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

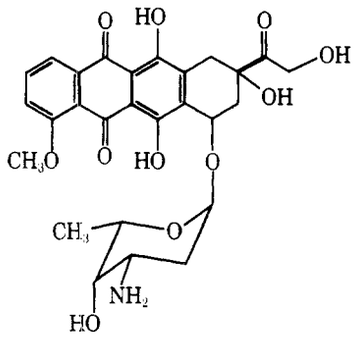
Michael E. Jung* and John A. Lowe

Contribution No. 3780 from the Department of Chemistry, University of California, Los Angeles, California 90024

Received March 15, 1977

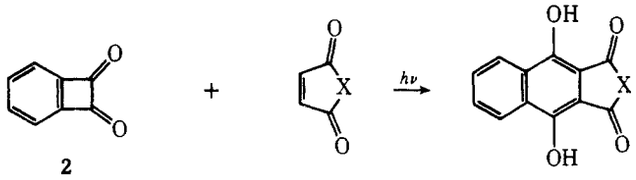
Oxidation of 5-hydroxy-2,3-dihydro-1,4-phthalazinedione (**7**), prepared from 3-nitrophthalic acid in four steps in 67% overall yield, with lead tetraacetate in the presence of anthracene afforded the Diels–Alder adduct **9** (R = H) in good yield. Protection of the phenolic hydroxyl group could be easily accomplished under base-catalyzed conditions to furnish the methoxymethyl **9** (R = CH_2OCH_3) and methyl **9** (R = CH_3) ethers. Vapor phase pyrolysis of these two compounds afforded the corresponding 3-alkoxybenzocyclobutene-1,2-diones, **2** (R = CH_2OCH_3 and CH_3). 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 = CH_2OCH_3) 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 digitopurpone (**12b**).

The broad spectrum of antineoplastic activity and effectiveness in combination chemotherapy of adriamycin (**1**) make



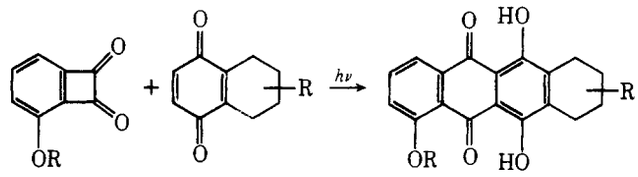
1

it one of the most useful chemotherapeutic agents available.[1] The principal limit on its utility is its high cardiotoxicity.[2] This fact, combined with an inefficient biosynthetic process for its production,[3] has stimulated considerable work recently on the synthesis of adriamycin and its analogues.[4] Some time ago, 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.[5] Despite the low yield in the case of



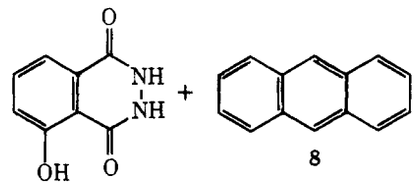
2 **3a**, X = O; b, X = *o*-C_6H_4 **4a**, 67%; b, 13.5%

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 digitopurpone (**12b**).[6]

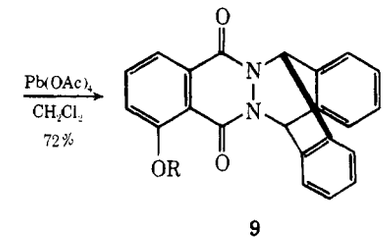


2 **5** **6**

The synthesis of the requisite benzocyclobutene-1,2-diones **2** was accomplished via McOmie's modification[7] of Rees' procedure.[8] Thus the readily available 5-hydroxy-2,3-dihydro-1,4-phthalazinedione (**7**), prepared from 3-nitrophthalic acid in four steps in 67% overall yield, was treated with lead tetraacetate in the presence of anthracene (**8**)[10] to furnish the Diels-Alder adduct **9** (R = H). The adduct **9** (R = H) could be

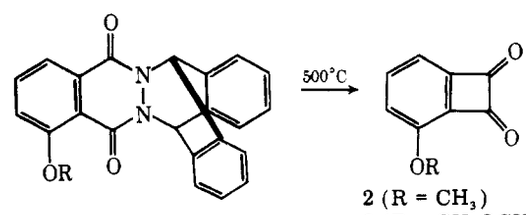


7 **8**



9

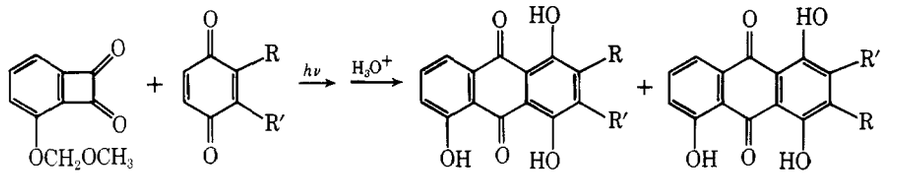
protected as its methyl or methoxymethyl ether (in yields of 67 and 89%, respectively) and then pyrolyzed in the vapor phase at 500 °C to furnish the required 3-alkoxybenzocyclobutene-1,2-dione **2** in up to 61% yield. The free phenol, **2** (R



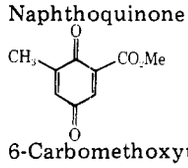
9 (R = CH_3); **9** (R = CH_2OCH_3)

2 (R = CH_3); **2** (R = CH_2OCH_3)

Table I. Photolysis of 2 with Quinones



2 10 11 12

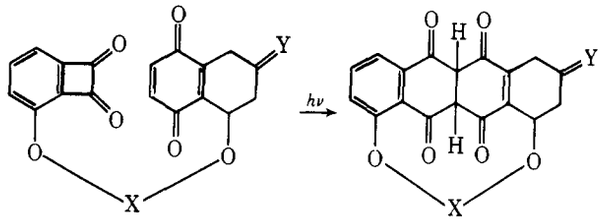
Quinone 10	Time,[a] h	Products	Yield,[b] %
a, R = R′ = H Benzoquinone	9	11a[c]	4, 8[g]
b, R = Me; R′ = H 2-Methylbenzoquinone	12	11b[d] + 12b[d] (1:1)	8
c, R = CH_2OH; R′ = H 2-Hydroxymethylbenzoquinone	9	11b[e] + 12b[e] (1:1)	9
d, R = R′ = –CH=CHCH=CH– Naphthoquinone	12	11d[f]	13.5
e  6-Carbomethoxytoluquinone	3.5		

[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 H_2 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 = CH_2OCH_3), 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 = CH_2OCH_3) is 56%].[11] Interestingly, the phenol **2** (R = H) exhibits a pK_a value of 5.8 ± 0.2, making it a very acidic phenol, though not quite as acidic as 4,5-dihydroxybenzocyclobutene-1,2-dione (pK_a = 4.48).[7]

Irradiation of the methoxymethyl ether **2** (R = CH_2OCH_3) in CH_2Cl_2 in the presence of various quinones **10a–e** furnished the expected adducts (**11a–d, 12b**) as listed in Table I. After hydrolysis 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,[12] 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 benzylic hydroxyl function in the case of **10c**) were a 1:1 mixture of the natural products, islandicin (**11b**) and digitopurpone (**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-toluquinone[13] (**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



13 (X = CO, CH_2, $SiMe_2$, etc.) 14

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 137B spectrophotometer. NMR spectra were measured on a Varian T-60 spectrometer and are reported in parts per million downfield from internal tetramethylsilane, 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-Hydroxyphthalazine-1,4-dione (9, R = H). To a stirring solution of 0.64 g (3.60 mmol) of 5-hydroxy-2,3-dihydro-1,4-phthalazinedione (**7**),[9] 0.71 g (4.00 mmol) of anthracene, and 0.5 mL of acetic acid in 35 mL of CH_2Cl_2 at 25 °C under N_2 was added 1.60 g (3.60 mmol) of lead tetraacetate in small portions every 15 min for 1.5 h. To the final dark brown mixture was added 4

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 CCl_4 to remove anthracene. Elution with CH_2Cl_2 gave 916 mg (72%) of nearly white, crystalline solid: mp 288–290 °C dec; IR (KBr) $\nu_{C=O}$ 1630, 1600 cm^{-1}; ν_{OH} 3400 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 354 (5), 179 (21) and 178 (100). Anal. Calcd for $C_{22}H_{14}N_2O_3$: C, 74.56; H, 3.98. Found: C, 74.50; H, 3.98.

Anthracene Adduct of 5-(Methoxymethyloxy)phthalazine-1,4-dione (9, R = CH_2OCH_3). 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 N_2 was added 790 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 CH_2Cl_2 and H_2O and evaporation of the CH_2Cl_2 layer left 0.67 g of crude solid which was chromatographed on SiO_2 eluting with mixtures of CH_2Cl_2 and ether to give 625 mg (89%) of white, crystalline solid: mp 244–246 °C dec; IR (KBr) $\nu_{C=O}$ 1635 cm^{-1}, ν_{C-O} 1025 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 398 (9), 192 (3), 191 (4), 179 (16), 178 (100), 177 (6), and 176 (5); NMR ($CDCl_3$) δ 3.52 (3 H, s), 5.30 (2 H, s), 7.7–7.2 (13 H, m). Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55. Found: C, 72.29; H, 4.63.

Anthracene Adduct of 5-Methoxyphthalazine-1,4-dione (9, R = CH_3). To a stirring suspension of 403 mg (1.14 mmol) of adduct **9** (R = H) in 40 mL of dry THF at 25 °C under N_2 was added 512 mg (4.56 mmol) of potassium *tert*-butoxide. The mixture was stirred at 25 °C for 40 min, and then 0.28 mL (4.56 mmol) of iodomethane was added and the mixture heated at reflux for 40 h. It was then cooled and rotary evaporated, and the solids chromatographed on SiO_2, eluting with mixtures of CH_2Cl_2 and Et_2O to give 280 mg (67%) of white, crystalline solid: mp 297–299 °C dec; IR (KBr) $\nu_{C=O}$ 1630 cm^{-1}, ν_{C-O} 1065 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 368 (6), 179 (26), 178 (100), 134 (15), 133 (5), and 104 (8). Anal. Calcd for $C_{23}H_{16}N_2O_3$: C, 74.98; H, 4.38. Found: C, 75.00; H, 4.36.

3-(Methoxymethyloxy)benzocyclobutene-1,2-dione (2, R = CH_2OCH_3). The pyrolysis apparatus was a horizontal 1.7-cm diameter quartz tube wrapped with nichrome wire over a 20-cm length. Pyrolyses were carried out at 500 °C (±20 °C) by reducing the pressure to 7 μ (±3 μ) and heating the anthracene adduct **9** (R = CH_2OCH_3) until it sublimed and passed through the tube. The solids that were trapped were chromatographed on SiO_2. Elution with CH_2Cl_2 furnished the product. From 137 mg (0.344 mmol) of **9** (R = CH_2OCH_3) there was obtained 40 mg (61%) of yellow solid: mp 80.5–82 °C; IR (KBr) $\nu_{C=O}$ 1780 cm^{-1}; NMR ($CDCl_3$) δ 3.60 (3 H, s), 5.52 (2 H, s), 7.5–7.2 (1 H, m), 7.8–7.6 (2 H, m); UV λ_{max} 413 nm (ϵ 53), 296 (3960); mass spectrum (70 eV) *m/e* (rel intensity 192 (1), 191 (2), 164 (9), 163 (12), 162 (9), 161 (90), 147 (4), 136 (2), 135 (5), 134 (57), 133 (13), 132 (4), 120 (3), 119 (14), 106 (12), 105 (100), 104 (20), 103 (8), 93 (2), 92 (3), and 91 (14). Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.19. Found: C, 62.53; H, 4.12.

3-Methoxybenzocyclobutene-1,2-dione (2, R = CH_3). Pyrolysis of anthracene adduct **9** (R = CH_3) was carried out as for **9** (R = CH_2OCH_3) and the crude solids were chromatographed on SiO_2. Elution with CH_2Cl_2 gave the product. From 126 mg of **9** (R = CH_3) there was obtained 18 mg (33%) of yellow solid: mp 112.5–113.5 °C; IR (KBr) $\nu_{C=O}$ 1780 cm^{-1}; NMR ($CDCl_3$) δ 4.16 (3 H, s), 7.6–7.0 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 162 (14), 135 (3), 134 (65), 133 (25), 106 (6), 105 (10), 104 (31), 91 (5), 78 (8), 77 (11), 76 (100), 75 (9), and 74 (8); UV λ_{max} 411 nm (ϵ 78), 299 (3690). Anal Calcd for $C_9H_6O_3$: C, 66.66; H, 3.73. Found: C, 66.59; H, 3.94.

3-Hydroxybenzocyclobutene-1,2-dione (2, R = H). A solution of 40 mg (0.208 mmol) of 3-(methoxymethyloxy)benzocyclobutene-1,2-dione (**2**, R = CH_2OCH_3), 1 mL of concentrated HCl, and 4 mL of H_2O in 30 mL of MeOH was stirred at reflux for 3 h. The solution was cooled and partitioned between CH_2Cl_2 and H_2O. The phases were separated and the aqueous layer washed with 2 × 10 mL of CH_2Cl_2. The combined organic phase was washed with 3 × 15 mL of saturated aqueous $NaHCO_3$ solution and the aqueous layer washed with 2 × 15 mL of CH_2Cl_2. The aqueous layer was then acidified with concentrated HCl to pH 1 and extracted with 3 × 15 mL of CH_2Cl_2. The organic phase was dried over Na_2SO_4 and rotary evaporated to leave 25 mg (81%) of pale yellow solid: mp 177–178 °C dec; IR (KBr) $\nu_{C=O}$ 1760 cm^{-1}, ν_{OH} 3340 cm^{-1}; NMR (acetone-d_6) δ 7.3–7.6 (m); mass spectrum (70 eV) *m/e* (rel intensity 148 (17), 121 (9), 120 (100), 119 (6), and 92 (56); UV λ_{max} 411 nm (ϵ 53), 297 (3610); pK_a = 5.8 ± 0.2. Anal. Calcd for $C_8H_4O_3$: C, 64.87; H, 2.72. Found: C, 64.69, H, 2.69.

The same procedure was utilized with the crude pyrolysate to give 56% overall yield of the phenol **2** (R = H) from **9** (R = CH_2OCH_3).

Photoreactions of 3-(Methoxymethyloxy)benzocyclobutene-1,2-dione (2, R = CH_2OCH_3). 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 CH_2Cl_2, for the period indicated in Table I. 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 251-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**, 23214-92-8; **2** (R = H), 62416-21-1; **2** (R = Me), 62416-22-2; **2** (R = CH_2OMe), 62416-23-3; **7**, 7600-08-0; **9** (R = H), 62416-24-4; **9** (R = Me), 62416-25-5; **9** (R = CH_2OMe), 62416-26-6; **10a**, 106-51-4; **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 methyl ether, 107-30-2; iodomethane, 74-88-4.

References and Notes

(1) S. Carter, *Cancer Chemother. Rep., Part 3*, **6**, 389 (1975).
(2) G. Rosen, N. Wollner, C. Jan, S. Wu, S. Hadju, W. Cham, G. D'Angio, and M. Murphy *Cancer*, **33**, 384 (1974).
(3) F. Arcamore, G. Cassinelli, G. Fantini, A. Grein, P. Orezzi, C. Pol, and C. Spalla, *Biotech. Bioeng.*, **11**, 1101 (1969).
(4) For example, see (a) T. Ross Kelly, R. Goerner, J. Gillard, and B. Prazak, *Tetrahedron Lett.*, 3869, 3873 (1976); (b) R. Gleim, S. Trenbleath, R. Mittal, and C. J. Sih, *ibid.*, 3385 (1976); (c) A. S. Kende, Y. Tsay, and J. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976); (d) W. Lee, A. Martinez, J. Smith, and D. Henry, *J. Org. Chem.*, **41**, 2296 (1976); (e) F. Arcamore, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A. Casazza, G. Pratesi, and P. Reggiani, *Cancer Treat. Rep.*, **60**, 829 (1976); (f) A. S. Kende, J. Belletire, J. Bentley, E. Hume, and J. Airey, *J. Am. Chem. Soc.*, **97**, 4425 (1975).
(5) H. Staab and J. Ipaktschi, *Chem. Ber.*, **101**, 1457 (1968).
(6) Recently an excellent regiospecific synthesis of both islandicin and digitopurpone has been reported: A. S. Kende, J. L. Belletire, J. L. Herrmann, R. F. Romanet, E. L. Hume, R. H. Schlessinger, J. Fayos, and J. C. Clardy, *Synth. Commun.*, **3**, 387 (1973).
(7) J. McOmie and D. Perry, *J. Chem. Soc., Chem. Commun.*, 248 (1973).
(8) D. Forster, J. Gilchrist, C. Rees, and E. Stanton, *J. Chem. Soc., Chem. Commun.*, 695 (1971).
(9) H. Drew and F. Pearman, *J. Chem. Soc.*, 26 (1937).
(10) R. Clement, *J. Org. Chem.*, **27**, 1115 (1962).
(11) The overall yield of **2** (R = H) from 3-nitrophthalic acid via eight steps is thus 24%.
(12) J. Finkelstein and J. Romano, *J. Med. Chem.*, **13**, 568 (1970).
(13) W. Nudenberg, A. Gaddis, and L. Butz, *J. Org. Chem.*, **8**, 500 (1943).