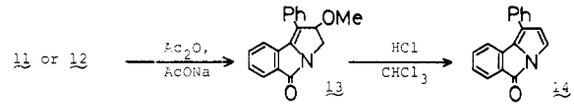
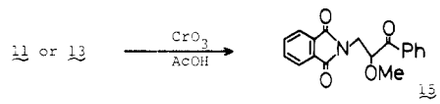
189–191 °C). On refluxing **11** and **12** in acetic anhydride and sodium acetate for 0.5 h, respectively, we readily obtained the same dehydrated product **13** (pale yellow crystals, mp 164–166 °C). The product **13** was further converted to **14** (orange

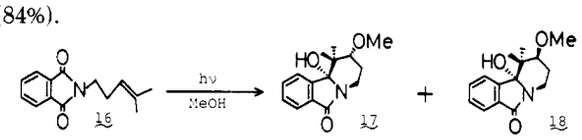


crystals, mp 113–115 °C) by treating with hydrochloric acid in chloroform. The main photoproduct **11** was quantitatively oxidized to **15** (mp 135–136 °C) by chromic acid oxidation in acetic acid. In a similar manner, **13** was oxidized to **15** (50%).



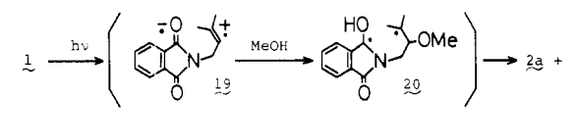
The structure of **11** was confirmed by X-ray diffraction. The stereochemistry of **12** is assigned on the basis of its ^{1}H NMR spectra compared with that of **11**: partial ^{1}H NMR (δ) of **11**, 4.1–4.4 (m, 2 H, two methine), 3.78 (m, 2 H, NC**H**$_2$); **12**, 4.92 (m, 1 H, **H**COMe), 3.74 and 3.50 (two dd, 2 H, NC**H**$_2$), 2.76 (d, 1 H, **H**CPh). On irradiation of **10** in methanol, the presence of a triplet quencher (penta-1,3-diene, 1 mol/L) did not significantly affect the rate of formation of the photoproducts, analogous to the case of photolysis of *N*-(dibenzylaminomethyl)phthalimide.[1e]

Irradiation of *N*-(4-methyl-3-pentenyl)phthalimide (**16**) in methanol gave the corresponding isomers **17**/**18** = 1:1 (84%).



These intramolecular photocyclizations of phthalimides may be reasonably explained by a mechanism involving initial one-electron transfer.[4] Thus, for example, in the photocyclization of **1**, the primary photoprocess may be one-electron transfer from the double bond (**1** → **19** in Scheme I) followed by polar addition of methanol to give a diradical (**19** → **20**)[5] which cyclizes to produce **2a** and **3a**.[6]

Scheme I



The reaction pattern of the photocyclization of *N*-alkenylphthalimide described above seems to be novel in the widely studied photochemistry of carbonyl compounds with olefins. The scope, limitation, and detailed mechanism of this reaction are under investigation.

Acknowledgment. We are indebted to Professor Masao Kakudo and Dr. Nobuo Tanaka of Osaka University (the Institute for Protein Research) for X-ray diffraction analysis.

References and Notes

(1) (a) Y. Kanaoka, *Yuki Gosei Kagaku Kyokai Shi*, **33**, 949 (1975), and papers cited therein; (b) Y. Sato, H. Nakai, T. Mizoguchi, and Y. Kanaoka, *Tetrahedron Lett.*, 1889 (1976); (c) Y. Sato, H. Nakai, T. Mizoguchi, Y. Hatanaka, and Y. Kanaoka, *J. Am. Chem. Soc.*, **98**, 2349 (1976); (d) H. J. Roth and D. Schwarz, *Arch. Pharm.*, **308**, 631 (1975); (e) J. D. Coyle and G. L. Newport, *Tetrahedron Lett.*, 899 (1977).

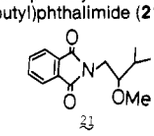
(2) Light-induced reaction of *N*-methylphthalimide with cycloalkenes has been reported, but the report described only an α-hydrogen abstraction from cycloalkenes.[2a] Photochemical oxetane formation of *N*-2-alkenyl alicyclic imides[2b] and photoaddition of dienes to *N*-methylphthalimide[2c] have been reported. (a) Y. Kanaoka and Y. Hatanaka, *Chem. Pharm. Bull.*, **22**, 2205 (1974); (b) K. Maruyama and Y. Kubo, *J. Org. Chem.*, **42**, 3215 (1977); (c) P. H. Mazzocchi, M. J. Bowen, and N. K. Narain, *J. Am. Chem. Soc.*, **99**, 7063 (1977).

(3) All new compounds gave satisfactory analytical results as well as reasonable spectral properties (IR, NMR, UV, and mass spectra).

(4) It is reported that in the photochemical reaction of aromatic esters with olefins in polar solvents, the exciplexes, once formed, dissociate into the radical ions.[4a-c] Furthermore, in the photohydrogen abstraction reaction of phthalimides, electron transfer (or CT) mechanisms are often regarded as playing an important role.[1] (a) R. A. Neunteufel and D. R. Arnold, *J. Am. Chem. Soc.*, **95**, 4080 (1973); (b) Y. Shigemitsu and D. R. Arnold, *J. Chem. Soc., Chem. Commun.*, 407 (1975); (c) A. J. Maroulis, Y. Shigemitsu, and D. R. Arnold, *J. Am. Chem. Soc.*, **100**, 535 (1978).

(5) Photosensitized anti-Markownikoff addition of alcohols (involving electron transfer) to olefins has been reported[4a-c] and the protonation of a carbonyl group from a CT complex by methanol has been postulated.[5a] The diradical is also a presumed intermediate in the intramolecular δ-hydrogen abstraction reaction of *N*-alkylphthalimides.[1] (a) P. J. Wagner and D. A. Ersfeld, *J. Am. Chem. Soc.*, **98**, 4515 (1976).

(6) Another mechanism for the photolysis of **1** is the possible intermediacy of *N*-(2-methoxy-3-methylbutyl)phthalimide (**21**) (via sensitized anti-Markownikoff addition of methanol to the double bond) followed by δ-hydrogen abstraction to **2a** and **3a**. However, in our hands **21** could not be isolated under various conditions. Furthermore, a photoreaction of **21** is anticipated to occur with preferential γ-hydrogen rather than δ-hydrogen abstraction as is observed in the photolysis of *N*-(3-methylbutyl)phthalimide.[1a]



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Diels–Alder Reaction of 1,4-Quinone Monobenzenesulfonimides

Summary: The Diels–Alder cycloaddition of a series of 1,4-quinone monobenzenesulfonimides with various 1,3-butadienes was investigated. The objective was to determine the influence of the benzenesulfonimide group on the regiochemistry of the cycloaddition as well as the relative dienophile double bond reactivity. The salient results are: (1) the regiochemistry of the cycloadditions is exclusively controlled by the benzenesulfonimide group; (2) the double bond in the quinone imine which is syn to the benzenesulfonimide is the more activated dienophilic position.

Sir: Synthetic strategy for the construction of a large number of naturally occurring quinones, including the biologically significant anthracycline antineoplastic antibiotics, utilizes a Diels–Alder cycloaddition of a quinone to a diene. However, this methodology often suffers both regiochemical and reactivity problems. That is, in the cycloaddition of a substituted benzoquinone with a substituted diene, the regiochemical problem concerns the orientation of the substituents in the final product, and the reactivity problem concerns the relative reactivity of the enone double bonds in the quinone dienophile.[1] These conflicts are dramatically illustrated in the elegantly simple synthesis of (±)-daunomycinone reported by Kende, Tsay, and Mills.[2] Here it was observed that the key intermediate, 5-methoxy-1,4,9,10-anthradiquinone (**1**), reacts with most electron-rich dienes at the internal 4a,9a double

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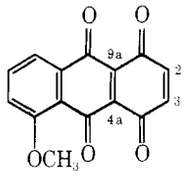


1

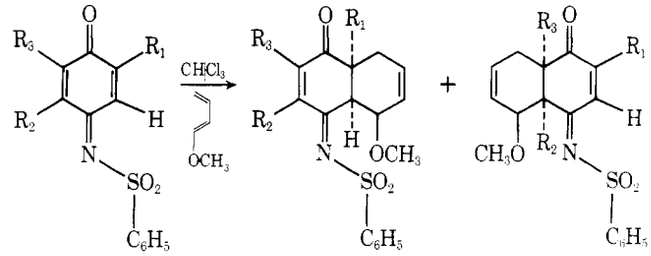
bond. The desired exclusive cycloaddition at the 2,3-double bond was accomplished with 2-acetoxy-1,3-butadiene, but both possible regioisomers resulted.

Our objectives concerning the above two problems were to study the Diels–Alder cycloadditions of a simple quinone derivative which could control both the regiochemistry and the double bond reactivity. Specifically, the cycloadditions of various 1,4-benzoquinone monobenzenesulfonimides with 1-methoxy-1,3-butadiene were initially investigated.[3] The salient results of this study are the following: (1) the benzenesulfonimide group markedly controls the regiochemistry of the reaction in that, for the examples described here, only those adducts **9** are formed which have the methoxy group at position 5 and the imide at position 4; (2) *remarkably, and counter to our initial expectation, the double bond which is syn to the benzenesulfonyl group is the more activated dienophile.*

When a chloroform solution of 1,4-benzoquinone monobenzenesulfonimide (**2**) and 10% molar excess of 1-methoxy-1,3-butadiene was allowed to stand at ambient temperature for 3 days, complete reaction occurred to give a 65% isolated yield of a mixture of the adducts **3** and **4** in a ratio of, respectively, 2:1.[4] Under these conditions the reaction is actually under thermodynamic control, since it was subsequently shown that the reaction is complete within 30 min and the ratio of **3/4** here is ~4:1. This kinetic ratio slowly changes to the equilibrium ratio of 2:1 as the reaction solution stands at ambient temperature over the 3-day period.[5] These isomers could not be separated by conventional methods, but the structural assignments were made (vide infra) on the basis of ^{1}H NMR analysis of the resulting mixture. No other regioisomers could be detected. Thus, the reaction appears to be regiospecific with respect to the electronic control of the imine vs. the carbonyl group, and regioselective with respect to the double bond reactivity. A complete stereochemical analysis of **3** and **4** has not been made. However, the indicated relative configuration of the chiral centers in the molecules is anticipated based upon the principle of endo cycloaddition. The stereochemistry of the imine moieties is readily assigned from the fact that the absorption for the vinyl proton at position 3 in the minor product, **4**, is deshielded relative to the analogous absorption in **3**. These appear respectively at δ 8.1 and 6.7. That the deshielded absorption is due to the *syn*-vinyl proton (with respect to the benzenesulfonyl group) is based upon the observation that the chemical shifts of the *syn*-vinyl protons in the quinone imines **2** and **5–8** all appear between δ 8.1 and 8.2.[6] Therefore, it is apparent that the proton on the syn double bond is experiencing a deshielding anisotropy effect of the benzenesulfonyl group.

In a manner analogous to the above, the cycloadditions of the quinone imines **5–8** with 1-methoxy-1,3-butadiene were investigated (3 days at ambient temperature), which gave, respectively, the adducts **9a,b, 9c,d, 9e,** and **9f** (Table I). Here again, the reactions were all observed to be regiospecific. For the symmetrical quinone imine **5**, where the difference in syn vs. anti double bond reactivity would be due only to the imine stereochemistry, the major isomer **9a** again was due to cycloaddition to the syn double bond as evidenced by the C-3 vinyl proton absorption at δ 8.1 for the minor isomer **9b** (25%), and δ 6.9 for the major isomer **9a** (49%). A reversal in the double bond reactivity was observed for the cycloaddition of

Table I



I 9 II

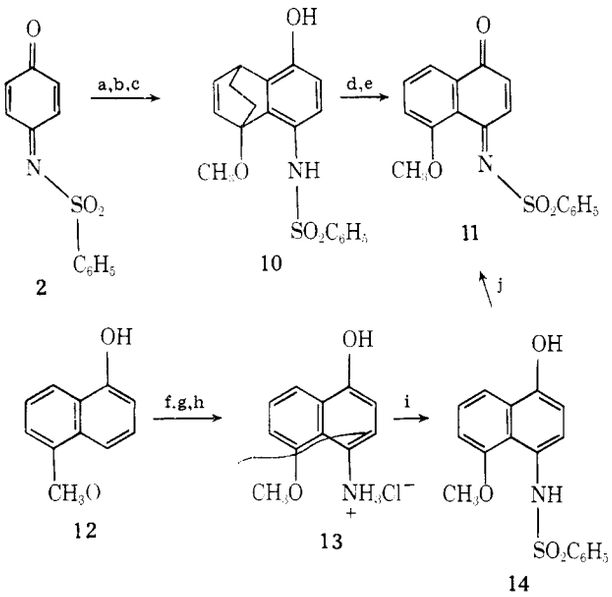
Quinone imine	R_1	R_2	R_3	I[c]	II[c]
2	H	H	H	**3,** 66%[a]	**4,** 33%[a]
2	H	H	H	**3,** 80%[b]	**4,** 20%[b]
5	CH_3	H	CH_3	**9a,**[8] 49%	**9b,**[8] 25%
6	CH_3	CH_3	H	**9c,** 27% (mp 173–175 °C)	**9d,** 55% (mp 121–123 °C)
7	H	CH_3	H	**9e,** 86% (mp 139–141 °C)	None
8	H	CH_3	CH_3	**9f,** 85% (mp 134–136 °C)	None

[a] NMR ratio after 3 days at room temperature. [b] NMR ratio after 30 min at room temperature. [c] All other % of I and II are actual isolated yield unless otherwise stated.

2,5-dimethyl-1,4-benzoquinone monobenzenesulfonimide (**6**). Here, the major product **9d** arises from cycloaddition to the anti double bond. This is not unexpected, since the 2,3-double bond (syn) would be activated by the benzenesulfonyl group, but deactivated by the methyl group at position 2. That is, for a cycloaddition occurring on the 2,3 double bond, "initial bond formation" would take place at position 2, and alkyl substitution at this site is known to retard the reaction.[7] The 5,6 double bond (anti), on the other hand, would gain no activation from the *anti*-benzenesulfonyl group, but would not be as greatly deactivated by the 5-methyl substituent, since "initial bond formation" would take place at the unsubstituted position 6. The influence of the methyl groups in **6** is apparently more important than the imine stereochemistry and thus preferential cycloaddition takes place at the anti-5,6 double bond to give **9d,** which shows the diagnostic low-field vinyl proton absorption at δ 8.1. For the quinone imines **7** and **8,** cycloaddition takes place, as expected, only at the unsubstituted syn double bond to give, respectively, **9e** and **9f.** Such assignments are clearly made by the fact that **9e** shows vinyl proton absorptions corresponding to three protons and **9f** to two protons.

To this point, the discussion has focused primarily upon the reactivity preference of the dieneophile double bond, and no persuasive arguments have been put forward regarding the regiospecificity of the cycloadditions. Such assignments of the regiostructures of **3, 4,** and **9a–f** are made on the basis of the following ^{1}H NMR data. Adduct **9d** shows a multiplet at δ 3.23 for the methine proton at position 5, which collapses to a singlet upon irradiation (decoupling) of the 6,7-vinyl protons. Adduct **9c** shows this same methine proton as a multiplet at δ 4.27, which collapses to a doublet (J = 5.5 Hz) upon decoupling the 6,7-vinyl protons. This resulting doublet is due to coupling to the methine proton at position 4a, which appears at δ 4.40 as a doublet (J = 5.5 Hz). Adduct **9f** shows the 5- and 4a-methine protons, respectively, as a multiplet at δ 4.28 and a doublet of doublets at δ 4.47. Decoupling in the 6,7-vinyl region causes the multiplet to collapse to a doublet (J = 3.9 Hz), and decoupling the 8a-methine proton at δ 2.81 results in collapse of the δ 4.47 doublet of doublets to a simple doublet (J = 3.9 Hz). The ^{1}H NMR spectrum of **3** and **9e** parallels that of **9f,** while **9b** is analogous to **9c.** Finally, the methine protons

Scheme I



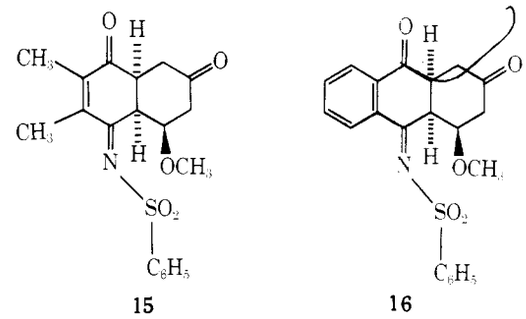
(a) $C_6H_7OCH_3/CHCl_3$/room temp. (b) KO*t*-Bu/THF. (c) H_3O^+. (d) $Pb(OCOCH_3)_4/CH_3CO_2H$. (e) C_6H_6, Δ. (f) $^+N_2C_6H_4SO_3^-$. (g) $Na_2S_2O_4/H_2O$. (h) Concentrated HCl. (i) $C_6H_5SO_2Cl$. (j) $Pb(OCOCH_3)_4$.

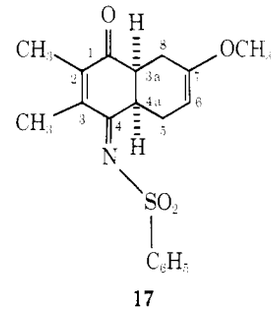
at position 5 in **4** and **9a**, which both appear at δ 3.60, collapse to doublets upon decoupling the 6,7-vinyl region. These data are consistent only with the indicated regiostructures of the adducts, i.e., **9a–f**.

In order to gain chemical conformation that the benzenesulfonimide group controls the regiochemistry of the cycloadditions, 1,4-benzoquinone monobenzenesulfonimide[6] (**2**) was treated with 1-methoxycyclohexa-1,3-diene to give the adduct which upon treatment with ^-O-*t*-Bu followed by acid workup to give the naphthol **10** in 35% yield (Scheme I):[9] mp 202–203 °C; NMR ($CDCl_3$) δ 9.3 (s, 1 H), 7.85 (s, 1 H). 7.8–6.7 (m, 7 H), 6.5–6.3 (m, 2 H), 4.13 (m, 1 H), 3.39 (s, 3 H), 1.9–1.0 (m, 4 H); IR (Nujol, cm^{-1}) 3315, 3500. This was oxidized with lead tetraacetate and pyrolyzed in refluxing benzene to give the quinone imine **11** (53%): mp 143–145 °C; NMR ($CDCl_3$) δ 8.5–7.2 (m, 8 H), 8.49 (d, 1 H, J = 10 Hz), 6.85 (d, 1 H J = 10 Hz), 3.7 (s, 3 H); IR (Nujol, cm^{-1}) 1650, 1600. This product was then independently synthesized starting with 1-hydroxy-5-methoxynaphthalene[10] (**12**). Here the naphthol was treated with *p*-sulfonylbenzenediazonium chloride and the resulting azo compound was reduced to the amine **13**, which was then treated with benzenesulfonyl chloride to give **14** (61%): mp 172–174 °C; NMR (acetone-d_6) δ 9.33 (s, 1 H), 8.75 (s, 1 H), 6.68–8.0 (m, 10 H), 3.81 (s, 3 H); IR (Nujol, cm^{-1}) 3600, 3510. Subsequent oxidation of **14** gave **11** in 90% yield.

In conjunction with our desire to utilize quinone imines as synthetic precursors to certain anthracycline antibiotics, it was of interest to see if 1,3-disubstituted-1,3-butadienes would undergo regiospecific cycloaddition. Thus, the reactions of 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene[11] with 2,3-dimethyl-1,4-benzoquinone monobenzenesulfonimide and 1,4-naphthoquinone monobenzenesulfonimide were studied. In both cases the reaction proceeds smoothly to give a single adduct which upon mild hydrolysis with 0.1 N HCl/THF results, respectively, in **15** (mp 170–172 °C) (75%) and **16** (mp 147–149 °C) (80%). Their structures are based upon spectral and elemental analyses which are consistent with the arguments previously presented.

Finally, it was of interest to see if the same high degree of regiochemical control would be observed for quinone imine cycloadditions to the less strongly directing 2-methoxy-1,3-butadiene. Thus, an acetonitrile solution of **8** containing a catalytic amount of hydroquinone was treated with excess diene at 55 °C (6 h). Here the resulting adduct, **17**, mp 142–144 °C, was obtained in 75% purified yield, and again only one regioisomer could be detected by NMR analysis of the crude solid product. Decoupling experiments of the 220-MHz spectrum of **17** revealed that the low-field C-4a methine proton (δ 4.25) and the vinyl proton at C-6 (δ 4.48) were both coupled to one of the methylene protons at C-5 (δ 2.74) and such a result is consistent for only the regioisomer **17**.





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(1) A number of unique resolutions to these problems have recently been reported. See, for example: W. W. Lee, A. P. Martinez, T. H. Smith, and D. W. Henry, *J. Org. Chem.*, **41**, 2296 (1976); T. R. Kelly, R. N. Goerner, Jr., J. W. Gillard, and B. K. Prazak, *Tetrahedron Lett.*, 3869 (1976); H. H. Inhoffen, H. Muxfeldt, V. Koppe, and J. H. Trosien, *Chem. Ber.*, **90**, 1448 (1957); R. A. Dickinson, R. Kubela, G. A. MacAlpine, Z. Stojanac, and Z. Valenta, *Can. J. Chem.*, **50**, 2377 (1972); N. Stojanac, A. Sood, Z. Stojanac, and Z. Valenta, *ibid.*, **53**, 616 (1975); T. R. Kelly, J. W. Gillard, R. N. Goerner, Jr., and J. M. Lyding, *J. Am. Chem. Soc.*, **99**, 5513 (1977); B.M. Trost, J. Ippen and W. C. Vladuchick, *ibid.*, **99**, 8117 (1977).

(2) A. S. Kende, Y. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976).

(3) The cycloadditions of quinone imines with dienes has previously been reported by R. Adams. However, the regio- and stereochemistry of the adducts were not determined, see: R. Adams and W. Reifschneider, *Bull. Soc. Chim. Fr.*, 23 (1958).

(4) All new compounds reported here showed spectral and analytical properties in complete accord with their proposed structures.

(5) It is, of course, possible that this equilibration takes place by a reversibility of the Diels–Alder reaction rather than isomerization of the time double bond. However, in view of the mild reaction conditions (ambient temperature), this appears unlikely.

(6) These quinone imines were all prepared according to the methods described by Adams and Reifschneider; see ref 3.

(7) M. F. Ansell and A. H. Clements, *J. Chem. Soc.*, 269 (1971).

(8) The mixture of **9a** and **9b** could not be separated. However, spectral analysis of the mixture readily allowed the structural assignments of the individual isomers.

(9) This transformation is analogous to that previously reported in the quinone series, see: R. G. F. Giles and G. H. P. Roos, *J. Chem. Soc., Perkin Trans. 1*, 2057 (1976).

(10) The naphthol was prepared in 82% overall yield from 1,5-dihydroxynaphthalene by dimethylation (CH_3I/K_2CO_3/acetone) followed by monodemethylation ($C_2H_5SH/NaH/DMF$).[3]

(11) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974).

(12) The authors are grateful to the National Cancer Institute (CA 11890) for financial support of this work.

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