

Periodate Oxidation of Phenols. XX.* Reactions of 5-Substituted 2,4-Cyclohexadienones with Dienophiles

GUNVOR ANDERSSON

Department of Organic Chemistry, Chalmers University of Technology and University of Göteborg, Fack, S-402 20 Göteborg 5, Sweden

2,4-Cyclohexadienones carrying a 5-substituent (CH_3 or OCH_3) do not dimerize, but undergo Diels-Alder addition to 2,3-dimethyl-*p*-benzoquinone, dimethyl acetylenedicarboxylate, maleic anhydride and bromomaleic anhydride. They failed, however, to add to the methyl, dimethyl and dichloro derivatives of maleic anhydride, *trans*-1,2-dicyanoethylene, tetracyanoethylene, and cyclopentadiene. The reasons for the resistance of the 5-substituted 2,4-cyclohexadienones to dimerization are discussed.

In a preceding paper,¹ the preparation of 2,4-cyclohexadienones carrying a small substituent (CH_3 or OCH_3) in the 5-position, such as compounds *1a-e*, was reported. These dienones were stable as monomers even when heated at 110 °C and thus differed from the analogues lacking the 5-substituent which readily dimerize by Diels-Alder addition in a stereospecific and regiospecific manner.² Further investigation of the ability of 5-substituted 2,4-cyclohexadienones to undergo Diels-Alder reactions therefore seemed of interest, and the present study deals with the behaviour

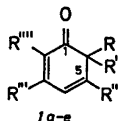
of compounds *1a-e* towards a number of dienophiles.

RESULTS

6-Ethoxy-5,6-dimethyl-2,4-cyclohexadienone (*1c*) reacted with 2,3-dimethyl-*p*-benzoquinone in refluxing toluene to give a fair yield of the Diels-Alder adduct *2c*. A small amount of this adduct, in addition to other products, had also been obtained on oxidation of 2,3-dimethylphenol with sodium periodate in water/ethanol.¹ It has been shown earlier³ that 2-methylphenols with free 3-positions, when oxidized with periodate in the presence of *p*-benzoquinones, yield *o*-quinol-*p*-quinone adducts similar to *2c* in addition to the *o*-quinol dimers. The formation of *2c* then indicates that the diene activity of the 5-substituted *o*-quinol ether *1c* is comparable to that of *o*-quinols carrying a hydrogen atom in position 5.

Diels-Alder additions of 2,4-cyclohexadienones to acetylenedicarboxylic esters, as well as to maleic anhydride, have been reported.⁴ As illustrated by the formation of *3e* from the *o*-quinone ketal *1e*, as well as the production of the adducts *4a-e* from compounds *1a-e*, these reactions are not inhibited by the presence of a 5-substituent in the dienone. (The steric arrangement of the geminal bridge substituents indicated in adducts *2c* and *4a-d* has not been investigated but has been assumed to be analogous to that found for other *o*-quinol-*p*-quinone adducts³ and for 2,4-cyclohexadienone dimers.⁵⁻⁹)

Neither methylmaleic anhydride nor dimethylmaleic anhydride, which are comparatively

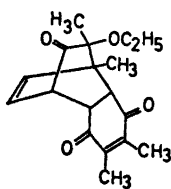


- 1a-e*
- a R=OH; R', R'', R'''=CH₃; R''''=H
 - b R=OCH₃; R', R'', R'''=CH₃; R''''=H
 - c R=OC₂H₅; R', R''=CH₃; R''', R''''=H
 - d R, R''=OCH₃; R'=CH₃; R''', R''''=H
 - e R, R', R''=OCH₃; R''', R''''=H

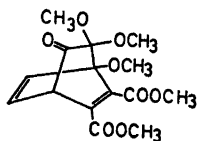
* Part XIX, see Ref. 1.

weak dienophiles,¹⁰ added to the 5-substituted cyclohexadienones. However, bromomaleic anhydride, which has about the same dienophilic reactivity as maleic anhydride,¹⁰ added to *1e* to give *7e*, whereas dichloromaleic anhydride, expected to be a strong dienophile, was unreactive.

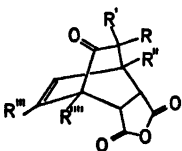
trans-1,2-Dicyanoethylene, a dienophile which, in its additions to cyclopentadiene or 9,10-dimethylantracene, is about 50 times less reactive than maleic anhydride,¹¹ did not react with *1e*, and the highly reactive tetracyanoethylene (rate constants about 500 times larger than with maleic anhydride¹¹) also failed to add to *1e*.



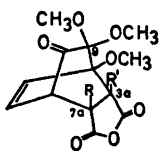
2c



3e

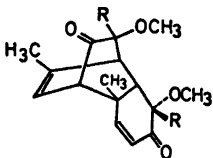


4a-e

(5e R=CH₃, R'=H)(6e R=R'=CH₃)

(7e R=Br, R'=H)

(8e R=R'=Cl)

9 R=OCH₃10 R=CH₃

Cyclopentadiene has been reported to add as dienophile to a number of 5-unsubstituted 2,4-cyclohexadienones⁴ but proved to be unreactive when heated together with the methoxy analogue of *1c*¹ or with *1d*.

DISCUSSION

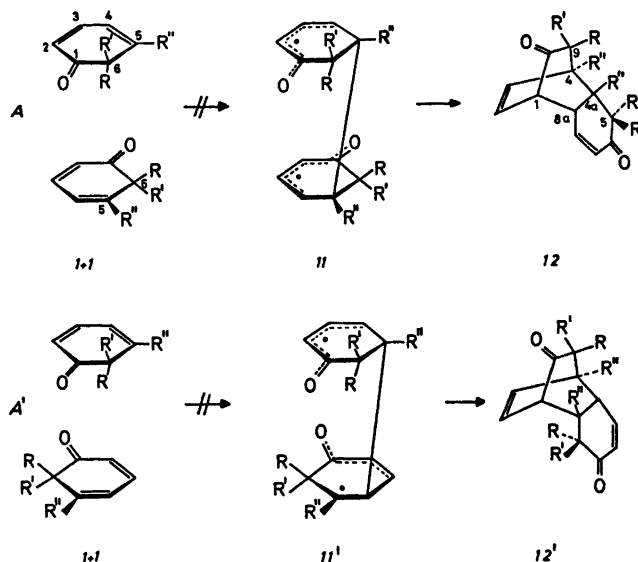
Addition of methylmaleic anhydride to the 5-substituted 2,4-cyclohexadienones did not take place although it seemed to be sterically possible. Reaction with *1e*, for instance, could

be expected to give adduct *5e* with the methyl substituent in position 7a; dimers 9^a and 10,⁵ with CH₃ in a similar position, are known. Since bromomaleic anhydride reacted to give adduct *7e*, and methyl and bromine are of comparable size, the different behaviour of the two monosubstituted maleic anhydrides can be assumed to be due mainly to the opposite electronic effects of the two substituents.

Apparently, the steric effect of the 5-substituent of the dienes is strong enough to hinder the approach of comparatively weak dienophiles, such as methylmaleic anhydride, *trans*-1,2-dicyanoethylene and cyclopentadiene. This effect is overcome by stronger dienophiles with comparable steric requirements, such as 2,3-dimethyl-*p*-benzoquinone, maleic anhydride and bromomaleic anhydride. However, dienophiles with a fully substituted double bond (dimethylmaleic anhydride, dichloromaleic anhydride, tetracyanoethylene) fail to react, because the 3a-substituent of the hypothetical adducts as illustrated by formulae *6e* and *8e* would be in steric opposition to the 9-substituent *anti* to the ethylenic bond.

The latter type of steric interaction is also responsible for the failure of the 5-substituted 2,4-cyclohexadienones to dimerize.^{1,4} Inspection of Dreiding models of the (nonexisting) dimers of type *12* (Scheme 1A) indicates severe steric opposition between groups R(9) and R''(4a), as well as between groups R(5) and R''(4).

The stereochemical and structural orientations of the monomers presented in Scheme 1A are those established for the dimers of 5-unsubstituted 2,4-cyclohexadienones.^{5-9,12} It would seem, however, that an orientation of the monomers as depicted in Scheme 1A' might result in dimerization, since no critical steric interaction would be involved. The fact that dimerizations of type A' do not take place—even if there is no 5-substituent (R'')—may be understood from recent mechanistic considerations. According to Epiotis,¹³ perturbation theory applied to Diels-Alder reactions between dienes and dienophiles carrying substituents of similar electronic properties led to false predictions of the regioselectivity, if a fully concerted mechanism was assumed. The orientations found experimentally were consistent, however, with a highly unsymmetrical,



Scheme 1.

biradical-like transition state. In a theoretical study of three typical Diels-Alder reactions, Dewar, Griffin and Kirschner¹⁴ similarly concluded that the transition states of these reactions were "very unsymmetrical, corresponding to biradicaloid structures." The transition states of reactions *A* and *A'* (Scheme 1) are, for simplicity, given as fully developed biradicals. As indicated by their hybrid structures, *11* is more stable than *11'*. This is in harmony with the fact that 5-unsubstituted monomers always give dimers of type *12* ($R'' = H$), whereas isomers of type *12'* have not been observed,⁵⁻⁹ and also with the fact that the 5-substituted analogues fail to dimerize according to *A'* although the latter reaction, contrary to reaction *A*, would seem sterically possible.

EXPERIMENTAL

UV spectra were run in ethanol on a Cary model 15, and IR spectra were recorded in KBr on a Beckman 9A instrument, unless otherwise stated. UV data are given as λ_{\max} values in nm, with log ϵ values in parentheses, IR data as ν_{\max} values in cm^{-1} . ^1H NMR spectra were taken in CDCl_3 on a Varian A-60 spectrometer. Analytical and preparative TLC, as well as column chromatography, were performed on silica gel with benzene/ethyl acetate (4:1) as mobile phase.

10-Ethoxy-1,4,4a,8a-tetrahydro-1,6,7,10-tetra-methyl-1,4-ethanonaphthalene-5,8,9-trione (2c). A solution of 6-ethoxy-5,6-dimethyl-2,4-cyclohexadienone (*1c*)¹ (350 mg = 2 mmol) and 2,3-dimethyl-*p*-benzoquinone (400 mg = 3 mmol) in toluene (15 ml) was refluxed for 15 h. (After a heating period of 3 h, TLC indicated the presence of some unchanged *1c*.) The solvent was removed and the remaining solid recrystallized from ethyl acetate to give *2c* (410 mg, 65%), identical by m.p. (160–161°C), mixed m.p. and IR spectrum with the same compound obtained according to Ref. 1.

Dimethyl 1,7,7-trimethoxy-8-oxobicyclo[2.2.2]octa-2,5-diene-2,3-dicarboxylate (3e). A solution of 5,6,6-trimethoxy-2,4-cyclohexadienone (*1e*)¹ (500 mg = 2.7 mmol) and dimethyl acetylenedicarboxylate (700 mg = 5.5 mmol) in toluene (25 ml) was refluxed for 8 h. Column chromatography of the product obtained after removal of the solvent gave (1) unchanged acetylenedicarboxylate; (2) compound *3e*, 640 mg (71%) of colourless crystals of m.p. 112–113°C after recrystallization from isopropyl ether; (3) 85 mg (17%) of unchanged *1e*. Compound *3e* was further characterized as follows. (Found: C 55.44; H 5.59. Calc. for $\text{C}_{18}\text{H}_{18}\text{O}_8$: C 55.21; H 5.56). UV sh 240 (3.42), sh 305 (2.40). IR 1730 (CO), 1718 (α,β -unsat. ester), 1655 and 1602 (C=C). NMR δ 3.46, 3.53, 3.69, 3.78, 3.88 (3 H each, 5 OCH_3). H-6, H-5 and H-4 give rise to an ABX pattern: 4.48 (dd, 1 H, H-4), 6.52 (dd, 1 H, H-5), 6.82 (dd, 1 H, H-6); $J_{4,5} = 6$ Hz, $J_{4,6} = 2$ Hz, $J_{5,6} = 8$ Hz.

Adducts of 2,4-cyclohexadienones 1a–e with maleic anhydride (general procedure). A solution

of the cyclohexadienone¹ (2–5 mmol) and a twofold excess of maleic anhydride in toluene (10–25 ml) was refluxed for 6 h. (After a reaction time of 3 h, some unchanged dienone was still present according to TLC.) The reaction mixture was evaporated under vacuum. Excess maleic anhydride was removed from the resulting solid by sublimation and subsequent extraction of the residue with boiling ether. The remaining crude adduct was purified by recrystallization. Yields given below refer to recrystallized product.

3a,4,7,7a-Tetrahydro-9-hydroxy-4,6,9-trimethyl-4,7-ethanoisobenzofuran-1,3,8-trione (4a).

From 6-hydroxy-3,5,6-trimethyl-2,4-cyclohexadienone (*1a*) and maleic anhydride in 70 % yield; m.p. 182–183 °C (ethyl acetate-hexane). (Found: C 62.57; H 5.67. Calc. for C₁₅H₁₄O₅: C 62.39; H 5.64). UV 205 (3.61), 308 (2.11) (β,γ -enone system). IR (CHCl₃) 1738 s (CO), 1780 s and 1860 m (five-membered cyclic anhydride), 3430 (OH).

3a,4,7,7a-Tetrahydro-9-methoxy-4,7,9-trimethyl-4,7-ethanoisobenzofuran-1,3,8-trione (4b).

From 6-methoxy-2,5,6-trimethyl-2,4-cyclohexadienone (*1b*) and maleic anhydride in 90 % yield, m.p. 150–152 °C (isopropyl ether). (Found: C 63.84; H 6.20; OCH₃ 11.93. Calc. for C₁₄H₁₆O₅: C 63.63; H 6.10; OCH₃ 11.74).

9-Ethoxy-3a,4,7,7a-tetrahydro-4,9-dimethyl-4,7-ethanoisobenzofuran-1,3,8-trione (4c).

From 6-ethoxy-5,6-dimethyl-2,4-cyclohexadienone (*1c*) and maleic anhydride in 82 % yield; m.p. 115–116 °C (isopropyl ether). (Found: C 63.77; H 6.09. Calc. for C₁₄H₁₆O₅: C 63.63; H 6.10). IR (CHCl₃) 1730 s, 1780 s, 1855 m.

3a,4,7,7a-Tetrahydro-4,9-dimethoxy-9-methyl-4,7-ethanoisobenzofuran-1,3,8-trione (4d).

From 5,6-dimethoxy-6-methyl-2,4-cyclohexadienone (*1d*) and maleic anhydride in 80 % yield; m.p. 164–165 °C (benzene-hexane). (Found: C 58.80; H 5.17; OCH₃ 23.09. Calc. for C₁₅H₁₄O₅: C 58.64; H 5.30; OCH₃ 23.31). IR 1730 s, 1801 s, 1872 m.

3a,4,7,7a-Tetrahydro-4,9,9-trimethoxy-4,7-ethanoisobenzofuran-1,3,8-trione (4e).

From 5,6,6-trimethoxy-2,4-cyclohexadienone (*1e*) and maleic anhydride in 74 % yield; m.p. 150–151 °C (benzene-hexane). (Found: C 55.33; H 4.82; OCH₃ 32.68. Calc. for C₁₅H₁₄O₇: C 55.32; H 5.00; OCH₃ 32.98). IR (CHCl₃) 1746 s, 1786 s, 1870 m.

7a-Bromo-3a,4,7,7a-tetrahydro-4,9,9-trimethoxy-4,7-ethanoisobenzofuran-1,3,8-trione (7e).

From *1e* and bromomaleic anhydride as described above for the maleic anhydride adducts, but reaction time 75 h. (After 24 h, some unchanged *1e* was detected by TLC.) Compound *7e* was separated from excess bromomaleic anhydride by column chromatography. Yield, 77 %; m.p. 124–125 °C (isopropyl ether). (Found: C 43.22; H 3.71; Br 22.08. Calc. for C₁₅H₁₃O₇Br: C 43.23; H 3.63; Br 22.12). UV 320 (1.97). IR 1745 s, 1803 s, 1870 m. NMR δ 3.57 (s, 6 H, 2 OCH₃), 3.83 (broadened s, overlapping the upfield doublet due to H-7,

about 3.5 H, OCH₃); the downfield doublet of H-7 is found at 3.92; 4.45 (s, 1 H, H-3a). The signals of H-5 and H-6 constitute the AB part of an ABX spectrum (X=H-7): 6.21 (dd, 1 H, H-6), 6.49 (dd, 1 H, H-5). $J_{6,7}$ = 6 Hz, $J_{5,7}$ = 1.5 Hz, $J_{5,6}$ = 8.5 Hz.

Unsuccessful attempts to add methylmaleic anhydride, dimethylmaleic anhydride, dichloromaleic anhydride, *trans*-1,2-dicyanoethylene, tetracyanoethylene and cyclopentadiene to *1a-e* in toluene solution at room temperature, as well as at reflux temperature, were made using prolonged reaction times.

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