been postulated as reactive intermediates in organic reactions for many years.[2] A quinone methide with an unsubstituted methylene group has not been isolated except at low temperatures[3] or in the case of highly hindered molecules.[4] Filar and Winstein[5] have shown the existence of a *p*-quinone methide in dilute solution.

A quinone methide intermediate is usually identified from product studies. Balon[6] has reported the oxidation of 4-substituted 2,6-dimethylphenols with various oxidizing agents such as silver oxide in methanol to form 4-substituted 2-methoxymethyl-6-methylphenols by trapping the *o*-quinone methide with the nucleophilic methanol. *o*-Quinone methide intermediate formation was subsequently confirmed by the formation of a [4+2] cycloadduct with reactive dienophiles to form chromane skeletons.[7]

We recently found that the oxidation of 5,13-di-*tert*-butyl-8,16-dihydroxy[2.2]MCP (MCP = metacyclophane) **1a** with $K_3Fe(CN)_6$ afforded the intramolecular O–C coupling product **2a** having a spiro skeleton.[8–11] Compound **2a** corresponds to the intramolecular [4+2] cycloadduct of the bis(*o*-quinone methide) **3a**. Here we report the cycloreversion of **2** with mild heating to generate **3** and the reaction of **2** with alcohols, acetic acid and ethenes. The effects on strain with increasing methylene bridge length of the cycloreversion product are also investigated.



Scheme 1



Scheme 2

Table 1 Reaction of **2a** with methanol, ethanol and acetic acid

Reagent	*T*/°C	*t*/h	Products (%)[a]
MeOH	reflux	3	**4a** (76)
EtOH	reflux	2	**5a** (96)
HOAc	100–105	2	**6a** (84)

[a]Isolated yields.

Oxidation of 5,13-di-*tert*-butyl-8,16-dihydroxy[2.2]MCP **1a**[12] in refluxing benzene by Ag_2O, as well as by aqueous $K_3Fe(CN)_6$, for 3 h afforded the intramolecular O–C coupling product **2a** in 70% yield (Scheme 1). When methanol was used instead of benzene, an unexpected product **4a**, which corresponds to a 1:2-adduct of **3a** and methanol, was obtained in 76% yield. The formation of **4a** suggests that the spiro compound **2a** produced in the oxidation of **1a** by Ag_2O reacted with methanol. Therefore, **2a** was treated separately with methanol, ethanol and acetic acid. When **2a** was treated with boiling methanol, the expected **4a**, whose structure was determined by its spectral data, was obtained in 76% yield. Ethanol similarly reacted with **2a** to give **5a** in good yield. Compound **2a** reacted with acetic acid to give diester **6a** in good yield.

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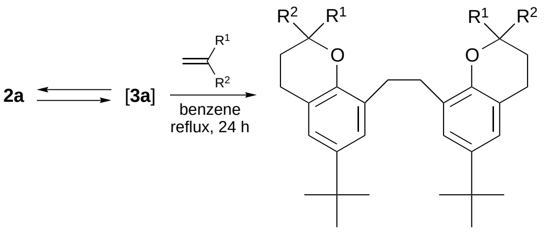
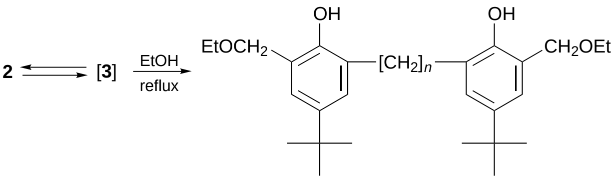


8a $R^1 = H, R^2 = OEt$ (96%)
b $R^1 = Me, R^2 = Ph$ (99%)

Scheme 3

The above results suggest the intermediate formation of the bis(*o*-quinone methide) **3a** from the spiro metacyclophane **2a**. In order to confirm this, reactions of **2a** with electron-rich dienophiles[3] such as ethyl vinyl ether (**7a**) and α-methylstyrene in refluxing benzene (**7b**) were investigated. The expected [4 + 2] cycloadducts, **8a** and **8b**, were obtained in 96 and 99% yield, respectively.

The reaction of **2a** with electron-deficient dimethyl acetylenedicarboxylate did not give the expected cycloadduct; instead a complex mixture of unidentified products was obtained.



5a $n = 2$
b $n = 3$
c $n = 4$
d $n = 5$

Scheme 5

In conclusion, the spiro compound **2a** is a convenient precursor of the bis(*o*-quinone methide) **3a**, generated after mild heating of **2a**.

These novel ring fissions, generating bis(*o*-quinone methide) intermediate **3a** after mild heating of **2a**, might occur as a result of releasing the strain in the spiro compound **2a**. Thus, there is substantial interest in investigating the effects on strain of increasing the length of the methylene bridge of spiro [*n*.2]cyclophanes by the formation of bis(*o*-quinone methide) intermediates.

When 5′,6-di-*tert*-butyl-3′,8-propanospiro[chromane-2,1′-cyclohexa-3′,5′-dien]-2′-one **2b** was treated with boiling ethanol for 2 h, the expected product **5b** derived from a bis(*o*-quinone methide) intermediate was obtained in 13% yield along with 87% recovery of the starting compound. Prolonged reaction times led to complete formation of **5b**. Similar treatment of the larger-ring-sized spiro compound **2c** ($n = 4$) with boiling ethanol afforded only **5c** in 16% yield, while with the larger-ring spiro compound **2d** only recovered starting material was obtained.

Table 2 Reaction of **2** with EtOH

Substrate **2**	*t*/h	Products **5** (%)[a]	Recovd.
a	2	(100)	(0)
b	2	(13)	(87)
b	36	(100)	(0)
c	36	(16)	(84)
d	36	(0)	(100)

[a] Yields were determined from ^1H NMR spectroscopy.

Although Biali *et al.*[14] reported the preparation of bis(spirodienone) derivatives of *p*-*tert*-butylcalix[4]arene and various reactions in protic media, the present novel ring fission to generate bis(*o*-quinone methide) intermediates has not been observed so far. Therefore, the above results suggest that the effects of strain in [*n*.2]cyclophanes having a spiro skeleton **2** do exist. Thus, the generation of a bis(*o*-quinone methide) on mild heating is possible for [2.2]cyclophane **2a** and [3.2]cyclophane **2b** having a spiro skeleton and can be attributed to the strain of a medium ring which can be released by conversion into the strain-free bis(*o*-quinone methides) **3a** and **3b**.

We conclude that the spiro compounds **2** obtained in the oxidation of dihydroxy[*n*.2]MCPs **1** with $K_3Fe(CN)_6$, readily generate a bis(*o*-quinone methide) **3** on mild heating, which is trapped with methanol, ethanol and acetic acid to give diarylalkanes.

Techniques used: ^1H NMR, IR, MS, VPC

References: 14

Tables: 2

Schemes: 5

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References cited in this synopsis

1 Part 39: T. Yamato, K. Fujita, T. Ando, S. Ide, Y. Nagano and M. Tashiro, *J. Chem. Res.*, 1996, (*S*) 264; (*M*) 1434.
2 A. B. Turner, *Quart. Rev.*, 1964, **28**, 347.
3 (*b*) A. Merrijan, B. A. Shoulders and P. D. Gardner, *J. Org. Chem.*, 1963, **28**, 2148.
4 A. Bistrzycki and C. Herbst, *Chem. Ber.*, 1903, **36**, 2335.
5 L. J. Filar and S. Winstein, *Tetrahedron Lett.*, 1960, **25**, 9.
6 D. A. Balon, *J. Org. Chem.*, 1970, **35**, 715.
7 D. A. Balon, *J. Org. Chem.*, 1970, **35**, 3666.
8 M. Tashiro, T. Yamato, S. Horie and S. Mataka, *Chem. Pharm. Bull.*, 1984, **32**, 1641.
9 T. Yamato, J. Matsumoto, K. Tokuhisa, K. Suehiro, S. Horie and M. Tashiro, *J. Org. Chem.*, 1992, **57**, 6368.
10 T. Yamato, J. Matsumoto, K. Tokuhisa, K. Suehiro and M. Tashiro, *J. Chem. Soc., Chem. Commun.*, 1992, 865.
11 T. Yamato, K. Fujita, J. Matsumoto, M. Sato, Y. Nagano and M. Tashiro, *J. Chem. Res. (S)*, 1996, 262.
12 (*b*) M. Tashiro, K. Koya and T. Yamato, *J. Am. Chem. Soc.*, 1982, **104**, 3707.
14 A. M. Litwak, F. Grynszpan, O. Aleksiuk, S. Cohen and S. E. Biali, *J. Org. Chem.*, 1993, **58**, 393.