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J. Nat. Prod., **1993**, 56 (5), 722-730• DOI:
10.1021/np50095a009 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 56, No. 5, pp. 722-730, May 1993

IDENTIFICATION AND CHARACTERIZATION OF NATURALLY OCCURRING RUBIADINS

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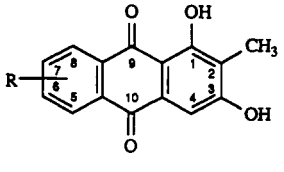
ABSTRACT.—An attempt has been made to resolve many of the inconsistencies that appear in descriptions of alleged naturally occurring rubiadins, 1,3-dihydroxy-2-methyl anthraquinones [**1**]. Using an unambiguous approach, a number of substances having the proposed structures do in fact show well-defined characteristics, mainly in the ^{1}H-nmr spectra of the pigments as well as in the ^{1}H-nmr and ^{13}C-nmr spectra of their peracetates. Correlations using uv or mass spectroscopy data were not particularly useful.

Rubiadins present a wide array of physical and spectroscopic characteristics (1,2). For instance, to rubiadin [**1**] itself (R=H) and its 6-hydroxy (**20**) and 8-methoxy (**16**) derivatives have been attributed melting points of 280–283° (3) or < 300° (4), 167–168° (5) or 236–238° (6), and 215° (7) or 238–240° (8), respectively, while the frequently encountered 8-hydroxy compound **12** has variously been described as dark brown (9), reddish brown (10), orange (11), or bright yellow (12) in color although the corresponding melting points are identical. Proof of structure is really convincing in only a few cases, such as for the 5-hydroxy (13) (non-natural), 6-hydroxy (**20**) (6), 5,6-dihydroxy (**27**) (4), and 6-methoxy-5-hydroxy (**26**) derivatives (14). Conversely, the identity (9) of important 8-hydroxyrubiadin [**12**] is deduced solely on the basis of a zinc dust distillation (a β-methyl group), the ir and uv spectra (a 1,8-dihydroxyanthraquinone), and the solubility in aqueous carbonate and the Shibata test (a 3-hydroxyl group). The natural product has been obtained by demethylation of the corresponding 8-methyl (7,8) and 3,8-dimethyl (15) ethers, and the structure of the latter has been confirmed by synthesis (15), yet considerable doubt remains as to the identity of the parent compound (1,16).

^{1}H- and ^{13}C-nmr spectra of rubiadins or of their derivatives should provide a number of the required reference values corresponding to the common substitution pattern. A single ^{13}C-nmr spectrum is known in this area, that of the 6-hydroxy compound (6), but isomeric substances, i.e., 2-methylquinizarins [**2**] [δ ($CDCl_3$) 2.36–2.38 (2-Me), 7.08–7.16 (H-3)] (17) and 3-methylalizarins [**3**] [δ ($CDCl_3$) 2.38–2.40



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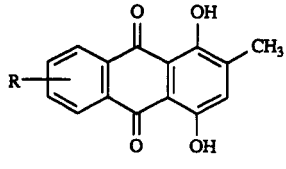

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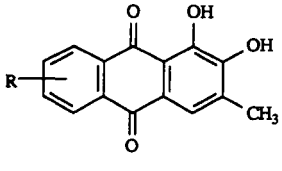

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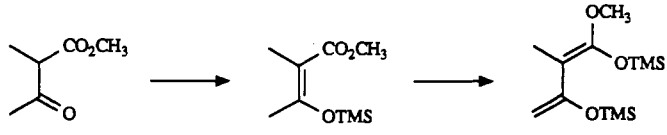
(3-Me), 7.69–7.72 (H-4)] (B. Montminy and P. Brassard, unpublished results) among others, do provide characteristic ^{1}H-nmr resonances. As for rubiadins, the data, when available show with few exceptions little consistency. Many spectra have been recorded in $CDCl_3$, in which such synthetic materials are insoluble.

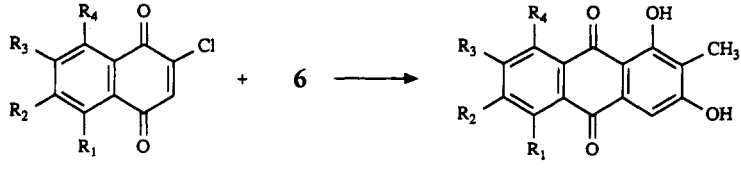
The validity of structures proposed for most anthraquinones is now securely established by several methods and particularly by applications of the Diels-Alder approach involving halogenated quinones and electron-rich dienes (18). The required reagent in most instances, 1-methoxy-1,3-bistrimethylsilyloxy-2-methylbutadiene [**6**], has been prepared previously (19,20) but for this investigation the starting material, methyl 2-methylacetoacetate [**4**], was conveniently obtained by alkylation of the parent pyrrolidine enamine with MeI (21,22). Consecutive enolsilylations using hexamethyldisilazane and imidazole (92%) followed by LDA and chlorotrimethylsilane (95%), as previously prescribed (20), provided the appropriate diene **6** (Scheme 1). In contrast to earlier observations, it was found that this compound could not be distilled without considerable rearrangement to the C-silylated product. Indeed, half of the reagent decomposes within 24 h at room temperature or within 1 month at −25°. Cycloadditions were therefore carried out between −5 and +5° in either CH_2Cl_2 or C_6H_6 using the freshly prepared diene which contained about 30% of the inert rearranged product.



4 **5** **6**

SCHEME 1

The first group of rubiadins was obtained straightforwardly by cycloaddition of diene **6** to the appropriate naphthoquinones **7–11**. Aromatization of the adduct with concentrated HCl in THF was generally rapid, leaving small amounts of a by-product, the 1-methyl ether, which was eliminated by refluxing the crude material in concentrated HBr and HOAc (overall yields 50–84%). In this approach, exemplified by Scheme 2, the nucleophilic end C-4 of the diene is known to combine with the quinonic carbon adjacent to the halogen-substituted position. Naphthoquinone substrates are therefore chosen in which the electronic effects present are complementary and hence facilitate the regiospecific process (23,24). [It is well established that

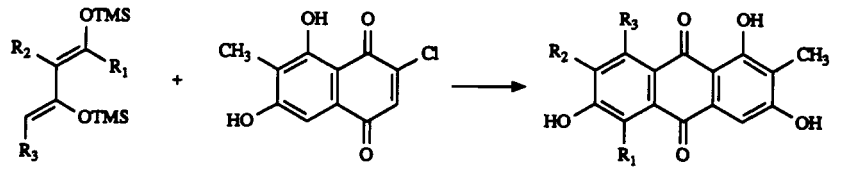


	R_1	R_2	R_3	R_4	
7	H	H	H	OH	**12**
8	H	OMe	H	OH	**13**
9	OH	H	H	OH	**14**
10	H	H	OH	H	**15**
11	H	H	H	OMe	**16**

SCHEME 2

nucleophilic attack on 3-halogenojuglones occurs at C-2 as a result of intramolecular hydrogen bonding and the effect of the halogen atom, while in 2-halogenojuglone ethers electron release to the 4-carbonyl and again the position of the halogen favor reaction at C-3. The electronic effects of substituents in these two cases can then be said to be complementary.] In one instance, however, the only convenient substrate, juglone methyl ether [**11**], gave the sole regioisomeric arrangement of **16** in spite of an unfavorable disposition of substituents [the isomeric 5-methoxyrubiadin having been obtained earlier (1)]. The incidental 1-methyl ether could obviously not be cleaved in the usual way (concentrated HBr/HOAc) without affecting the substituent at C-8, but separation of the corresponding 3-methoxymethyl derivatives by chromatography, followed by hydrolysis, was found to be effective (Scheme 2).

In cases where the foregoing device entails hindrance to the final cycloaddition, it becomes advisable to reverse the sequence of steps. By preparing first 3-chloro-6-methyl-7-hydroxyjuglone [**19**] from 2,6-dichlorobenzoquinone and diene **6**, a final reaction with diene **17** becomes particularly advantageous. Moreover, since 4-oxygenated dienes do not combine satisfactorily with benzoquinones, access to 5,6,7,8-tetrahydroxyrubiadin [**22**] involving the novel diene **18** [prepared from 2,4-dimethoxyacetoacetate (25) by double enolsilylation] is limited to this strategy (Scheme 3).



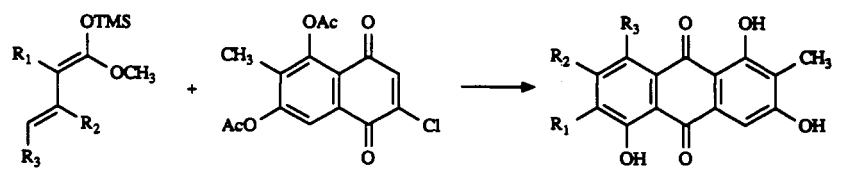
	R_1	R_2	R_3
17	H	H	H
18	OMe	OMe	OMe

19

	R_1	R_2	R_3
20	H	H	H
21	OMe	OMe	OH
22	OH	OH	OH

SCHEME 3

Finally, a number of rubiadins show substitution patterns that require 2-halogenated juglones as substrates, and although this arrangement is unfavorable it is well established that the electronic effect can be reversed by acetylating or otherwise blocking the phenolic groups. This was effectively carried out in the synthesis of knoxiadin [**26**] and 3-hydroxymorindone [**27**] starting from the naphthoquinone **25**. Although another similar approach could also have been successful in this case, this avenue is once again the only practical one for obtaining the rubiadin **28** (Scheme 4).



	R_1	R_2	R_3
23	OMe	H	H
24	H	Me	OTMS

25

	R_1	R_2	R_3
26	OMe	H	H
27	OH	H	H
28	H	Me	OH

SCHEME 4

Besides providing a number of precise criteria for the identification of novel rubiadins [i.e., the ^{1}H-nmr spectra of the pigments in DMSO (Table 1), the ^{1}H-nmr and ^{13}C-nmr spectra of their peracetates in $CDCl_3$ (Tables 2 and 3)], the present exercise also permits the drawing of some definitive conclusions as to the validity of some structures proposed earlier. As expected, the nature of knoxiadin [**26**] and 3-hydroxy-

TABLE 1. ^{1}H-nmr Chemical Shifts of Rubiadins (recorded at 200 MHz in DMSO-d_6).[a]

Compound	Substituent							
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
12	12.48 s	2.05 s	—	7.23 s	7.64 dd (7.3,1.5)	7.74 dd (8.2,7.3)	7.32 dd (8.2,1.5)	12.08 s
13	12.42 s	2.02 s	11.97	7.17 s	7.05 d (2.6)	3.88 s	6.76 d (2.6)	12.19 s
14	12.51 s	2.05 s	—	7.28 s	12.76 s	7.35 s		12.23 s
15	13.06 s	2.05 s	11.02 or 11.18 s	7.22 s	8.01 d (8.4)	7.17 dd (8.8,2.6)	11.02 or 11.18 s	7.49 d (2.6)
16	13.56 s	2.04 s	11.02 s	7.15 s	7.77 m	7.80 dd (8.1,7.7)	7.55 dd (8.1,1.8)	3.93 s
20	13.25 s	2.01 s	10.99 br s	7.16 s	7.39 d (2.2)	10.99 br s	7.17 dd (8.6,2.4)	8.01 d (8.8)
22	13.65 s	2.07 s	10.50 br s	7.31 s	12.67 or 12.76 s	10.50 or 11.22 s		12.67 or 12.76 s
26	13.37 s	2.06 s	12.78 or 12.79 s	7.28 s	12.78 or 12.79 s	3.92 s	7.41 d (8.4)	7.73 d (8.4)
27	13.37 s	2.02 s	11.10 br s	7.21 s	12.65 s	11.10 br s	7.15 d (8.1)	7.59 d (8.1)
28	12.50 s	2.00 s	11.30 s	7.16 s	12.78 s	7.16 s	2.20 s	12.35 s

[a]Chemical shifts in δ (ppm), coupling constants (Hz) in parentheses.

morindone [**27**] was fully confirmed by excellent agreement between the physical and spectral properties of the natural and those of the synthetic products. Although both 6-hydroxyrubiadin [**20**] and 7-hydroxyrubiadin [**15**] have been prepared, their physical and spectral properties do not agree with the extensive published values ascribed to

TABLE 2. ^{1}H-nmr Chemical Shifts of Rubiadin Acetates (recorded at 200 MHz in $CDCl_3$).[a]

Compound	Substituent							
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
12	2.43 or 2.47 s	2.13 s	2.37 s	7.91 s	8.17 dd (7.8,1.6)	7.73 t (8.2)	7.38 dd (7.8,1.6)	2.43 or 2.47 s
13	2.43 or 2.47 s	2.13 s	2.38 s	7.90 s	7.65 d (2.7)	3.95 s	6.88 d (2.7)	2.43 or 2.47 s
14	2.42,2.45 or 2.46 s	2.12 s	2.36 s	7.81 s	2.42,2.45 or 2.46 s	7.38 s		2.42,2.45 or 2.46 s
15	2.52 s	2.16 s	2.35 or 2.40 s	7.98 s	8.29 d (8.4)	7.48 dd (8.4,2.2)	2.35 or 2.40 s	7.93 d (2.6)
16	2.52 s	2.12 s	2.36 s	7.85 s	7.86 dd (7.4,1.2)	7.64 dd (8.4,7.7)	7.29 dd (8.4,1.1)	3.99 s
20	2.53 s	2.16 s	2.36 or 2.40 s	7.97 s	7.95 d (2.6)	2.36 or 2.40 s	7.51 dd (8.8,2.6)	8.24 d (8.4)
22	2.42,2.44 or 2.45 s	2.13 s	2.34 or 2.37 s	7.82 s	2.34 (or 2.37), 2.42, 2.44, 2.47			
26	2.47 or 2.52 s	2.14 s	2.37 s	7.88 s	2.47 or 2.52 s	3.95 s	7.30 d (8.8)	8.20 d (8.8)
27	2.46 or 2.51 s	2.15 s	2.36 or 2.38 s	7.89 s	2.46 or 2.51 s	2.36 or 2.38 s	7.60 d (8.4)	8.20 d (8.4)
28	2.41 or 2.44 s	2.11 s	2.36 s	7.79 s	2.41 or 2.44 s	7.25 s	2.30 s	2.41 or 2.44 s

[a]Chemical shifts in δ (ppm), coupling constants (Hz) in parentheses.

TABLE 3. ^{13}C-nmr Chemical Shifts of Rubiadin Acetates (A-Ring) (recorded at 50.3 MHz in $CDCl_3$)[a].

Compound	Position				
	C-1	C-2	C-3	C-4	C-2a
12	149.80 or 149.89	132.46 or 132.77	153.56	118.66	10.46
13	149.83	132.52 or 132.84	153.22	118.66	10.48
14	149.28	132.43	153.69	118.53	10.37
15	150.05	132.43 or 132.59	153.93	119.09 or 120.13	10.41
16	149.52	132.35 or 132.52	152.91	118.29 or 119.31	10.48
20	150.05	132.66	153.76	119.09 or 119.58	10.46
22	149.83	132.94 or 133.39	154.22	118.87	10.12
26	149.09	132.08	153.60	118.93	10.35
27	149.82	132.39 or 132.84	154.00	119.06	10.42
28	149.22	132.19	153.60	118.42	10.39

[a]Chemical shifts in δ (ppm).

compound **20** (6). Compounds described as the 8-hydroxy (**12**) (9–12), 8-methoxy (**16**) (7,8), and 5,8-dihydroxy (**14**) (26,27) derivatives of rubiadin must be considered to have been incorrectly identified in view of the discrepancies which now become apparent between their descriptions in the literature and those of synthetic materials. The status of compounds **13** (28,29), **22** (30,31), and **28** (32,33) remains ambiguous by reason of a dearth of comparable data or the unavailability of authentic samples.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were taken in capillary tubes with a Thomas-Hoover apparatus and are not corrected. The uv spectra were determined on a Hewlett-Packard 8450A spectrophotometer and the ir spectra on a Beckman Model IR-4250 instrument. Nmr spectra were recorded with Varian XL-200 and Varian GEMINI 300 spectrometers using TMS as an internal standard. Mass spectra were obtained with a Hewlett-Packard 5995A spectrometer. Merck Si gel 60F_{254} for dry cc and ICN SiliTech 32-63 60A for flash chromatography were used throughout in a product-to-adsorbent ratio of 1:50–100. A deactivated absorbent was obtained from Si gel (300 g) and 2% aqueous oxalic acid (800 ml). Elemental analyses were carried out by Galbraith Laboratories, Knoxville, TN.

PREPARATION OF DIENES.—*Methyl 2-methylacetoacetate* [**4**].—To a boiling mixture of the pyrrolidine enamine of methyl acetoacetate (34) (84.6 g, 0.50 mol) in MeCN (300 ml) was added MeI (46.7 ml, 0.75 mol) in the same solvent (100 ml). The solution was refluxed for 20 h while three more portions of MeI (12.5 ml in 60 ml of MeCN) were added at regular intervals. HOAc (30 ml) in H_2O (90 ml) was introduced and heating continued for an additional 2 h. Upon concentration for the reaction mixture under vacuum, extraction with CH_2Cl_2 (3 × 200 ml), and distillation of the residue, pure ester **4** (50.9 g, 78%) was obtained: bp 78–80°/20 mmHg); ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.36 (3H, d, J = 7.0 Hz, 2-Me), 2.25 (3H, s, H-4), 3.53 (1H, q, J = 7.0 Hz, H-2), 3.75 (3H, s, 1-OMe).

Methyl 2-methyl-3-trimethylsilyloxy-2-butenoate [**5**].—A mixture of methyl ester **4** (39.3 g, 0.30 mol), imidazole (1.23 g, 0.018 mol), and hexamethyldisilazan (35) (53.3 g, 0.33 mol) was heated to reflux for 2.5 h, stirred at room temperature for 16 h, and concentrated under vacuum. Distillation of the residue gave enol ether **5** (55.9 g, 92%), bp 60–62°/0.6 mmHg, as a 1:1 mixture of diastereomers: ir ν max (film) 1740 (sh), 1700, 1615, 890 (br) cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.21 (18H, s, 3-OTMSi), 1.73, 1.74 (2 × 3H, 2s, 2-Me), 2.23, 2.24 (2 × 3H, 2s, H-4), 3.67 (6H, s, 1-OMe).

1-Methoxy-2-methyl-1,3-bistrimethylsilyloxy-1,3-butadiene [**6**].—To a solution of LDA (44.4 mmol) in

THF (130 ml) at −78° was added dropwise under N_2 chlorotrimethylsilane (6.33 g, 58.2 mmol) in the same solvent (10 ml) and then ester **5** (7.50 g, 37.1 mmol) in THF (10 ml) (1 h) (36). After stirring for 1 h, the mixture was allowed to warm to room temperature, concentrated under vacuum, diluted with petroleum ether, bp 35–60° (250 ml), and filtered (this operation was repeated until salts no longer separated). The residue then consisted of a 3:1 mixture of diene **6** (as a single detectable stereomer) and methyl 2-methyl-4-trimethylsilyl-3-trimethylsilyloxy-2-butenoate (9.60 g): ^{1}H nmr (200 MHz, $CDCl_3$) δ for diene **6** 0.18, 0.21 (2 × 9H, 2s, 1,3-OTMSi), 1.63 (3H, s, 2-Me), 3.53 (3H, s, 1-OMe), 4.27, 4.40 (2H, 2s, H-4); for the 4-TMSi ester 0.02, 0.21 (2 × 9H, 2s, 4-TMSi and 3-OTMSi), 1.75 (3H, s, 2-Me), 2.39 (2H, br s, H-4), 3.65 (3H, s, 1-OMe).

Methyl 2,4-dimethoxy-3-trimethylsilyloxy-2-butenoate.—To a suspension of anhydrous $ZnCl_2$ (225 mg) in triethylamine (15.3 g, 0.150 mol) were added dropwise methyl 2,4-dimethoxyacetoacetate (25) (12.3 g, 0.070 mol) in C_6H_6 (20 ml) (1 h) and chlorotrimethylsilane (14.9 g, 0.137 mol) (1 h) (37). The reaction mixture was stirred at 45° for 12 h, cooled, filtered, concentrated under vacuum, diluted with petroleum ether (bp 35–60°), and again filtered (this was repeated until salts no longer precipitated). Distillation of the residue provided the title compound (14.3 g, 82%): bp 72°/0.2–0.3 mmHg; ir ν max (film) 1705, 1610, 840 cm^{-1}; ^{1}H nmr (200 MHz; $CDCl_3$) δ 0.24 (9H, s, 3-OTMSi), 3.35, 3.56, 3.77 (3 × 3H, 3s, 1,2,4-OMe), 4.36 (2H, s, H-4). Exact mass calcd for $C_{10}H_{20}O_5Si$, 248.1080; found 248.1071.

1,2,4-Trimethoxy-1,3-bistrimethylsilyloxy-1,3-butadiene [**18**].—In a preparation analogous to that of diene **6**, LDA (0.050 mol) in THF (130 ml), chlorotrimethylsilane (6.52 g, 0.060 mol), and methyl 2,4-dimethoxy-3-trimethylsilyloxy-2-butenoate (12.4 g, 0.050 mol) in THF (10 ml) gave diene **18** (14.5 g, 97%) as a 4:3 mixture of two stereomers: ^{1}H nmr (200 MHz, $CDCl_3$) δ major isomer 0.14, 0.18 (2 × 9H, 2s, 1,3-OTMSi), 3.45, 3.49, 3.71 (3 × 3H, 3s, 1,2,4-OMe), 5.92 (1H, s, H-4); minor isomer 0.16, 0.20 (2 × 9H, 2s, 1,3-OTMSi), 3.45, 3.56, 3.64 (3 × 3H, 3s, 1,2,4-OMe), 5.78 (1H, s, H-4).

QUINONES.—*3-Chloro-5,7-dihydroxy-6-methylnaphthoquinone* [**19**].—Diene **6** (9.33 mmol) was added dropwise to 2,6-dichlorobenzoquinone (1.06 g, 6.00 mmol) at 0° in dry CH_2Cl_2 (6 ml). The solution was stirred for 30 min and evaporated under vacuum (below 20°). After concentrated HCl (12 ml) in THF (60 ml) was added to the residue, the resulting mixture was stirred at room temperature for 2 h, heated to reflux for 30 min, diluted with H_2O (600 ml), and extracted with EtOAc (2 × 400 ml). Purification of the crude product by flash chromatography [CH_2Cl_2, then CH_2Cl_2-EtOAc (1:1)] gave quinone **19** (after rinsing with light petroleum ether) (918 mg; 64%), which decomposes at ca. 198° (EtOAc/petroleum ether, bp 80–110°): uv λ max (MeOH) (log ε) 222 (4.49), 272 (4.18), 440 (3.62), 656 (1.79) nm; ir ν max (KBr) 3390, 1650, 1620, 1580 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ 2.01 (3H, s, 6-Me), 7.00 (1H, s, H-8), 7.30 (1H, s, H-2), 11.29 (1H, s, 7-OH), 12.02 (1H, s, 5-OH); ms *m/z* [M]$^+$ 238. *Anal.* calcd for $C_{11}H_7O_4Cl$, C 55.37, H 2.96; found C 55.49, H, 3.20.

2-Chloro-5,7-dihydroxy-6-methylnaphthoquinone (parent compound of **25**).—According to the foregoing procedure, diene **6** (8.00 mmol) and 2,5-dichlorobenzoquinone (6.00 mmol) were allowed to react in CH_2Cl_2 (12 ml). After hydrolysis and aromatization of the adduct, the crude product, triturated with petroleum ether (bp 35–60°) and recrystallized from petroleum ether (bp 65–110°) afforded the title compound (1.016 g; 71%), which decomposes at ca. 228°: uv λ max (MeOH) (log ε) 222 (4.53), 272 (4.19), 442 (3.65), 658 (1.95) nm; ir ν max (KBr) 3450 br, 1665, 1625, 1575 cm^{-1}; ^{1}H-nmr (200 MHz, DMSO-d_6) δ 2.03 (3H, s, 6-Me), 7.11 (1H, s, H-8), 7.36 (1H, s, H-3), 11.22 (1H, s, 7-OH), 12.24 (1H, s, 5-OH). *Anal.* calcd for $C_{11}H_7O_4Cl$, C 55.36, H 2.96; found C 55.56, H 2.99. Acetate **25** (Ac_2O/H_2SO_4): mp 201–202° (EtOH); ^{1}H nmr (200 MHz, $CDCl_3$) δ 2.13 (3H, s, 6-Me), 2.39, 2.47 (2 × 3H, 2s, 5, 7-OAc), 7.06 (1H, s, H-3), 7.83 (1H, s, H-8).

1,3,8-Trihydroxy-2-methylanthraquinone (8-hydroxyrubiadin) [**12**].—Diene **6** (1.50 mmol) was added to 3-chlorojuglone [7] (38) (208 mg, 1.00 mmol) in CH_2Cl_2 (6 ml) at 0° followed after 12 h and 22 h by two more portions of 0.50 mmol each. When the cycloaddition was complete (tlc), the mixture was evaporated and the residue treated with concentrated HCl (2 ml) in THF (10 ml) for 2 h at room temperature and 30 min at reflux. The crude product was recovered and purified as in the preceding paragraph, providing 8-hydroxyrubiadin [**12**] (134 mg, 50%), which decomposes at ca. 310° [lit. (9,10) mp 232°; (12,39,40) 230°; (11) 229°]: uv λ max (MeOH) (log ε) 247 (4.16), 278 (4.52), 434 (4.00) nm; ir ν max (KBr) 3390, 1665, 1615, 1595, 1580 cm^{-1}; ms *m/z* [M]$^+$ 270 (100). *Anal.* calcd for $C_{15}H_{10}O_5$, C 66.65, H 3.74; found C 66.67, H 3.71. Acetate (Ac_2O/H_2SO_4): mp 216–217° (EtOH) [lit. (9,12,39,40) 205°].

1,3,8-Trihydroxy-6-methoxy-2-methylanthraquinone (8-hydroxy-6-methoxyrubiadin) [**13**].—As in the foregoing procedure, diene **6** (3.00 mmol and, after 30 min, 0.75 mmol) and 3-chloro-7-methoxyjuglone [**8**] (41) (477 mg; 2.00 mmol) in CH_2Cl_2 (12 ml) (1 h), with an analogous workup, provided anthraquinone **13** (502 mg, 84%), which decomposes at ca. 290° [lit. (28,29) mp 250°]: uv λ max (MeOH) (log ε) 220 (4.41), 228 (4.37), 315 (3.98), 446 (3.95) nm; ir ν max (KBr) 3410, 1668, 1620, 1560 cm^{-1};

ms *m/z* $[M]^+$ 300 (54), 55 (100). Acetate (Ac_2O/H_2SO_4): mp 216–217° (EtOH) [lit. (29) mp 213°]. *Anal.* calcd for $C_{16}H_{12}O_6$, C 61.97, H 4.26; found C 61.78, H 4.25.

1,3,5,8-Tetrahydroxy-2-methylanthraquinone (5,8-dihydroxyrubiadin) [**14**].—The adduct obtained from chloronaphthazarin [**9**] (42) (449 mg, 2.00 mmol) and diene **6** (2.50 mmol and 3 additional portions of 0.75 mmol) (4.5 h) in C_6H_6 (15 ml) at 5° was hydrolyzed and aromatized in the usual way. The crude product was separated by chromatography [CH_2Cl_2, then CH_2Cl_2-EtOAc (1:3), and finally MeOH], heated to reflux (3 h) in a mixture of 48% HBr (30 ml) and HOAc (20 ml), and recovered by diluting with H_2O (250 ml) and extracting with EtOAc (2 × 250 ml). The residue, washed with light petroleum ether (3 × 250 ml) and recrystallized from EtOAc/petroleum ether (bp 80–110°), provided the required anthraquinone **14** (464 mg, 81%): mp 281–282° [lit. (43) mp 276–277°; (26) 220°]; uv λ max (MeOH) (log ε) 220 (4.38), 280 (4.31), 488 (4.12) nm; ir ν max (KBr) 3410, 1655, 1589 cm^{-1}; ms *m/z* $[M]^+$ 286 (100). *Anal.* calcd for $C_{15}H_{10}O_6$, C 62.94, H 3.53; found C 62.85, H 3.58. Acetate (Ac_2O/H_2SO_4): mp 232–234° (EtOH) [lit. (43) mp 223°; (26) mp 185°].

1,3,7-Trihydroxy-2-methylanthraquinone (7-hydroxyrubiadin) [**15**].—Diene **6** (2.50 mmol) in CH_2Cl_2 (6 ml) was added to 3-chloro-6-hydroxynaphthoquinone [**10**] (44) (414 mg, 2.00 mmol) in the same solvent (6 ml) at −30°. After evaporation of the solvent under vacuum, the residue was treated with 5% HCl (6 ml) in THF (20 ml) for 6 h at room temperature and 1 h under reflux. The crude product, recovered in the usual way (EtOAc), was washed with light petroleum ether (2 × 250 ml) and heated to reflux with 48% HBr (30 ml) in HOAc (20 ml) (1.5 h). Dilution of the mixture with H_2O and extraction with EtOAc gave anthraquinone **15** (382 mg, 71%), which decomposes at ca. 336° (MeOH/C_6H_6): uv λ max (MeOH) (log ε) 280 (4.54), 333 (4.04), 388 (3.91) nm; ir ν max (KBr) 3440, 3340, 1660, 1585, 1570 cm^{-1}; ms *m/z* $[M]^+$ 270 (100). Exact mass calcd for $C_{15}H_{10}O_5$, 270.0528; found 270.0576. Acetate (Ac_2O/H_2SO_4): mp 220–221° (EtOH).

1,3-Dihydroxy-8-methoxy-2-methylanthraquinone (8-methoxyrubiadin) [**16**].—In a similar reaction, diene **6** (3.00 mmol) and 3-chloro-5-methoxynaphthoquinone [**11**] (443 mg; 2.00 mmol) [prepared from **7** (MeI, Ag_2O, $CHCl_3$, 97%), mp 164–166°] in dry C_6H_6 (6 ml) at 6° (1 h) gave an adduct which was stirred with 10% HCl (4 ml) in THF (20 ml) at room temperature for 20 h and for 2 h more after addition of concentrated HCl (4 ml). The crude product was purified by flash chromatography [CH_2Cl_2, then CH_2Cl_2-EtOAc (4:1)] and gave a mixture (468 mg) of **16** and the corresponding 1-methyl ether. The anthraquinones were converted to their MOM-derivatives [diisopropylamine (0.4 ml), chloromethoxymethane (1.5 ml), THF (7 ml)] and separated by flash chromatography (CH_2Cl_2). The 3-methoxymethyl ether of **16** (219 mg) and the 1-methyl ether (180 mg) were hydrolyzed by heating to reflux with concentrated HCl (0.5 ml) in MeOH (30 ml) (1 h) to give quinone **16** (150 mg, 26%), which decomposes at ca. 313° (EtOAc) [lit. (7) mp 215°; (8) 238–240°]: uv λ max (MeOH) log 245 (4.33), 278 (4.40), 420 (4.00) nm; ir ν max (KBr) 3400 br, 1660 sh, 1615, 1580 cm^{-1}; ms *m/z* $[M]^+$ 284 (100). Acetate (Ac_2O/H_2SO_4): mp 224–225° (EtOH) [lit. (7) mp 195°; (8) 140–144°]. *Anal.* calcd for $C_{16}H_{12}O_5$, C 65.21, H 4.39; found C 65.45, H 4.31.

1,3,6-Trihydroxy-2-methylanthraquinone (6-hydroxyrubiadin) [**20**].—Diene **17** (45,46) (576 mg, 2.50 mmol) in C_6H_6 (6 ml) was added to naphthoquinone **19** (477 mg, 2.00 mmol) in the same solvent (6 ml) at 5°. The mixture was stirred at room temperature (18 h) and heated to reflux; additional portions of the diene (200 mg) were added after 24 h and 48 h of heating. Aromatization was carried out in the usual way with 5% HCl (9 ml) in THF (30 ml), stirring at room temperature for 2 h, and heating to reflux for 1 h. The crude product after rinsing with light petroleum ether (3 × 200 ml) gave 6-hydroxyrubiadin [**20**] (405 mg, 75%): mp ca. 340° (dec) [EtOAc/petroleum ether (bp 65–110°)] [lit. (6) mp 236–238°; (5) 167–168°]; uv λ max (MeOH) (log ε) 276 (4.55), 334 (3.81), 4.26 (3.77) nm; ir ν max (KBr) 3405, 1665, 1625, 1592 cm^{-1}; ms *m/z* $[M]^+$ 270 (100). *Anal.* calcd for $C_{15}H_{10}O_5$, C 65.65, H 3.74; found C 66.21, H 3.78. Acetate (Ac_2O/H_2SO_4): mp 238–239° (EtOH) [lit. (5) mp 180°].

1,3,5,6,7,8-Hexahydroxy-2-methylanthraquinone (5,6,7,8-tetrahydroxyrubiadin) [**22**].—A solution of diene **18** (244 mg; 0.748 mmol) in dry CH_2Cl_2 (3 ml) was added at 0° to a suspension of naphthoquinone **19** (119 mg, 0.499 mmol) in the same solvent (5 ml). The mixture was stirred at room temperature for 72 h, additional portions of diene (500 mg, 1.67 mmol) being added after 24 and 48 h. Upon evaporation of the solvent, a solution of the adduct in a mixture of 5% HCl (2 ml) and THF (10 ml) was stirred at room temperature for 24 h, diluted with H_2O, and extracted with EtOAc. The crude quinone **21** in EtOAc (30 ml) was precipitated by addition of petroleum ether (bp 35–60°) (150 ml) and demethylated at 180° in a melt of $AlCl_3$ (20 g) and NaCl (4 g). Hydrolysis of the cooled reaction mixture and extraction with EtOAc provided anthraquinone **22** (40 mg, 25%): no mp (sinters at 155° and decomposes at ca. 308°) [EtOAc/petroleum ether (bp 65–110°)]; uv λ max (MeOH) (log ε) 220 (4.17), 287 (4.33), 333 (3.84), 480 (3.90) nm; ir ν max (KBr) 3160 br, 1610 sh, 1585 cm^{-1}; ms *m/z* $[M]^+$ 318 (100). Acetate (Ac_2O/H_2SO_4): mp 232–233° (EtOH). Exact mass calcd for $C_{15}H_{10}O_8$, 318.0375; found 318.0361.

1,3,5-Trihydroxy-6-methoxy-2-methylanthraquinone (5-hydroxy-6-methoxyrubiadin) (knoxiadin) [**26**].—To naphthoquinone **25** (322 mg, 1.00 mmol) in dry C_6H_6 (5 ml) at room temperature was added 1,2-dimethoxy-1-trimethylsilyloxybutadiene [**23**] (41) (445 mg, 2.20 mmol) followed after 12 h and 24 h by two more portions of the diene (222 mg, 1.10 mmol each). The adduct was then aromatized by slow percolation through a column of Si gel [C_6H_6, then C_6H_6-EtOAc (1:1)]. The 5-methyl ether was eliminated by treating the crude product with a refluxing mixture of 48% HBr (10 ml) and HOAc (6 ml). Recovery of the product by the usual means provided knoxiadin [**26**] (252 mg, 84%): mp ca. 344° (dec) (EtOAc) [lit. (14) mp >310°]; uv λ max (MeOH) (log ε) 225 (4.47), 276 (4.49), 315 (4.06), 444 (4.08) nm; ir ν max (KBr) 3420, 1620 (sh), 1595 cm^{-1}; ms *m/z* $[M]^+$ 300 (96), 55 (100). *Anal.* calcd for $C_{16}H_{12}O_6$, C 63.99, H 4.03; found C 63.87, H 4.03. Acetate (Ac_2O/H_2SO_4): mp 238–239° (EtOH) [lit. (14) mp 226–228°].

1,3,5,6-Tetrahydroxy-2-methylanthraquinone (5,6-dihydroxyrubiadin)(3-hydroxymorindone) [**27**].—The mixture of anthraquinones obtained in the preceding paragraph (after hydrolysis and aromatization of the adduct) was introduced into a molten mixture of anhydrous $AlCl_3$ (20 g) and NaCl (4 g) at 180°. Hydrolysis of the cooled melt and extraction with EtOAc gave 3-hydroxymorindone [**27**] (202 mg, 71%), which decomposes at ca 320° [EtOAc/petroleum ether (bp 80–110°)] [lit. (4) mp ≥ 300°; (14) 314–315°]; uv λ max (MeOH) (log ε) 226 (4.40), 275 (4.48), 316 (4.09), 456 (3.92) nm; ir ν max (KBr) 3440, 1600, 1485 cm^{-1}; ms *m/z* $[M]^+$ 286 (100). *Anal.* calcd for $C_{15}H_{10}O_6$, C 62.94, H 3.53; found C 62.52, H 3.55. Acetate (Ac_2O/H_2SO_4): mp 256–257° (EtOH) [lit. (4) mp 255–256°; (14) 248–250°].

1,3,5,8-Tetrahydroxy-2,7-dimethylanthraquinone (5,8-dihydroxy-7-methylrubiadin) [**28**].—The adduct obtained from diene **24** (47) (1.098 g, 4.00 mmol) in dry C_6H_6 (3 ml) and naphthoquinone **25** (645 mg, 2.00 mmol) in the same solvent (5 ml) at room temperature (5 h) was heated to reflux with concentrated HCl (4 ml) in THF (20 ml) (3.5 h). The crude product recovered in the usual way (H_2O, EtOAc) was treated with a boiling mixture of 48% HBr (30 ml) and HOAc (20 ml) (3 h) and gave anthraquinone **28** (435 mg, 72%), which decomposes at ca. 300° [EtOAc/petroleum ether (bp 80–110°)]; uv λ max (MeOH) (log ε) 227 (4.70), 258 (4.51), 280 (4.51), 486 (4.10), 518 (3.97) nm; ir ν max (KBr) 3400 (br), 1650 (sh), 1600, 1560 cm^{-1}; ms *m/z* $[M]^+$ 300 (100). Acetate (Ac_2O/H_2SO_4): mp 231–232° (EtOH) [lit. (32) mp 225–227°]. *Anal.* calcd for $C_{24}H_{20}O_{10}$, C 61.53, H 4.31; found C 61.60, H 4.34).

ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from NSERC (Canada) and FCAR (Quebec).

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Received 14 September 1992