Erythrina Alkaloids and a Pterocarpan from the Bark of *Erythrina subumbrans*†

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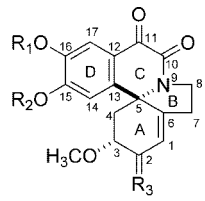
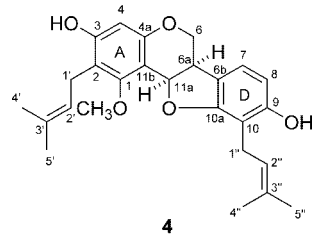
Three new erythrina alkaloids, (+)-10,11-dioxoerythratine (**1**), (+)-10,11-dioxoepierythratidine (**2**), and (+)-10,11-dioxoerythratidinone (**3**), and a new pterocarpan, 1-methoxyerythrabyssin II (**4**), were isolated from the bark of *Erythrina subumbrans*, together with seven known pterocarpans, erythrabyssin II, erybraedin A, erystagallin A, erycristagallin, erythrabissin-1, eryvarin A, and hydroxycristacarpone, three flavanones, 5-hydroxysophoranone, abyssinone V, and lespedezaflavanone B, three triterpenes, sophoradiol, soyasapogenol B, and lupeol, and one isoflavanone, vogelin C. Their structures were elucidated on the basis of spectroscopic data. Some isolates were tested for antiplasmodial, antimycobacterial, and cytotoxic activities.

As part of our continuing investigation on the traditional medicinal plants of Thailand, the bark of *Erythrina subumbrans* Merr. (Leguminosae) was investigated. Recently, we described the isolation of some pterocarpans, flavanones, an isoflavone, triterpenes, and steroids from the stems of this plant and their antibacterial, antiplasmodial, antimycobacterial, and cytotoxic activities.[1,2] In this paper, we report the isolation and structure elucidation of three new erythrina alkaloids and a new pterocarpan, designated (+)-10,11-dioxoerythratine (**1**), (+)-10,11-dioxoepierythratidine (**2**), (+)-10,11-dioxoerythratidinone (**3**), and 1-methoxyerythrabyssin II (**4**), along with 14 known compounds. The structures of compounds **1**−**4** were elucidated by spectroscopic data interpretation. Some of the isolates were evaluated for antiplasmodial, antimycobacterial, and cytotoxic activities.



1 $R_1 + R_2 = CH_2$, R_3 = β-OH, H
2 $R_1 = R_2 = CH_3$, R_3 = β-OH, H
3 $R_1 = R_2 = CH_3$, R_3 = O



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Compound **1** was obtained as a pale yellow, amorphous solid. The APCI-TOFMS displayed a $[M + H]^+$ ion peak at *m/z* 344.1128, consistent with the molecular formula $C_{18}H_{17}NO_6$. The IR spectrum showed the presence of OH (3460 cm^{-1}) and carbonyl (1686 and 1655 cm^{-1}) groups. The ^1H NMR spectrum exhibited signals of an olefinic proton [δ 6.01 (H-1)], four aliphatic protons in the A ring [δ 2.05 (H-4a), 2.13 (H-4e), 3.30 (H-3), and 4.35 (H-2)], four aliphatic protons in the B ring [δ 2.48 (H-7), 3.37 (H-8b), and 4.24 (H-8a)], a methoxy group [δ 3.17 (3-OCH_3)], a methylenedioxy group (δ 6.08 and 6.10), and two singlet aromatic protons [δ 6.92 (H-14) and 7.38 (H-17)]. The stereochemistry at C-2 and C-3 was deduced from the coupling constants $J_{2,3}$ (6.6 Hz), $J_{3,4eq}$ (4.2 Hz), and $J_{3,4ax}$ (11.8 Hz) in the ^1H NMR spectrum. These results were consistent with the OH group at C-2 and the methoxy group at C-3 and with both groups equatorial or in a *trans* relationship. Further support for this arrangement came from the NOESY spectrum, which displayed NOE correlations between H-2/H4a, H-3/H-14, and H-4e/3-OCH_3. The ^{13}C NMR spectrum revealed the presence of two carbonyl carbons at δ 159.1 (amide) and 180.6 (α,β-unsaturated ketone). In addition, the ^{13}C NMR spectrum of the partial structure (C-1−C-8) was similar to that of (+)-epierythratidine[3] except for reversal of the chemical shift assignments for C-2 (δ 72.6) and C-3 (δ 80.5) in **1** as compared to the values of C-2 (δ 81.0) and C-3 (δ 72.7) in (+)-epierythratidine. However, the lower values of carbon signals C-4, C-7, and C-8 in **1** might result from the deshielding effect of the carbonyl groups at C-10 and C-11. The ^1H and ^{13}C NMR spectra of the rest of the structure (C-10−C-17) were in good agreement with those of (+)-10,11-dioxoerythraline.[4] Biogenetic considerations on erythrina alkaloids[5,6] and the positive optical rotation value[3] suggested that **1** has an *S* configuration at C-5. Compound **1** was thus identified as (+)-10,11-dioxoerythratine.

Compound **2** was obtained as a pale yellow, amorphous solid whose molecular formula was $C_{19}H_{21}NO_6$ by APCI-TOFMS ($[M + H]^+$, *m/z* 360.1444). The IR spectrum showed absorption bands at 3474 (OH) and 1686 and 1650 cm^{-1} (C=O). The ^1H and ^{13}C NMR data of **2** were similar to those of **1**, with the only difference being that the latter contained two methoxy groups (δ 3.93 and 3.96) in place of a methylenedioxy group (δ 6.08 and 6.10). Compound **2** was therefore identified as (+)-10,11-dioxoepierythratidine.

Compound **3** had the molecular formula $C_{19}H_{19}NO_6$ by APCI-TOFMS ($[M + H]^+$, *m/z* 358.1288). The IR spectrum showed the presence of carbonyl groups (1670 cm^{-1}). The ^1H and ^{13}C NMR data of **3** were similar to those of **2**, except for the absence of the carbinolic proton at δ 4.38 and the presence of an additional carbonyl carbon at δ 196.8 assignable to C-2. Compound **3** was therefore identified as (+)-10,11-dioxoerythratidinone.

Compound **4** had the molecular formula $C_{26}H_{31}O_5$ as indicated by the APCI-TOF mass spectrum ($[M + H]^+$, *m/z* 423.2180). The UV and ^1H NMR spectra (δ 3.38, 3.57, 4.14, and 5.59) suggested that **4** was a pterocarpan derivative. In the ^1H NMR spectrum of **4**, two OH groups (δ 5.29, 5.47), two prenyl groups (δ 1.71, 1.75, 3.32, and 5.29; δ 1.74, 1.82, 3.35, and 5.22), a singlet aromatic proton (δ 6.25), and two *ortho*-coupled aromatic protons (δ 6.35 and 6.94) on rings A and D were assigned by comparison of the ^1H and ^{13}C NMR spectra with those of erythrabyssin II.[7] Placement of the methoxy group at C-1 was determined from a HMBC correlation between the methoxy signal and C-1. Further support for the C-1 methoxy group was obtained by the NOESY experiment, which revealed NOE interactions between OCH_3/H-1′, H-11a/OCH_3, and H-2′/OCH_3. The absolute configuration at C-6a and C-11a was assigned as *R* from its negative optical rotation value.[8] Compound **4** was therefore identified as (6a*R*,11a*R*)-3,9-dihydroxy-

† This work is dedicated to Professor Apichart Suksamrarn in honor of his 60th birthday.

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2,10-di(3,3-dimethylallyl)-1-methoxypterocarpane and named 1-methoxyerythrabyssin II.

The known compounds were identified as erythrabyssin II,[7] erybraedin A,[9] erystagallin A,[10] erycristagallin,[11] erythrabissin-1,[12] eryvarin A,[13] hydroxycristacarpone,[14] 5-hydroxysophoranone,[15,16] abyssinone V,[17,18] lespedezaflavanone B,[19] sophoradiol,[20,21] soyasapogenol B,[21–23] lupeol,[24] and vogelin C[25] by comparison of their spectroscopic data with reported values.

Compounds **1**−**3** are the first examples of alkenoid-type erythrina alkaloids with carbonyl groups at both the C-10 and C-11 positions. The known compound lespedezaflavanone B was identified for the first time from the genus *Erythrina*. Compounds **1**, **2**, **4**, eryvarin A, hydroxycristacarpone, abyssinone V, lespedezaflavanone B, and vogelin C were evaluated for antiplasmodial, antimycobacterial, and cytotoxic activities. Vogelin C exhibited the highest antiplasmodial activity against *Plasmodium falciparum* with an IC_{50} value of 2.8 μg/mL, whereas lespedezaflavanone B and abyssinone V exhibited lower activity, with IC_{50} values of 3.7 and 7.0 μg/mL, respectively. Compound **4** exhibited moderate antimycobacterial activity against *Mycobacterium tuberculosis* (H37Ra strain) with an MIC value of 50 μg/mL, whereas lespedezaflavanone B, eryvarin A, and abyssinone V showed weak activity (MIC 100−200 μg/mL). Compounds **4** and lespedezaflavanone B showed moderate to weak cytotoxicity against KB, BC, and NCI-H187 cells (IC_{50} 7.6−19.1 μg/mL), whereas vogelin C exhibited only weak activity against BC cells (IC_{50} 18.4 μg/mL). Compounds **1** and **2** were inactive in all tests.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO-1020 polarimeter. UV spectra were measured with a JASCO V-530 spectrophotometer. IR spectra were obtained using a Perkin-Elmer FT-IR Spectrum BX spectrophotometer. 1D and 2D NMR spectra were recorded on a Bruker AVANCE 400 NMR spectrometer. Chemical shifts (δ) are expressed in ppm with reference to the solvent signals. ACPI-TOFMS were recorded on a microTOF Bruker Daltonics mass spectrometer. Quick column chromatography (QCC) and column chromatography (CC) were carried out using Merck silica gel 60 PF_{254} and silica gel 60 (<0.063 mm), respectively. For TLC Merck precoated silica gel 60 F_{254} plates were used. Spots on TLC were visualized under UV light and by spraying with anisaldehyde-H_2SO_4 reagent followed by heating.

Plant Material. The bark of *E. subumbrans* was collected from Kangkajan National Park, Kangkajan District, Phetchaburi Province, Thailand. A voucher specimen (No. BKF 091954) has been deposited at the herbarium of the Royal Forest Department, Ministry of Agriculture and Cooperatives, Bangkok.

Extraction and Isolation. The air-dried, powdered bark of *E. subumbrans* (0.93 kg) was Soxhlet extracted successively with *n*-hexane, CH_2Cl_2, and MeOH. The hexane, CH_2Cl_2, and MeOH extracts were filtered and concentrated to dryness under reduced pressure.

The hexane extract (14.9 g) was subjected to QCC, using a gradient solvent system of hexane, hexane−EtOAc, and EtOAc in increasing proportions of the polar solvent to afford 13 fractions (H1−H13). Fraction H5 (1 g) was subjected to CC twice in succession, using CH_2Cl_2 and hexane−CH_2Cl_2−MeOH (3:2:1) to give nine fractions (H14−H22). Fractions H16 and H20 yielded sophoradiol (5 mg) and 5-hydroxysophoranone (60 mg), respectively. Fraction H7 (1 g) was chromatographed twice in succession, using a gradient solvent system of hexane−EtOAc in increasing polarity and hexane−CH_2Cl_2 (20:80) to afford 14 fractions (H23−H36). Fraction H24 furnished erybraedin A (3 mg), whereas H29 (15 mg) was further purified by CC, using hexane−CH_2Cl_2 (20:80), to yield 1-methoxyerythrabyssin II (**4**) (6 mg). Fraction H8 (1.2 g) was separated by CC three times in succession, using EtOAc−hexane (15:85), CH_2Cl_2−hexane (20:80), and CH_2Cl_2, to give erythrabyssin II (18 mg).

The CH_2Cl_2 extract (25 g) was subjected to QCC, using a gradient solvent system of hexane, hexane−EtOAc, and EtOAc in increasing polarity, to give 11 fractions (C1−C11). Fraction C4 (968 mg) was subjected to repeated CC, using EtOAc−hexane (5:95), to afford abyssinone V (13 mg). Fraction C5 (3.8 g) was further fractionated by QCC, using a gradient solvent system of hexane, hexane−EtOAc, and EtOAc in increasing proportions of the polar solvent, to yield nine fractions (C12−C20). Fraction C14 (626 mg) was subjected to CC, using EtOAc−hexane (10:90), to furnish lespedezaflavanone B (20 mg). Fractions C16 and C17 were separately subjected to repeated CC, using MeOH−CH_2Cl_2 (1:99), to give vogelin C (4 mg) and erystagallin A (5 mg), respectively. Fraction C6 (3.9 g) was rechromatographed, using a gradient solvent system of CH_2Cl_2, CH_2Cl_2−EtOAc, and EtOAc in increasing polarity, to afford fractions C21−C27. Fraction C22 (367 mg) was purified by CC, using CH_2Cl_2–EtOAc (6:94), to furnish erycristagallin (264 mg). Fraction C25 (1.2 g) was chromatographed twice, using MeOH−CH_2Cl_2 (1:99), to give erythrabissin-1 (89 mg). Fraction C8 (4.6 g) was subjected to repeated CC, using EtOAc−hexane (40:60), to afford soyasapogenol B (20 mg).

The MeOH extract (26 g) was subjected to QCC, using a gradient of CH_2Cl_2, CH_2Cl_2−EtOAc, EtOAc, EtOAc−MeOH, and MeOH in increasing proportions of the polar solvent, to give 14 fractions (M1−M14). Fraction M2 (173 mg) was purified by CC, using CH_2Cl_2, to furnish lupeol (6 mg). Fraction M6 (482 g) was separated by repeated CC, using hexane−EtOAc (50:50), to yield eryvarin A (3 mg). Fraction M7 (1 g) was chromatographed twice in succession, using MeOH−CH_2Cl_2 (1:99) and hexane−EtOAc (40:60), to give fractions M15−M21. Fraction M17 yielded hydroxycristacarpone (6 mg). Fraction M21 (23.7 mg) was further fractionated, using a gradient solvent system of hexane−EtOAc in increasing polarity, to give fractions M22−M25. Fraction M23 (4.8 mg) was purified by CC, using hexane−EtOAc (20:80), to furnish (+)-10,11-dioxoerythratine (**1**) (3 mg), whereas M25 (7.1 mg) was purified by CC, using MeOH−CH_2Cl_2 (0.1:99.9), to give (+)-10,11-dioxoepierythratidine (**2**) (4 mg) and (+)-10,11-dioxoerythratidinone (**3**) (1.5 mg).

(+)-10,11-Dioxoerythratine (1): pale yellow, amorphous solid; $[\alpha]^{31}_D$+132.9 (*c* 0.17, CH_3OH); UV (MeOH) λ_{max} (log ϵ) 219 (3.41), 249 (3.38), 289 (3.13), 352 (2.83) nm; IR (KBr) ν_{max} 3460, 2919, 1686, 1655, 1605, 1504, 1482, 1424, 1379, 1290, 1209, 1124, 1092, 1032, 929, 887 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (1H, s, H-17), 6.92 (1H, s, H-14), 6.10 and 6.08 (each 1H, br s, OCH_2O), 6.01 (1H, dd, J = 3.6, 0.8 Hz, H-1), 4.35 (1H, br t-like, J = 4.4 Hz, H-2), 4.24 (1H, dd, J = 11.2, 7.0 Hz, H-8a), 3.37 (1H, ddd, J = 11.2, 11.2, 6.0 Hz, H-8b), 3.30 (1H, ddd, J = 11.8, 6.6, 4.2 Hz, H-3), 3.17 (3H, s, OCH_3-3), 2.48 (2H, m, H-7), 2.13 (1H, dd, J = 11.8, 4.2 Hz, H-4eq), 2.05 (1H, t, J = 11.8 Hz, H-4ax); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.6 (C-11), 159.1 (C-10), 151.9 (C-15), 148.4 (C-16), 141.8 (C-13), 140.7 (C-6), 126.5 (C-12), 126.0 (C-1), 108.3 (C-17), 105.5 (C-14), 102.5 (O*C*H$_2$O), 80.5 (C-3), 72.6 (C-2), 64.7 (C-5), 57.2 (O*C*H$_3$-3), 46.7 (C-4), 46.3 (C-8), 31.1 (C-7); APCI-TOFMS *m*/*z* 344.1128 (calcd for $C_{18}H_{17}NO_6$+H, 344.1129).

(+)-10,11-Dioxoepierythratidine (2): pale yellow, amorphous solid; $[\alpha]^{31}_D$ +92.8 (*c* 0.17, CH_3OH); UV (MeOH) λ_{max} (log ϵ) 246 (3.77), 291 (3.76), 352 (3.72) nm; IR (KBr) ν_{max} 3474, 2907, 1686, 1650, 1595, 1508, 1454, 1426, 1357, 1301, 1283, 1224, 1200, 1099, 1036, 930 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45 (1H, s, H-17), 6.99 (1H, s, H-14), 6.02 (1H, d, J = 4.4 Hz, H-1), 4.38 (1H, br t-like, J = 5.0 Hz, H-2), 4.29 (1H, m, H-8a), 3.96 (3H, s, OCH_3-15), 3.93 (3H, s, OCH_3-16), 3.41 (1H, m, H-8b), 3.33 (1H, m, H-3), 3.15 (3H, s, OCH_3-3), 2.50 (2H, m, H-7), 2.14 (1H, dd, J = 11.6, 4.4 Hz, H-4eq), 2.06 (1H, t, J = 11.6 Hz, H-4ax); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.4 (C-11), 159.1 (C-10), 153.1 (C-15), 149.3 (C-16), 141.7 (C-6), 139.1 (C-13), 125.4 (C-1), 124.4 (C-12), 110.4 (C-17), 107.8 (C-14), 81.1 (C-3), 72.7 (C-2), 64.7 (C-5), 57.2 (O*C*H$_3$-3), 56.5 (O*C*H$_3$-16), 56.3 (O*C*H$_3$-15), 46.9 (C-4), 46.1 (C-8), 31.4 (C-7); APCI-TOFMS *m*/*z* 360.1444 (calcd for $C_{19}H_{21}NO_6$+H, 360.1442).

(+)-10,11-Dioxoerythratidinone (3): pale yellow, amorphous solid; $[\alpha]^{28}_D$ +16.3 (*c* 0.16, CH_3OH); UV (MeOH) λ_{max} (log ϵ) 244 (3.81), 288 (3.54), 352 (3.33) nm; IR (KBr) ν_{max} 2924, 2852, 1670, 1595, 1509, 1459, 1384, 1300, 1228, 1203, 1176, 1113, 1076, 1017, 879, 799 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.53 (1H, s, H-17), 6.57 (1H, s, H-14), 6.40 (1H, s, H-1), 4.47 (1H, m, H-8a), 3.94 (3H, s, OCH_3-16), 3.87 (3H, s, OCH_3-15), 3.57 (1H, m, H-8b), 3.52 (1H, dd, J = 11.8, 5.1 Hz, H-3), 3.39 (3H, s, OCH_3-3), 2.79 (2H, m, H-7), 2.53 (1H, t, J = 11.8 Hz, H-4ax), 2.44 (1H, dd, J = 11.8, 5.1 Hz, H-4eq); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.8 (C-2), 179.5 (C-11), 161.8 (C-6), 158.3 (C-10), 153.4 (C-15), 149.9 (C-16), 136.4 (C-13), 125.3 (C-1), 124.8 (C-12), 111.5 (C-17), 105.3 (C-14), 77.2 (C-3), 64.8 (C-5), 59.1 (O*C*H$_3$-3), 56.5* (O*C*H$_3$-15), 56.4* (O*C*H$_3$-16), 49.4 (C-4), 45.3 (C-8), 32.3 (C-7) (*assignments may be interchanged); APCI-TOFMS *m*/*z* 358.1288 (calcd for $C_{19}H_{19}NO_6$+H, 358.1291).

1-Methoxyerythrabyssin II (4): pale yellow, amorphous solid; $[\alpha]^{31}_{D}$ −176.7 (*c* 0.17, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 239 (3.79), 285 (3.80) nm; IR (KBr) ν_{max} 3421, 2918, 1616, 1448, 1352, 1262, 1166, 1127, 1075, 1034, 906, 847 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.94 (1H, d, J = 8.0 Hz, H-7), 6.35 (1H, d, J = 8.0 Hz, H-8), 6.25 (1H, s, H-4), 5.59 (1H, d, J = 6.4 Hz, H-11a), 5.47[a] (1H, s, OH-9), 5.29 (1H, t, J = 7.2 Hz, H-2″), 5.29[a] (1H, s, OH-3), 5.22 (1H, t, J = 7.2 Hz, H-2′), 4.14 (1H, dd, J = 11.0, 4.8 Hz, H-6), 3.95 (1H, s, OCH_3-1), 3.57 (1H, t-like, J = 11.0 Hz, H-6), 3.38* (1H, m, H-6a), 3.35* (2H, m, H-1′), 3.32* (2H, m, H-1″), 1.82 (3H, s, H-4′), 1.75 (3H, s, H-4"), 1.74 (3H, s, H-5′), 1.71 (3H, s, H-5″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.6 (C-1), 158.5 (C-10a), 157.2 (C-3), 155.7 (C-9), 155.3 (C-4a), 135.2[b] (C-3′), 135.0[b] (C-3″), 122.3 (C-7), 122.1 (C-2′), 121.4 (C-2″), 118.7 (C-6b), 114.0 (C-2), 110.1 (C-10), 108.0 (C-8), 107.1 (C-11b), 100.3 (C-4), 75.6 (C-11a), 66.2 (O*C*H$_3$-1), 39.4 (C-6a), 25.79[c] (C-5″), 25.76[c] (C-5′), 23.3 (C-1″), 22.9 (C-1′), 17.9 (C-4′), 17.8 (C-4″) (*partially overlapping signals; [a,b,c]assignments may be interchanged); APCI-TOFMS *m*/*z* 423.2180 (calcd for $C_{26}H_{31}O_5$+H, 423.2166).

Antiplasmodial Activity Test. Antiplasmodial activity was evaluated against the parasite *Plasmodium falciparum* (K1, multidrug-resistant strain), which was cultured continuously according to the method of Trager and Jensen.[26] Quantitative assessment of antiplasmodial activity *in vitro* was determined by means of the microculture radioisotope technique based upon the method described by Desjardins et al.[27] The inhibitory concentration (IC_{50}) represents the concentration that causes 50% reduction in parasite growth as indicated by the *in vitro* uptake of [^{3}H]-hypoxanthine by *P. falciparum*. An IC_{50} value of 1 ng/mL was observed for the standard compound dihydroartemisinin in the same test system.

Antimycobacterial Activity Test. The antimycobacterial activity was assessed against *Mycobacterium tuberculosis* H37Ra strain using the microplate Alamar blue assay (MABA).[28] The lowest drug concentration effecting an inhibition of ≥90% was considered the MIC. The standard drugs rifampicin, isoniazid, and kanamycin sulfate showed MIC values of 0.004, 0.06, and 2.5 μg/mL, respectively.

Cytotoxicity Activity Test. Cytotoxicity assays against oral human epidermal carcinoma (KB), human breast cancer (BC), and human small cell lung cancer (NCI-H187) cells were performed employing the colorimetric method.[29] The standard drug ellipticine exhibited IC_{50} values against these cell lines of 1.33, 1.46, and 0.39 μg/mL, respectively.

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