g) was further purified by successive chromatography over Sephadex LH-20 (500 g; methanol/chloroform, 1:1) and silica gel (200 g; hexane/EtOAc, 9:1) to give pure **1** (1.41 g; 17%) as a white crystalline solid.

(7*E*,1*S*,3*S*,4*R*,12*S*,13*R*,14*R*)-13-Acetoxy-3,4-epoxycembra-7,15-dien-16,14-olide [Eupalmerin Acetate (1)]. The solid was recrystallized twice from hexane/benzene mixtures: mp 151-153 °C (lit.[4] mp 157-159 °C); $[\alpha]_D^{25} = +8.26°$ (c = 1.76 g/100 mL, $CHCl_3$) (lit.[4] $[\alpha]_D^{25} = +8°$); λ_{max} ($CHCl_3$) 242 nm (ϵ 300); IR (KBr) 1772 (s), 1736 (s), 1669 (w), 1459 (w), 1384 (m), 1234 (s), 1106 (s), 1048 (s), 1040 (s), 1032 (s), 970 (m), 940 (m), 925 (m), 814 (m), 679 (m), 580 (m) cm^{-1}; HREIMS M^+, 1%, m/z obsd 376.2240, $C_{22}H_{32}O_5$ requires 376.2250, 334 (4), 316 (7), 298 (4), 122 (36), 107 (58), 94 (100), 81 (97), 69 (53), 55 (87); ^1H and ^{13}C NMR (see Table I). In vitro screening data for eupalmerin acetate show potent cytotoxicity against CHO-K1 cells (ED_{50} = 9.3 μg/mL) and antimicrobial activity against *Shigella flexneri* and *Proteus vulgaris* (MIC = 1 μg/mL).

Acknowledgment. We thank Dr. P. Yoshioka of La Parguera Marine Biological Station, University of Puerto Rico at Mayagüez, for identification of the gorgonian, J. J. Morales, M. A. Medina, and G. Cabrera for help with collections, and M. Ortiz for continuous technical assistance. Special thanks are extended to P. J. Scheuer and W. P. Niemczura for the use of 500-MHz NMR instrumentation and A. Báez for performing the CHO-K1 cytotoxicity tests. High-resolution mass spectral determinations were performed by the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Facility (Grant No. CHE8211164). This study was supported in part by the National Science Foundation EPSCoR Program (Grant No. R118610677) and the University of Puerto Rico FIPI Program.

Registry No. I, 37299-08-4.

Supplementary Material Available: 500-MHz ^1H NMR and COSY spectra of compound 1 (2 pages). Ordering information is given on any current masthead page.

Reactions of 2,3-Dihydro-9,10-dihydroxy-1,4-anthracenedione (Leucoquinizarin) with Hydrazine and Substituted Hydrazines

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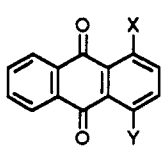
Received March 1, 1990

Introduction

Our previous attempts to prepare 1,4-bis(hydrazino)-anthracene-9,10-dione (**1a**) by ipso substitutions of the fluorides of **1b** by *N,N*-dimethylhydrazine have been unsuccessful.[1] The N-N bond cleavage products **1c** (48%) and **1d** (40%) were isolated from this reaction.



1a, X = Y = $NHN(CH_3)_2$
b, X = Y = F
c, X = F, Y = $N(CH_3)_2$
d, X = Y = $N(CH_3)_2$
e, X = Y = NH_2
f, X = OH, Y = NH_2

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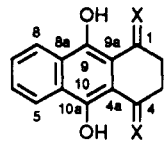
Treatment of 2,3-dihydro-9,10-dihydroxy-1,4-anthracenedione (**2a**) (leucoquinizarin) with primary amines leads to the corresponding bis(imines). These



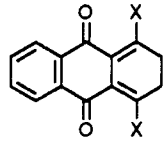
2a, X = O
b, X = NNH_2
c, X = $NNHCH_3$
d, X = $NN{=}C(CH_3)_2$

bis(imines) generally undergo facile air oxidations to yield the 1,4-bis(aminoalkyl)anthracene-9,10-diones. Numerous anthracene-9,10-dione analogues have been prepared by this procedure for antitumor evaluations.[2]

A literature survey uncovered only one related process in which a product formulated as **2b** was obtained by treatment of **2a** with aqueous hydrazine.[3] No evidence was presented for the structure being this particular tautomeric form. We report our results of an investigation of the reactions of **2a** with hydrazine and substituted hydrazines, which has uncovered some interesting N-N bond cleavages.

Results and Discussion

Treatment of **2a** with hydrazine or methylhydrazine at room temperature yielded bis(hydrazones) **2b** and **2c**, respectively. Both are rather unstable and quite difficult to purify. Attempts to oxidize these compounds to the corresponding 1,4-bis(hydrazino) 9,10-diones were unsuccessful. However, **2b** on treatment with acetone formed a crystalline derivative formulated as **2d**. These structures rather than the alternative tautomeric forms **3a-c** are



3a, X = $NHNH_2$
b, X = $NHNHCH_3$
c, X = $NHN{=}C(CH_3)_2$

based on ^1H NMR and ^{13}C NMR data. In particular, since the resonance peak for the carbonyl carbon (C-9,10) of an anthracene-9,10-dione is characterized by an absorption at about 180 ppm,[4-8] the absence of this peak would appear to exclude these structures.

The pertinent ^{13}C data are tabulated in Table I.

When hydrazine was refluxed with **2a**, a complex reaction mixture was obtained that proved difficult to char-

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0022-3263/90/1955-4960$02.50/0

Table I. ^{13}C NMR Data for 2a–d

	C-1,4	C-2,3	C-5,8	C-6,7	C-9,10	C-8a,I0a	C-4a,9a	other
2a[a]	200.8	35.7	124.4	130.4	154.9	129.1	107.3	
2b[b]	149.5 (s)[c]	20.0 (t)	122.3 (d)	125.9 (d)	146.5 (s)[c]	125.3 (s)	108.0 (s)	
2c[d]	148.2[c]	20.1	122.2	125.3	146.2[c]	125.8	107.5	30.72[e]
2d[b,f]	164.4 (s)	23.1 (t)	123.9 (d)	128.1 (d)	154.5 (s)	128.0 (s)	106.1 (s)	*g*, *h*

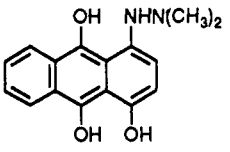
[a] $CDCl_3$.[5] [b] DMSO-d_6, proton coupled. [c] Assignments may be reversed. [d] DMSO-d_6, proton decoupled. [e] Methyl group bonded to nitrogen. [f] Reference 9 reports data for $(CH_3)_2C{=}NN(CH_3)_2$, azines, and other hydrazones. [g] $-N{=}C(CH_3)_2$ (q) for anti CH_3 at 25.62; (q) for syn CH_3 at 18.96. See ref 9. [h] $-C{=}N(CH_3)_2$, 166.07 for hydrazone carbon, may be reversed with C-1,4.

acterize. On the other hand, when **2a** was refluxed in methylhydrazine, 1,4-diaminoanthracene-9,10-dione (**1e**) was obtained (30%).

Treatment of **2a** with *N,N*-dimethylhydrazine at room temperature led to 1-amino-4-hydroxyanthracene-9,10-dione (**1f**; 59%). A small amount of the desired bis(hydrazine) **1a** (10%) was also isolated. In this case, the same **1f**:**1a** product ratio also resulted if the reaction was conducted at reflux.

While the formation of hydrazones **2b** and **2c** is unexceptional, the observation that they exist predominantly as these tautomers is of interest.

A N–N bond cleavage of a hydrazine intermediate has been found in the conversion of a 1,2,3,4-tetrahydro-β-carboline to a 4-amino-β-carboline.[10] A mechanism has been proposed for this transformation. In the formation of **1f** from *N,N*-dimethylhydrazine and **2a**, an intermediate such as **4** might be involved which could undergo a N–N bond cleavage to **5** followed by a tautomerization to **1f**.



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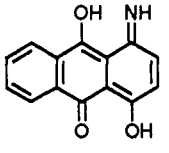

5

The formation of the double N–N cleavage product **1e** from **2a** and methylhydrazine is interesting, but mechanistic speculation about its formation would appear to be unwarranted at this time.

Experimental Section

Melting point were determined on a Thomas-Hoover apparatus and are uncorrected. ^1H NMR were run on a Bruker WM-250 pulsed Fourier transform spectrometer. TLC precoated silica gel plates (Eastman chromagram sheets with fluorescent indicator) were used to monitor reactions. For column chromatography Baker analyzed 80–200-mesh silica gel was utilized. Microanalyses were performed by Robertson Laboratories, Madison, NJ.

2,3-Dihydro-9,10-dihydroxy-1,4-anthracenedione Bis(hydrazone) (2b). Leucoquinizarin (**2a**; 1 g, 4.1 mmol) and anhydrous hydrazine (24 g, 757 mmol) were stirred at room temperature under nitrogen for 3.5 h. The reaction mixture was poured into brine and filtered to yield a brownish solid (1.02 g, 91%). Analysis by TLC (silica gel, 95% $CHCl_3$/MeOH) showed one major yellow spot, a minor red spot, and traces of other components: ^1H NMR (DMSO-d_6) δ 2.77 (s, 4 H), 6.68 (s, 4 H), 7.45 (m, 2 H), 8.15 (m, 2 H), 14.32 (s, 2 H).

Column chromatography (silica gel, 95% $CHCl_3$/MeOH) of 210 mg of the crude product gave a yellow solid (100 mg) and a red uncharacterized solid (20 mg). The yellow solid changed to red on standing in air for 1 day and had an ^1H NMR similar to that of the crude reaction product.

Bis(acetone hydrazone) 2d. Crude **2b** (212 mg, 0.78 mmol) was refluxed in acetone (20 mL) for 4 h. Crystalline purple needles were collected upon cooling (177 mg, 65%) and were identified as **2d**: ^1H NMR ($CDCl_3$) δ 2.01 (s, 6 H), 2.20 (s, 6 H), 3.25 (s, 4 H), 7.6 (m, 2 H), 8.4 (m, 2 H), 15.34 (s, 2 H); mp 208–211 °C. Anal. Calcd for $C_{20}H_{22}N_4O_2$: C, 68.57; H, 6.28; N, 16.00. Found: C, 68.34; H, 6.51; N, 15.73.

2,3-Dihydro-9,10-dihydroxy-1,4-anthracenedione Bis(2-methylhydrazone) (2c). Leucoquinizarin (**2a**; 0.5 g, 2.1 mmol) and methylhydrazine (8.7 g, 190 mmol) were stirred at room temperature for 18 h. The mixture was poured into saturated brine, and a brown solid was collected (0.5 g, 80%). Analysis by TLC (silica gel, $CHCl_3$) showed the presence of a major yellow compound: ^1H NMR (DMSO-d_6) δ 2.79 (s, 4 H), 2.99 (s, 6 H), 6.59 (s, 2 H), 7.48 (m, 2 H), 8.15 (m, 2 H), 14.08 (s, 2 H); mp 120–128 °C (attempts at purification led to decomposition).

1,4-Bis(*N,N*-dimethylhydrazino)anthracene-9,10-dione (1a) and 1-Amino-4-hydroxyanthracene-9,10-dione (1f). (a) Reflux Conditions. Leucoquinizarin (**2a**; 500 mg, 2 mmol) and *N,N*-dimethylhydrazine (4.0 g, 16 mmol) were stirred at reflux under nitrogen for 4 h. The mixture was poured into ice–water, and a purple solid (510 mg) was collected. A 200-mg portion of this crude solid was crystallized from benzene to yield dark red needles with a greenish metallic luster of **1f**: 116 mg, 59%; mp 208–209 °C (lit.[11] mp 206 °C); ^1H NMR ($CDCl_3$) δ 7.01 (d, 1 H), 7.20 (d, 1 H), 7.80 (m, 2 H), 8.35 (m, 2 H), 13.56 (s, 1 H). Analysis of the crude product by TLC (silica gel, $CHCl_3$) indicated the presence of yellow, blue, and red components (**1f**). Chromatography ($CHCl_3$, silica gel) yielded a yellow compound, which was not characterized, and a blue compound was identified as **1a**: 10%; mp 152–154 °C (EtOH/H_2O); ^1H NMR ($CDCl_3$) 2.69 (s, 12 H), 7.72 (m, 2 H), 7.95 (s, 2 H), 8.30 (m, 2 H), 10.98 (s, 2 H). Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.64; H, 6.21; N, 17.28. Found: C, 66.48; H, 6.14; N, 17.08. The red component **1f** was also isolated.

(b) Room-Temperature Conditions. Leucoquinizarin (**2a**; 1 g, 4.1 mmol) and *N,N*-dimethylhydrazine (12 g, 197 mmol) were stirred at room temperature for 19 h. The mixture was poured into brine to yield a purple solid (1 g). Analysis by TLC and R_f comparisons showed **1a** and **1f** to be present. Analysis by ^1H NMR ($CDCl_3$) indicated a **1a**:**1f** ratio of 1:2.8.

1,4-Diaminoanthracene-9,10-dione (1e). Leucoquinizarin (**2a**; 300 mg, 1.24 mmol) was refluxed in methylhydrazine (3 mL) for 4 h under nitrogen. The purple solution was poured into brine, and a purple solid (295 mg) was collected. Crystallization from pyridine/water gave **1e**: 89 mg, 30%; mp 247–251 °C (lit.[12] mp 263 °C); ^1H NMR δ 6.91 (s, 2 H), 7.07 (s, 4 H), 7.71 (m, 2 H), 8.33 (m, 2 H).

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On the Resonance Energy of Methylenecyclopropene and Cyclopropenone

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Received February 5, 1990

The aromaticity of methylenecyclopropene (**1**) and cyclopropenone (**2**) have been discussed and debated over many years.[1-8] The arguments revolve about the defi-

