(M^+), 324 ($M^+ - CH_3CONH_2$), 309, 293; high resolution mass spectroscopy (*m/e*) 383.1745, calcd for $C_{22}H_{25}NO_5$ 383.1733; 324.1365, calcd for $C_{20}H_{20}O_4$ 324.1362.

(3,4-Dimethoxyphenyl)acetaldoxime (45). This compound was prepared from the aldehyde via its bisulfite addition complex by the known method.[34]

Reaction of 45 with Trimethylsilyl Iodide. The oxime **45** (97.5 mg, 0.5 mmol) in $CHCl_3$ was treated with 1 equiv of trimethylsilyl iodide at room temperature for 2 h. After workup and preparative TLC (solvent $CHCl_3$), 40 mg of the corresponding nitrile, (3,4-dimethoxyphenyl)-acetonitrile, were isolated.

3-Hydroxy-1,2:5,6-dibenzocycloocta-1,5,7-triene (49). Treatment of the ether **48**[3] (100 mg, 0.45 mmol) with 2 equiv of *n*-butyllithium, under the identical conditions as described above for the preparation of **13** from **12**, gave after preparative TLC (solvent $CHCl_3$) 83.5 mg of alcohol **49** (83.5%): mp 119-120 °C (lit.[25] mp 120-121 °C).

3-(Iodomethyl)-1,2:4,5-dibenzocyclohepta-1,4,6-triene (50). Treatment of the alcohol **49** (50 mg, 0.225 mmol) in EtOH (4 mL) with concentrated HI (2 mL) under the conditions described above for preparation of **17c** from **13** gave 87.1 mg of crude iodide **50**. The iodide could be recrystallized from ethanol. Identity was established by comparison of the NMR with that of the tetramethoxy case: NMR δ 7.2-7.4 (8 H, m), 6.95 (2 H, s), 4.34 (1 H, t, $J \approx 8.3$ Hz), 3.56 (2 H, d, $J \approx 8.3$ Hz).

Acknowledgment. We thank the National Cancer Institute and the National Science Foundation for their generous support of our synthetic program. The Bruker 200-MHz NMR instrument was purchased with funds provided by a major instrument grant from the National Science Foundation.

Simple *o*-Quinodimethane Route to (±)-4-Demethoxydaunomycinone

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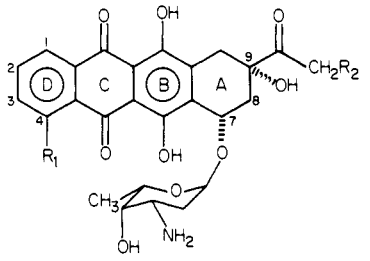
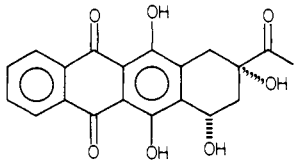
Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received August 25, 1980*

Abstract: The anthracycline antibiotics daunorubicin and adriamycin are important clinically useful drugs in the treatment of a number of human cancers. The structurally simplified synthetic analogues 4-demethoxydaunorubicin and 4-demethoxyadriamycin show much clinical promise. The synthesis of the corresponding aglycone (±)-4-demethoxydaunomycinone from the inexpensive dye intermediate quinizarin, utilizing *o*-quinodimethane intermediates, is discussed.

The anthracycline antibiotics daunorubicin (**1**) and adriamycin (**2**) are of great current interest in view of their activity against various experimental tumors, as well as their clinical effectiveness in the treatment of many types of human cancer.[1]



1, $R_1 = OCH_3$; $R_2 = H$
2, $R_1 = OCH_3$; $R_2 = OH$
3, $R_1 = R_2 = H$



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The antineoplastic acitivity of these compounds can be improved by structural modification, as shown by the recent report that the totally synthetic analogue 4-demethoxydaunorubicin (**3**) is 4-8 times more active than daunorubicin itself.[2] Although several syntheses of the corresponding aglycone 4-demethoxydaunomycinone (**4**) have been described,[3] a simple and practical route for a larger scale preparation of **4** has yet to be devised. The work reported in this paper represents our initial efforts toward the attainment of this goal.[4]

Results and Discussion

About 2 decades ago, studies in our laboratory,[5,6] as well as those of Jensen[7] and Alder,[8] showed that unstable *o*-quinodimethane intermediates could be trapped by suitable dienophiles: these early observations have since formed the basis for a powerful new technique for the synthesis of a variety of natural products from benzocyclobutene precursors.[9]

Our present synthetic strategy has centered upon the concept of constructing ring A of an anthracyclinone system by the

(1) (a) Arcamone, F.; Francheschi, G.; Crezzi, P.; Cassinelli, G.; Barbiere, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334. (b) Bernard, J.; Paul, R.; Boiron, M.; Jaquillat, C., Maral R., Eds.; "Rubidomycin"; Springer-Verlag: New York, 1969. (c) Arcamone, F.; Francheschi, G.; Penco, S. *Tetrahedron Lett.* **1969**, 1007. (d) Ghione, M. *Cancer Chemother. Rep.* **1975**, Part 3, 83.

(2) Arcamone, F.; Bernardi, L.; Giardino, P.; Patelli, B.; DiMarco, A.; Casazza, A. M.; Pratesi, G.; Reggiani, P. *Cancer Treatment Rep.* **1976**, *60*, 829.

(3) (a) Wong, C. M.; Popien, D.; Schwenk, R.; Te Raa, J. *Can. J. Chem.* **1971**, *49*, 2412. (b) Arcamone, F.; Bernardi, L.; Patelli, B.; DiMarco, A. British Patent 2 601 785 (Jan 22, 1975). (c) Suzuki, F.; Glein, R. D.; Trenbeath, S.; Sih, C. J. *Tetrahedron Lett.* **1977**, 2303. (d) Jackson, D. K.; Narashimhan, L.; Swenton, J. S., *J. Am. Chem. Soc.* **1979**, *101*, 3989. (e) Kende, A. S.; Curran, D. P.; Tsay, Y. G.; Mills, J. E. *Tetrahedron Lett.* **1977**, 3537. (f) Wiseman, J. R.; French, N. I.; Hallmark, R. K.; Chiong, K. G. *Ibid.* **1978**, 3765. (g) Kelly, T. R.; Tsong, W. G. *Ibid.* **1978**, 4457. (h) Garland, R. B.; Palmer, J. R.; Schultz, J. A.; Sollman, P. B.; Pappo, R. *Ibid.* **1978**, 3669. (i) Krohn, K.; Tolkiehn, K. *Ibid* **1978**, 4023.

(4) Kerdesky, F. A. J.; Cava, M. P. *J. Am. Chem. Soc.* **1978**, *100*, 3635.

(5) Cava, M. P.; Deana, A. A. *J. Am. Chem. Soc.* **1959**, *81*, 4266.

(6) Cava, M. P.; Deana, A. A.; Muth, K. *J. Am. Chem. Soc.* **1959**, *81*, 6458.

(7) Jensen, F. R.; Coleman, W. E. *J. Am. Chem. Soc.* **1958**, *80*, 6149.

(8) Alder, K.; Fremery, M. *Tetrahedron* **1961**, *14*, 190.

(9) (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 29.

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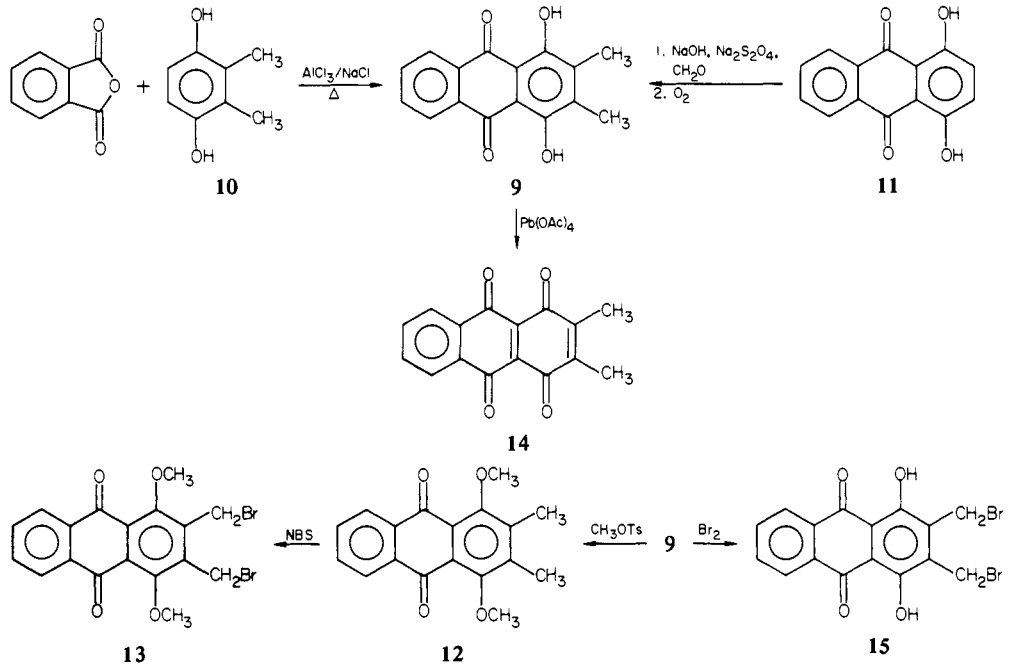
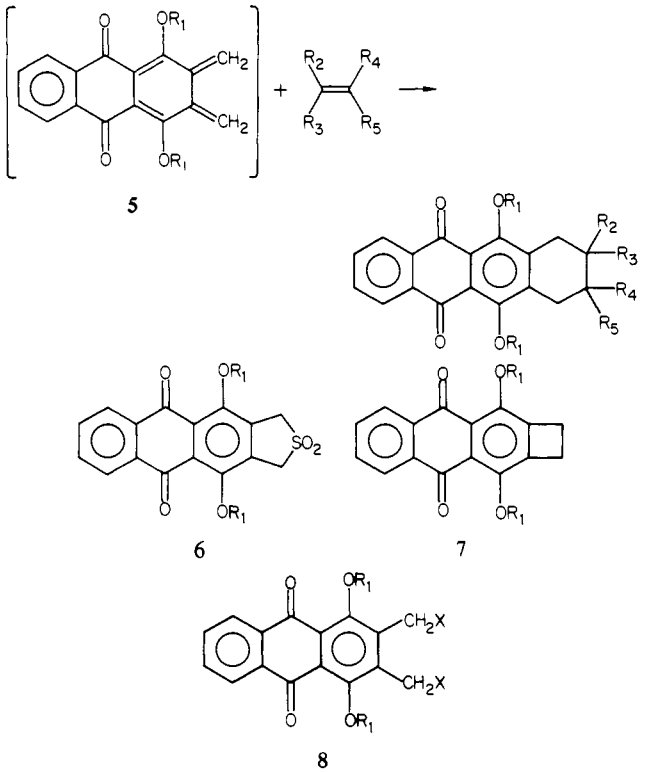
Scheme I



10 9 11 14 13 12 15

trapping of an anthraquinone-derived *o*-quinodimethane intermediate (**5**) by a dienophile, as shown below.[10] Possible precursors



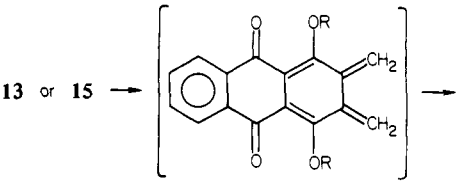
5 6 7 8

of **5** would be a sulfone (**6**), a cyclobutene (**7**), or a dihalide (**8**). Since both **6** and **7** would be most readily obtained from **8**, the synthesis and direct halogenation of several halides of this type were chosen as the subject of our initial studies.

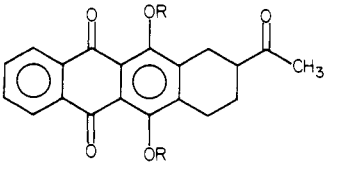
Our starting material was 1,4-dihydroxy-2,3-dimethylanthraquinone (2,3-dimethylquinizarin, **9**), which we initially prepared in good yield (81%) by the one-step condensation of phthalic anhydride with 2,3-dimethylhydroquinone (**10**)[11] in a melt of $AlCl_3/NaCl$ at 190 °C (Scheme I). Quinone **9** had already been reported by Marschalk in 1936 as the product of the reductive alkylation of quinizarin (**11**) by formaldehyde, followed by air oxidation.[12] We have found Marschalk's synthesis, which can be readily scaled up, to be the most practical procedure, since it employs only cheap starting materials and gives a product which is easily purified. O-Methylation of **9** was sluggish and was best carried out by using methyl tosylate and K_2CO_3 in a mixture of dimethylformamide (DMF) and 2-butanone to give (81%) the yellow dimethyl ether **12**, mp 159–160 °C. Light-catalyzed NBS bromination of **12** afforded (78%) the corresponding α,α'-dibromo derivative **13**, mp 171–173 °C.

Lead tetraacetate oxidation of 2,3-dimethylquinizarin (**9**) takes place readily to give, in almost quantitative yield, the corresponding diquinone **14**.[13] Photochemical bromination of **9** (best with bromine in tetrachloroethylene) does not lead to the formation of **14**, however; only side-chain bromination takes place with the formation of the red crystalline dibromide **15** (mp 290 °C dec) in good yield.

Both of the dibromides **13** and **15** reacted with activated zinc



16, R = CH_3
17, R = H



18, R = CH_3
19, R = H

in DMF solution to generate the corresponding *o*-quinodimethanes

(10) Wiseman et al.[3f] have reported an alternate *o*-quinodimethane approach to anthracyclinones in which ring C is constructed in the Diels–Alder step.

(11) Nilsson, J. L. G.; Sievertsson, H.; Selander, H. *Acta Pharm. Suec.* **1968**, *5*, 215.

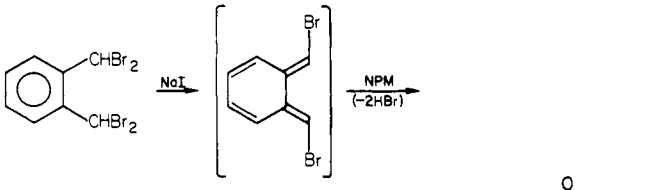
(12) Marschalk, C.; Koenig, F.; Ouroussoff, N. *Bull. Soc. Chim. Fr.* **1936**, *3*, 1545.

(13) Gorelik, M. U.; Zaitseu, B. E. *Probl. Poluch. Poluprod. Prom. Org. Sin. Akud. Nauk, SSSR, Otd. Obstach., Tekh., Khim.* **1967**, 212.

(16 and 17), as evidenced by their successful trapping by excess methyl vinyl ketone to give the tetracyclic ketones **18** and **19**, respectively. In our initial experiments yields of **18** (from **13**) as high as 52% were obtained, but subsequently this yield could not be reproduced, and often none of the desired product could be isolated. The formation of **19** from dibromide **15** was somewhat less capricious, and yields up to 28% were not uncommon. The course of these reactions seemed to be dependent in a complex way upon such factors as solvent purity, rate of stirring, and especially the quality of each batch of zinc employed. The poorest reactions were those which quickly developed a purple color, suggestive of reduction of the quinizarin system to the leuco form by the zinc.

Our attention then turned to seeking a method for the generation of *o*-quinodimethane **17** from dibromide **15** under homogeneous reaction conditions, using a reagent which would be incapable of reducing the anthraquinone carbonyl groups. Sodium iodide seemed to be a potentially ideal reagent for this purpose.

Many years ago, we demonstrated that the reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene with sodium iodide leads to the clean generation of α,α'-dibromo-*o*-quinodimethane (**20**), as evidenced



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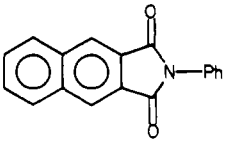

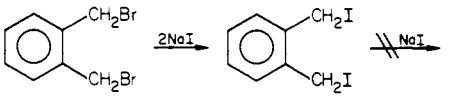

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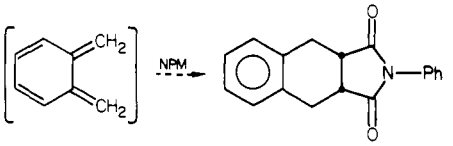
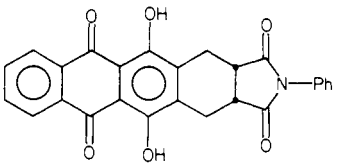


by the efficient trapping of this intermediate by various dienophiles, such as *N*-phenylmaleimide (NPM).[6] On the other hand, the simple α,α'-dibromo-*o*-xylene reacts readily with iodide ion to give the corresponding diiodide (**21**).[14] Although the latter undergoes a slow thermal decomposition with the liberation of iodine, no evidence for the generation of the parent *o*-quinodimethane could be obtained by trapping experiments with NPM,[15] an observation which we have now confirmed. Apparently, a certain degree of stabilization of the *o*-quinodimethane system by appropriate substituents is necessary if this system is to be generated from a benzenoid precursor under the mild conditions of a Finkelstein iodide elimination.

We were gratified to find that the tricyclic *o*-quinodimethane **17** is in fact sufficiently stabilized to be generated under very mild conditions from dibromide **15**. Thus, the reaction of **15** with a large excess of sodium iodide in dimethylacetamide (DMA) in the presence of NPM at 65 °C for 45 min afforded the pentacyclic imide **22** in about 80% yield. The corresponding debromination of **15** in the presence of excess methyl vinyl ketone was studied in some detail. The reaction, which was essentially complete after only 30 min at 69 °C, gave the important anthracyclinone intermediate **19** in reproducible yields of 63–65%; the product could be purified by a simple crystallization. The dimethoxy dibromide **13** similarly afforded ketone **18** in 73% yield. Ketone **18** was also obtained (55%) by direct O-methylation of ketone **19**.

(14) Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528.
(15) Mitchell, M. J. Thesis, The Ohio State University, 1960.



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Oxygenation of the anion of **18** at −20 °C in the presence of triethyl phosphite **15** gave, in 55% yield,[16] the corresponding 9-hydroxy derivative **23**; aluminum chloride demethylation of **23** afforded, in high yield, 4-demethoxy-7-deoxydaunomycinone **24**. The conversion of **23** and **24** to 4-demethoxydaunomycinone (**4**) has already been described;[2,3a,e] our synthesis of these compounds constitutes a new synthesis of **4**.

Finally, we have investigated the direct synthesis of **24** by trapping the quinodimethane **17** with 3-[(trimethylsilyl)oxy]-3-buten-2-one (TBO), followed by acetic acid desilylation. The best results were obtained by iodide debromination of dibromide **15** in the presence of a large excess of TBO. Even under these conditions, however, the yield of **24** was only 12%, reflecting the somewhat sluggish behavior of TBO as a dienophile.[17] A highly insoluble byproduct from this reaction proved to be the quinodimethane dimer **25**. This compound also constituted the major byproduct in the synthesis of **19** from **15**.

In view of the ready accessibility of the tetracyclic ketones **18** and **19**, we have initiated an extensive study of alternate and improved methods for the stereoselective introduction of hydroxyl groups at C-7 and C-9. the successful solution of this study would indeed provide a practical route to 4-demethoxydaunomycinone (**4**).

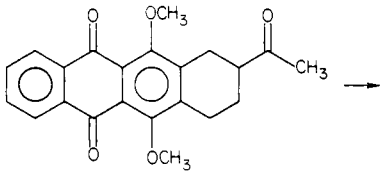
Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass, infrared (KBr), and ultraviolet spectra were determined, with Perkin-Elmer 270B, 137, and 202 spectrometers, respectively. NMR spectra were recorded on Varian-60, EM-360, and Bruker 250-MHz FT instruments ($CDCl_3$ solutions (unless otherwise stated) containing Me_4Si internal standard) and are reported in δ units. Elemental analyses were performed by Galbraith Laboratories. All organic extracts were washed and dried over anhydrous Na_2SO_4 prior to filtration and evaporation. Zinc dust was activated by stirring with saturated NH_4Cl solution, followed by decantation and successive washings with water, ethanol, ether, and DMF.

1,4-Dihydroxy-2,3-dimethylanthraquinone (9). Method A. A mixture of anhydrous aluminum chloride (56 g) and sodium chloride (10 g) was melted in an Erlenmeyer flask at 160 °C. The melt was allowed to cool to 140 °C and an intimate mixture of phthalic anhydride (7 g) and 2,3-dimethylhydroquinone (6 g) was added. The reaction mixture was heated rapidly to 190 °C and kept at that temperature for 2 min. The resulting red melt was cooled, added to ice and hydrochloric acid (25 mL), and heated on a steam bath for 2 h. The resulting red precipitate was filtered, dried, and crystallized from acetic acid to afford **9** as red needles (10.8 g, 81%): mp 152–153 °C (lit.[11] mp 153 °C); NMR δ 2.35 (s, 6 H, 2 CH_3), 7.88 (m, 2 H, Ar), 8.37 (m, 2 H, Ar), 13.69 (s, 2 H, OH).

Method B (Marschalk Reaction). Sodium dithionite (100 g, 0.57 mol) was dissolved in 1.5% sodium hydroxide solution (5 L). Quinizarin (50 g, 0.21 mol) was added to the basic dithionite solution and the reaction mixture was allowed to stand under nitrogen for 30 min. Next, 37% formaldehyde solution (100 g), diluted with water (300 mL), was added. The reaction mixture was then heated at 90 °C for 1 h. After the mixture cooled to room temperature, a current of air was passed into the solution for 16 h. The reddish violet precipitate was recovered, washed with cold water, and added to water (4 L). The pH of the system was adjusted to 4 by addition of concentrated hydrochloric acid, the suspension was heated for 1 h on a steam bath and then cooled, and the red precipitate was collected. The crude dimethylquinizarin (**9**) was dried in an oven. A methylene chloride solution of crude **9** was filtered through a short column of Florisil to purify the compound. Evaporation of the organic solvent gave pure red needles of 1,4-dihydroxy-2,3-dimethylanthraquinone (**9**) (41.7 g, 74%).

(16) The procedure followed was that employed with representative 20-keto steroids: Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294.
(17) Ardecky, R. J.; Kerdesky, F. A. J.; Cava, M. P. *J. Org. Chem.*, in press.



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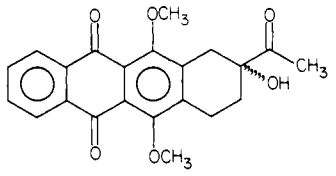

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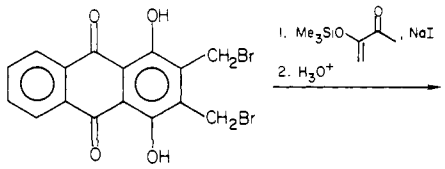

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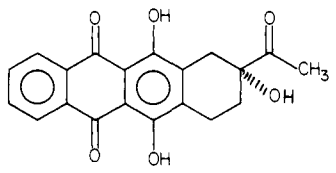

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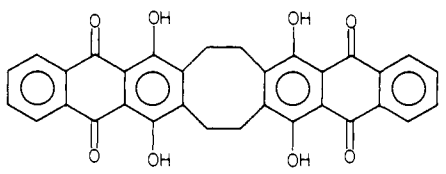

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1,4-Dimethoxy-2,3-dimethylanthraquinone (12). A mixture of the anthraquinone **9** (5 g), anhydrous potassium carbonate (20 g), dry DMF (100 mL), dry 2-butanone (100 mL), and methyl tosylate (25 mL) was stirred under reflux for 3 h. The initial reddish black color turned yellowish orange. Excess water was added to the cooled mixture, and the yellow precipitate was filtered, washed, and dried. Crystallization from 95% ethanol yielded the dimethyl ether **12** as yellow needles (4.5 g, 81%): mp 159–160 °C; NMR δ 2.33 (s, 6 H, 2 OMe), 3.88 (s, 6 H, 2 OMe), 7.70–8.38 (m, 4 H, Ar); UV-vis, $\lambda_{max}^{ethanol}$ 240 (sh) (log ϵ 4.45), 256 (4.59), 362 nm (3.71); MS *m/e* 296 (M^+, 100), 265 (44), 234 (16). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41. Found: C, 72.84; H, 5.50.

1,4-Dimethoxy-2,3-bis(bromomethyl)anthraquinone (13). A mixture of anthraquinone **12** (6 g), *N*-bromosuccinimide (7.2 g), and benzoyl peroxide (~0.4 g) in CCl_4 (300 mL) was refluxed with irradiation, using a sunlamp for 6 h. After the mixture cooled, the succinimide was filtered off, and the solvent was evaporated in vacuo. The residue (8.4 g) upon crystallization from CH_2Cl_2–hexane furnished the dibromide **13** as bright yellow needles (7.2 g, 78.4%): mp 174–176 °C; NMR δ 4.09 (s, 6 H, 2 OMe), 4.80 (s, 4 H, 2 CH_2Br), 7.73–8.40 (m, 4 H, Ar); UV-vis, λ_{max}^{MeCN} 240 (sh) (log ϵ 4.39), 252 (4.46), 372 nm (3.70); MS *m/e* 454 (M^+, 100), 374 (80), 294 (100). Anal. Calcd for $C_{18}H_{14}Br_2O_4$: C, 47.58; H, 3.08; Br, 35.24. Found: C, 47.46; H, 3.08; Br, 35.54.

2,3-Dimethylanthra-1,4,9,10-diquinone (14). Anthraquinone **9** (268 mg) and lead tetraacetate (540 mg) were dissolved in toluene (500 mL). The solution was heated at 100 °C for 6 h. After the mixture cooled, the organic solvent was filtered and washed with dilute acetic acid and water. the solvent was removed under reduced pressure. Recrystallization of the solid residue from benzene/petroleum ether gave yellow needles of 2,3-dimethyl-1,4,9,10-anthradiquinone (**14**) (227 mg, 85%): mp 192–193 °C (lit.[12] mp 193 °C); NMR δ 2.43 (s, 6 H, 2 CH_3), 7.25–7.91 (m, 4 H, Ar); IR 1680 (C=O), 1645 (C=O) cm^{-1}.

1,4-Dihydroxy-2,3-bis(bromomethyl)anthraquinone (15). A solution of bromine (4 mL) in tetrachloroethylene (40 mL) was added dropwise to a gently refluxing solution of 2,3-dimethylquinizarin (**9**, 10 g) in tetrachloroethylene (500 mL) containing benzoyl peroxide (0.5 g) under irradiation with a sunlamp. Irradiation was continued for 20 h, at the end of which, upon cooling, the dibromide **15** separated as dark red chunky crystals, mp 285 °C dec (13.2 g, 82.5%), sufficiently pure for the next reaction. A sample recrystallized from excess benzene melted at 290 °C dec: NMR δ 4.61 (s, 4 H, 2 CH_2Br), 7.71–8.30 (m, 4 H, Ar), 13.69 (s, 2 H, 2 OH); UV-vis, λ_{max}^{MeCN} 225 (log ϵ 4.54), 285 (4.00), 468 nm (3.96); MS *m/e* 426 (M^+, 35), 346 (35), 266 (100). Anal. Calcd for $C_{16}H_{10}Br_2O_4$: C, 45.07; H, 2.3; Br, 37.56. Found: C, 44.87; H, 2.3; Br, 37.85.

8-Acetyl-7,8,9,10-tetrahydro-6,11-dimethoxy-5,12-naphthacenedione (18). Method A. Dibromide **13** (230 mg) was added portionwise over a period of 30 min to a mixture of methyl vinyl ketone (300 mg), hydroquinone (10 mg), and activated zinc dust (300 mg) in dimethylformamide (10 mL). The reaction mixture was stirred for 6 h at 25 °C. At 1-h intervals, fresh zinc dust (50 mg) was added to the system. The product was worked up by filtering off the zinc and evaporating the organic solvent under reduced pressure. The solid residue was washed with water and dried. Chromatography (SiO_2, $CHCl_3$) and crystallization from acetic acid afforded ketone **18** as yellow needles (90 mg, 52%): mp 147–149 °C; NMR δ 1.60 (m, 2 H, CH_2), 2.10 (m, 1 H, CH), 2.27 (s, 3 H, $COCH_3$), 3.89 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 7.71–8.18 (m, 4 H, Ar); UV-vis $\lambda_{max}^{CH_3CN}$ 228 (log ϵ 4.57), 258 (4.56), 275 (4.48), 360 nm (3.87); MS *m/e* 364 (M^+, 100), 336 (15), 321 (37). Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.52; H 5.5. Found: C, 72.82; H, 5.5.

Method B. To a stirred solution of dibromide **13** (1.8 g) and excess methyl vinyl ketone (6 mL) in DMA (60 mL) at 65–70 °C was added an excess of sodium iodide (10 g) in one lot. After stirring at 70 °C for 1 h, the dark mixture was cooled and diluted with water (200 mL). The dark yellow precipitate was filtered and taken up in CH_2Cl_2. The organic extract was shaken with aqueous sodium thiosulfate and water successively. Evaporation, followed by crystallization of the residue from methanol, furnished ketone **18** (1.1 g, 75.3%), mp 145–146 °C, identical with the sample prepared by method A as described.

Adduct 22. To a stirred mixture of dibromide **15** (0.45 g) and *N*-phenylmaleimide (0.20 g) in DMA (10 mL) at 65–70 °C was added sodium iodide (1.5 g) in one portion. After the mixture was heated and stirred at 65–70 °C for 45 min, it was cooled and diluted with water carefully to the crystallization point. The red crystals were filtered under suction, dried, and recrystallized from 1,2-dichlorobenzene to yield adduct **22** (350 mg, 75.4%): mp >290 °C dec; IR 5.70 μm >CO; MS *m/e* 439 (M^+, 100), 292 (68), 274 (63).

8-Acetyl-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (19). Method A. Dibromide **15** (426 mg) was added portionwise over a period of 5 min to a mixture of methyl vinyl ketone (1.0 g), activated zinc dust (1.0 g), and 10 mL of dry DMF. The reaction mixture was stirred for 30 min at 25 °C, and the zinc was filtered off. The remaining solution was added to 100 mL of H_2O, and the precipitate was filtered and dried. Chromatography (SiO_2, CH_2Cl_2–10% EtOAc) and recrystallization from acetic acid yielded ketone **19** as red needles: mp 198–202 °C; NMR δ 1.90 (m, 2 H, CH_2), 1.95 (m, 1 H, CH), 2.31 (s, 3 H, $COCH_3$), 2.75 (m, 2 H, benzylic), 3.10 (m, 2 H, benzylic), 7.80 (m, 2 H, Ar), 8.30 (m, 2 H, Ar), 13.49 (s, 1 H, OH), 13.52 (s, 1 H, OH); UV-vis $\lambda_{max}^{CH_3CN}$ 243 (log ϵ 3.06), 252 (3.07), 286 (2.40), 330 (1.78), 449 (2.35), 475 (2.45), 507 nm (2.26); MS *m/e* 336 (M^+, 100), 293 (100). Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.41; H, 4.80. Found: C, 71.33; H, 4.84.

Method B. To a stirred mixture of dibromide **15** (8.52 g) and methyl vinyl ketone (50 mL) in DMA (350 mL) at 65–70 °C was added excess sodium iodide (40 g) in one lot. After 30 min, the dark mixture was poured into water and the red-orange precipitate was filtered and washed with water under suction. It was then extracted into glacial acetic acid (~400 mL), filtered free of highly insoluble material (1 g), and diluted with water cautiously to the crystallization point. Ketone **19** (4.65 g, 69.2%) crystallized in small red needles, mp 198–202 °C dec and was identical with a sample prepared by method A.

The acetic acid insoluble material was crystallized from 1,2-dichlorobenzene to furnish dimer **25**, mp >300 °C (0.7 g; 13%) UV-vis $\lambda_{max}^{CH_2Cl}$ 249 (log ϵ 3.02), 254 (3.07), 283 (2.81), 405 (2.49), 425 (2.54), 478 (2.45), 511 nm (3.1); MS *m/e* 532 (M^+, (100), 514 (30), 504 (20), 266 (45). Anal. Calcd for $C_{32}H_{20}O_8$: 532.1158. Found: 532.1156.

Methylation of 19. A mixture of ketone **19** (0.336 g), anhydrous potassium carbonate (4 g), and methyl tosylate (2 mL) in DMF/2-butanone (1:1, 50 mL) was stirred under reflux for 1.5 h. The dark brown mixture was poured into water and the precipitate was filtered, washed, and extracted into CH_2Cl_2. The dried, filtered extract was passed through a short column of alumina, collecting the first yellow fraction. Crystallization from methanol of the residue from this fraction afforded ketone **18** (0.187 g, 55.6%), mp 145–146 °C.

8-Acetyl-8-hydroxy-7,8,9,10-tetrahydro-6,11-dimethoxy-5,12-naphthacenedione (23). Sodium *tert*-butoxide (50 mg, 4 mmol) was dissolved in *tert*-butyl alcohol (1 mL) and dimethylformamide (4 mL). To this solution was added freshly distilled triethyl phosphite (1 mL) in

dimethylformamide (4 mL). After the mixture was cooled to -20 °C, oxygen was bubbled through it and 8-acetyl-7,8,9,10-tetrahydro-6,11-dimethoxy-5,12-naphthacenedione (**18**) (150 mg, 2.5 mmol) in dimethylformamide was added. After 1 h, the reaction mixture was acidified with acetic acid and poured into water and the precipitate was collected. The crude residue was chromatographed (SiO_2, 2% CH_3OH-$CHCl_3$) and recrystallized from methanol to give pale yellow needles of 8-acetyl-8-hydroxy-7,8,9,10-tetrahydro-6,11-dimethoxy-5,12-naphthacenedione (**23**) (80 mg, 55%): mp 184-186 °C (lit.[3a] mp 184-186 °C); NMR δ 2.27 (s, 3 H, $COCH_3$), 3.09 (m, 4 H, benzylic), 1.80 (s, 1 H, OH), 3.85 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 7.66-8.27 (m, 4 H, Ar); IR 3510 (OH), 1710 (C=O), 1670 (C=O), 1600 (Ar) cm^{-1}; MS *m/e* 380 (M^+, 18), 362 (21), 337 (100).

8-Acetyl-6,8,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (24). Method A. Hydroxyketone **23** (38 mg) was dissolved in benzene (25 mL) to which aluminum chloride (67 mg, 0.5 mmol) was added. The reaction mixture was stirred at room temperature for 16 h and poured into water. The benzene extract was evaporated. Recrystallization of the residue from methanol afforded red needles of 4-demethoxy-7-deoxydaunomycinone (**24**) (33 mg, 94%): mp 160-162 °C (lit.[3e] mp 160-162 °C); NMR δ 2.40 (s, 3 H, $COCH_3$), 2.99 (m, 4 H, benzylic), 1.96 (m, 2 H, aliphatic), 3.71 (s, 1 H, OH), 7.84 (m, 2 H, Ar), 8.36 (m, 2 H, Ar), 13.54 (s, 2 H, OH); IR 3510 (OH), 1710 (C=O), 1628 (C=O), 1585 (Ar); MS *m/e* 352 (M^+, 17), 334 (18), 309 (100), 291 (25). The synthesized **24** was identical (IR, TLC, MS, mp) with an authentic sample of **24** supplied by Dr. A. S. Kende of the University of Rochester.

Method B. To a mixture of dibromide **15** (430 mg) and TBO (1.5 mL) in DMA (25 mL) was added sodium iodide (2 g). After 1 h at 70 °C, the mixture was poured into aqueous acetic acid and warmed on a steam bath. The resulting red precipitate was extracted into chloroform and chromatographed (SiO_2, $CHCl_3$/$CHCl_3$-EtOAc (5%)) to yield the hydroxy ketone **24** (42.2 mg, 12%), mp 190-193 °C. The mass and NMR spectra of this sample were identical with those of the sample, mp 160 °C, obtained in method A.

The chloroform-insoluble portion was recrystallized from 1,2-dichlorobenzene to yield dimer **25**, mp >300 °C (100 mg).

Reaction of *o*-Xylylene Dibromide and NPM in the Presence of NaI. A mixture of *o*-xylylene dibromide (0.56 g) and NPM (0.5 g) in DMA (10 mL) at 70 °C was treated with NaI (2 g). Monitoring of aliquots at intervals showed no trace of the expected product by TLC against a comparison sample. Workup of the dark mixture at the end of 5 h gave a dark intractable powder, traces of the diiodide, and NPM.

Acknowledgment. This investigation was supported by Grant CA-24199, awarded by the National Institutes of Health.

Lewis Acid Promoted Decomposition of Unsaturated α-Diazo Ketones. 1. An Efficient Approach to Simple and Annulated Cyclopentenones

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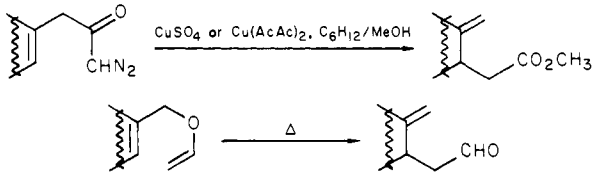
Abstract: The preparation and Lewis acid promoted decomposition of some 24 β,γ- and γ,δ-unsaturated α-diazo ketones are described. The resulting products, summarized in Tables I-III, were found to be simple and annulated cyclopentenone derivatives. In addition, the first examples of polyolefinic cationic cyclization initiated by the α-diazo ketone functionality are described.

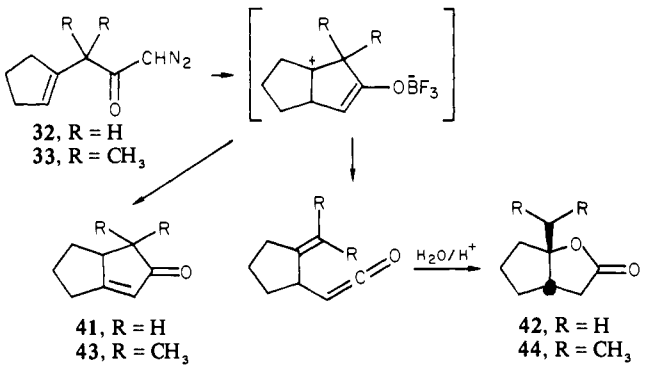
Introduction

During the past several years we have engaged in a systematic study of the chemistry of β,γ-unsaturated diazo ketones. Two principal discoveries have emanated from this effort. First, we observed that β,γ-unsaturated diazo ketones in the presence of a copper catalyst [i.e., $CuSO_4$ or $Cu(AcAc)_2$] efficiently led, via



a novel skeletal rearrangement, to γ,δ-unsaturated acid derivatives.[2,3] This transformation, a synthetic alternative to the Claisen rearrangement of enol vinyl ethers, was termed by us the vinylogous Wolff Rearrangement. Second, we demonstrated that β,γ-unsaturated diazo ketones are synthetically useful precursors of simple[4] and annulated[5] cyclopentenone derivatives, as well as

Scheme I



polycyclic[6] cyclopentanoid systems. That is, the *α-diazo ketone functionality represents an effective initiator of both mono- and polyolefinic cationic cyclization.*

In this, the first of three full accounts of our work in this area, we record the utility of the acid-promoted decomposition of β,-

(1) Camille and Henry Dreyfus Teacher-Scholar, 1978-1983; Recipient of a National Institutes of Health Career Development Award, 1980-1985.
(2) A. B. Smith, III, *J. Chem. Soc., Chem. Commun.*, 695 (1974). Also see J. P. Lokensgard, J. O'Dea, and E. A. Hill, *J. Org. Chem.*, **39**, 3355 (1974).
(3) A. B. Smith, III, B. H. Toder, and S. J. Branca, *J. Am. Chem. Soc.*, **98**, 7456 (1976).
(4) A. B. Smith, III, S. J. Branca, and B. H. Toder, *Tetrahedron Lett.*, 4225 (1975).
(5) A. B. Smith, III, *J. Chem. Soc., Chem. Commun.*, 274 (1975).
(6) A. B. Smith, III, and R. K. Dieter, *J. Org. Chem.*, **42**, 396 (1977).

0002-7863/81/1503-1996$01.25/0