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Novel Stereoselective Addition of Some Nucleophiles to 2,3-Bis(methylsulfanyl)norbornenobenzoquinone.

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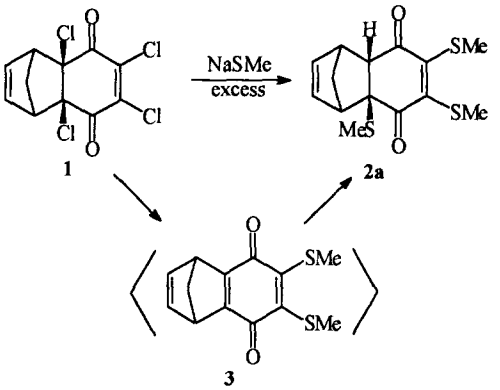
Abstract: 2,3-Bis(methylsulfanyl)norbornenobenzoquinone undergoes reaction with nitrogen, oxygen, sulfur or carbon nucleophiles to give the trisubstituted adducts containing the new substituent at the ring junction. Their configurations are assigned by ^{1}H NMR spectroscopy and NOE enhancement experiments. © 1997 Elsevier Science Ltd.

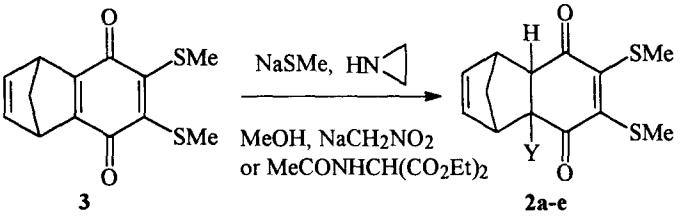
In the course of our studies[1] of the reaction of chloranyl-cyclopentadiene Diels-Alder adduct **1** with excess of sodium methyl sulfide, leading to the corresponding 2,3,5-tris(methylsulfanyl)-derivative **2a**, we became interested in investigating the addition of nucleophilic reagents to 2,3-bis(methylsulfanyl)norbornenobenzoquinone[2] **3**, a probable intermediate in the above reaction (Scheme 1).



Scheme 1

It is noteworthy that the intermediate quinone **3** has not been reported in the literature and that also little attention was given in the literature to the corresponding unsubstituted derivative.[3]

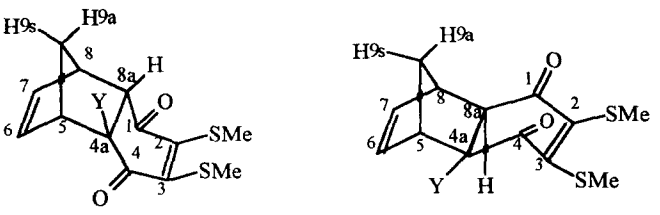
Compound **3**, obtained by oxidation of the enolized 2,3-bis(methylsulfanyl)-benzoquinone-cyclopentadiene adduct,[4] was submitted to the reaction with sulfur, nitrogen, oxygen and carbon nucleophiles such as sodium methyl sulfide, aziridine, methanol, the sodium salt of nitromethane and ethyl acetamidomalonate carbanion.[5a-e] In all cases the corresponding trisubstituted derivatives **2a-e**, containing the new substituent group at the ring junction[1], were obtained (Scheme 2).



Y = SMe (**a**); N (**b**); OMe (**c**); CH_2NO_2 (**d**); $C(CO_2Et)_2NHCOMe$ (**e**)

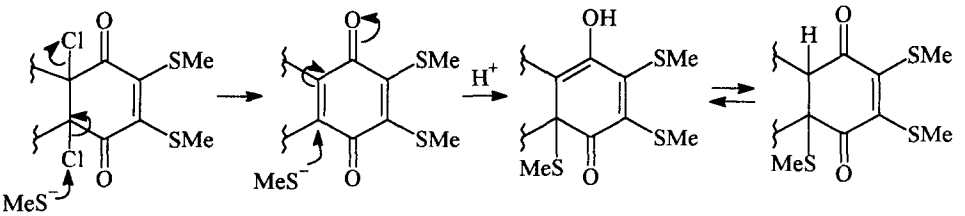
Scheme 2

However, although reactions with sodium methyl sulfide and ethyl acetamidomalonate carbanion lead only to one adduct **2a** (81%) and **2e** (71%) in the case of methanol, aziridine and the sodium salt of nitromethane, besides adducts **2b** (49%), **2c** (68%) and **2d** (34%), the main products of these reactions, small amounts of adducts **2'b** (12%), **2'c** (23%) and **2'd** (6%) were also isolated. Our supposition that the latter were stereoisomers of the adducts **2b-d** was confirmed by analysis of the values of the coupling constants[6] for the ring junction protons and NOE enhancement experiments,[5] which indicated that adducts **2a-e** contain *cis-exo* H and Y substituents, but that in adducts **2'b-d** they are *cis-endo* (Figure).



Figure

The fact that for **2a**, obtained from the chloranyl adduct **1**, H and SMe were also *cis-exo*[1] suggests that compound **3** is an intermediate in the above reaction. It seems reasonable to propose that the double bond in the latter would be formed by initial attack of MeS^- on the chlorine atom at the ring junction,[7] followed by elimination of Cl^-. The addition of MeS^- would occur via a Michael-type reaction, the hydrogen being attached through tautomeric equilibrium. As a consequence the final product would assume the thermodynamically more stable configuration (Scheme 3).



Scheme 3

Further studies on the application of this addition reaction to the synthesis of trisubstituted benzoquinones of potential biological activity, employing the retro-Diels-Alder procedure,[4] are in progress.

In summary, we have shown that the addition of nucleophiles to the bis(methylsulfanyl)norbornenobenzoquinone is stereoselective, giving exclusively, or at least predominantly, the adducts of the *cis-endo* configuration.

Acknowledgements
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References and Notes

1. Wladislaw, B.; Di Vitta; C.; Marzorati, L.; de Arruda Campos, I. P.; *J. Chem. Research (S)* 1994, 438.
2. Synthesis of norbornenoquinone **3**: The enolized 2,3-bis(methylsulfanyl)-benzoquinone-cyclopentadiene adduct (1.3 g; 4.9 mmol) was suspended in MeOH (10 mL) and treated with a saturated aqueous solution of $Fe(NO_3)_3$ (20 mL). The resulting purple solid (0.80 g; 3.0 mmol; m. p.: 128-130°C) was filtered and washed with cold water. C, H, (%) 59.0, 4.7 (calc.: 59.1, 4.6). ^1H NMR (δ, $CDCl_3$): 6.86(2H, m), 4.09(2H, m), 2.63(6H, s), 2.28(2H, m).
3. Mehta, G.; Padma, S.; Karra, S. R.; Gopdas, K. R.; Cyr, D. R.; Das, P. K.; George, M. V.; *J. Org. Chem.* 1989, *54*, 1342.
4. Wladislaw, B.; Marzorati, L.; Di Vitta, C.; *Synthesis* 1983, 464.
5. a) Reaction of **3** with sodium methyl sulfide: To a solution of quinone **3** (0.10 g; 0.38 mmol) in MeOH (2 mL) was added NaSMe (4.3 mmol) dissolved in MeOH (2 mL). After disapearance of the characteristic purple colour of the quinone (5 min.), the mixture was poured into saturated NH_4Cl solution (20 mL) and the

product collected by filtration. Recrystalization from MeOH yielded a yellow solid (0.096 g) with physical and spectroscopic data identical to those described for **2a**[1]. b) Reaction of **3** with aziridine: Quinone **3** (0.50 g; 1.9 mmol) was dissolved in Et_2O (10 mL), and treated with freshly destilled aziridine (1.2 g; 28 mmol). After colour fading (5 h), the mixture was poured into saturated NH_4Cl solution (20 mL) and the organic layer was separated, dried and concentrated. The resulting resinous solid was chromatographed on silica gel (Et_2O) giving: i) **2b** (*cis-exo*; 0.29 g; m. p.: 119-120°C); C, H, N (%) 58.8, 5.6, 4.6 (calc.: 58.6, 5.5, 4.6); ^1H NMR (δ, $CDCl_3$): 6.16 (1H, m, H7), 5.95 (1H, m, H6), 3.42 (1H, m, H8), 3.20 (1H, d, H8a, $^3J_{8a,8}$=3.8 Hz[6]), 3.00 (1H, m, H5), 2.53 and 2.49 (6H, s, SMe), 2.03 (1H, m, H9a), 1.78 (4H, m, NC_2H_4), 1.60 (1H, m, H9s). NOE experiments[1] (irradiation on H / % of enhancement observed at H'): NC_2H_4 / 2 % at H9a, 3 % at H8a; H9a / 3 % at H8a; H8a / 2 % at H9a. ii) **2'b** (*cis-endo*; 0.07 g; oil); C, H, N (%) 58.9, 5.7, 4.7 (calc.: 58.6, 5.5, 4.6); ^1H NMR (δ, C_6D_6): 6.43 (1H, m, H7), 6.27 (1H, m, H6), 3.48 (1H, m, H8), 3.46 (1H, m, H5), 2.53 and 2.52 (6H, s, SMe), 2.29 (1H, d, H8a, $^4J_{8a,9s}$ = 2.4 Hz[6]), 1.60 (4H, m, NC_2H_4), 1.46 (1H, m, H9s), 1.12 (1H, m, H9a); NOE experiments (irrad. on H / % of enhanc. obs. at H'): NC_2H_4/ 6 % at H8a, 2 % at H6; H8a / 2 % at NC_2H_4, 1 % at H7; H7 / 1 % at H8a. c) Reaction of **3** with methanol: Quinone **3** (1.5 g; 5.7 mmol) was refluxed in MeOH (20 mL) during 1 h. After concentration, a yellow solid was collected and chromatographed on silica gel (C_6H_6) yielding: i) **2c** (*cis-exo*; 1.15 g; m. p.: 106-108°C); C, H (%) 56.5, 5.5 (calc.: 56.8; 5.5); ^1HNMR (δ, $CDCl_3$): 6.25(1H, m, H7), 5.92(1H, m, H6), 3.45(1H, m, H8), 3.35(1H, m, H5), 3.33(3H, s, OMe), 3.06 (1H, d, H8a, $^3J_{8a,8}$=3.7Hz[6]), 2.51 and 2.47 (6H, s, SMe), 1.85(1H, m, H9a), 1.69(1H, m, H9s); ii) **2'c** (*cis-endo*; 0.39 g; oil); C, H (%) 57.0, 5.7 (calc.: 56.8; 5.5); ^1H NMR (δ; $CDCl_3$): 6.49(1H, m, H7), 6.18(1H, m, H6), 3.64(1H, m, H8), 3.45(1H, m, H5), 3.19(3H, s, OMe), 2.51 and 2.48(6H, s, SMe), 2.38(1H, d, H8a, $^4J_{8a,9s}$=2.9Hz[6]), 1.60 (1H, m, H9s), 1.22 (1H, m, H9a); d) Reaction of **3** with sodium salt of nitromethane: Nitromethane (2 mL) was slowly added dropwise over oil-freed NaH (0.040 g; 1.7 mmol) suspended in DMSO (2.0 mL). The resulting suspension was added, via syringe, to a solution of quinone **3** (0.26 g; 1.0 mmol) in C_6H_6 (5 mL). After colour fading (1 h) the mixture was poured into saturated NH_4Cl solution (15 mL) and extracted with CH_2Cl_2. The extract was dried and concentrated resulting in an oil. Separation using preparative TLC (C_6H_6) afforded: i) **2d** (*cis-exo*; 0.11 g; m.p.: 89-91°C); C, H, N (%) 51.5, 4.5, 4.3 (calc.: 51.7, 4.6, 4.3); ^1H NMR (δ, $CDCl_3$): 6.20 (1H, m, H7), 6.12 (1H, m, H6), 5.33 (1H, d, $CH\underline{a}Hb NO_2$, J_{ab} = 14 Hz), 4.44 (1H, d, $CHaH\underline{b}NO_2$, J_{ab}=14 Hz), 3.52(1H, m, H8), 3.25 (1H, d, H8a, $^3J_{8,8a}$=3.7 Hz[6]), 3.14(1H, m, H5), 2.52 (6H, s, SMe), 1.65 (2H, m, H9s and H9a); NOE experiments (irrad. on H / % of enhanc. obs. on H'): H8a / 2 % at H9a, 3 % at $CH\underline{a}HbNO_2$, 4 % at $CH\underline{b}HaNO_2$; $CH\underline{b}HaNO_2$ / 2 % at H9a, 3 % at H8a; ii) **2'd** (*cis-endo*; 0.020 g; m.p.: 125-127°C); C, H, N (%) 51.8, 4.5, 4.2 (calc.: 51.7, 4.6, 4.3); ^1H NMR (δ, $CDCl_3$): 6.56 (1H, m, H6), 6.24 (1H, m, H7), 5.11 (1H, d, $CH\underline{a}HbNO_2$, J_{ab} = 14 Hz), 4.06 (1H, d, $CHaH\underline{b}NO_2$, J_{ab} = 14 Hz), 3.26 (1H, m, H5), 3.21 (1H, m, H8), 2.57 and 2.56 (6H, s, SMe), 2.50 (1H, d, H8a,$^4J_{8a,9s}$ = 1.5 Hz[6]), 1.73(1H, m, H9a), 1.56 (1H, m, H9s); NOE experiments (irrad. on H / % of enhanc. obs. at H'): H8a / 6 % at $CH\underline{b}HaNO_2$; $CH\underline{b}HaNO_2$ / 4 % at H8a. e) Reaction of **3** with ethyl acetamidomalonate: Quinone **3** (0.19 g; 0.71 mmol), anhydrous potassium carbonate (0.40 g; 3.0 mmol), ethyl acetamidomalonate (0.25 g; 1.1 mmol) and a catalytic amounth of TEBAC, in dry benzene (25 mL), were stirred 5h at room temperature. The organic phase was washed three times with water (25 mL), dried and concentrated. Separation by preparative TLC (C_6H_6/AcOEt), yielded the starting quinone **3** (0.050 g; 0.19 mmol) and **2e** (*cis-exo*; 0.19 g; 0.41 mmol; yellow oil); C, H, N (%) 53.3, 5.5, 3.2 (calc.: 52.9, 5.9, 2.8 for the monohydrate form); ^1H NMR (δ, $CDCl_3$): 6.98 (1H, m, H-N), 6.03 (1H, m, H6), 5.99 (1H, m, H7), 4.19-3.99 (4H, m, $OC\underline{H}_2Me$), 4.06 (1H, d, H8a, $^3J_{8a-8}$= 3.8Hz[6]), 3.45 (1H, m, H5), 3.27 (1H, m, H8), 2.50 and 2.40 (6H, s, SMe), 1.97 (3H, s, Me-CO), 1.38 (2H, m, H9a and H9s), 1.18 and 1.15 (6H, t, $OCH_2\underline{Me}$); NOE experiments (irrad. on H / % of enhanc obs. on H'): H-N/ 1% at H9a and H9s; H9a and H9s/ 8 % at H8a.

6. Coupling constants values for the *exo* ($^3J_{8a-8}$) and *endo* ($^4J_{8a-9s}$) ring-junction protons are in accordance with those reported for the *endo* and *exo* 2,3-epoxides of some Diels-Alder adducts of 1,4-benzoquinones (Gates Jr., J. W.; O'Brien, D. D.; *J. Org. Chem.* 1965, *30*, 2593; Youngquist, M. J.; O'Brien, D. F.; Gates Jr., J.W.; *J.Am.Chem.Soc.* 1966, *88*, 4960; *see also* Marchand, A.P.; *Methods Stereochem. Anal.* 1982, *1*, 1).
7. Oki, M.; Furakoshi, W.; Nakamura, A.; *Bull.Chem.Soc. Japan* 1971, *44*, 828.

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