Asian Journal of Chemistry Vol. 22, No. 3 (2010), 2058-2072

Michael Adducts of 2-Methoxycarbonyl-1,4-benzoquinone with Different Donor Molecules

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The main objective of the present work is the synthesis of Michael adducts from 2-methoxycarbonyl-1,4-benzoquinone as acceptor and malonitrile, *p*-cresol and thiophenol as donors, using a number of different bases such as 2-methoxypyridine, 4-dimethyl-aminopyridine, 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 18-crown-6 + potassium fluoride. The results obtained had shown that the reactions of 2-methoxycarbonyl-1,4-benzoquinone with the donor molecules and also the separation of the products were much more difficult than the corresponding reactions with 2-acetyl-1,4-benzoquinone. Spiro[4.1.2]hepta-1,3-diene and spiro[4.1.4]nona-1,3-diene were used in order to direct the Diels-Alder cycloaddition reaction (due to steric effect) to the unsubstituted side of 2-methoxycarbonyl-1,4-benzoquinone, but results had shown that a mixture of addition reaction to both sides of the benzoquinone were obtained.

Key Words: Michael adducts, 2-Methoxycarbonyl-1,4-benzoquinone, 1,5-Diazabicyclo[5.4.0]undec-5-ene, 1,5-Diazabicyclo[4.3.0]non-5-ene.

INTRODUCTION

Michael reaction in its original form[1] is the addition of an addend or donor (A), containing an α-hydrogen atom in the system O=C-CH, to an acceptor (B) which is a C=C in a conjugated system of the general formulation C=C-C=O (Fig. 1). The addition takes place under the influence of alkaline reagents, typically alkali metal alkoxides. The range of addends is very broad. In principle, most carbanions and most α, β-unsaturated aldehydes, ketones and acid derivatives are acceptors. The function of the base is to remove the α-hydrogen as a proton and generate the electron rich carbanion. The carbanion adds to the most electron-poor carbon of the C=C-C=O to generate a new carbanion which absorbs another α-hydrogen atom from the donor molecule, because most often less than one equivalent of the base is needed.

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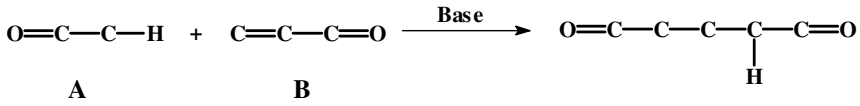


Fig. 1. Michael reaction

Generally, one would expect that the degree to which the Michael reaction takes place, as well as its rates, should be influenced by the acidity of the donor and the polarity of the C=C in the acceptor. The acidity of the hydrogen atom in the group R.C-H decreases in the following sequence: R = NO_2 > SO_3R > CN > CO_2R > CHO > COR.

1,4-Benzoquinones often behave in the Michael reaction as ethylenic ketones, as they do in many other reactions, *e.g.*, the Diels-Alder synthesis. Although the enols formed in the Michael addition to most α, β-ethylenic ketones ketonize spontaneously, the enols formed from quinones are hydroquinones and are stable. However, some of the hydroquinone products are dehydrogenated *in situ* by an excess of the original quinone, so that the newly formed quinone can undergo a second Michael addition[2]. Other hydroquinones undergo cyclization involving the hydroxyl group of the hydroquinone leading to condensed heterocyclic ring system[3] (Fig. 2).

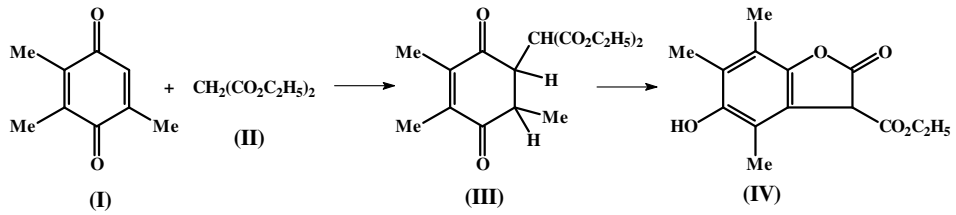


Fig. 2

Singh and Turner[4], reported a number of reactions between alkylbenzoquinones and alcohols, both catalyzed and uncatalyzed and mostly obtained two isomers in which the alkoxy groups were at the 5- or 6-positions, respectively. The reaction involves addition of the alcohol to the quinone to give an alkoxyhydroquinone, which is then oxidized by the excess of starting quinone, as this has a higher oxidation potential than the resulting alkoxyquinone. The overall reaction is shown in Fig. 3. They used zinc chloride and dichlorodicyanobenzoquinone (DDQ) as reagents. Singh and Turner[4] also reported the reaction between benzoyl-1,4-benzoquinone and methanol, both catalyzed and uncatalyzed and in each case obtained 2-benzoyl-3-methoxyhydroquinone. Here, C-3 is the most electrophilic carbon atom, being conjugated with the 1-carbonyl group and the side-chain carbonyl group.

Farina and Valderrama[5] have reported similar results with 2-acetyl-1,4-benzoquinone. This is attacked by variety of alcohols. They obtained good yield of the corresponding alkoxy-acetylquinone when equimolar amounts of reactants were

used in dry benzene (Fig. 4). The presence of the acetyl group in the quinone (**VIII**), enhances greatly the reactivity of the 3-position and nucleophilic addition takes place only at this position, under very mild conditions. The process involves a conjugate addition of the weakly nucleophile ROH to the C=C-C=O system of the quinone and does not require any catalysis. Farina and Valderrama[5] reported that *tert*-butyl alcohol does not react with acetyl-1,4-benzoquinone, probably due to steric factors.

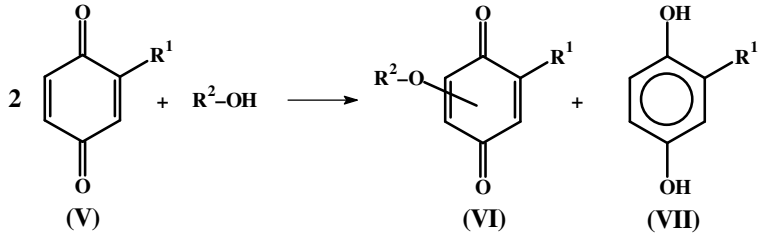


Fig. 3

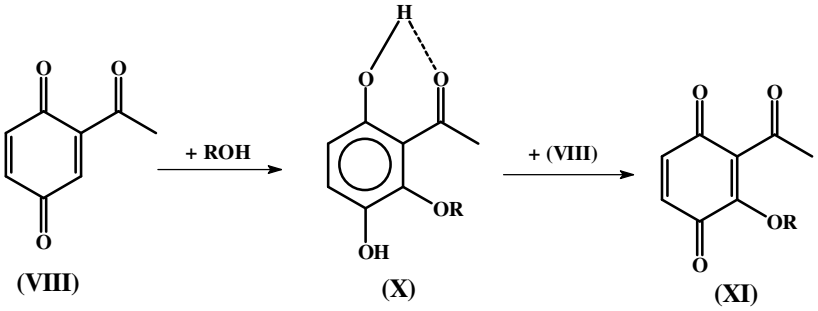
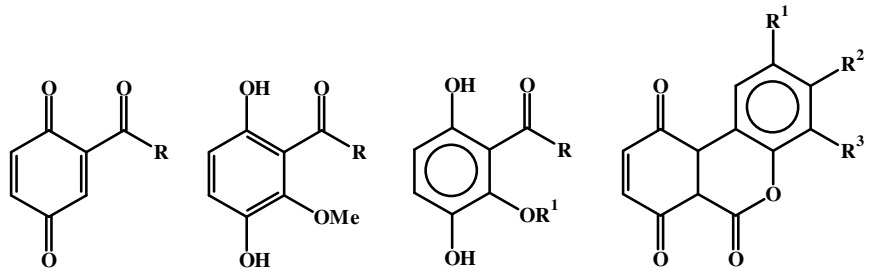


Fig. 4

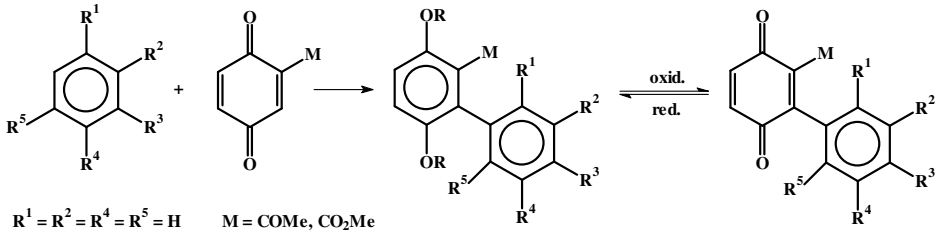
Coville[6] found that when the reaction between acetyl-1,4-benzoquinone (**IXa**; R = Me) and one equivalent of cyclopentadiene was carried out in either methanol or ethanol, the corresponding 2-acetyl-3-alkoxyquinols (**XII**; R = Me, R' = Me) and (**XII**; R = Me, R' = Et) were produced in respective yields of 22 and 52 %. A similar reaction using formyl-1,4-benzoquinone (**IXb**) gave (**XII**; R = H, R' = Et) in 22 % yield. Covill[6] explained these preliminary results by suggesting that the cyclopentadiene was acting as a catalyst. Brown[7] has continued Coville's work in more detail and used a number of quinones (**IX**; R = Me, Et, Pri, But, Ph). These could be left in solution in *t*-butyl alcohol without any reaction taking place. He concluded that the lack of reaction between 1,4-benzoquinone and the alcohols showed that activation of the 3-position of the quinone, *e.g.* by any acyl or other electron-withdrawing substituent at the 2-position, will be necessary if attack by an alcohol is to occur. However, Brown[7] has objected to Coville's suggestion[6] of the importance of cyclopentadiene as catalyst. He carried out the alkoxylation in the presence and absence of cyclopentadiene and found that it is not responsible for the alkoxylation.



(VIII) **(XI)** **(XII)** **(XVII)**

a. R = Me
b. R = H

Eugster *et al.*[8-10] have described reactions between a number of mono-substituted high potential quinones and various nucleophiles, notable the reaction of acetyl-1,4-benzoquinone with furans and thiophens. Eugster *et al.*[11] had investigated the acid-catalyzed addition of aromatic compounds such as (**XIII**) to acetyl- and methoxycarbonyl-1,4-benzoquinone to give biaryls such as (**XIV**) (Fig. 5).



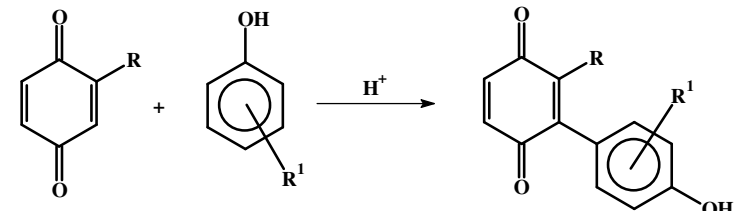
$R^1 = R^2 = R^4 = R^5 = H$
R^5 = OMe, $N(CH_3)_2$, etc.
(XIII)

M = COMe, CO_2Me

(XIV) **(XV)**

Fig. 5

Eugster and Bram[12] have described the acid catalyzed reaction of phenols with activated quinones, *e.g.* 2-methoxycarbonyl-1,4-benzoquinone and its 5-methoxy- and 6-methoxy-derivatives and 2-acetyl-1,4-benzoquinone, which leads to substituted biphenyl-derivatives (C-C-addition). The general reaction is given in Fig. 6. When the quinone carries a methoxycarbonyl group and addition occurs at the *o*-position of the phenol, the products are benzocoumarins (**XVII**)[13].



R = COMe, CO_2Me R^1 = H, Alkyl, OMe **(XVI)**

Fig. 6

Eugster *et al.*[14] have also reported the base catalyzed reaction of methoxycarbonyl-1,4-benzoquinone with a number of nucleophilic reagents such as phenols, alkylphenols, methoxyphenol, arylthiols, N-methyl-N-arylamines. The bases they used were 2-methoxypyridine and 4-dimethylaminopyridine. O,C-, S,C- and N,C-addition occurred readily. The resulting substituted diphenyl ethers, diarylthioethers and N-methyl-N,N-diarylamines can serve as convenient starting materials for regiospeceific synthesis of substituted heterocycles, as shown in Fig. 7.

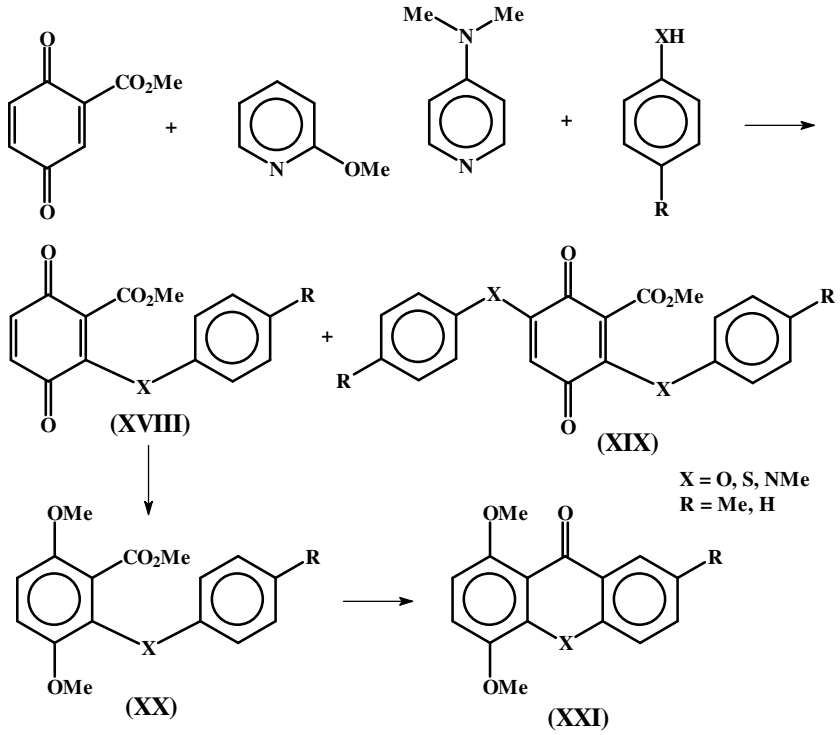


Fig. 7

EXPERIMENTAL

Nuclear magnetic resonance (NMR) spectra were recorded with Perkin-Elmer R12B (60 MHz), R32 (90 MHz) and R34 (220 MHz) spectrometers, respectively. Tetramethylsilane (TMS) was used as an internal standard and coupling constants (J) are expressed in Hz. Infrared spectra were measured using a Pye Unicam SP3-200 Spectrophotometer. Low resolution electron impact (EI) mass spectra were recorded on AEI MS30 and Kratos MS25 instruments; mass measurements (MM) were made on the former and chemical ionization (CI) spectra were recorded on the latter using ammonia as the reagent gas. Sublimation and bulb-to-bulb distillation temperature are those of the Buchi Oven (heating bath). All solvents, liquid reagent and starting material were distilled prior to use. Irradiation with visible light was

carried out at 15 °C, using tungsten-filament lamps. Analytical and preparative TLC were carried out with Merck silica gel plates (5 × 10 cm × 0.25 mm and 10 × 20 cm × 0.25 mm), type $60F_{254}$.

Methyl 2,5-dihydroxybenzoate: To a solution of 2,5-dihydroxybenzoic acid (5 g, 32.47 mmol), in absolute methanol (130 mL), conc. sulphuric acid (3.5 mL) was added cautiously and the mixture was refluxed for 9 h. Progress of the reaction was monitored by TLC using 1:1 light petroleum (40-60 °C)-ether and showed one spot after all the starting material had been consumed. The removal of most of the solvent gave a yellow oily liquid. Water (*ca.* 30 mL) was added and the mixture was extracted with ether (3 × 30 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate and then with water. The fine white crystals were filtered (4.7 g, 86 %), m.p. 80-82 °C. Recrystallization from cyclohexane gave white crystals (4.5 g, 83 %), m.p. 83-85 °C (lit.[15], 87.8 °C). It had δ (4 %, $CDCl_3$, 60 MHz) 10.42 (s, 2-OH), 7.23 (d, J = 3, H-6), 7.0 (dd, J_1 = 9, J_2 = 3, H-4), 6.83 (d, J = 9, H-3), 5.25 (bs, 5-OH), 3.88 (s, OMe); [10 %, $(CD_3)_2CO$, 60 MHz] 12.09 (s, 2-OH), 10.21 (s, 5-OH), 7.21 (d, J = 3, H-6), 6.4 (dd, J_1 = 9, J_2 = 3, H-4); ν (cm^{-1}, Nujol) 3340 (s), 3125 (w), 1690 (s), 1615 (m), 1500 (m), 1215 (s), 1080 (sh); m/z 168 (M^+, 37), 136); [($M-MeOH)^+$, 100 %], 108); [($136-CO)^+$, 23].

2-Methoxycarbonyl-1,4-benzoquinone: Methyl 2,5-dihydroxybenzoate (4 g, 23.81 mmol), silver oxide (40 g) (commercial or freshly prepared and dried), anhydrous sodium sulphate (40 g) (baked at 100-200 °C) and freshly distilled benzene (150 mL) in a 500 mL round-bottomed flask wrapped with aluminium foil to exclude light, were shaken together for 4 h. The mixture was filtered through Celite and the cake washed with dry benzene (until no coloured solution passed through). The removal of the solvent gave orange crystals (3.75 g, 85 %), m.p. 49-50 °C (lit.[16], 53.5-54 °C). Recrystallization from cyclohexane afforded orange crystals (3 g, 76 %), m.p. 51-52 °C. It had δ (4 %, $CDCl_3$, 60 MHz) 2.95 ['s', with slight splitting, H-3), 3.22 (s, H-5 or H-6), 3.24 (s, H-6 or H-5), 6.13 (s, CO_2Me)]; [10 %, $(CD_3)_2CO$, 60 MHz] 2.94 (d, J = 2, H-3), 3.10 ('s', with slight splitting, H-5 + H-6), 6.16 (s, CO_2Me); ν (cm^{-1}, CH_2Cl_2) 3050 (sh), 2980 (sh), 1740 (s), 1665 (sh), 1600 (w), 1260 (s); m/z 168 [($M+2)^+$, 6], 166 [(M^+, 84], 136 [($M+2-MeOH)^+$, 100], 135 [($M-MeO)^+$, 92], 107 [($M-CO_2Me)^+$, 38],), 79 [($M-CO_2Me$ -$CO)^+$, 29]. Sublimation of the crude product at 90 °C/0.3 mmHg gave orange crystals, m.p. 51-52 °C.

Reaction of 2-methoxycarbonyl-1,4-benzoquinone with *p*-cresol: (a) 2-Methoxycarbonyl-1,4-benzoquinone (250 mg, 1.506 mmol) in benzene (3 mL) was added to a mixture of *p*-cresol (0.2 g), 2-methoxypyridine (0.5 mL) and anhydrous magnesium sulphate (0.5 g) over 20 min at room temperature and then stirred for 2 h. Filtration and removal of the solvent gave a deep-red mobile oil (646 mg). NMR spectroscopy showed a mixture. TLC on silica gel in 10:1 toluene-ethyl acetate showed starting material and two new spots. Preparative TLC gave five bands, each of which was separated. TLC of each band showed a mixture of 2-3 spots. Therefore, a good separation could not be achieved. The crude product, silver oxide (1.5 g), anhydrous

magnesium sulphate (1.5 g) and methylene chloride (20 mL) were shaken together for 1 h. NMR spectroscopy showed a mixture. Its MS had m/z 438 {[$CH_3.C_6H_4O.C_6HO_2(CO_2Me).O.C_6H_3(OH)$ $(CO_2Me)]^+$, 17}, 406 [$(438\text{-}MeOH)^+$, 5], 378 {[$CH_3.C_6H_4O.C_6HO_2(CO_2Me).O.C_6H_4CH_3]^+$, 42}, 332 [$C_6H_2O_2(CO_2Me).O.C_6H_3(OH)(CO_2Me)]^+$, 42}, 300 [$(332\text{-}MeOH)^+$, 24], 272 [$(300\text{-}CO)^+$, 21], 271 [$(378\text{-}CH_3.C_6H_4O)^+$, 34], 119 (100). Column chromatography through silicic acid using benzene-ethyl acetate (10:1) as solvent gave three eluates, only the second of which showed one spot on TLC. The second eluate had δ (4 %, $CDCl_3$, 60 MHz) 7.0 (AA'BB' system, 4H, aromatic), 6.77 (s, 2H, H-5 + H-6), 3.58 (s, 3H, OMe), 2.32 [s, 3H, Me-C(4')]; m/z 274 (M^+, 7), 242 [$(274\text{-}MeOH)^+$, 33], 241 [$(M\text{-}MeO)^+$, 12], 119 (35), 94 (100), 77 (21), 65 (32). These data are consistent with this fraction being 3-(4'-methylphenoxy)-2-methoxycarbonyl-1,4-benzoquinone.

(b) Reaction (a) was carried out at room temperature for 4 h without using anhydrous magnesium sulphate. 2-Methoxypyridine (0.2 equ.) and *p*-cresol (1 equ.) were used. A deep red suspension was obtained. It was filtred and the two phases were collected as follow: (i) Solid phase, m.p. 278-284 °C, m/z (EI) 243 (55), 242 (100), 214 (14); (C.I.) 275 (0.5), 244 (51), 243 (100), 242 (54). (ii) Deep red solution. The removal of the solvent gave a deep-red sticky oil. NMR spectroscopy showed a mixture of the starting materials and the desired addition product as its hydroquinone. Resonances due to the addition hydroquinone were δ (8 %, $CDCl_3$, 60 MHz) 10.25 (bs, OH), 6.65-7.60 (6H aromatic protons + OH, overlapped with absorptions due to the starting materials), 3.64 (s, 3H, OMe), 2.37 [s, 3H, Me-C(4')]; m/z (EI) 274 (M^+, 44), 242 [$(M\text{-}MeOH)^+$, 100], 168 [$(C_6H_2(OH)_2(CO_2Me)^+$, 15], 136 (27), 108 (48), 107 (44); (CI) 381 (24), 335 (37), 275 [$(M+H)^+$, 100], 274 (50), 243 (75), 242 (72), 169 (76), 108 (67).

Reaction between 2-methoxycarbonyl-1,4-benzoquinone and malononitrile: 2-Methoxycarbonyl-1,4-benzoquinone (83 mg, 0.5 mmol) in benzene (2 mL) was added to a solution of malononitrile (33 mg, 1 equ.) and 2-methoxypyridine (11 mg, 0.2 equ.) in benzene (1 mL) at room temperature and left for 2 h. After 2 min, a dark coloured mixture was formed. The removal of the solvent gave a dark solid (99 mg). It was partially soluble in $CDCl_3$. The soluble portion had δ (3 %, $CDCl_3$, 60 MHz) 10.35 (bs, OH), 6.80-7.50 (m), 4.07 [s, $(CN)_2CH$], 3.95 (s, CO_2Me); m/z (EI) 168 [$HO.C6H_3(CO_2Me).OH)^+$, 15], 136 [(168-MeOH), 60], 108 [$(136\text{-}CO)^+$, 18], 80 [$(108\text{-}CO)^+$, 12], 52 [$(80\text{-}CO)^+$, 18], 40 (100); (CI) 312 (51), 310 (90), 250 [$(M+18)^+$, 100], 233 [$(M+18)^+$, 83], 169[$(168+H)^+$, 53]. This may have been a mixture of isomeric mono-adducts.

Methyl 2,5-dihydroxy-6-phenylthiobenzoate: 2-Methoxycarbonyl-1,4-benzoquinone (498 mg, 3 mmol) in methylene chloride (3 mL) was added to a solution of thiophenol (330 mg, 3 mmol) and 2-methoxypyridine (65 mg, 0.2 equ.) in methylene chloride (2 mL) at room temperature. A yellow solution was obtained and this was stirred at room temperature for 4 h. Removal of the solvent gave a yellow-brown oil (843 mg) which solidified on standing. TLC in 10:1 toluene-ethyl acetate showed

two spots, a small one probably due to methyl gentisate and a large one due to the product. Sublimation at 100-110 °C/0.1 mmHg gave white-pale yellow soft crystalline compounds (311 and 442 mg, respectively). IR, NMR, mass spectra and microanalyses of the two sublimates were identical and consistent with fractions being almost pure mono-adduct (753 mg, 91 %), m.p. 68-70 °C. NMR showed that the product was a mixture of 93:7 of adduct and methyl gentisate, respectively (Found: C, 61.25; H, 4.4; S, 11.5; $C_{14}H_{12}O_4S$ requires: C, 60.87; H, 4.35; S, 11.6 %). It had δ (7 %, $CDCl_3$, 90 MHz) 10.23 (s, 2×OH), 6.80-7.35 (m, 7×H, aromatic + 5-OH), 3.74 (s, CO_2Me); δ (6 %, C_6D_6, 90 MHz) 10.65 (s, 2×OH), 7.04 (AB-q, J = 9 Hz, H-3 + H-4), 6.94 (bs, 5×H, aromatic + 5-OH), 3.28 (s, CO_2Me); ν (cm^{-1}, Nujol) 3380 (m), 3125 (w), 1665 (s), 1585 (m), 1220 (s); m/z (EI) 276 (M^+, 100), 245 [$(M\text{-}MeO)^+$, 71], 244 [$(M\text{-}MeOH)^+$, 95], 216 [$(244\text{-}CO)^+$, 26], 110[(PhSH), 14], 77 [$(C_6H_5)^+$, 21]; (CI) 312 (51), 294 [$(M+18)^+$, 45], 277 [$(M+18)^+$, 100], 276 [M^+, 43], 245 [$(277\text{-}MeOH)^+$, 41], 244 [$(M\text{-}MeOH)^+$, 48].

2-Methoxycarbonyl-3-phenylthio-1,4-benzoquinone: Methyl 2,5-dihydroxy-6-phenylthiobenzoate (50 mg, 0.181 mmol), freshly prepared silver oxide (750 mg, 15 equ.), anhydrous sodium sulphate (750 mg) and methylene chloride (30 mL) were shaken together for 4 h. Filtration through celite, washing the cake with methylene chloride and removal of the solvent gave a red sticky oil (44 mg, 89 %) (Found: C, 60.6; H, 3.8; S, 12.2; $C_{14}H_{10}O_4S$ requires: C, 61.3; H, 3.7; S, 11.7 %). It had δ (6 %, $CDCl_3$, 60 MHz) δ 7.40 (m, 5×H, aromatic), 6.75 (bs, H-5 + H-6), 3.37 (s, CO_2Me). After keeping for 1 week, NMR spectroscopy then showed that the product was a 4:1 mixture of the quinone and hydroquinone, respectively. The quinone had δ (7 %, $CDCl_3$, 90 MHz) 7.15-7.65 (m, 5×H, aromatic), 6.68 (d, J = 10.8 Hz, H-5 or H-6), 6.80 (d, J-10.8 Hz, H-6 or H-5), 3.40 (s, CO_2Me); δ (6 %, C_6D_6, 90 MHz) 7.32 (m, 2×H, aromatic), 6.95 (m, 3×H, aromatic), 5.90 (s, H-5 + H-6), 3.24 (s, CO_2Me); ν (cm^{-1}, film) 3060 (w), 2960 (w), 1670 (s), 1565 (m); m/z (EI) 276 (MH_2^+, 32), 274 (M^+, 15), 244 [$(276\text{-}MeOH)^+$, 50], 215 [$(M\text{-}CO_2Me)^+$, 54], 187 [$(215\text{-}CO)^+$, 47], 159 [$(187\text{-}CO)^+$, 9], 133 [$(159\text{-}C_2H_2)^+$, 13], 109 [(PhS)., 20], 82 [$(M\text{-}PhS.C{\equiv}C.CO_2Me)^+$, 100], 77 [(109-S), 73], 31 (MeO, 97); (CI) 294 [$(MH_2{+}18)^+$, 25], 292 [$(M+18)^+$, 25], 275[$(M+H)^+$, 54].

Attempted preparation of 1,4-dihydroxythioxanthenone

By polyphosphoric acid (PPA): Methyl-2,5-dihydroxy-3-phenylthiobenzoate (90 mg, 0.326) was added to PPA (10.8 g, excess). The suspension was mechanically stirred at 120 °C for 4 h. Water was added to disperse acid and the mixture was cooled to room temperature. The suspension was extracted with ether (3×25 mL) and the extracts were combined, washed with water and dried over anhydrous magnesium sulphate. The removal of ether gave a yellow-orange semi-solid (20 mg, 0.082 mmol, 25 %). Attempted purification by TLC and by sublimation resulted in decomposition. It had δ (2 %, $CDCl_3$, 90 MHz) 7.0-7.65 (m), d (2 %, C_6D_6, 90 MHz) 6.70-7.50 (m); m/z (EI) 246 [$(M+2)^+$, 4], 245 [$(M+1)^+$, 16], 244 [M^+, 100], 218 [$(M\text{-}C_2H_2)^+$,

34], 216 [(M-CO)$^+$, 14], 187 [(216-CHO)$^+$, 26], 158 [(187-CHO)$^+$, 9], 109[(PhS), 84]; (CI) 262 [(M+18)$^+$, 2], 245 [(M+H)$^+$, 100], 244 (M$^+$, 66), 218 (56), 110 (PhSH, 11), 109 (49).

By boron tribromide: Boron tribromide (326.8 mg, 4 equ.) was added to a solution of methyl 2,5-dihydroxy-3-phenylthiobenzoate (90 mg, 0.326 mmol) in methylene chloride (3 mL) at room temperature and left for 4 h. Water (29 mL, 5 equ.) was added and stirred until a solution obtained. Organic layer was separated and the solvent removed, a pale-yellow crystalline compound was formed (57 mg). NMR spectroscopy showed that a 70:30 mixture of the cyclization product and starting material had been formed. Separation by sublimation was unsuccessful.

Reaction of 2-methoxycarbonyl-1,4-benzoquinone with spiro[4.1.2]hepta-1,3-diene

At room temperature in benzene: Spiro[4.1.2]hepta-1,3-diene (92 mg, 1 equ.) (the spiro-compound was a 2:1 mixture with ethylene bromide; 260 mg of the mixture was used) was added to a solution of 2-methoxycarbonyl-1,4-benzoquinone (166 mg, 1 mmol) in benzene (5 mL) at room temperature and left for 64 h. The removal of the solvent gave a brown oil. NMR spectroscopy showed that the product was a mixture of ethylene bromide and two mono-adducts addition of spiro-compound on substituted side (B) and unsubstituted side (A), respectively. It had d (7 %, $CDCl_3$, 60 MHz) 6.86 (s, H-3, A), 6.66 (s, H-2 + H-3, B), 6.24 (m, H-6 + H-7, A, + H-6 + H-7, B), 3.87 (s, CO_2Me, B), 3.77 (s, CO_2Me, A), 3.67 (s, $BrCH_2CH_2Br$), 3.44 (m, H-8a + H-5 + H-8, B), 2.94 (m, H-4a + H-5 + H-8 + H-8a, A), 0.58 (2×H-10 + 2×H-11, A, + 2×H-10 + 2×H-11, B). Integration showed that the mono-adducts (A) and (B) were in a 1:1 ratio. In order to remove ethylene bromide, the mixture was dissolved in freshly distilled carbon tetrachloride. The removal of the carbon tetrachloride and ethylene bromide gave an oil. This was repeated three times. The NMR spectrum (5 %, $CDCl_3$, 60 MHz) then showed identical resonances to those described above, except that absorption due to ethylene dibromide had been remove. 30 mg of the mixture (A+B), was dissolved in d_6-benzene in an NMR sample tube and immersed in boiling methanol (64 °C). Every 1.5 h, NMR spectrum of the mixture was taken; no significant change was observed after 4.5 h. This was repeated in boiling ethanol (78 °C) for 6 h. NMR spectroscopy showed the formation of a new isomer, possibly an exo isomer of B.

At 80 °C in benzene: Spiro[4.1.2]hepta-1,3-diene (92 mg, 1 equ.) (260 mg of the mixture with ethylene bromide) was added to a refluxing solution of 2-methoxycarbonyl-1,4-benzoquinone (166 mg, 1 mmol) in benzene (5 mL). The mixture was refluxed (80 °C) for 1 h. The removal of the solvent gave a honey-like compound. It had δ (10 %, $CDCl_3$, 90 MHz) 6.79 (s, H-3, A), 6.59 (s, H-2 + H-3, B), 6.09 (m, sharpened on irradiation at δ 3.70, 3.50, 2.85, split to a doublet, J = 1.5, on irradiation at δ 3.35, H-6 + H-7, A, + H-6 + H-7, B), 3.81 (s, CO_2Me, B), 3.70 (s, CO_2Me, A), 3.30 (m, partially overlapped with absorption due to H-8a + H-5 + H-8, B), 3.45 (d,

J = 4, H-8a, B), 2.90 (m, H-4a + H-5 + H-8, A), 0.54 (m, 2×H-10 + 2×H-11, A, + 2×H-10 + 2×H-11, B); δ (10 %, C_6D_6, 90 MHz) 6.59 (s, H-3, A), 6.18 (s, H-2 + H-3, B), 5.97 (m, sharpened on irradiation at δ 2.88, 2.60, H-6 + H-7, A, + H-6 + H-7, B), 3.73 (d, *J* = 4, collapsed to a singlet on irradiation at δ 2.60, H-8a, B), 3.38-3.53 (H-4a or H-8a, A, buried under CO_2Me absorption), 3.45 (s, CO_2Me, B), 3.28 (s, CO_2Me, A), 2.88 (m, slightly sharpened on irradiation at δ 5.97, H-5, B + H-8 or H-5, A), 2.60 (m, slightly sharpened on irradiation at δ 5.97, 3.73, H-8, B, + H-5 or H-8 + H-8a or H-4a, A), (2×H-10 + 2×H-11, A, + 2×H-10 + 2×H-11, B, signals were not recorded). Integration indicated that the mixture was 6:5, A and B, respectively. Also, NMR spectroscopy showed that a very small amount of the exo isomer was formed.

At 130 °C in chlorobenzene: Reaction (b) was exactly repeated but in refluxing chlorobenzene. The results had shown that some thermal decomposition had taken place, but the mono-adducts were remarkably stable. It was also concluded that the ratio of A:B increased to 2:1; that is at higher temperature addition at the unsubstituted side is favoured.

With trifluoroacetic acid: Reaction (a) was exactly repeated but trifluoroacetic acid (114 mg), was added as well. The results had shown that the ratio of B:A had increased, but some decomposition had taken place. The reaction was repeated by using only 5 mg trifluoroacetic acid. The results had shown that the ratio of A:B was *ca.* 1:1.

Formation of cage compound from addition between 2-methoxycarbonyl-1,4-benzoquinone and spiro[4.1.2]hepta-1,3-diene: A mixture (50 mg) of the two mono-adducts from the addition of spiro[4.1.2]hepta-1,3-diene to the substituted and unsubstituted sides of 2-methoxycarbonyl-1,4-benzoquinone was dissolved in C_6D_6 (0.5 mL) and placed in an NMR sample tube. The mixture was irradiated with tungsten filament light at 20 °C and the progress of the reaction was monitored by NMR spectroscopy. Rapid photocyclization took place, showing that both mono-adducts were *endo*-ismers.The irradiation was continued for 17 h and the solution then had δ (10 %, $CDCl_3$, 90 MHz) 3.86 (s, CO_2Me, A), 3.83 (s, CO_2Me, B), 2.02-3.62 (m, 14×H, A+B), 0.79 (s, 2×H-12+12×H-13, B), 0.76 (s, 2×H-12+12×H-13, A; δ (10 %, C_6D_6, 90 MHz) 3.47 (s, CO_2Me, A), 3.45 (s, CO_2Me, B), 1.30-3.40 (m, 14×H, A+B), 0.24 (s, 2×H-12+12×H-13, A, + 2×H-12+12×H-13, B); m/z (EI) 259 [$(M+1)^+$, 34], 258 [M^+, 44], 230 [$(258\text{-}CO)^+$, 20], 227 [$(M\text{-}MeO)^+$, 17], 226 [$(M\text{-}MeOH)^+$, 14], 199[$(M\text{-}CO_2Me)^+$, 13], 198 [$(M\text{-}HCO_2Me)^+$, 20], 171[$(199\text{-}CO)^+$, 22], 170 [$(198\text{-}CO)^+$, 23], 115 [$(143\text{-}CO)^+$, 48], 92 ($(C_7H_8)^+$, 67), 91 [$(92\text{-}H)^+$, 100], 65 [$(91\text{-}C_2H_2)^+$, 25].

Attempted preparation of *bis*-adduct of spiro[4.1.2]hepta-1,3-diene and 2-methoxycarbonyl-1,4-benzoquinone: Spiro[4.1.2]hepta-1,3-diene (222 mg, 10 equ.) was added to a solution of 2-methoxycarbonyl-1,4-benzoquinone (40 mg, 0.241 mmol) in benzene (1 mL) at room temperature and left for 14 h. The removal of the solvent and the excess of spiro[4.1.2]hepta-1,3-diene gave a yellow oil (83.5 mg). Its NMR spectrum was almost identical with those obtained for the mono-adducts. m/z (CI) 276 [$(M+18)^+$,12], 259 [$(M+H)^+$, 48], 93 [$(C_7H_8+H)^+$, 100].

Reaction of 2-methoxycarbonyl-1,4-benzoquinone with spiro[4.1.4]nona-1,3-diene

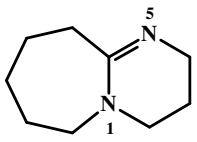
At 0 °C: Spiro[4.1.4]nona-1,3-diene (60 mg) (the spiro-compound was a 1:1 mixture with 1,4-dibromobutane; 120 mg of the mixture was used) was added to a solution of 2-methoxycarbonyl-1,4-benzoquinone (83 mg, 0.5 mmol) in methylene chloride (3 mL) at °C and left for 4 h. The removal of the solvent gave a yellow-brown sticky oil (220.6 mg). NMR spectroscopy showed that the product consisted of two mono-adducts (addition of spiro-compound on the substituted side of the quinone, B and unsubstituted side, A), in the ratio of 62:38 A to B, respectively. It had δ (8 %, $CDCl_3$, 60 MHz) 6.76 (s, H-3, A), 6.56 (bs, H-2 + H-3, B), 6.0 (m, H-6 + H-7, A, + H-6 + H-7, B), 0.8-4.0 (m, H-4a +H-8 + H-5 + H-8a + 2×H-10 + 2×H-11 + 2×H-12 + 2×H-13, A, +H-8a + H-5 + H-8 + 2×H-10 + 2×H-11 + 2×H-12 + 2×H-13, B), 3.84 (s, CO_2Me, A), 3.71 (s, CO_2Me, B).

At 40 °C: Reaction (a) was repeated, but with refluxing for 4 h. The removal of the excess of spiro-compound and the solvent gave a yellow-brown sticky oil. NMR spectroscopy showed that the product was a mixture, in which a particular adduct could not be identified.

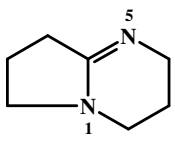
At room temperature: Reaction (a) was repeated at room temperature. The same results as in (b) were obtained.

RESULTS AND DISCUSSION

The main objective of the present work was the synthesis of Michael adducts from 2-methoxycarbonyl-1,4-benzoquinone as acceptor and malonitrile, *p*-cresol and thiophenol as donors, using a number of different bases such as 2-methoxypyridine, 4-dimethylaminopyridine, 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (**XXII**), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (**XXIII**), 18-crown-6 + potassium fluoride (**XXIV**). In general, the nucleophilic character of C, S >> O (*ca.* 10^4 times). However, successful reactions can occur with poor nucleophiles if the acceptor is powerful, *e.g.* a quinone such as methoxycarbonyl-1,4-benzoquinone in which conjugation of C-3 is with both the carbonyl group of the substituent and the C-1 carbonyl group in a planar system. Therefore, reactions between nucleophile and methoxycarbonyl-1,4-benzoquinone were attempted in the hope of obtaining 1:1 adducts which could subsequently be cyclized to regiospecifically substituted heterocycles.



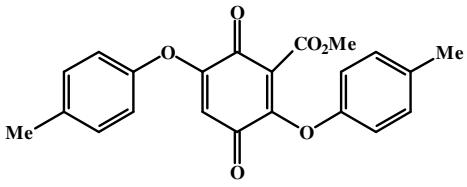
(XXII)



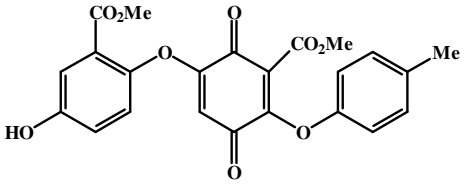
(XXIII)

p-Cresol was chosen because the methyl group provides a useful marker for ^1H NMR study of the products. Thus, a solution of methoxycarbonyl-1,4-benzoquinone in benzene was added to a mixture of *p*-cresol, 2-methoxypyridine and anhydrous

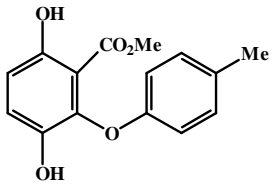
magnesium sulphate in benzene at room temperature; a deep red oil was finally obtained, but TLC and PLC (preparative liquid chromatography) on silica gel failed due to decomposition of the adduct(s) and unchanged starting material on the plate. Therefore, the crude product was oxidized with silver oxide in an attempt to convert the possible hydroquinones to the corresponding quinones. Mass spectrometry of the product showed m/z at 378 and 438, indicating the presence of (**XXV**) and (**XXVI**), respectively. Compound (**XXV**) arises from oxidation of the mono-adduct (**XXVII**) to the quinone (**XXVIII**) and addition of a second molecule of *p*-cresol. Compound (**XXVI**) is formed similarly, but the second Michael addition is of the hydroquinone of the initial quinone. These compounds could not be isolated in a pure state.



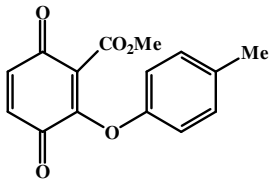
(XXV)



(XXVI)

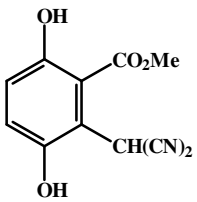


(XXVII)



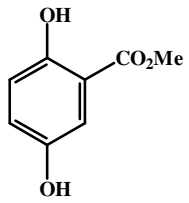
(XXVIII)

Eugster *et al.*[14] have also reported the isolation of mono- and *bis*-adducts (**XXVIII**) and (**XXV**), respectively. Repetition of the experiment under a variety of different conditions afforded only crude methyl 2,5-dihydroxy-6-*p*-tolyloxybenzoate (**XXVII**) in poor and variable yield. Therefore, other nucleophiles, such as malononitrile and thiophenol, were tried. In the case of malononitrile a dark solid material was obtained, which was only partially soluble in *d*-chloroform and could not be certainly identified, although its mass spectrum (CI, NH_3) showed m/z 250 [$(M+18)^+$, 100] and 233 [$(M+H)^+$, 83], possibly indicating the formation of compound (**XXIX**).



(XXIX)

Thiophenol reacted with methoxycarbonyl-1,4-benzoquinone in methylene chloride, using 2-methoxypyridine as base, to give a yellow brown oil which solidified on standing. TLC on silica gel showed two spots, a small and a large, the former due to methyl gentisate (**XXX**) resulting from reduction of some of the quinone. The major product was, on the basis of its spectroscopic and microanalysis results, methyl 2,5-dihydroxy-6-phenylthiobenzoate (**XXXI**).



(XXX)

Other bases such as DBN, DBU, 4-dimethylaminopyridine and 18-crown-6 + KF were tried in the thiophenol reaction with methoxy-1,4-benzoquinone, but the best condition was that described above. 2-Methoxycarbonyl-3-phenylthio-1,4-benzoquinone (**XXXIV**) was obtained from oxidation of (**XXXI**) with silver oxide.

Treatment of (**XXXI**) with polyphosphoric acid at 120 °C gave a yellow-orange semi-solid, indicated by ^{1}H NMR and mass spectra to be the thioxantenone (**XXXIII**). The yield was 25 %. Attempted purification by TLC and sublimation resulted in decomposition. Therefore, the reaction was repeated using boron tribromide instead of polyphosphoric acid; a 70:30 mixture of (**XXXIII**) and (**XXXI**) was obtained, but separation was unsuccessful.

On the basis of the above results, in order to achieve a good single Michael addition to methoxycarbonyl-1,4-benzoquinone, the unsubstituted C=C must be protected, which prevent the formation of *bis*-adducts. A convenient protection is *via* the Diels-Alder reaction, which is reversible. However, a problem is that simple dienes such as cyclopentadiene add to the ester-substituted side, giving the wrong protection. It is necessary to direct a protecting group to the unsubstituted C=C. This could be achieved by conversion of the electron-withdrawing ester group into an electron-donor group from which the ester group can later be regenerated. Al-Hamdany[17] has reported a related reaction with acetyl-1,4-benzoquinone in order to obtain the addition of cyclopentadiene on the unsubstituted side of the quinone. First he converted 2-acetylhydroquinone (**XXXIV**) to the ketal (**XXXV**) using ethylene glycol in the presence of toluene-*p*-sulphonic acid, then oxidized (**XXXV**) to the corresponding quinone (**XXXVI**); treatment of this with cyclopentadiene then gave the adduct (**XXXVII**), which could be deketalized with dilute sulphuric acid and the desired mono-adduct (**XXXIII**) obtained in 40 % yield. The general reaction is shown in Fig. 8. A similar route in the present case would require protection of the ester group which is more difficult. Because of the difficulties, an alternative approach

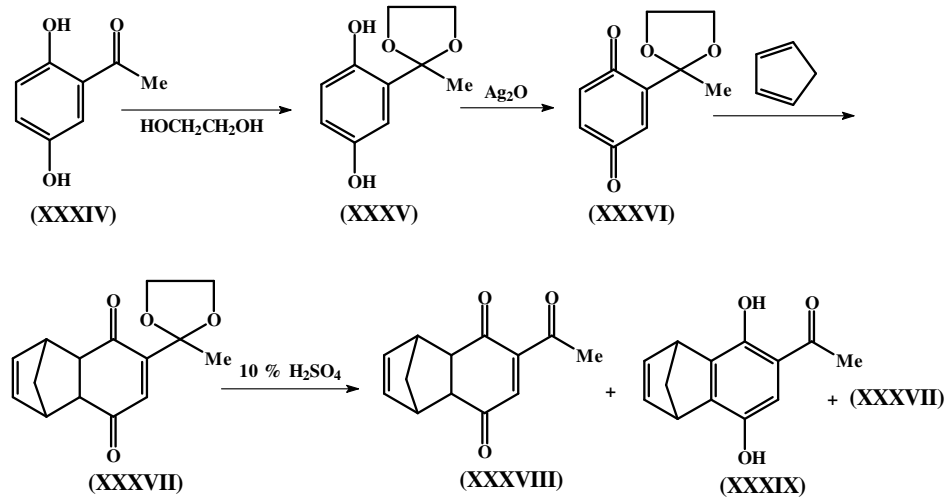
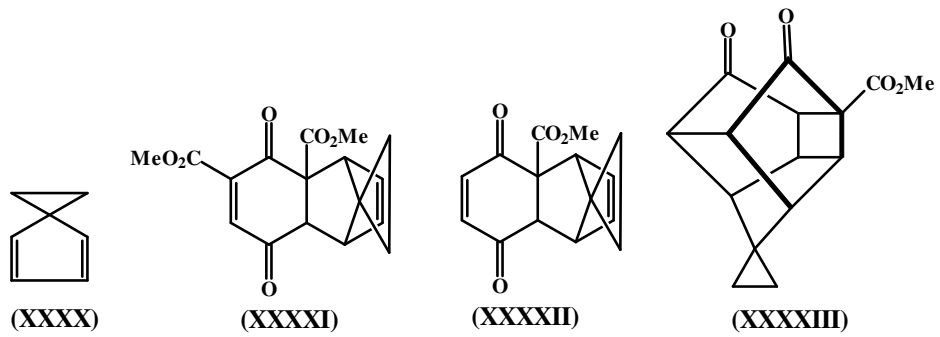
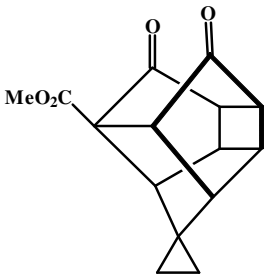


Fig. 8

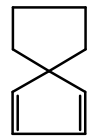
was adopted. This involved increasing the steric requirement of the diene. Cyclopentadiene adds to the substituted side of the quinone giving the endo isomer which is kinetically favoured. Hence, it was decided to use spiro[4.1.2]hepta-1,3-diene (**XXXX**) which is easy to make and is stable. Addition of one equivalent of spiro[4.1.2]hepta-1,3-diene (**XXXX**) to methoxycarbonyl-1,4-benzoquinone in benzene at room temperature resulted in a 1:1 mixture of two mono-adducts shown by NMR spectroscopy to be (**XXXXI**) and (**XXXXII**) referred to as (A) and (B), respectively in the Experimental Section. These compounds could not be separated. Photoisomerization of the mixture gave the "box compounds" (**XXXXIII**) and (**XXXXIV**), respectively, confirming that both (**XXXXI**) and (**XXXXII**) have the endo-configuration. The fact that a 1:1 mixture of two mono-adducts is formed shows that under kinetic conditions the steric factor is not strong enough to overcome the electronic factor which favours the formation of (**XXXXII**). In an attempt to obtain greater regioselectivity of mono-adduct formation, addition of spiro[4.1.4]-hepta-1,3-diene (**XXXXV**)[18] was tried, this diene having a greater steric requirement



than (**XXXX**). Some problems were encountered. The diene (**XXXXV**) was more difficult to make than (**XXXX**) and was not obtained pure, but NMR spectroscopy showed that addition still occurs on both sides of methoxycarbonyl-1,4-benzoquinone. Addition in methylene chloride at 0, 20 and 40 °C gave a 62:38 mixture of the two mono-adducts (**XXXXVI** = A) and (**XXXXVII** = B). Separation of the mixture was unsuccessful. It is therefore, apparent that the selective protection of the unsubstituted ethene linkage of methoxycarbonyl-1,4-benzoquinone by the Diels-Alder reaction will require highly susbstituted dienes which are unlikely to be readily available. This approach was therefore not further examined.



(XXXXIV)



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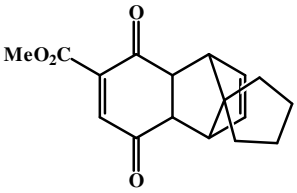

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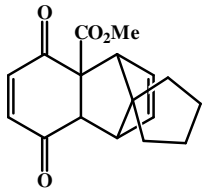

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(*Received*: 25 May 2009; *Accepted*: 26 November 2009) AJC-8095