PHOTOINDUCED MOLECULAR TRANSFORMATIONS.[1] PART 160. FURAN ANNELATION OF 2-HYDROXYNAPHTHOQUINONE INVOLVING PHOTOCHEMICAL ADDITION AND RADICAL FRAGMENTATION: EXCLUSION OF THE INTERMEDIACY OF [2+2] CYCLOADDUCT IN A ONE-POT FORMATION OF FURANOQUINONES BY THE REGIOSELECTIVE 3+2 PHOTOADDITION OF HYDROXYQUINONES WITH ALKENES

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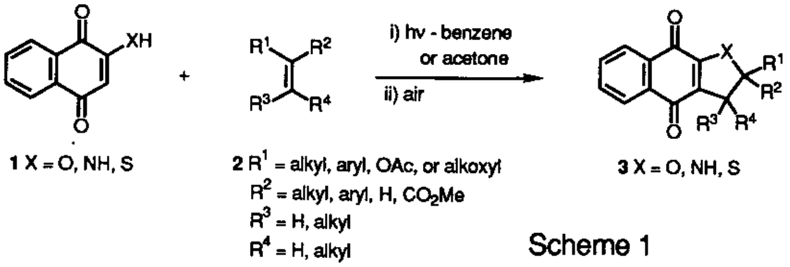
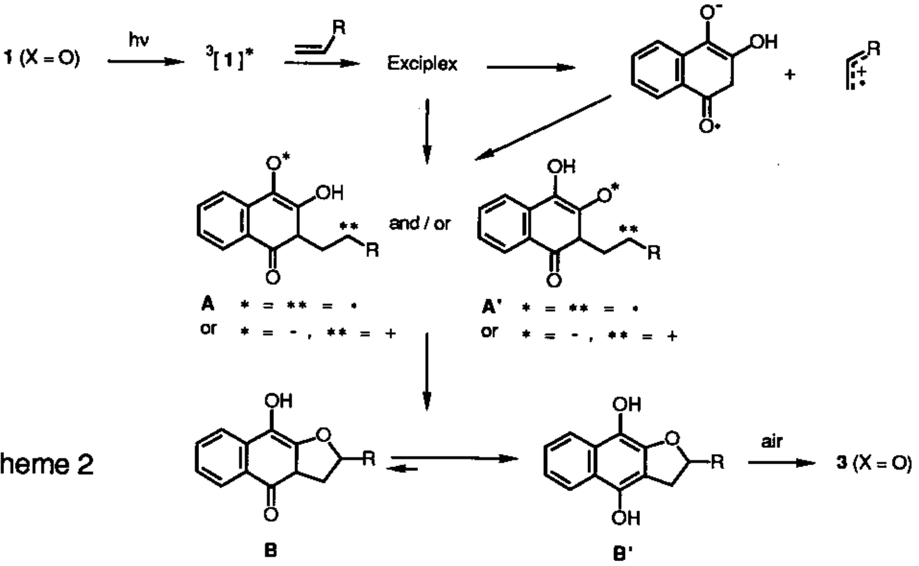
Abstract- 2-Acetoxy-1,4-naphthoquinone underwent [2+2] photoaddition to 2-methylpropene, giving a cyclobutanol acetate exclusively. Hydrolysis of the acetate with acid gave the corresponding cyclobutanol, which was stable under the conditions of an alkene-quinone photoaddition; hydrolysis with a base gave a fused 1-indanone derivative. Photolysis of the hypoiodite generated from the cyclobutanol derivative with mercury(II) oxide-iodine in benzene induced a β-scission of the cyclobutanoxyl radical to give a 2,3-dihydronaphtho[2,3-*b*]furan-4,9-dione and its [1,2-*b*]furan-4,5-dione isomer.

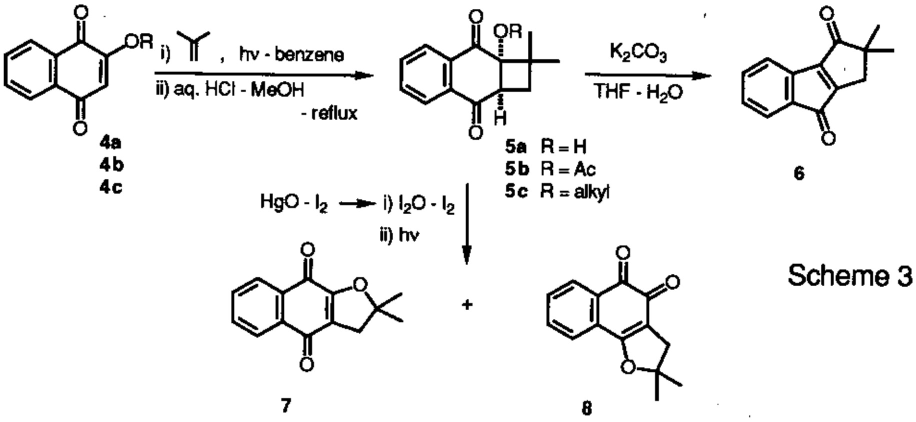
The common reaction of photochemically excited 1,4-quinones with alkenes is a [2+2] cycloaddition with either their carbonyl group or a carbon-carbon double bond, giving spirooxetanes and/or cyclobutane derivatives.[2,3] We found, however, that the excited 1,4-quinones, having a hydroxyl, amino or thio group at their C-2 position, react with alkenes in a distinctly different manner. We have thus reported that 3+2 adducts instead of [2+2] cycloadducts, 2,3-dihydronaphtho[2,3-*b*]furan-4,9-diones (**3** : R = O), are



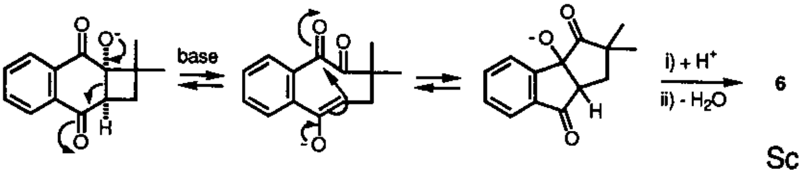
Scheme 1



Scheme 2



Scheme 3



Scheme 4

formed exclusively in high yields when 2-hydroxy-1,4-naphthoquinone (**1** : X = O) and alkenes in acetone or benzene are irradiated with Pyrex-filtered light (Scheme 1).[4] We subsequently found that 3+2 adducts, 2,3-dihydro-1*H*-benz[*f*]indole-4,9-diones (**3** : X = NH)[5] and 2,3-dihydronaphtho[2,3-*b*]thiophene-4,9-diones (**3** : X = S),[6] can be similarly formed by the photoaddition of 2-aminonaphthoquinone (**1** : X = NH) and of photogenerated 2-mercapto-1,4-naphthoquinone (**1** : X = S) with alkenes. Although the photochemistry of 1,4-quinones with alkenes suffers by a simultaneous formation of several products,[2,3] none of the [2+2] cycloadducts were formed in these 3+2 photoadditions. Thus, these selective 3+2 photoadditions of 1,4-quinones, having a 2-hydroxy-, 2-amino-, or 2-thio- group, are among the most synthetically useful photoreactions in the 1,4-quinone photochemistry.

We have confirmed that the furoquinones (**3**) are produced through air oxidation of the initially formed furohydroquinones (**B** and **B'**) by an intramolecular reaction of the intermediary 1,4-biradicals or 1,4-zwitterions (**A** and **A'**), as outlined in Scheme 2.[4]

The present work had two purposes: (1) To exclude the possibility of the involvement of a [2+2] cycloadduct in the path of the formation of 2,3-dihydronaphtho[2,3-*b*]furan-4,9-diones (**3** : R = O)[4] (the unlikely suggestion that the furoquinones (**3** : R = O) might be formed *via* a secondary rearrangement of an excited or ground-state species of an initially formed [2+2] photocycloadduct was made by one reviewer when we submitted a paper reporting on the path for the formation of the furoquinones (**3** : R = O) in the photoaddition[4]). (2) An application of our furan annelation[7, 8] through a combined process of [2+2] cycloaddition and radical fragmentation, to a naphthoquinone skeleton in order to extend the generality of this synthetically useful furan annelation; interesting biological activities of the derivatives of 1,2- and 1,4-naphthoquinones related to lapachol attracted attentions.[9]

Results and Discussion

The irradiation of 2-acetoxynaphthoquinone (**4b**) and excess of 2-methylpropene in benzene through a Pyrex filter at room temperature gave a single cycloadduct (**5b**) in 41% yield (Scheme 3). A spectroscopic analysis indicated that the cycloadduct (**5b**) was a head-to-head [2+2] cycloadduct. The cyclobutane and cyclohexane rings of the adduct (**5b**) should be *cis*-fused based on a steric consideration.

The cyclobutanol derivative (**5b**) was recovered unchanged when its solution was irradiated under the conditions for the photoaddition of 2-hydroxynaphthoquinone with alkenes giving furoquinones (**3**).[4]
The hydrolysis of the cycloadduct (**5b**) with aq. hydrochloric acid in methanol under reflux for 2.5 h gave the corresponding cyclobutanol (**5a**) in 90% yield. On the other hand, a treatment of the cycloadduct (**5b**) in aq. THF containing potassium carbonate at room temperature for 2 h resulted in the formation of a single crystalline product in 75% yield. A combustion analysis and mass spectrometry indicated that it had a molecular formula of $C_{14}H_{12}O_2$. The ir spectrum exhibited the presence of two bands at 1676 and 1662 cm^{-1} due to a conjugated enedione group, and the absence of any band due to a hydroxyl group. The ^1H nmr spectrum exhibited one singlet (6H) at δ 1.51 and another (2H) at δ 2.85, which were assignable to the *gem* dimethyl and methylene protons. These spectral results and the formation mechanism indicated the structure to be a cyclopentanoindanone (**6**). It is produced by a retro aldol condensation, followed by an intramolecular aldol condensation accompanied by a loss of water, as outlined in Scheme 4.

The irradiation of cyclobutanol (**5a**) in benzene containing mercury(II) oxide and iodine (each 3 equiv.)[7, 8] through a Pyrex filter with a 100-W high-pressure mercury arc under a nitrogen atmosphere for 6h gave two crystalline products (**7** and **8**) in 20 and 12% yields (Scheme 3). A combustion analysis and mass spectrometry indicated that both products had the molecular formula $C_{14}H_{12}O_3$. A spectral analysis and a direct comparison established that product (**7**) was 2,2-dimethyl-2,3-dihydronaphtho[2,3-*b*]furan-4,9-dione (**7**),[4] obtained by the cycloaddition of quinone (**1a**) with 2-methylpropene; product (**5**) was its angular isomer,[8,10] which exhibited a ^{13}C nmr spectrum identical to that given in the literature.[11]

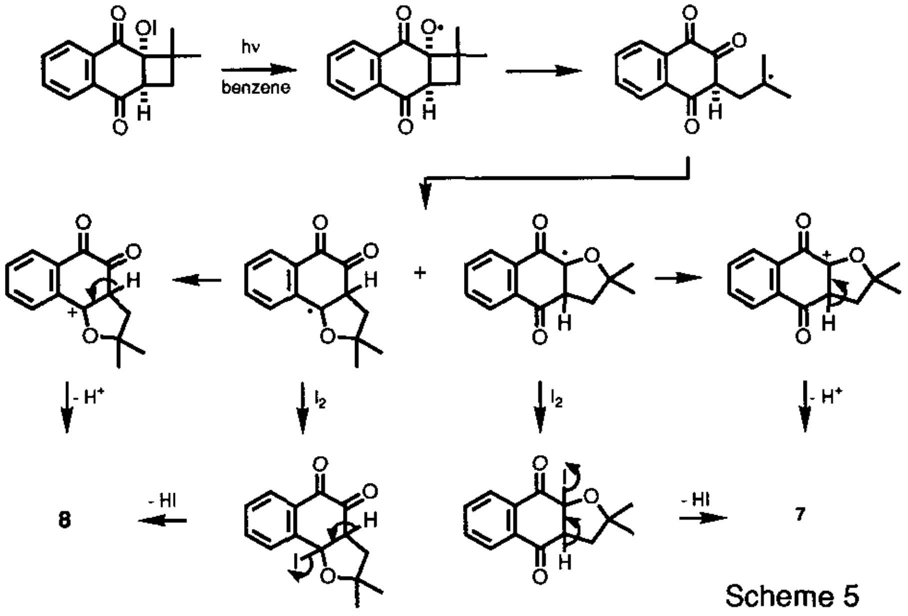
In contrast to the photoaddition of 1,4-naphthoquinone to 2-methylpropene, which was reported to give a 1:3.3 mixture of the spirooxetane and cyclobutane derivatives in 70% yield,[2] the above-mentioned photoaddition of 2-acetoxy-1,4-naphthoquinone to 2-methylpropene gave a cyclobutane derivative as the exclusive product. The lack of photoaddition to the carbonyl group in the present photoaddition is parallel to the results of the photoaddition of 2-hydroxynaphthoquinones, giving 3+2 photoadduct.[4-6] It is inferred that the energies of the n,π^* and π,π^* triplet states of 1,4-quinones may be appreciably influenced by the introduction of an acetoxy, hydroxy, amino, or thio group to their C-2, thus lowering the energy of the π, π^* triplet states relative to the n,π^* triplet states.

The foregoing experiments have unambiguously confirmed that the cyclobutanol (**5a**) is not an intermediate in the photoaddition giving furonaphthoquinone (**3**).[3]

We note that the cyclobutanol (**5a**) formed from 2-acetoxynaphthoquinone is a molecule suitable for preparing the alkoxyl derivative (**5c**), which was either a missing intermediate or was obtained as a mixture with a secondary photochemical product in the [2+2] cycloaddition of 2-alkoxynaphthoquinone (**4c**) with alkenes,[12] since the photocycloaddition invariably leads to a secondary photochemical reaction of the initially formed [2+2] cycloadduct (**4c**).[12]

The experiments described above have also revealed that the naphthofurandione (**3**) can alternatively be obtained by furan annelation [6,7] to the quinone skeleton through the combined process of [2+2] photoaddition and fragmentation, as has been found for a variety of heterocyclic compounds.[6,7]

Scheme 5 outlines the proposed formation mechanisms of the furonaphthoquinones (**7** and **8**).[8]



Scheme 5

EXPERIMENTAL

Mps were determined with a Yanagimoto mp apparatus, and are uncorrected. The ir spectra were determined for Nujol mulls with a JASCO IR-810 infrared spectrophotometer. The ^{1}H nmr spectra were determined in $CDCl_3$ ($SiMe_4$ as internal reference) with a JEOL JNM-JX 270 high-resolution spectrometer operating at 270 MHZ. The *J*-values are in Hz. The mass spectra were recorded using a

JEOL JMS-DX303 or JMS-HX110 spectrometer (70 eV). Elemental analyses were performed by the staff of the analytical laboratory of the Faculty of Pharmaceutical Sciences. Preparative tlc was carried out with Merck Kiesel gel 60PF$_{254}$. The photoaddition was carried with a 500-W high-pressure Hg arc lamp (Eikosha EHB-WI-500). The photolysis of the hypoiodites was carried out with a 100-W high-pressure Hg arc lamp (Eikosha EHB-WU-100).

2-Acetoxy-1,4-naphthoquinone (4b). This compound was prepared by acetylating commercially available Lawsone by the standard method.

1,1-Dimethyl-8a-acetoxy-1,2-dihydrocyclobuta[*b*]naphthalene-3,8 (2a*H*, 8a*H*)-dione (5b) by [2+2] Cycloaddition of 2-Acetoxy-1,4-naphthoquinone (4b) with 2-Methylpropene. A solution of naphthoquinone (**4b**) (800 mg, 3.7 mmol) and 2-methylpropene (3.82 g, 68 mmol) in benzene (74 ml) was irradiated through a Pyrex-filter with a 500-W high pressure Hg arc at room temperature for 7h. Removal of the solvent and excess 2-methylpropene left a residue which was subjected to preparative tlc on silica gel (1:2 ethyl acetate - hexane) to give [2+2] photoadduct (**5b**) (412 mg, 41%). mp 166-167°C (from hexane-CH_2Cl_2) Anal. Calcd for $C_{16}H_{16}O_4$: C: 70.57, H: 5.92: Found: C: 70.45, H: 6.00. ^{1}H Nmr; δ_H 1.02 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.83 (1H, dd, J = 8.91 and 11.72), 2.10 (3H, s, CH_3COO), 2.30 (1H, dd, J = 10.55 and 11.72), 3.57 (1H, dd, J = 8.91 and 10.55, 2aH), 7.73-7.81 (2H, m), 8.04-8.07 (1H, m), and 8.12-8.15 (1H, m); ir; 1734 and 1695 cm^{-1}; ms *m*/*z* (EI) 272 (M^+, 0.59), 230 (52), 175 (68), and 43 (100%).

1,1-Dimethyl-8a-hydroxy-1,2-dihydrocyclobuta[*b*]naphthalene-3,8 (2a*H*, 8a*H*) dione (2a). Aqueous HCl (15 ml of a 20% solution) was added to the photoadduct (**5b**) (320 mg, 1.18 mmol) in methanol (20 ml) and then the mixture was heated under reflux for 2.5 h. Evapolation of the solvent left a residue which was extracted with ether (20 ml x 3). The combined organic phases were washed successively with water and brine, and dried over anhydrous Na_2SO_4. The product was subjected to preparative tlc with silica gel (1:3 ethyl acetate-hexane) to give cyclobutanol (**5a**) (243 mg, 90%). mp 69-71°C (from hexane-CH_2Cl_2) Anal. Calcd for $C_{14}H_{14}O_3$: C: 73.02, H: 6.13. Found:C: 72.95, H: 6.20. ^{1}H Nmr; δ_H 0.78 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.61 (1H, dd J = 12.2 and 1.32), 2.27 (1H, dd, J = 12.2 and 8.91), 3.17 (1H, br.s, OH), 3.69 (1H, dd, J = 8.91 and 1.32, 2aH), 7.49 (1H, dt J = 7.92 and 1.32), 7.70 (1H, dt J = 7.59 and 7.92), 7.81 (1H, dd J = 7.92 and 0.66), and 8.06 (1H, dd J = 7.59 and 1.32); ir; 3462 and 1694 cm^{-1}; ms *m*/*z* (EI) 230 (M^+, 9.18), 212 [$(M-H_2O)^+$, 61.98), and 146 (100%).

The Formation of Cyclopentanoindene Derivative (6) by Treatment of Cycloadduct (5b) with Potassium Carbonate. Potassium carbonate (25 mg, 0.18 mmol) in water (20 ml) was added to a solution of photoadduct (**5b**) (46 mg, 0.17 mmol) in THF (7 ml). The mixture was then stirred at room temperature for 2 h. Evaporation of the solvent left a residuewhich was extracted with ether (25 ml x 3). The combined ether phases were washed successively with water and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude product which was subjected to preparative tlc with silica gel (1:4 ethyl acetate - hexane) to give cyclopentanoindene (**6**) (27 mg, 75%). mp 127-128.5°C (hexane - CH_2Cl_2) Anal. Calcd for $C_{14}H_{12}O_2$: C: 79.22, H: 5.70. Found; C: 79.07, H: 5.89. ^{1}H Nmr; δ_H 1.51 (6H, s, CH_3), 2.85 (2H, s, 3-H), 7.65-7.72 (2H, m), and 8.01-8.06 (2H, m); ir; 1676 and 1662 cm^{-1}; ms *m/z* (EI) 212 (M^+, 80.0), 210 (100), and 197 [$(M-CH_3)^+$, 99%].

The Formation of 2,2-Dimethyl-2,3-dihydronaphtho[2,3-*b*]furan-4,5-dione (7) and 2,2-Dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,9-dione (8) by the Photolysis of the Hypoiodite of Cyclobutanol (5a). Mercury (II) oxide (509 mg, 2.35 mmol) and iodine (596 mg, 2.35 mmol) were added to a solution of cyclobutanol (**5a**) (180 mg, 0.83 mmol) in benzene (39 ml). The solution was flashed with nitrogen and irradiated for 6 h through a Pyrex filter while being cooled with water. The reaction mixutre was filtered through a Celite and organic layer was washed successively with 5% $Na_2S_2O_3$, water and brine. After dryness over anhydrous Na_2SO_4, the solvent was removed *in vacuo*. The product was subjected to preparative tlc with silica gel, (1:3 ethyl acetate - hexane) to give two fractions. The more mobile fraction (36 mg, 20%) was naphtho[2,3-*b*]furan-4,9-dione (**4**),[4a] mp 187.5°C (from hexane-CH_2Cl_2) (lit.,[4a] mp 188-190°C), which was identical with an authentic sample obtained by the 3+2 photoaddition. The less mobile fraction (22 mg, 12%) was naphtho[1,2-*b*]furan-4,5-dione(**8**).[10] mp 155-157°C (From hexane-CH_2Cl_2).(lit.,[10] mp 120°C). ^{1}H Nmr: δ_H 1.61 (6H, s, CH_3), 2.95 (2H, s, 3H) 7.5-7.7 (3H, m, aromatic H), and 8.08 (1H, dd, *J* = 9.9 and 7.26, 6-H);^{13}C nmr:[11] δ_C 28.4 (CH_3), 39.3 (CH_2), 93.7 (C), 115.0 (C), 124.6 (CH), 128.0 (C), 129.4 (CH), 130.9 (C), 131.9 (CH), 134.4 (CH), 168.8 (C), 175.7 (C), 181.3 (C); ms *m/z* (EI) 228 (M^+, 16.1), 213 [$(M-CH_3)^+$, 17.2], 200 [$(M-CO)^+$, 40.2], 185 [$(M-CO-CH_3)^+$, 19.5], 174 (69.7), 159 (69.8), and 104 (100%).

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