Journal of Natural Products
Vol. 58, No. 11, pp. 1772-1775, November 1995

SYNTHESIS OF (±)-PLOIARIQUINONES A AND B

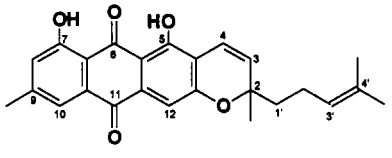
ALLA Y. TCHIZHOVA, VICTOR P. ANUFRIEV,* VLADIMIR A. DENISENKO, and VYACHESLAV L. NOVIKOV

Pacific Institute of Bioorganic Chemistry, Far East Division, Russian Academy of Sciences, 690022, Vladivostok-22, Russia

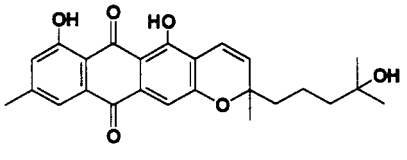
ABSTRACT.—Citral was reacted with emodin [**3**] in the presence of pyridine to give (±)-ploiariquinone A [**1**]. Oxymercuration of **1** using $Hg(OAc)_2$ followed by reduction of the mercurial intermediate by $NaBH_4$ yielded a complex mixture from which (±)-ploiariquinone B [**2**] was isolated. Ploiariquinones A and B have been isolated previously from *Ploiarium alternifolium*.

Anthraquinones bearing 2,2-dialkylpyran rings are extremely rare natural products (1,2). Ploiariquinones A [**1**] and B [**2**] were the first naturally occurring anthra[2,3-b]pyran-6,11-diones to be isolated, and are the pigments of the bark of the cicada tree, *Ploiarium alternifolium* (3). Ploiariquinone B [**2**], unlike the pigment **1**, is the minor component and contains an hydroxy group in the side-chain. We now report the first synthesis of ploiariquinones A and B and provide some reasoning relative to the origin of ploiariquinone B.

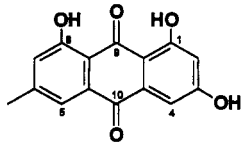
Retrosynthetically, ploiariquinone A [**1**] can be produced by the reaction of 1,2-addition of emodin [**3**] to citral followed by dehydration and hetero-Diels-Alder cyclization of the resulting dienone. This approach has been used previously for the synthesis of some other natural products (4–6).



1



2



3

The nucleophility of the aromatic nucleus of emodin [**3**] is reduced because of the electron-withdrawing influence of the 9,10-carbonyl groups. Therefore, we failed to perform this reaction successfully under acidic catalysis (4). However, citral condenses with emodin [**3**] under pyridine catalysis (5,6) to give the desired product **1**. The ^{13}C-nmr spectrum of **1** agreed with that of natural ploiariquinone A [**1**] (3). However, in the ^{1}H-nmr spectrum of **1** (in $CDCl_3$), the signals due to the aromatic protons H-12 (δ 7.25) and H-10 (δ 7.61) differed from those reported (3) for ploiariquinone A (δ 7.12 and δ 7.46, respectively). Therefore, additional proof of the structure of the synthetic material was required.

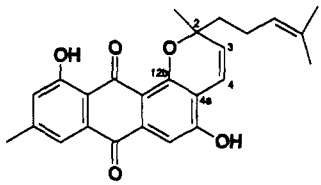
The ^{1}H-nmr spectrum of product **1** showed signals due to two chelated hydroxy groups (δ 12.13 and 12.59) that helped eliminate the possibility of the formation of the 4a,12b-pyran structure **4** (Table 1). The chemical shifts of H-3 and H-4 in the chromene system precluded the possibility of the isomeric 4a,12a-pyran structure **5** because, in that case, the carbonyl group would significantly deshield H-4 [to ca. δ 7.83 (7)]. In the ^{1}H-nmr spectrum of **1**, the signal of

TABLE 1. ^{1}H-Nmr Data of Compounds **1**, **6–8**, **10a**, and **10b** in $CDCl_3$ [δ (*J*, Hz)].[a]

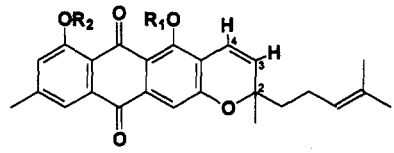
Position	Compound				
	1	**6**	**7**	**8**	**10a, 10b**
3	5.69 d (10.1)	5.80 d (10.1)	5.82 d (10.1)	5.68 d (10.1)	5.67 d (10.0)
4	6.80 br d (10.1)	6.52 br d (10.1)	6.54 br d (10.1)	6.80 br d (10.1)	6.81 br d (10.0)
5	12.59 s (OH)	2.48 s (OAc)	2.49 s (OAc)	13.25 s (OH)	12.60 s (OH)
7	12.13 s (OH)	2.47 s (OAc)	12.76 s (OH)	2.45 s (OAc)	12.12 s (OH)
8	7.06 d (1.5)	7.98 d (1.5)	7.06 d (1.5)	8.03 d (1.5)	7.06 d (1.5)
10	7.61 d (1.5)	7.17 d (1.5)	7.58 d (1.5)	7.19 d (1.5)	7.61 d (1.5)
12	7.25 br s	7.53 br s	7.59 br s	7.20 br s	7.22 br s
3′	5.09 br t (7.0)	5.07 br t (7.0)	5.08 br t (7.0)	5.08 br t (7.0)	4.32 t (6.4) [3.90 t (6.4)][b]
4′	1.57 br s	1.56 br s	1.57 br s	1.57 br s	1.72 br s
5′	1.66 br s	1.65 br s	1.66 br s	1.66 br s	5.03 m

[a]The resonances of Me groups at positions 2 and 9 for all compounds were observed at δ 1.45–1.49 and δ 2.42–2.45, respectively.

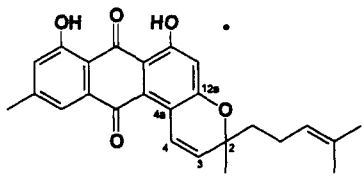
[b]For compound **10b**.



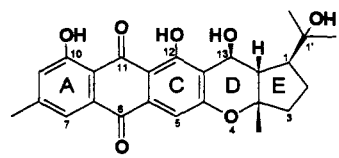
4



6 $R^1=R^2=Ac$
7 $R^1=Ac, R^2=H$
8 $R^1=H, R^2=Ac$



5



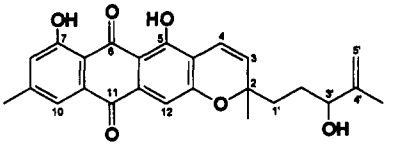
9

H-4 was observed at δ 6.80. The structure of **1** was further supported by examining the changes in chemical shift of the H-3 and H-4 protons produced on acetylation. Merlini *et al.* (8) have collated nmr data proving that when H-4 of the chromene ring is peri to a hydroxy group, acetylation causes an upfield shift ($\Delta\delta \approx 0.3$ to 0.4) while H-3 changes by $\delta \approx 0.1$. In the present case, the relevant nmr data of the corresponding di- and monoacetates **6–8** are shown in Table 1. They are consistent only with structure **1**. In addition, comparison of the ^{1}H-nmr data of compounds **1**, **7**, and **8** allowed unambiguous assignment of the signals due to the peri hydroxy groups OH-5 and OH-7 of ploiariquinone A [**1**] (δ 12.59 and δ 12.13, respectively).

Oxymercuration of **1** using $Hg(OAc)_2$ in aqueous THF followed by the *in situ* reduction of the mercurial intermediate by alkaline $NaBH_4$ afforded a complex mixture. Chromatography on Si gel and elution with hexane/Me_2CO gave three zones. The first zone was identified as unreacted ploiariquinone A [**1**]. The second constituent was the cyclopentapyranoquinone **9** (8%), which was purified by further prep. tlc. Structure **9** was established on the basis of ^{1}H-nmr investigations (decoupling, INDOR)

as well as ir and ms data. In the ^{1}H-nmr spectrum of **9** (in C_6D_6) the signal due to H-13a appeared as a triplet at δ 2.17. From the H-13a/H-13 and H-13a/H-1 coupling constants (8.2 Hz for each signal), the trans-orientation of the proton at C-13a to the adjacent H-13 and H-1 could be deduced. A strong nOe between the methyl group at C-3a and the proton at C-13a showed clearly the cis-linkage of rings D and E in **9**. Finally, the third zone was purified further by prep. tlc to yield two compounds. The ^{1}H-nmr spectrum of the less polar compound proved to be similar to that of ploiariquinone A [**1**]. However, among the signals associated with the side-chain, some important differences are noted: (a) the disappearance of the signal at δ 5.09 (1H, br t); (b) the replacement of the methyl signal at δ 1.57 (or δ 1.66) by two exomethylene group resonances at δ 5.02 and 5.04 (2H, m for each signal); (c) the appearance of signals at δ 4.32 and 3.90 (1H, br t, J=6.4 Hz for each) (Table 1). These results are consistent with the identity of this compound as a mixture (ca. 1:1) of the diastereoisomers **10a** and **10b** (22%). The more polar of the two compounds proved to be identical in all respects (except optical rotation) with ploiariquinone B [**2**] (44%).

It should be noted that small amounts of **2** were found when the solution of **1** in EtOAc was worked up using H_2O or when chromatographic purification was carried out according to Bennett's procedure (3). Taking into account the apparent ease of conversion of **1** to **2** under these conditions it may be suggested that quinone **2** is, at least in part, an artifact of the isolation or chromatographic procedure.



10a 2 (*R**), 3′ (*R**)
10b 2 (*R**), 3′ (*S**)

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mps were determined with a Boethius apparatus and are uncorrected. The ir spectra were measured on a Specord M82. All nmr experiments were run on a Bruker WM-250 instrument using $CDCl_3$ or C_6D_6 as solvent and TMS as an internal reference (δ 0). Eims were taken on a LKB-9000S mass spectrometer (direct inlet probe, ionizing energy 70 eV). Silufol® plates were used for tlc and R_f values for all compounds were determined using hexane-EtOAc (3:1). Prep. tlc and cc were performed on Si gel L [Chemapol, Czechoslovakia] 5/40 and 40/100 (μm), respectively.

(±)-PLOIARIQUINONE A [**1**].—A mixture of emodin [**3**] (540 mg, 2.0 mmol), freshly distilled citral (3.4 ml, 20.0 mmol), and anhydrous pyridine (0.4 ml, 5.0 mmol) was heated at 150° for 12 h. The excess of pyridine and citral was evaporated off under reduced pressure and the residue was chromatographed on a Si gel column using a gradient of Me_2CO in hexane (1:20→1:5). The zone (R_f 0.78) was collected and crystallized from Me_2CO to yield orange crystals of 5,7-dihydroxy-2,9-dimethyl-2-(4′-methylpent-3′-en-1′-yl)-2H-anthra[2,3-b]pyran-6,11-dione [(±)-ploiariquinone A] [**1**] (25%), mp 139–142° [lit. (3) mp 144–146°]; ^{1}H-nmr data, see Table 1; eims *m/z* 404 $[M]^+$ (9), 389 (4), 361 (4), 321 (100); *anal.*, found C, 74.1, H, 6.2; calcd for $C_{25}H_{24}O_5$ C, 74.2, H, 6.0%.

ACETYLATION OF **1**.—Ploiariquinone A [**1**] (80.8 mg, 0.2 mmol) in anhydrous pyridine (0.75 ml) was treated with a mixture of Ac_2O (1.0 ml) and pyridine (0.75 ml) at 0°. The reaction mixture was stirred at room temperature for 12 h, poured in ice-H_2O and extracted with Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), filtered, and concentrated. The diacetate **6** and a mixture of monoacetates [**7**, **8**] were separated by prep. tlc with hexane-Et_2O-HCOOH (8:5:1).

5,7-Diacetoxy-2,9-dimethyl-2-(4′-methylpent-3′-en-1′-yl)-2H-anthra[2,3-b]pyran-6,11-dione [**6**].—27%, mp 70–72°; R_f 0.38; ^{1}H-nmr data, see Table 1; eims *m/z* 488 $[M]^+$ (7), 446 (9), 431 (7), 405 (22), 396 (17), 378 (17), 363 (88), 321 (100); *anal.*, found: C, 71.1, H, 6.1; calcd for $C_{29}H_{28}O_7$: C, 71.3, H, 5.8%.

5-Acetoxy-7-hydroxy-2,9-dimethyl-2-(4′-methylpent-3′-en-1′-yl)-2H-anthra[2,3-b]pyran-6,11-dione [**7**] and *7-acetoxy-5-hydroxy-2,9-dimethyl-2-(4′-methylpent-3-en-1′-yl)-2H-anthra[2,3-b]pyran-6,11-dione* [**8**].—[2.5:1, respectively (^{1}H nmr)] (55%); R_f 0.58; ^{1}H-nmr data, see Table 1.

OXYMERCURATION OF **1**.—Ploiariquinone A [**1**] (404 mg, 1.0 mmol) in THF (15.0 ml) was added to a stirred solution of $Hg(OAc)_2$ (319 mg,

1.0 mmol) in H_2O (2.0 ml). The reaction mixture was stirred at room temperature for 2 h and NaOH (1.0 ml; 3.0 M) was added, followed by a solution (1.0 ml) of $NaBH_4$ (0.5 M) in NaOH (3.0 M). After 15 min, the reaction mixture was carefully acidified with diluted HCl to pH 7–8. NaCl was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed over a Si gel column with hexane-Me_2CO (4:1) to yield three fractions. The first of these was identical with ploiariquinone A [**1**] (0.48 mmol), R_f 0.78.

The component of intermediate polarity was purified by further prep. tlc with hexane-Me_2CO (4:1) to yield (1α,3aβ,13α,13aβ)-2,3,3a,13a-tetrahydro-10,12,13-trihydroxy-1-(1′-hydroxy-1′-methylethyl)-3a,8-dimethyl-1H,13H-cyclopenta[e]anthra[2,3-b]pyran-6,11-dione [**9**] (8%), mp 246–251°; R_f 0.58; ir ν max ($CHCl_3$) 3617 (free OH), 3100 (br, chelated OH), 1677 (C=O), 1626 (chelated C=O), 1601 (C=C), 1565, 1471 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.31 (3H, s, Me at C-3a), 1.38 (3H, s, Me), 1.40 (3H, s, Me), 1.60–1.95 (3H, m), 2.08 (1H, m, H_{eq}-3), 2.45 (3H, s, Me), 2.70 (1H, m, ΣJ=31.2 Hz, H-1), 2.80 (1H, t, J=8.4 Hz, H-13a), 5.28 (1H, d, J=8.4 Hz, H-13), 7.08 (1H, d, J=1.6 Hz, H-9), 7.33 (1H, s, H-5), 7.62 (1H, d, J=1.6 Hz, H-7), 12.14 (1H, s, OH-10), 12.87 (1H, s, OH-12); ^1H nmr (C_6D_6) δ 1.09 (3H, s, Me at C-3a), 1.17 (6H, s, 2×Me), 1.23–1.41 (3H, m), 1.75 (1H, m), 2.05 (1H, m, J=31.0 Hz, H-1), 2.17 (1H, t, J=8.2 Hz, H-13a), 5.29 (1H, d, J=8.2 Hz, H-13), 6.78 (1H, d, J=1.8 Hz, H-9), 7.58 (1H, d, J=1.8 Hz, H-7), 7.65 (1H, s, H-5), 12.21 (1H, s, OH-10), 13.00 (1H, s, OH-12); eims *m/z* 422 [M^+-CH_4] (5), 421 [M^+-OH] (12), 420 [M^+-H_2O] (43), 406 [M^+-CH_3OH] (18), 405 [M^+-OH, CH_4] (7), 366 (8), 364 (17), 362 (10), 322 (12), 321 (47), 285 (35), 284 (100); *anal.*, found C, 68.4, H, 6.1; calcd for $C_{25}H_{26}O_7$ C, 68.5, H, 6.0%.

The more polar constituent was chromatographed a further three times (prep. tlc) using CH_2Cl_2-hexane (5:1). A yellow band (R_f 0.37) afforded 5,7-dihydroxy-2,9-dimethyl-2-(3′-hydroxy-4′-methylpent-4′-en-1′-yl)-2H-anthra[2,3-b]pyran-6,11-dione [**10**] as a mixture of diastereoisomers (22%), mp 116–119°; ir ν max ($CHCl_3$) 3615 (free OH), 3538 (OH), 3210 (OH), 3105 (br, chelated OH), 3075 (=CH_2), 1671 (C=O), 1645 (=CH_2), 1616 (chelated C=O), 1601 (C=C), 1561, 1470, 900 (=CH_2) cm^{-1}; ^1H-nmr data, see Table 1; eims *m/z* 420 $[M]^+$ (12), 322 (24), 321 (100); *anal.*, found C, 71.2, H, 6.0; calcd for $C_{25}H_{24}O_6$ C, 71.4, H, 5.8%.

A yellow-orange band (R_f 0.34) yielded a product that in all respects (except for optical rotation) was identical with 5,7-dihydroxy-2,9-dimethyl-2-(4-hydroxy-4′-methylpent-1′-yl)-2H-anthra[2,3-b]pyran-6,11-dione [(±)-ploiariquinone B] [**2**] (44%), mp 166–168° ($CHCl_3$) [lit. (3) mp 168–169°].

ACKNOWLEDGMENTS

We are greatly indebted to Drs. Ludmila S. Stepanenko and Nataliya P. Mischenko of the Pacific Institute of Bioorganic Chemistry for the supply of emodin [**1**].

LITERATURE CITED

1. R.H. Thomson, "Naturally Occurring Quinones," Academic Press, London, 1971, 2nd Ed.
2. R.H. Thompson, "Naturally Occurring Quinones," Chapman and Hall, London, 1987, 3rd Ed.
3. G.L. Bennett, L.J. Harrison, M.-S. Lim, K.-Y. Sim, E.-C. Tan, and J.D. Connolly, *Phytochemistry*, **30**, 3141 (1991).
4. G. Appendino, G. Cravotto, S. Tagliapietra, G.M. Nano, and G. Palmisano, *Helv. Chim. Acta*, **73**, 1865 (1990).
5. L. Crombie and R. Ponsford, *J. Chem. Soc. (C)*, 796 (1971).
6. W.M. Bandaranayake, L. Crombie, and D.A. Whiting, *J. Chem. Soc. (C)*, 804 (1971).
7. J.R. Cannon, K.R. Joshi, I.A. McDonald, R.W. Retallack, A.F. Sierakowski, and L.C.H. Wong, *Tetrahedron Lett.*, 2795 (1975).
8. A. Arnone, G. Cardillo, L. Merlini, and R. Moondelli, *Tetrahedron Lett.*, 4201 (1967).

Received 21 April 1995