Synthetic Approaches to Adriamycin Involving Diels–Alder Reactions of Photochemically Generated Bisketenes. Total Synthesis of Islandicin and Digitopurpure

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Oxidation of 5-hydroxy-2,3-dihydro-1,4-phthalazinedione (7), prepared from 3-nitrophthalic acid in four steps in 67% overall yield, with lead tetraacetate in the presence of anthracene afforded the Diels–Alder adduct 9 (R = H) in good yield. Protection of the phenolic hydroxyl group could be easily accomplished under base-catalyzed conditions to furnish the methoxymethyl 9 (R = CH₂OCH₃) and methyl 9 (R = CH₃) ethers. Vapor phase pyrolysis of these two compounds afforded the corresponding 3-alkoxybenzocyclobutene-1,2-diones, 2 (R = CH₂OCH₃ and CH₃). Hydrolysis of the former afforded the phenol 2 (R = H) in high yield. As a test of the utility of these systems in a photochemical synthetic approach to the potent antineoplastic agent, adriamycin (1), the ether 2 (R = CH₂OCH₃) was photolyzed in the presence of several quinones 10a–e. The desired anthraquinone products 11 and 12 were obtained (as a regiochemical mixture where possible) in low yields. The use of 2-methylbenzoquinone (10b) and 2-hydroxymethylbenzoquinone (10c) permitted a straightforward total synthesis of the natural products, islandicin (11b) and digitopurpure (12b).

The broad spectrum of antineoplastic activity and effectiveness in combination chemotherapy of adriamycin (1) make it one of the most useful chemotherapeutic agents available. The principal limit on its utility is its high cardiotoxicity. This fact, combined with an inefficient biosynthetic process for its production, has stimulated considerable work recently on the synthesis of adriamycin and its analogues. Staab and Ipaktschi reported that benzocyclobutene-1,2-dione (2) undergoes Diels–Alder reactions with electron-deficient olefins [maleic anhydride (3a) and naphthoquinone (3b)] upon irradiation to afford the Diels–Alder adducts 4a and 4b, respectively. Despite the low yield in the case of naphthoquinone, which the authors attribute to having to terminate the irradiation prematurely due to the intense absorption by the product, it seemed possible that an appropriately substituted benzocyclobutene-1,2-dione 2 might undergo Diels–Alder reaction with an appropriately substituted quinone 5 to produce a compound 6 which might be easily converted into the aglycone of adriamycin, adriamycinone. We now report our initial results in this area, to include (1) the synthesis of 3-substituted benzocyclobutene-1,2-diones 2, (2) their photoreactions with quinones, and (3) the total synthesis of islandicin (11b) and digitopurpure (12b).

![Chemical structures](image-url)
Table I. Photolysis of 2 with Quinones

<table>
<thead>
<tr>
<th>Quinone 10</th>
<th>Time, h</th>
<th>Products</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a, R = R' = H</td>
<td>9</td>
<td>11a</td>
<td>4, 8f</td>
</tr>
<tr>
<td>Benzoquinone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b, R = Me; R' = H</td>
<td>12</td>
<td>11b + 12b (1:1)</td>
<td>8</td>
</tr>
<tr>
<td>2-Methylbenzoquinone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c, R = CH₃OH; R' = H</td>
<td>9</td>
<td>11b + 12b (1:1)</td>
<td>9</td>
</tr>
<tr>
<td>2-Hydroxymethylbenzoquinone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d, R = R' = -CH=CH-CH=CH-</td>
<td>12</td>
<td>11d</td>
<td>13.5</td>
</tr>
<tr>
<td>Naphthoquinone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td></td>
<td>6-Carbomethoxytoluquinone</td>
<td></td>
</tr>
</tbody>
</table>

a The length of time irradiation was carried out. b Yields are given for isolated purified products, all of which exhibit spectral data in accord with their structures. c Identified by comparison with melting point and IR spectrum as given in H. Brockmann and B. Franck, Chem. Ber., 88, 1792 (1955). d Identified as the triacetates by comparison with NMR of authentic samples of the triacetates and as given in Y. Ogihara, N. Kobayashi, and S. Shibata, Tetrahedron Lett., 1881 (1968). e Identified as in c, following hydrogenolysis with 10% Pd/C and 1 atm H₂ at 25 °C for 4 h. f Identified by comparison with melting point and UV spectrum as given in H. Brockmann and W. Müller, Chem. Ber., 92, 1164 (1959). g Using the free phenol, 2 (R = H), in the presence of triethylamine.

= H), could be obtained by acid hydrolysis of the methoxymethyl ether 2 (R = CH₃OCH₃), or, more conveniently, by treating the crude pyrolysis product with acid and isolating the phenol by extraction with aqueous bicarbonate [overall yield of 2 (R = H) from 9 (R = CH₃OCH₃) is 56%]. Interestingly, the phenol 2 (R = H) exhibits a pKᵢ value of 5.8 ± 0.2, making it a very acidic phenol, though not quite as acidic as 4,5-dihydroxybenzocyclobutene-1,2-dione (pKᵢ = 4.48). h

Irradiation of the methoxymethyl ether 2 (R = CH₃OCH₃) in CH₂Cl₂ in the presence of various quinones 10a–e furnished the expected adducts (11a–d, 12b) as listed in Table I. After photolysis of the protecting group, the products were isolated by preparative thin layer chromatography and compared with melting points and spectra given in the literature or from authentic samples. While the yield of adduct 11d, a compound possessing marked activity against the solid form of Ehrlich carcinoma, was the same as that reported by Staab for the parent compound, the yields of the other adducts were somewhat lower and there was no starting material left to be recovered. In the case of the 2-methylbenzoquinone 10b and the 2-hydroxymethylbenzoquinone 10c, the products after hydrolysis (and hydrogenolysis of the benzyl hydroxyl function in the case of 10c) were a 1:1 mixture of the natural products, islandicin (11b) and digitopurpure (12b). We detect no directing effect of methyl or hydroxymethyl on the regiochemistry of this Diels–Alder reaction. The last entry in Table I reflects an attempt to overcome the intense absorption by the product as a possible problem by blocking the usually facile aromatization with an ester function. However, irradiation in the presence of 6-carbomethoxy-1,4-tolquinone (10e) followed by acidic or basic hydrolysis failed to produce any of the desired anthraquinone. Also, irradiation of the phenol 2 (R = H) in the presence of triethylamine (via the phenolate ion) and benzoquinone gave only 8% yield of the desired adduct, 11a.

Thus, although we have demonstrated the viability of the proposed synthetic scheme, the yields obtained are far too low to be synthetically useful, especially inasmuch as no starting material is left to be recycled. The possibility that other absorbing chromophores besides the benzocyclobutene-1,2-dione might be causing harmful side reactions is suggested by preliminary experiments which indicate that maleic anhydride gives an appreciably better yield. Therefore research is continuing to explore reaction with other dienophiles in order to improve the synthetic utility of the photoprocess. Especially interesting is the possibility of photolyzing bridged intermediates, e.g., 13, which might then afford products, e.g., 14, with the correct regiochemical placement of groups in significantly higher yields.

Experimental Section

General. Melting points were taken on a Büchi melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 107B spectrophotometer. NMR spectra were measured on a Varian T-60 spectrometer and are reported in parts per million downfield from internal tetrarnethylsilane, except for the spectra of 11b and 12b, which were measured as the triacetates at 251 MHz. Mass spectra were recorded on an MS-9 instrument. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Anthracene Adduct of 5-Hydroxypthalazine-1,4-dione (9, R = H). To a stirring solution of 0.64 g (8.60 mmol) of 5-hydroxy-2,3-dihydro-1,4-phthalazinedione (7) 0.71 g (4.00 mmol) of anthracene, and 0.5 mL of acetic acid in 35 mL of CH₂Cl₂ at 25 °C under N₂ was added 1.80 g (3.60 mmol) of lead tetraacetate in small portions every 15 min for 1.5 h. To the dark brown mixture was added 4
Synthetic Approaches to Adriamycin

g of activity V neutral alumina (Merck) and the mixture rotary evaporated to dryness. The solids were placed atop a column of 70 g of activity V neutral alumina (Merck) and eluted with CCl4 to remove anthracone. Elution with CH2Cl2 gave 916 mg (72%) of nearly white, crystalline solid: mp 163-165 °C dec; IR (KBr) ν = 1780 cm⁻¹; mass spectrum (70 eV) m/e (relative intensity) 349 (1), 179 (19) and 178 (100). Anal. Caled for C23H16N2O3: C, 74.98; H, 4.38. Found: C, 75.00; H, 4.36.

Anthracene Adduct of 5-(Methoxymethyl)oxyphenanthroline-1,4-dione (9, R = CH2OCH3). To a stirring suspension of 623 mg (1.76 mmol) of adduct 9 (R = H) in 40 mL of dry THF at 25 °C under N2 was added 290 mg (7.05 mmol) of potassium tert-butoxide. The mixture was stirred at 25 °C for 40 min, and then 0.51 mL (7.05 mmol) of chloromethyl methyl ether was added with gradual formation of a white precipitate as it was stirred at 25 °C for 3 h. Partitioning between CH2Cl2 and H2O and evaporation of the CH2Cl2 layer left 0.67 g of activity V neutral alumina (Merck) and the mixture rotary evaporated to dryness. The solids were trapped were chromatographed on SiO2. Elution with CH2Cl2 and H2O and evaporation of the CH2Cl2 layer left 0.67 g of activity V neutral alumina (Merck) and the mixture rotary evaporated to dryness. The solids were placed atop a column of 70 g of anthracene. Elution with CH2Cl2 gave 916 mg (72%) of nearly white, crystalline solid: mp 163-165 °C dec; IR (KBr) ν = 1780 cm⁻¹; mass spectrum (70 eV) m/e (relative intensity) 349 (1), 179 (19) and 178 (100). Anal. Caled for C23H16N2O3: C, 74.98; H, 4.38. Found: C, 75.00; H, 4.36.

Anthracene Adduct of 3-(Methoxymethoxy)benzocyclobutene-1,2-dione (2, R = CH2OCH3). Irradiation was carried out in a Pyrex flask, placed approximately 5 cm from a 550-W Hanovia medium-pressure Hg arc, in approximately 10⁻² M solutions of CH2Cl2, for the period indicated in Table 1. The products were generally hydrolyzed as in the preparation of 3-hydroxybenzocyclobutene-1,2-dione and isolated by preparative TLC.

Acknowledgments. We wish to thank Dr. A. S. Kende for authentic samples of digitopurpone trimethyl ether and triacetate and islandicin. Dr. R. Helgeson for helpful advice, and Dr. F. A. L. Anet and Mr. M. Squillacote for 255-MHz NMR spectra. We also wish to thank the University of California Cancer Research Coordinating Committee for partial support of this work.

Registry No.—1, 22314-92-2; 2 (R = H), 62416-21-1; 2 (R = Me), 62416-22-2; 2 (R = CH2OCH3), 62416-23-3; 7, 7,600-08-0; 9 (R = H), 62416-24-4; 9 (R = Me), 62416-25-5; 9 (R = CH2OCH3), 62416-26-6; 10a, 10b-61-4; 10b, 553-97-9; 10c, 644-17-7; 10d, 130-15-4; 10e, 62416-27-7; 11b, 476-56-2; 12b, 34425-57-5; anthracene, 120-12-7; chloromethyl ether, 107-30-2; iodomethane, 74-88-4.

References and Notes

(7) Recently an excellent regiospecific synthesis of both oxfordin and digi-}
(11) The overall yield of 2 (R = H) from 3-nitrohippuric acid via four steps is thus 24%.