Timothy B. Patrick of the Chemistry Department, Southern Illinois University at Edwardsville, and the technical assistance of Mr. Mitch Sasa.

Registry No.—1, 64-85-7; 2, 58958-13-7; 3, 58958-14-8; 4, 58958-15-9; 5, 58958-16-0; 6, 58958-17-1; 8, 58958-18-2; 9, 58958-19-3; *p*-toluenesulfonyl chloride, 98-59-9; 2-mercaptoethanol, 60-24-2.

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Daunomycinone Analogues via the Diels–Alder Reaction. Synthesis and Chemistry of Some 6,11-Dihydroxy-5,12-naphthacenediones[1]

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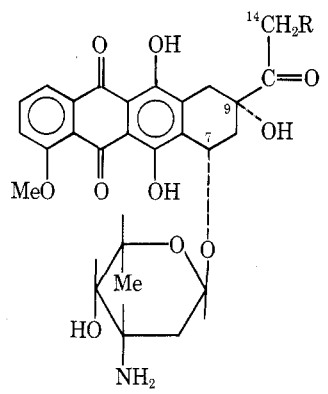
Received May 21, 1975

Quinizarinquinone reacts with 1,3-butadiene and 1-acetoxy-1,3-butadiene, but not 2-methoxy-1,3-butadiene, mainly at the external double bond to give end adducts **5a** and **5b**, respectively. Their transformation into, and the chemistry of, various dihydroxynaphthacenedione derivatives are described. These include **13d** (a simplified aglycone of daunomycinone), the 5,6,11,12-tetramethoxynaphthacenes, **17** and **19a**, and the oxidative demethylation of **17** to a 5,6,11,12-naphthacenetetrone, **18**, as well as the dihydroxytrione **22b**.

The anthracycline antibiotics daunorubicin (**1**) and adriamycin (**2**) have shown promise for clinical use against a variety of tumors, including solid ones.[2] In addition, daunorubicin benzhydrazone (**3**, methyl ketone O of **1** replaced by $NNHCOC_6H_5$) has clinical activity against acute myeloblastic and lymphoblastic leukemia.[3] Thus, various changes in this system appear compatible with retention of antitumor properties.



1, R = H, daunorubicin
2, R = OH, adriamycin

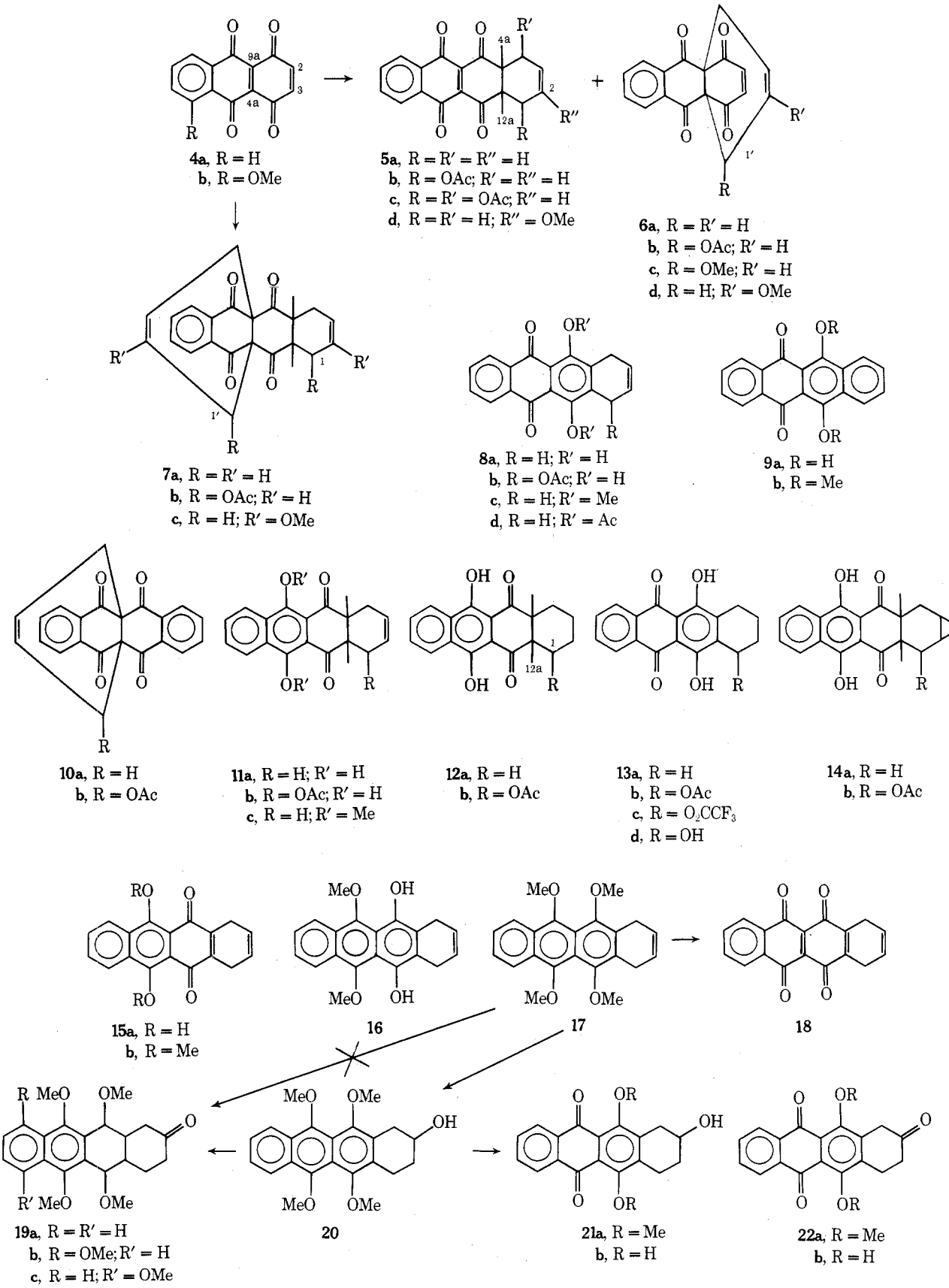
A number of derivatives at the ketone and amine functions of daunorubicin and adriamycin synthesized in our laboratories[4] and elsewhere[5,6] show a modified spectrum of both toxicity and antitumor activity against various experimental tumors in mice. These results led us to examine other structural variations and also routes that may lead to a synthesis of **1** and **2**.

This paper reports some studies on (1) the Diels–Alder reaction as a route to the 6,11-dihydroxy-5,12-naphthacenedione ring system of **1** and **2**, (2) some chemistry of, and blocking methods for, the quinizarin system of these rings, (3) an assessment of this route to the aglycones of **1** and **2** and their analogues.

The Diels–Alder reaction of quinizarinquinone (**4a**) with suitable butadienes offers a possible quick entry into the dihydroxynaphthacenedione ring system if addition occurs at the C-2 double bond. Inhoffen et al.[7] studied the reaction of several dienes with **4** and observed that the internal double bond competed with the double bond at C-2. Only with 1,4-diacetoxybutadiene was any end adduct **5c** isolated. In the other cases, they found that the formation of an internal adduct (e.g., **6c**) or diadduct (e.g., **7b**[8] or an isomer; isolated as **10b**) predominated. We find that under proper reaction conditions, the desired end adducts of structure **5** may become the predominant products for some, but not all, butadienes.

Reaction of quinizarinquinone (**4a**) with excess 1,3-butadiene in hot benzene for several hours afforded the red end adduct **5a** as the main product, the pale-beige internal adduct **6a** as a minor product, and only TLC and mass spectral indications of the diadduct **7a**. Unlike butadiene, excess 1-acetoxy-1,3-butadiene[9] reacted with **4a** in hot benzene to give mainly the diadduct **7b**, essentially as reported.[7] However, **4a** and a limited excess of 1-acetoxy-1,3-butadiene reacted in acetonitrile to afford primarily **5b**,[8] together with some internal adduct **6b**[8] and some diadduct **7b**.

The reaction of **4a** with 2-methoxybutadiene was disappointing. Under a wide variety of conditions, the major product was the center adduct **6d**, accompanied by some diadduct **7c**. The desired end adduct **5d** was never formed in sufficient quantity to warrant attempts at its separation from the major product **6d**. Compound **5d** is wanted as the precursor to the versatile ketone **22b**. Thus the reaction of butadienes with **4** cannot always be directed to give the end ad-



duct by choice of reaction conditions. The products formed depend also on the nature of the substituents of the butadiene.[10]

The structural assignments in the above series of Diels–Alder reactions were based on the chemistry and spectral properties of the products. When the end adduct **5a** was heated in xylene, it tautomerized to the quinizarin form **8a.** Adduct **5a** also could be aromatized to **9a.** In the acetoxybutadiene series, the end adduct **5b** readily lost acetic acid and aromatized to **9a** under a wide variety of conditions. Only by carefully heating **5b** in acetonitrile containing molecular sieves was tautomerization to the quinizarin form, **8b,** achieved. Heating the diadduct **7b** in xylene and acetic acid caused aromatization to **10b.**[7] In contrast to **5b,** the internal adduct **6b** was only slowly changed by hot methanolic sodium methoxide to give anthraquinone.

Table I. NMR Data[a]

Compd	Allyl H	Vinyl H	H-4a,12a	Other
4a		6.90 s 2[b,c]		
5a	2.37 m 4	5.67 m 2	3.51 m 2	
5b	2.0–2.3 m 2	6.00 m 2	3.62 m 2	1.68 s 3 OAc
	5.37 m 1			
6a	2.66 d 4	5.72 t 2		
		6.78 s 2[b]		
6b	2.12 m 1[d]	6.64 d 1[b,e]		1.88 s 3 OAc
	3.24 m 1[d]	7.11 d 1[b,e]		
	6.06 m 3			
6d	2.70 m 4	4.60 t 1		3.50 s 3 OMe
		6.79 s 2[b]		
7b	1.7–4.0 m 6[f]	5.97 m 4	*f*	1.27 s 3 OAc
	5.72 m 2			1.88 s 3 OAc
8c	3.48 d 4	5.92 t 2		3.92 s 6 OMe
8d	3.34 br s 4	5.87 br s 2		2.51 s 6 OAc
10b	1.5–3.7 m 2	6.05 m 2		1.28 s 3 OAc
	6.18 m 1			
11a	2.45 m 4	5.72 m 2	3.30 m 2	13.35 s 2 OH[g]
11b	1.5–3.2 m 2	6.06 m 2	3.42 m 2	1.40 s 3 OAc
	5.54 m 1			13.08 s 1 OH
				13.52 s 1 OH
11c	2.4–3.1 m 6[f]	5.78 m 2	*f*	4.07 s 6 OMe
12b	1.5–3.0 m 6[h]		3.22 m 2	1.42 s 3 OAc
	5.35 m 1[i]			13.30 s 1 OH
				13.60 s 1 OH
14b	5.68 m 1[i]			1.43 s 3 OAc
	1.5–3.32 m 6[h]			13.00 s 1 OH
				13.50 s 1 OH
15b	3.20 s 4	5.80 s 2		4.02 s 6 OMe
16	3.52 d 4	6.01 m 2		9.55 s 2 OH[g]
17	3.62 d 4	6.04 m 2		3.86 s 6 OMe
				4.00 s 6 OMe

[a] See Experimental Section for details. Results are given in the order δ, multiplicities and number of protons; and s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Aromatic protons are omitted. [b] Quinone H-2, 3 protons. For 1,4-benzoquinone, these appear at δ 6.72. [c] Acetone-d_6 was solvent. [d] $J_{4'}$ geminal = 18 Hz. [e] $J_{2,3}$ = 10 Hz. [f] These 6 include 4 allyl and 2 H-4a,12a protons. [g] All OH in table are phenolic OH. All are chelated with quinone except those for **16** which are hydrogen bonded to OMe. [h] These include all other aliphatic protons except those listed. [i] H-1 proton.

The ir spectra of **5a** and **5b** had carbonyl adsorption at 5.8–6.0 μ instead of the chelated hydroxy quinone absorption at 6.1–6.3 μ shown by **8a, 8b,** and quinizarin. The NMR spectra of both **5a** and **5b** showed clearly the protons H-4a and H-12a and lacked the phenolic protons of quinizarin, which are chelated with the quinone oxygens. The NMR spectra of the internal adducts **6a, 6b,** and **6d** clearly showed the H-2 and H-3 protons typical of quinones that were absent from the NMR spectra of **5a** and **5b.** Table I presents the NMR data. The ir spectra of **6a** and **6b** are distinguishable from those of **5a** and **5b,** although they all show carbonyl bands in the same region. The mass spectral fragmentation patterns are also distinctive and helpful in making the structural assignments. Thus, end adduct **5b** tends to lose acetic acid to give **9a,** whereas internal adduct **6b** tends to undergo a reverse Diels–Alder reaction that ultimately gave quinizarin while losing acetic acid to a lesser extent. Likewise, **6d** tends to reverse to quinizarin.

We next chose to demonstrate that **5b** could be converted into the trihydroxynaphthacenedione **13d** that had been prepared previously in our laboratories.[11] Compound **8b** could not be reduced successfully to **13b;** acetic acid was eliminated rapidly to form **9a** under all the reaction conditions studied. However, **5b** rapidly absorbed 1 mol of hydrogen with a variety of catalysts to give **11b** in which the double bond still remained at C-2. Introduction of 2 mol of hydrogen was achieved by hydrogenation of **5b** in benzene in the presence of palladium black. The product **12b** could be reoxidized to **13b** by the use of silver oxide in benzene. Application of the previously developed[11] transesterification procedure to form **13c** and subsequent hydrolysis afforded the desired **13d.** Less effectively **12b** could be air oxidized by treatment with sodium carbonate in acetonitrile to give a mixture of **13b** and **13d.** The whole mixture could be treated with trifluoroacetic acid and hydrolyzed to afford **13d.** Compared with the original synthesis,[11] the reaction sequence to **13d** via **4a, 5b, 12b,** and **13b** is shorter and affords a greater yield (about 18% overall from **4a**). Farina and Vega[12] have recently prepared the methyl ether of **13d** (where R = OMe) by another route. The coupling of **13d** with daunosamine to give the simplified analogue of **2** has already been reported[13] using the techniques recently developed for the successful coupling of daunomycinone and daunosamine to afford **2.**[13,14]

The catalytic hydrogenation of **5a** did not proceed selectively. After the uptake of 1 mol of hydrogen, **11a** and **12a** were both present according to NMR data. Complete hydrogenation to **12a** was accomplished with palladium black as catalyst. Pure **11a** was obtained readily by chemical reduction of **5a** with zinc and acetic acid. With proper care, this reagent combination also could be applied to **5b** for the preparation of **11b** without appreciable aromatization of **5b** to **9a.**

The C-2 double bond of **5, 8,** and **11** would seem to provide the means for further modification of these molecules. However, **5** and **8** were very insoluble compounds, and **5b** and **8b** lost acetic acid very easily. Compounds **11a** and **11b** were more soluble and more stable. Both **11a** and **11b** have been successfully converted to the 2,3-epoxides, **14a** and **14b,** respectively, by the action of peracid. Surprisingly, they were not oxidized from the leuco to the quinizarin form. The diacetyl quinizarin **8d,** a protected and more soluble form of **8a,** was

obtained readily by treatment of **5a** with trifluoroacetic anhydride and acetic acid.

Leuco **12b** is completely converted by treatment with triethylamine in benzene into quinizarin **13a.** This transformation probably begins with the elimination of acetic acid from **12b** to afford the $\Delta^{1(12a)}$ olefin. This isomerizes to a quinone—**15a** without the Δ^2 double bond—which in turn readily tautomerizes to the quinizarin **13a.** This sequence follows the suggested mechanism by which the condensation of leucoquinizarin with aldehydes affords 2-alkyl quinizarins.[15]

Ketone **22b,** or an appropriately protected form, appears to be a versatile intermediate. It seems suitable not only for conversion to the 4-demethoxy derivatives of daunomycinone[16] and adriamycinone, but the carbonyl group seems suitable for transformation into widely different kinds of side chains also. Protection of the quinizarin system of **22b** by conversion to the tetramethoxy derivative **19a** may be practical, providing that the mild, oxidative demethylation procedure for dimethyl ethers of hydroquinones[17,18] is applicable. To test this, we proceeded as follows.

Methylation of leuco **11a** in acetone with methyl sulfate and barium oxide as base gave consistent yields (50–57%) of tetramethoxy **17.** When potassium carbonate was used as base, the yields of **17** were erratic and dimethyl products leuco **11c,** leuco tautomer **16,** and quinone **15b** were isolated, depending on reaction conditions. The presence of these compounds show that the tetramethyl **17** is formed in a stepwise fashion, e.g., **11a** → **11c** → **16** → **17.** Product is lost when leuco **11c** or **16** is oxidized to quinone **15b.** Interestingly, the formation of **15b** is suppressed, but not eliminated, when zinc dust is added to the reaction mixture.

Assignment of structure to leuco **11c** was on the same basis as for leuco **11a** and **11b.** Initial assignment of structure to **15b** was based on its rapid isomerization in acid (with concomitant air oxidation) to **9b,** and was confirmed by the synthesis of the different dimethyl **8c** from **8a.** Dimethyl **8c** was unaffected by the acid conditions that converted **15b** to **9b.** The structure of **16** was assigned on the basis of its ir that showed the presence of OH (3 μ) and absence of C=O, its NMR that showed two phenolic H (δ 9.55)[19] and two methoxy groups, as well as its MS (*m/e* 322, M^+, 100% rel abundance) and analysis. Furthermore, when a solution of **16** was left in air, it was converted to quinone **15b.** A solution of **16** left overnight in an NMR tube was only half oxidized; its spectrum showed **16** and **15b** in a 1:1 ratio, perhaps stabilized as a molecular complex like quinhydrone.

The four methyl groups in **17** were readily removed by silver(II) oxide[17] treatment to give a high yield of the diquinone **18** whose ir spectrum was similar to that of **4a** and lacked the chelated quinone adsorptions of **8a** and **9a.** Two of the methyl groups in **17** were readily removed by a number of reagents (see Experimental Section) as well as by treatment with (1) mercuric acetate, palladium chloride, and cupric chloride in methanol,[20] or (2) one-pot treatment with sodium borohydride–zinc chloride and then chromic acid,[21] two sets of reagents that are used to convert olefins to ketones; ketone **19a** was not obtained. The product was **8c.**

The four methyl groups remained intact when **17** was converted to the alcohol **20** by hydroboration and subsequent oxidation with alkaline hydrogen peroxide. Alcohol **20** was best oxidized to tetramethoxy ketone **19a** (50% yield) with dimethyl sulfoxide (Me_2SO)–dicyclohexylcarbodiimide (DCC) in the presence of pyridinium trifluoroacetate.[22] Crystalline ketone **19a** was stable. It was unstable in solution or in the noncrystalline but chromatographically homogeneous form and decomposed rapidly to give a mixture of several components by TLC.

Oxidative demethylation[17] of **20** gave only the partially demethylated **21a** instead of a diquinone that corresponded to **18,** the diquinone that was smoothly obtained from **17.** However treatment of **20** with aluminum chloride in nitrobenzene afforded the completely demethylated **21b** in over 90% yield.

Work in this area is being discontinued in view of concurrent work elsewhere[10] and plans to examine a stereospecific route to daunomycinone and adriamycinone. Results thus far show that the Diels–Alder reaction of quinizarinquinone with various butadienes is a possible but not general entry to dihydroxynaphthacenediones. Results also show that a quinizarin system can be protected as the tetramethoxy derivative, e.g., as in **17, 19a,** and **20,** but the usefulness of these blocking groups is somewhat limited by their instability and by methods for their removal.

Twenty-four compounds have been evaluated under the auspices of the National Cancer Institute against lymphoid leukemia L1210 in the mouse. All were found inactive at doses ranging as high as 400 mg/kg. The compounds tested were **4a, 5a, 5b, 6a, 6b, 6d, 7b, 8a–d, 9a, 9b, 11a, 11b, 12a, 12b, 14a, 16, 17, 19a, 20, 21a,** and **21b.**

Experimental Section

Melting points were taken on a Fisher-Johns hot stage and were not corrected. Ultraviolet–visible spectra (methanol solution, Cary 11 instrument), infrared spectra (Nujol, Beckman IR-4 instrument), and 60-MHz NMR (Varian Associates, A-60 spectrometer) measurements were made by the Pharmaceutical Analysis Group under the direction of Dr. Peter Lim. Measurements of 100-MHz NMR were performed by Mr. L. Cary, using a Varian XL-100 spectrometer. The NMR spectra were run in $DCCl_3$ as solvent, unless otherwise noted, with Me_4Si as internal solvent. Elemental microanalyses were provided by Ms. E. M. McCarthy. Mass spectra were recorded by Dr. D. W. Thomas on an LKB Model 9000 mass spectrometer at 12 eV.

For thin layer chromatography, silica gel HF-254 plates were used and visualized with uv or iodine. The solvent systems used were (A) acetone–cyclohexane (20:80); (B) methylene chloride; (B-1) same solvent as B except with a silica gel slurry for plates, prepared with 0.05 M KH_2PO_4 instead of water, as suggested by Dr. Carol Mosher; (C) tetrahydrofuran–CH_2Cl_2 (30:70); (C-1) same as C but a silica gel slurry, prepared with 0.05 M KH_2PO_4 instead of water; (D) CH_2Cl_2; (E) acetone–cyclohexane (40:60); (F) $CHCl_3$, plates as in B-1; (G) THF–benzene (1:4), plates as in B-1. All evaporations were carried out in a spin evaporator at a bath temperature of 45 °C under vacuum (either water aspirator and/or mechanical pump, as required), unless specified otherwise. Anhydrous Na_2SO_4 was used for drying solutions, unless otherwise specified.

1,4,4a,12a-Tetrahydro-5,6,11,12-naphthacenetetrone (5a). A cooled, stainless steel bomb was loaded with 50 g (0.21 mol) of quinizarinquinone, 300 ml of benzene, and 42 ml (0.48 mol) of 1,3-butadiene, heated for 20 h at 45–50 °C with stirring, and evaporated to afford 44.8 g of crude product. This was stirred with 1.0 l. of boiling acetone for 10 min to afford 25.13 g (41%) of **5a:** mp >315 °C; ir max 5.81, 6.00, 6.26, and 7.79 μ; uv max 315 nm (ϵ 4100), 253 (14 700), 230 sh (16 700), 213 (20 700); MS *m/e* 292 (M^+, 90), 290 (30), 274 (40), 240 (quinizarin, 20); R_f 0.23 in solvent A. Anal. Calcd for $C_{18}H_{12}O_4 \cdot \frac{1}{2}H_2O$: C, 72.3; H, 3.70; Found: C, 72.3; H, 3.70.

4a,9a-[2]Buteno-1,4,9,10-anthracenetetrone (6a). The organic liquors from the purification of 60.0 g of **5a** were evaporated to dryness, and the residues were triturated with 200 ml of tetrahydrofuran to give crystalline quinizarin, 31.2 g. The liquors were concentrated to 50 ml to yield 7.35 g of crude **6a.** Recrystallization from 75 ml of tetrahydrofuran and 150 ml of cyclohexane afforded the off-white solid **6a,** 2.82 g (1.9%), mp 205–207 °C. One recrystallization from ethanol afforded the analytical sample of **6a:** mp 207–208 °C; ir max 5.85, 5.95 (C=O), 7.95 μ; uv max 296 nm (ϵ 6300), 245 sh (30 000), 227 (44 700); MS *m/e* 292 (M^+, 80), 274 (20), 264 (40), 210 (64), 134 (100); R_f 0.46 in solvent A. Anal. Calcd for $C_{18}H_{12}O_4$: C, 74.0; H, 4.14. Found: C, 74.0; H, 3.84.

The crystallization liquors from **6a** on concentration afforded crude **6a** containing some diadduct **7a** (1,4,4a,12a-tetrahydro-5a,11a-[2]-buteno-5,6,11,12-naphthacentetrone) which was detected by TLC (R_f 0.07 in solvent A) and characterized by MS, *m/e* 346 (M^+, 2) and 292 (100).

1,4,4a,12a-Tetrahydro-1-acetoxynaphthacene-5,6,11,12-tetrone (5b).[8] **A. Benzene Solvent.** A benzene solution of 0.22 g (2.0

mmol) of 1-acetoxy-1,3-butadiene and 0.48 g (2.0 mmol) of quinizarinquinone, (**4a**) in 35 ml of benzene reacted at 40 °C for 2 h to afford 0.35 g of crystalline product from cyclohexane. Recrystallization from acetone–cyclohexane (1:1) afforded 0.18 g (26%) of **5b**, a deep-red, crystalline material: mp ~150 °C, changes color, >315 °C; ir max 5.75, 5.82, 5.98, 6.25 μ; uv max 348 nm (ε 4200), 278 shoulder (11 100), 257 (17 400), 239 (17 700), 217 (17 400); MS *m/e* 290 (only major peak, M − HOAc); R_f 0.65 in solvent C. Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.6; H, 4.03. Found: C, 68.8; H, 4.09.

B. Acetonitrile Solvent. A mixture of 50.0 g (0.178 mol) of **4a** and 23.5 g (0.21 mol) of 1-acetoxy-1,3-butadiene in 250.0 ml of acetonitrile was heated for 20 min at 50 °C to afford 7.64 g (15.3%) of precipitated quinizarin, and a filtrate that afforded a red, slightly tacky solid. Trituration in 250 ml of ether afforded 45.64 g (76%) of **5b** that decomposed on TLC plates. Recrystallization from 25% methylene chloride in ethanol, 13.5 ml/g, afforded the pure product 58% yield: ir max 5.72, 5.80, 5.88 w, 5.97, 6.22 μ. The ir spectrum was different from that of the analytical sample, but the benzene reaction product gave the same ir when the workup was as above.

The purity of **5b** cannot be established by TLC and melting point since it decomposes to **9a**. The ir spectrum is helpful, but the NMR spectrum is essential to show that **5b** is free of quinizarin, quinizarinquinone, internal adduct **6b**, and diadduct **7b**.

11-Acetoxy-4a,9a-[2]buteno-1,4,9,10-anthracenetetrone (6b).[8] The mother liquors from the crystallization of **5b** (method B above) were evaporated to dryness, and the residue was extracted with ether. The ether-soluble material was recrystallized from methylene chloride–cyclohexane to afford crystalline, off-white **6b**: mp 207–208 °C; ir max 5.70 (C=O ester), 5.84 and 5.93 (C=O), 8.00, 8.18 (C–O–C); uv max 228 nm (ε 35 700), 310 (2200); MS (12 eV) *m/e* (rel intensity) 308 (M − CH_2O, 4), 290 (M − HOAc, 15), 240 (M − acetoxybutadiene, 70). Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.6; H, 4.03. Found: C, 68.5; H, 4.19.

Extended heating of **6b** in methanolic sodium methoxide afforded a high yield of anthraquinone, identical with authentic anthraquinone by ir, TLC, and melting point.

1,13-Diacetoxy-1,4,4a,12a-tetrahydro-5a,11a-[2]buteno-naphthacene-5,6,11,12-tetrone (Diadduct 7b).[8] A stirred mixture of 0.80 g (3.36 mmol) of **4a** and 0.90 g (8.0 mmol) of 1-acetoxy-1,3-butadiene in 25 ml of benzene was heated for 15 h in an oil bath of 38 °C. The homogeneous, reddish solution was diluted with 25 ml of carbon tetrachloride and evaporated to dryness. The residue was slurried in 25 ml of carbon tetrachloride and again evaporated to dryness to remove excess acetoxybutadiene. The residue was then stirred in 25 ml of carbon tetrachloride for 24 h. The tan, crystalline product **7b** was collected and dried to afford 1.13 g (74%), mp 175–178 °C, R_f 0.29 in B. One recrystallization afforded the crystalline analytical sample of **7b**: mp 162.0–163.5 °C; ir max 5.70, 5.75 (sh), 5.86, 6.25; uv max 305 nm (ε 2700), 260 (10 500), 232 (32 000); MS *m/e* 402 (M − HOAc); R_f 0.30 in solvent D. Anal. Calcd for $C_{26}H_{22}O_8$: C, 67.5; H, 4.80. Found: C, 67.5; H, 4.60.

4a,9a-[2]buteno-12-methoxy-1,4,9,10-anthracenetetrone (6d). Reaction of 2.1 g of 75% purity (58 mmol) of **4a** and 0.82 g (63 mmol) of 2-methoxybutadiene[23] in 10 ml of acetonitrile containing a little hydroquinone for 6 h at 55 °C afforded, after column chromatography (silica gel, 150, benzene) and crystallization from ether–petroleum ether (bp 30–60 °C), 0.85 g (41%) of pale orange **6d**: mp 68–70 °C; ir max 5.85, 5.95 (C=O), 6.28 (C=C), 7.95, 8.15 μ; uv max (95% EtOH) 2.98 nm (ε 2390), 253 (11 250), 227 (37 400); MS *m/e* 323 (M + 1, 11), 322 (M^+, 58), 240 (100). Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.81; H, 4.38. Found: C, 71.0; H, 4.45.

Use of other temperatures (23–160 °C), many other solvents (cyclohexane, benzene, DMF, etc.), various reaction times (up to 30 h), and different mole ratios all gave **6d** as the major product (81–100% of any reaction mixture) as indicated by examination of the NMR spectra. The presence of traces of end adduct (**5d**) was inferred. With large excesses of 2-methoxybutadiene (10 ×), the presence of some diadduct (**7c**) was observed (NMR and TLC) but no isolation was attempted.

7,10-Dihydro-6,11-dihydroxynaphthacene-5,12-dione (8a). A mixture of 0.70 g (2.39 mmol) of **5a** in 75 ml of xylene was heated for 20 h at reflux, and then chilled in ice. The crystalline material was collected and dried to afford 0.40 g (57%) of **8a** as dark-red needles, mp >310 °C, very insoluble in most solvents. Trituration with boiling chloroform and drying at 80 °C (1.0 mm pressure) afforded the analytical sample of **8a**: ir max 6.11, 6.28 μ (chelated C=O); MS *m/e* 290 (M − H_2, 52), 292 (M^+, 50). Anal. Calcd for $C_{18}H_{12}O_4$: C, 74.0; H, 4.14. Found: C, 74.2; H, 3.96.

7-Acetoxy-7,10-dihydro-6,11-dihydroxy-5,12-naphthacenedione (8b). A mixture of 0.20 g (0.57 mmol) of **5b** and 1.2 g of 3 A molecular sieves in 25 ml of acetonitrile was stirred for 20 h at ~30 °C in a stoppered flask. The reaction mixture was diluted with 50 ml of CH_2Cl_2 and filtered through a Celite pad. The filtrate was evaporated to dryness to afford 0.14 g (70%) of **8b**. Trituration of 0.11 g of the crude product with 20 ml of ether afforded 0.10 g (63%) of the analytically pure, red **8b**: mp >300 °C; ir max 5.75, 6.10, and 6.24 (chelated quinone), 7.88, 8.00 μ; uv max 251 nm (ε 37 000), 256 (36 100), 281 sh (9600); MS *m/e* 290 (M − HOAc, 100). Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.6; H, 4.03. Found: C, 69.1; H, 3.57.

No tautomerization of **5b** to **8b** occurred in acetonitrile alone or in acetone containing 3 A molecular sieves.

7,10-Dihydro-6,11-dimethoxy-5,12-naphthacenedione (8c). Methylation of 5.00 g of **8a** with 20 ml of methyl sulfate and 30 g of potassium carbonate in 200 ml of methyl ethyl ketone at reflux for 20 h afforded 3.14 g (58%) of **8c**, mp 190–191 °C. The product from an earlier run using acetone as a solvent (which gave lower yield) was recrystallized from methylene chloride–methanol (1:5) to afford the analytical sample of **8c**: mp 193–193.5 °C; ir max 6.00 (C=O), 6.28, 6.42, 7.46, 7.53, and 10.02 μ (this band not in **15**); uv max 376 nm (ε 8300), 261 (29 300); MS *m/e* 320 (M^+, 100); R_f 0.38 in solvent F. Anal. Calcd for $C_{20}H_{16}O_4$: C, 75.0; H, 5.04. Found: C, 74.8; H, 5.07.

This was identical by ir, TLC, and melting point with product formed from **17** by treatment (1) with mercuric acetate, palladium chloride, and cupric chloride[20] and (2) one-pot treatment with diborane (from $NaHB_4$ and $ZnCl_2$) and chromic acid.[21] Probably no reaction with diborane occurred and **17** was partially demethylated and oxidized to **8c** (cf. **20** giving **21a** with CrO_3).

7,10-Dihydro-6,11-diacetoxy-5,12-naphthacenedione (8d). A mixture of 300 mg (1.03 mmol) of **5a** in a solution of 5.0 ml of trifluoroacetic anhydride and 2.0 ml of glacial acetic acid was stirred for 15 min in a stoppered flask. The resulting red solution was poured with stirring into 100 ml of cold water to afford a yellow, crystalline precipitate. This was collected after 2 h, washed thoroughly with water, and dried to afford 0.34 g (88%) of **8d**, R_f 0.16 and 0.64 (trace) in solvent B-1. One recrystallization from methylene chloride–ethanol afforded **8d**: mp 256–257 °C; ir max 5.69, 5.99, 6.30, 7.47 μ; MS *m/e* 376 (M^+, 5), 334 (M − CH_2CO, 30), 292 (M − $2CH_2CO$, 100); R_f 0.04 in solvent B. Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.2; H, 4.29. Found: C, 70.4; H, 3.90.

6,11-Dihydroxy-5,12-naphthacenedione (9a). A mixture of 0.26 g (0.74 mmol) of **5b** and 0.50 g of commercial sponge nickel (water suspension) in 5.0 ml of DMF was stirred for 16 h at ambient temperature to afford 0.20 g (93%) of **9a**, mp >300 °C, homogeneous by TLC: R_f 0.55 in solvent E.

The analytical sample of **9a** obtained from a previous experiment had mp >315 °C (lit. mp 333[7] and 289–290 °C[24]); ir max no OAc at 5.75, 6.12, and 6.30 (chelated quinone), 6.61, 11.55, and 13.79 μ; uv max (cyclohexane) 452, 484, 508, and 518 as compared with literature values[24] of uv max (cyclohexane) 457, 488, 511, and 524 nm; MS *m/e* 290 (M^+, 100).

Compound **5b** also was converted completely to **9a** by boiling xylene (20 h), nitrobenzene at 100 °C, and methanolic sodium methoxide at reflux for 0.5 h. At 23 °C, aromatization to **9a** also occurred with nickel boride in 1,2-dimethoxyethane, potassium diazocarboxylate in acetonitrile, and trifluoroacetic acid in benzene for 1 h. A solution of **5b** in $(Me_2N)_3PO$–H_2O (10:1) was converted rapidly to **9a** by warming on a steam bath for 15 min; $(Me_2N)_3PO$ alone was ineffective.

6,11-Dimethoxy-5,12-naphthacenedione (9b). A solution of 200 mg of the dimethoxy quinone **15b** in 10 ml of trifluoroacetic acid was left for 20 h at room temperature, then the solvent was removed. The residue was crystallized from methylene chloride–petroleum ether, bp 65–110 °C (1:9), 20 ml, to afford 50 mg (25%) of **9b** as a bright yellow solid: mp 183–184 °C; ir max 6.00, 6.22 (weak), 6.25, 6.32 (weak), 7.43, 7.90 μ; uv max 403 nm (ε 71 300), 293 (18 500), 281 (20 000 sh), 249 (42 500); NMR δ 4.12 (s, 6 H, 2 OCH_3) and eight aromatic protons; MS *m/e* 318 (M^+, 100). Anal. Calcd for $C_{20}H_{14}O_4 \cdot \frac{1}{4}HO$: C, 74.5; H, 4.53. Found: C, 74.5; H, 4.80.

13-Acetoxy-5a,11a-[2]butenonaphthacene-5,6,11,12-tetrone (10b). A solution of 6.0 g (13.0 mmol) of **7b** in 400 ml of toluene and 32 ml of glacial acetic acid was heated for 20 h at 75 °C and then evaporated. The residue was triturated with 25 ml of carbon tetrachloride and crystallized from 100 ml of ethanol to afford 4.2 g (81%) of **10b**: mp 188–190 °C (lit.[7] mp 190 °C); R_f 0.25 in B, 0.25 in toluene, and 0.10 in acetone; ir max 5.69 (C=O, ester), 5.80, 5.90, 6.28 μ; uv max 313 nm (ε 5500), 262 (16 400), 232 (39 800); MS *m/e* 400 (M^+, 5), 357 (M − CH_3CO, 5), 340 (M − HOAc, 28), 290 (M − 1 − acetoxybutadiene, 25).

1,4,4a,12a-Tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (11a). A mixture of 1.50 g (5.12 mmol) of **5a** and 4.0 g of zinc dust in 50 ml of glacial acetic acid was stirred under nitrogen for 3.0 h to afford 1.20 g (79%) of yellow-green, homogeneous **11a**. This was recrystallized

once from 2-propanol–cyclohexane to afford the analytical sample of **11a:** ir max 6.10, 6.20, 6.35, 6.70 μ; MS *m/e* 294 (M^+, 100); R_f 0.69 in solvent B-1. Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.5; H, 4.80. Found: 73.7; H, 5.17.

1-(Acetoxy)-1,4,4a,12a-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (11b). To a 200-mg portion of 5% Pd/$BaSO_4$ in 50.0 ml of cold benzene, presaturated with hydrogen, was added 1.06 g (3.0 mmol) of **5b.** The cooled mixture was hydrogenated at 1 atm until hydrogen uptake ceased after 44 min. The catalyst was removed by filtration, and the filtrate was evaporated to afford 1.01 g of **11b,** which was freed of insoluble quinizarin (19%) by trituration with ether. The product was recrystallized twice from ether to afford analytically pure **11b:** mp 164–165 °C; ir max 5.75, 6.10, 6.20, 6.32, 6.65 (characteristic of leuco), 8.02, 8.15 μ; uv max 237 nm (ε 26 700), 252 (23 000), 277 (22 000), 285 (20 200), 397 (12 800), 417 (12 300); MS *m/e* 352 (M^+, 18), 292 (M − HOAc, 40), 240 (M − acetoxybutadiene, 68); R_f 0.70 in solvent E. Anal. Calcd for $C_{20}H_{16}O_6$: C, 68.2; H, 4.58. Found: C, 68.6; H, 4.80.

Reaction of **5b** to **11b** with zinc dust and acetic acid with toluene as solvent at 0 °C proceeded with aromatization to **9;** yields of **11b** ranged between 75 and 80%.

1,2,3,4,4a,12a-Hexahydro-6,11-dihydroxy-5,12-naphthacenedione (12a). Hydrogenation of 2.00 g (6.85 mmol) of **5a** with 0.20 g of palladium black (Engelhard's catalytic grade) in 100 ml of benzene at 1 atm, overnight, afforded 2.0 g (98%) of crude product, homogeneous by TLC. Recrystallization from methylene chloride and 2-propanol gave 138 mg (68%) of yellow-orange **12a:** mp 172–73 °C; ir max 6.11, 6.20, 6.30, 6.65 μ (characteristic of leuco compounds); NMR δ 1.3–3.5 m 10; 13.42 s ½ and 13.69 s 1½, phenolic H; MS *m/e* 296 (M^+, 100). Anal. Calcd for $C_{18}H_{16}O_4$: C, 73.0; H, 5.44. Found: C, 72.8; H, 5.17.

1-Acetoxy-1,2,3,4,4a,12a-hexahydro-6,11-dihydroxy-5,12-naphthacenedione (12b). A mixture of 1.5 g of palladium black (Engelhardt catalytic grade) in 250 ml of benzene was cooled to 10 °C while 15.0 g of **5b** was added. The cold mixture was hydrogenated at 48 psig. The hydrogen uptake showed that 83% of **5b** had been reduced to **11b** in 5 min. The theoretical amount of hydrogen for reduction to **12b** was taken up in 5 h. Recrystallization from tetrahydrofuran–cyclohexane (1:4) afforded 11.7 g (78%) of **12b:** mp 170–172 °C; ir max 5.75, 6.10, 6.20, 6.32, 6.64 (characteristic of leuco), 8.15, 11.92, 12.30 μ; uv max 417 nm (ε 12 500), 398 (13 100), 285 (20 500), 277 (22 000), 252 (23 600), 237 (27 100); MS *m/e* 354 (M^+, 6), 312 (M − CH_2CO, 2), 294 (M − HOAc, 100); R_f 0.37 in solvent B-1. Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.8; H, 5.12. Found: C, 68.8; H, 5.13.

7,8,9,10-Tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (13a). A stirred solution of 0.55 g (1.52 mmol) of **12b** in 50.0 ml of benzene was treated overnight at 20 °C with 5.0 ml of triethylamine. The red precipitate was collected, washed thoroughly with water (50 ml) and benzene (50 ml), then dried at 100 °C (1.0 mm) for 6 h to afford 0.425 g (93%) of the bright red **13a:** mp >300°; ir max 6.12, 6.28, 7.95, 12.0, 13.75 μ; NMR δ 1.85 m 4, 2.81 m 4, 7.80 q 2 (aryl), 8.35 q 2 (aryl), 14.1 s 2 (chelated OH); MS *m/e* 294 (M^+, 100). Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.5; H, 4.79. Found: C, 73.4; H, 4.84.

These properties agreed well with those of **13a** synthesized earlier.[11]

7-Acetoxy-6,11-dihydroxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (13b). A mixture of 6.68 g (18.9 mmol) of leuco **12b** and 10.0 g (43 mmol) of silver oxide in 500 ml of benzene was stirred and heated at reflux for 1 h, an additional 2.0 g (8 mmol) of silver oxide was added, and the reaction was continued for a total of 6.5 h. After filtration, the filtrate was saturated with H_2S and filtered, and the filtrate was evaporated to dryness. Recrystallization from absolute ethanol afforded 4.8 g (73%) of homogeneous **13b** in two crops (second crop, 15%), R_f 0.70 in solvent A-1 (developed twice) identical with that of authentic **13b**[10] by TLC and ir. Compound **13b** had ir max 5.75 (C=O ester), 6.15, 6.3, 8.1 μ; mp 210–212 °C, red melt. When the melt was cooled and reheated above 220 °C gradually, a solid glass formed and gave off the odor of acetic acid, and then decomposed >280 °C (lit.[11] mp 286 °C dec).

7,8,9,10-Tetrahydro-6,7,11-trihydroxynaphthacene-5,12-dione (13d). A. By Air Oxidation in Carbonate. A mixture of 0.50 g (1.4 mmol) of **12b** and 0.32 g (3.0 mmol) of sodium carbonate, anhydrous, in 25 ml of acetonitrile was heated for 18 h at 40 °C with stirring to afford 0.42 g of a mixture of acetoxy **13b** and the hydroxy **13d,** by TLC. This mixture was treated first with trifluoroacetic acid and then with cold methanolic sodium methoxide to afford 0.23 g (52%) of **13d,** ir and TLC identical with those of authentic **13d;** ir max 5.72 (C=O of OAc), 6.13 and 6.30; R_f 0.10 in B-1.

This procedure did not scale up well, probably because the rather insoluble **13d** tended to coat the reactants and reduce the likelihood for further reaction.

B. By Literature Method.[11] A mixture of 4.2 g (12.0 mmol) of **13b** and 90 ml of trifluoroacetic acid was stirred for 2.0 h at 25 °C. The mixture was diluted with 75 ml of toluene and evaporated to dryness. This was repeated to remove the excess trifluoroacetic acid, leaving 4.70 g of **13c.** The trifluoroacetate **13c** in 275 ml of cold methanol was treated with 110.0 ml of 1 N methanolic sodium methoxide for 1.5 h at ice-bath temperature, acidified with 25.0 ml of glacial acetic acid, and evaporated to dryness. The residue was triturated with 1.0 l. of water to afford 3.25 g of product. Recrystallization from 200 ml of 1,2-dichloroethanol afforded 2.40 g (64.5%) of **13d,** mp 278–279 °C, changing to dark needles which decomposed at 295 °C (lit. mp 292 °C dec);[11] R_f 0.25 in solvent C-1; MS *m/e* 310 (M^+, 40), 292 (M − H_2O, 100).

2,3-Epoxy-1,2,3,4,4a,12a-hexahydro-6,11-dihydroxy-5,12-naphthacenedione (14a). Reaction of 0.29 g (1.0 mmol) of **11a** with 0.20 g (1.16 mmol) of *m*-chloroperbenzoic acid in 100 ml of benzene with stirring at room temperature for 86 h in a stoppered flask afforded a yellow solid. This was collected and washed with cyclohexane to afford 100 mg of impure product. The mother liquors deposited a second yellow, crystalline crop of 50 mg (16%) of analytically pure **14a:** mp 187–188 °C; NMR δ 2.80–3.50 m 8, 13.30 s 2; MS *m/e* 310 (M^+, 100), 290 (20), 274 (22), 254 (30); R_f 0.63 in solvent C-1. Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.7; H, 4.55. Found: C, 69.9; H, 4.72. From the impure product and the mother liquors was obtained an additional 157 mg (49%) of **14a.**

1-Acetoxy-2,3-epoxy-1,2,3,4,4a,12a-hexahydro-6,11-dihydroxy-5,12-naphthacenedione (14b). A solution of **11b** in benzene was stirred with 40% aqueous peracetic acid for 5 days and worked up. Two recrystallizations from benzene afforded the analytical sample of **14b:** mp 264–265 °C; ir max 5.72, 6.10, 6.20, 6.31, 6.69 μ; MS *m/e* 368 (M^+, 100), 308 (M − HOAc, 60), 290 (M − HOAc − H_2O, 60); R_f 0.10 in solvent B. Anal. Calcd for $C_{20}H_{16}O_7$: C, 65.2; H, 4.38. Found: C, 65.3; H, 4.76.

1,4-Dihydro-5,6,11,12-tetramethoxynaphthacene (17). A mixture of 100 g of leuco **11a,** 320 g of barium oxide, 1.67 l. of acetone, and 322 ml of dimethyl sulfate was stirred under a nitrogen atmosphere at reflux for 5 h. The mixture was filtered (through Celite), the filter was thoroughly washed with acetone, and the combined filtrates were evaporated. The residue was diluted with 200 ml of acetone, kept overnight at 5 °C, and the precipitate was collected, washed (cold acetone), and air dried to give 68.5 g (57.6%) of orange-yellow, crystalline **17,** mp 191–193 °C. Recrystallization from methylene chloride–petroleum ether (bp 65–110 °C) afforded **17:** mp 197–198 °C; ir max 5.99, 6.19, 6.22, 6.91, 7.52 μ; uv max 420 nm (ε 6500), 397 (8000), 377 (7800), 359 (4300), 269 (107 000), 240 (27 800); MS *m/e* 350 (M^+, 100); R_f 0.70 and 0.55 in solvent D and F, respectively. Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.5; H, 6.33. Found: C, 75.6; H, 6.33.

The use of barium oxide gave very consistent results in experimants ranging in size from 3 g to 100 g of **11a.** Earlier experiments with calcined potassium carbonate instead of barium oxide required longer reaction times (40–89 h), and gave erratic yields (20–60%) of **17** and increasing amounts of leuco dimethyl **11c** with shorter reaction times. Overly long reaction times gave dimethyl **15b,** an oxidized form of **11c.** Addition of zinc dust to the reaction decreased the formation of **15b.**

The stability of **17** was examined. **17** was relatively unchanged (by TLC) by the following: 20-h reflux or 8 days at room temperature in 1 N NaOMe–MeOH; 48 h at room temperature in lithium aluminum hydride and diglyme; 24 h at room temperature in glacial acetic acid. **17** was all decomposed (by TLC) by the following at room temperature: 2 h in trifluoroacetic acid; 20 h in sodium hydride and DMF; 6 days (or less) in 1 N hydrochloric acid and 1,2-dimethoxyethane; and 4 days when a methylene chloride solution of **17** was exposed to air and repeatedly allowed to evaporate to dryness and then redissolved. In the last case, the product was **8c.** When **17** (30 mg) was treated with excess sodium hydride in DMF for 2 days, the homogenous (R_f 0.73 in chloroform) product (20 mg) appeared to be 5,6,11,12-tetramethoxynaphthacene (mp 158–170 °C from 2-propanol–cyclohexane) on the basis of its molecular weight [MS 348 (M^+, 100)], its symmetrical aryl and methyl protons by NMR (δ 4.06 s, 12 protons of 4 OMe; 7.37 q 4, aryl H; and 8.29 q, 4, aryl H), and analysis fitting solvated 5,6,11,12-tetramethoxynaphthacene (Anal. Calcd for $C_{22}H_{20}O_4$·*i*-PrOH·⅓C_6H_{12}: C, 74.3; H, 7.40. Found: C, 74.4; H, 7.67).

1,4-Dihydro-6,11-dimethoxy-5,12-naphthacenedione (15b). After 3.0 g (43%) of crystalline **17** had been obtained from a methylation of 5.8 g of **11a,** using K_2CO_3 and 89-h reaction time, the mother liquors were evaporated. Recrystallization of the residue from 25 ml of 1,2-dimethoxyethane afforded 1.02 g (16%) of orange-yellow **15b:** mp 196.5–197.5 °C; ir max 6.00 (s), 6.20, 6.33, 7.4 (s), 12.70 (this band not in **8c**); uv max 412 nm (ε 6600), 295 (15 600), 284 (16 200), 233

(50 400); MS *m/e* 320 (M^+, 100); R_f 0.37 in solvent F. Anal. Calcd for $C_{20}H_{16}O_4$ (320.3): C, 75.0; H, 5.04. Found: C, 75.1; H, 5.11.

6,11-Dimethoxy-1,4,4a,12a-tetrahydro-5,12-naphthacenedione (11c). After unreacted **4a** (recovered by base extraction) and 50 mg (14%) of crystalline **17** had been obtained from a methylation of 0.29 g of **11a** using K_2CO_3 and 18-h reaction time, the mother liquors (consisting of 1 ml of methylene chloride and 15 ml of 2-propanol) were diluted with an equal volume of cyclohexane to afford 30 mg (9%) of leuco dimethyl **11c:** mp 164–165 °C; ir max 5.92, 6.05 (C=O), 6.20, 6.37, 6.70, 6.89 μ; uv max 368 nm (ϵ 5000), 296 (6800), 263–267 (36 400), 235 (27 400); MS *m/e* 322 (M^+, 100); R_f 0.24 in solvent F. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.4; H, 5.62. Found: C, 74.4; H, 5.77.

1,4-Dihydro-5,12-dihydroxy-6,11-dimethoxynaphthacene (16). A mixture of 1.5 g (7.75 mmol) of leuco **11a,** 10.0 g of freshly calcined potassium carbonate, 25 ml of methyl ethyl ketone, and 10 ml of methyl sulfate was heated for 3 h at reflux temperature. Filtration of the salts and concentration of the solvent afforded a reddish-brown precipitate that was triturated with methanol and dried to give 1.38 g (55%) of **16,** identical by TLC and ir with the analytical sample of **16.** This was purified through a silica gel column (methylene chloride eluent) to yield brownish **16:** mp 162–163 °C; ir max 2.98 (OH), 6.05 (m), 7.35–7.40 (s), 8.00, 11.90 μ (not in **11c** or **15b**); uv max 413 nm (ϵ 5600), 272 (28 000), 218 (46 600); MS *m/e* 322 (M^+, 100); R_f 0.10 in benzene. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.5; H, 5.63. Found: C, 74.3; H, 5.71.

A solution of **16** in methylene chloride left open to air overnight was oxidized to **15** according to TLC and ir of the isolated product.

Smaller amounts of **16** was also formed in some methylations of **11a** with acetone as solvent, generally in cases where little **17** was formed.

1,4-Dihydro-5,6,11,12-naphthacenetetrone (18). The literature procedure[17] was followed. A mixture of 63 mg (0.18 mmol) of **17** and 262 mg (2.1 mmol) of silver(II) oxide was sonificated for 15 s, then treated with 0.40 ml of 85% H_3PO_4. After stirring at room temperature for 45 min, the mixture was diluted with 150 ml of water and extracted with methylene chloride (3 × 60 ml). Evaporation of the dried organic extracts left 52 mg (100%) of dull red **18:** mp 205 °C dec; ir max 5.87 (C=O), 6.00, 6.25, 7.72, 7.82 μ; uv max 315 nm (ϵ 4100), 252 (14 700), 230 (16 700 sh), 213 (20 700); MS *m/e* 290 (M^+, 100), 288 ($M - H_2$, 80). Anal. Calcd for $C_{18}H_{10}O_4 \cdot \frac{1}{2}H_2O$: C, 72.2; H, 3.70. Found: C, 72.3; H, 3.70.

1,2,3,4-Tetrahydro-2-hydroxy-5,6,11,12-tetramethoxynaphthacene (20). A tetrahydrofuran (THF) solution (20 ml) of diborane (1 M in BH_3) was added to a stirred solution of 4.20 g (12.0 mmol) of olefin **17** in 60 ml of THF under nitrogen. After 3.5 h, the solution was cooled (ice bath) and stirred while treated carefully with 14.5 ml of 30% hydrogen peroxide in 60 ml of 6 N sodium hydroxide. Most of the THF was removed and the aqueous solution was extracted with methylene chloride to afford 4.1 g (92%) of homogeneous (by TLC) **20.** Recrystallization from benzene gave yellow, crystalline **20:** mp 212–213 °C; ir max 2.85 μ (OH); NMR δ 3.83 (s, 6 H) and 3.99 (s, 6 H) of 4 OCH_3; uv max 430 nm (ϵ 6200), 396 (7900), 378 (7700), 359 (3900); NMR 1.3–3.0 m 8, 3.83 s 6 (2 OMe), 3.99 s 6 (2 OMe), and 4 aryl H; MS *m/e* 310 (M^+, 100); R_f 0.11 in solvent F. Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.7; H, 6.55. Found: C, 72.1; H, 6.70.

3,4-Dihydro-5,6,11,12-tetramethoxy-2(1*H*)-naphthacenone (19a). The literature procedure[22] was followed using 1.00 g (2.71 mmol) of alcohol **20,** 8 ml of dimethyl sulfoxide, 30 ml of benzene, 2 ml pyridine, and 1.0 ml of trifluoroacetic acid; 2.00 g of dicyclohexylcarbodiimide was added initially and 2.00 g more (total, 19.4 mmol) after 3.75 h. After a total reaction time of 5.75 h, no **20** was left (by TLC). The reaction mixture was treated with 6.0 g (67.5 mmol) of oxalic acid and 25 ml of methanol and worked up, using additional benzene to extract the product (1.77 g). This was chromatographed (100 g silica gel, 200–325 mesh, pretreated with KH_2PO_4 buffer; 2.25 × 47 cm column; 1% THF in benzene as eluent) to give 0.50 g (50%) of **19a,** homogeneous by TLC. Identical material from an earlier run was recrystallized from ether–hexane (1:5) to afford dark tan **19a:** mp 130 °C sintered; 142–145 °C dec; ir max 5.80 μ (C=O); uv max 413 nm (ϵ 5100), 390 (6200), 325 (5900), 266 (72 500), 227 (20 000); NMR δ 2.65 t 2, 3.48 t 2, 3.88 d 8 (2 OMe + benzylic CH_2), 4.04 d 6 (2 OMe), 7.52 q 2 (aryl), 8.36 q 2 (aryl); MS *m/e* 366 (M^+, 100); R_f 0.58 in solvent G. Anal. Calcd for $C_{22}H_{22}O_5 \cdot \frac{1}{4}H_2O$: C, 71.2; H, 6.10. Found: C, 71.1; H, 5.77.

6,11-Dimethoxy-8-hydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (21a). The literature procedure[17] used in preparing the naphthacenetetrone **18** was applied to 500 mg (1.36 mmol) of tetramethoxy **20** using 2.0 g (16.2 mmol) of silver(II) oxide, 30 ml of dioxane, and 3.2 ml of 85% phosphoric acid to afford the theoretical yield of **21a** that crystallized on standing. Recrystallization from acetonitrile–petroleum ether (bp 30–60 °C) afforded orange **21a:** mp 182–183 °C; ir max 2.88 (OH), 5.97 μ; uv max 370 nm (ϵ 5300), 260 (34 800), 223 (19 500); MS *m/e* 338 (M^+, 100), 320 ($M - H_2O$, 25); R_f 0.15 in solvent G. Anal. Calcd for $C_{20}H_{18}O_5$: C, 70.8; H, 5.35. Found: C, 70.6; H, 5.42.

The identical product (ir, TLC, MS) was obtained on treatment of **20** with either *N*-bromoacetamide in *tert*-amyl alcohol or with chromium trioxide in pyridine.

7,8,9,10-Tetrahydro-6,8,11-trihydroxy-5,12-naphthacenedione (21b). A mixture of 2.00 g (5.40 mmol) of **20,** 100 ml of nitrobenzene, and 10.0 g (75 mmol) of aluminum trichloride was stirred at ambient temperature for 20 h and then poured into a mixture of 500 g of ice, 200 ml of water, and 300 ml of concentrated hydrochloric acid. After the nitrobenzene was removed by ether extraction (2 × 600 ml), the aqueous phase stood for 12 days during which the precipitated 1.54 g (92%) of **21b** was collected. This was almost homogeneous (R_f 0.30 + trace at R_f 0.95). Trituration with boiling methylene chloride afforded red, crystalline **21b:** mp 313–315 °C dec; ir max 3.00 (OH), 6.15, 6.30 μ (phenolic OH chelated with quinone); uv max 514 nm (ϵ 6000), 481 (9700), 457 (8700), 287 (9600), 256 sh (38 600), 252 (39 700); NMR δ 2.0–3.2 m 6, 4.30 m 2, 7.84 q 2 (aryl), 8.38 q 2 (aryl), 13.62 s 2 (chelated OH); MS *m/e* 310 (M^+, 100); R_f 0.32 in solvent G. Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.7; H, 4.54. Found: C, 70.1; H, 4.80.

3,4-Dihydro-6,11-dihydroxy-5,8,12(1*H*)-naphthacenetrione (22b). By the procedure used to prepare **19a,** 0.35 g (1.13 mmol) of **21b** was allowed to react with 1.30 g (6.32 mmol) of dicyclohexylcarbodiimide and excess dimethyl sulfoxide for 3 h and worked up to afford 0.29 g (83%) of crude **22b,** still containing a trace of dicyclohexylurea according to its ir spectrum. Addition of water to a sulfolane solution of this afforded red crystals which were triturated with boiling methanol to afford the analytical sample of **22b:** mp >310 °C dec; ir max 5.79 (C=O), 6.15, 6.30 μ (chelated quinone); uv max 514 nm (ϵ 5300), 482 (7300), 457 sh (6400), 288 (7000), 256 (26 900), 252 (27 300); NMR δ 2.67 t 2 (H-9), 3.30 t 2 (H-10), 3.68 s 2 (H-7), 7.84 q 2 and 8.38 q 2 (aryl H), 13.35 s 1 and 13.45 s 1 (chelated OH) with MeOH solvate also detectable; R_f 0.65 in solvent G. Anal. Calcd for $C_{18}H_{12}O_5 \cdot 0.2CH_3OH$: C, 69.3; H, 4.09. Found: C, 69.1; H, 4.15.

Acknowledgment. This work was performed under Contract N01-CM-33742, Drug Research and Development, NCI, NIH, Public Health Service. We thank Mr. Ben Bicknell, Mr. Jim Williams, Mr. Mark Loza, and Mr. Juan Dulude for the large-scale preparation of intermediates, Mr. Cesar Villalba for assistance in some experiments, and the others mentioned in the Experimental Section.

Registry No.—**4a,** 1709-63-3; **5a,** 58976-81-1; **5b,** 58976-82-2; **6a,** 58976-83-3; **6b,** 58976-84-4; **6d,** 58976-85-5; **7b,** 58976-86-6; **8a,** 58976-87-7; **8b,** 58976-88-8; **8c,** 58976-89-9; **8d,** 58976-90-2; **9a,** 1785-52-0; **9b,** 36831-93-3; **10b,** 58976-91-3; **11a,** 58976-92-4; **11b,** 58976-93-5; **11c,** 58976-94-6; **12a,** 58976-95-7; **12b,** 58976-96-8; **13a,** 58976-97-9; **13b,** 58976-98-0; **13d,** 20494-73-9; **14a,** 58976-99-1; **14b,** 58977-00-7; **15b,** 58977-01-8; **16,** 58977-02-9; **17,** 58977-03-0; **18,** 58977-04-1; **19a,** 58977-05-2; **20,** 58977-06-3; **21a,** 58977-07-4; **21b,** 58977-08-5; **22b,** 58977-09-6; 1,3-butadiene, 106-99-0; 1-acetoxy-1,3-butadiene, 1515-76-0; 2-methoxybutadiene, 3588-30-5; 5,6,11,12-tetramethoxynaphthacene, 58977-10-9.

References and Notes

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Chemical Transformations of 7,9-Disubstituted Purines and Related Heterocycles. Selective Reduction of Imines and Immonium Salts

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Received October 17, 1975

Ten 7,9-disubstituted purines and related heterocycles were reduced with borohydride to afford the corresponding 7,8-dihydro species, a type of heterocycle which has not previously been studied in any detail. The reduced species were found to reoxidize quantitatively at rates characteristic of and predictable for the individual heterocycles; the reoxidation phenomenon was investigated and shown to involve reaction with water or oxygen. In solutions containing mixtures of reduced and oxidized heterocycles, the two species were found to be in rapid equilibrium, undoubtedly via hydride transfer. This observation prompted the utilization of the 7,8-dihydro-7,9-disubstituted heterocycles for the novel and selective reduction of imines and immonium salts. Benzylideneaniline, benzylidenebenzylamine, and cyclohexylidenepyrrolidinium perchlorate, e.g., were converted to their respective amines in excellent yields. Over the range of conditions employed for these transformations, no significant reduction of aldehydes, ketones, or several other common organic functional groups was observed, so the heterocycles may prove useful as selective reducing agents. The reactivity of the disubstituted heterocycles with nucleophiles was also studied. Certain of the oxidized compounds, e.g., were found to undergo ring opening at high pH, as has been observed previously. Treatment of the reduced, ribosylated species with aniline at pH 4.5 resulted in deribosylation of the nucleosides. This transformation, which previously has been possible only after opening of the imidazole moiety at high pH, should be of considerable utility to biochemists for the depurination of 7-methylguanosine moieties in transfer and messenger RNA's.

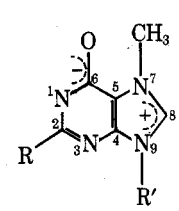
Many reports concerned with alkylated purines and their derivatives and analogues have appeared in recent years. These investigations have dealt with the synthesis of substituted heterocycles and with the effects of specific alkylating agents and reaction conditions on the position and extent of alkylation. The relevance of these alkylations as models for mutagenic change at the nucleic acid level has also been considered, as have the biological and physical properties of the alkylated species. However, substantially less work descriptive of the chemistry of the individual alkylated compounds themselves is available.

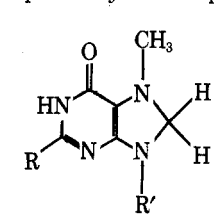
One alkylated nucleoside of special interest in this regard is 7-methylguanosine, which occurs in unique positions in certain transfer[3] and messenger[4] RNA's, and is the only naturally occurring nucleoside known to exist as a zwitterion at physiological pH. Owing to its zwitterionic character, 7-methylguanosine may undergo facile and reversible reduction,[5] a transformation first noted[6] for 1,3-dimethylbenzimidazolium iodide and 9-methylcaffeine perchlorate. 7-Methylguanosine also undergoes ring opening in strong aqueous base,[7] depurination in strong acid,[8] and selective demethylation in the presence of a powerful nucleophile.[9]

To determine the possible generality of these transformations for related heterocycles, as well as additional reaction pathways which may be available, we have studied the chemistry of ten 7,9-disubstituted purines and related compounds and report on the nature of the pH-dependent reoxidation of the reduced heterocycles, the utilization of the reduced species in the selective reduction of imines and immonium salts, and the interaction of certain of the oxidized and reduced heterocycles with strong bases and nucleophiles.

Results and Discussion

Synthesis of Disubstituted Heterocycles. The 7,9-disubstituted purines **1a–8a** were prepared by known proce-





	R	R′	
1a	NH_2	β-D-ribofuranosyl	**1b**
2a	NH_2	CH_3	**2b**
3a	H	β-D-ribofuranosyl	**3b**
4a	H	CH_3	**4b**
5a	OH	β-D-ribofuranosyl	**5b**
6a	OH	CH_3	**6b**

dures[10] and converted to the corresponding 7,9-disubstituted 7,8-dihydropurines by reduction with sodium borohydride in water. Isolation of the reduced purines free from boron hydrides was accomplished by concentration of the reaction mixtures to a small volume, treatment with acetone, and concentration to dryness under diminished pressure. This