TWO NEW ERYTHRINAN ALKALOIDS FROM *ERYTHRINA* X *BIDWILLII*

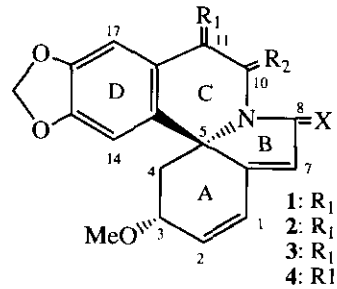
Hitoshi Tanaka, *[a] Toshihiro Tanaka,[b] Hideo Etoh,[c] Sachiko Goto,[a] and Yukimasa Terada[a]

[a]Faculty of Pharmacy, Meijo University, Yagoto, Tempaku-ku, Nagoya, 468-8503, Japan, [b]Gifu Pharmaceutical University, 6-1 Mitahora-higashi 5 chome, Gifu 502-8585, Japan, [c]Faculty of Agriculture, Shizuoka University, Shizuoka 422-8529, Japan

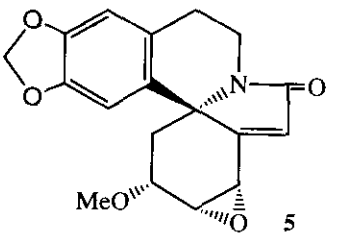
Abstract —Two new erythrinan alkaloids, 10,11-dioxoerythraline (**1**) and 8-oxoerythraline epoxide (**5**) have been isolated from flowers of *Erythrina* x *bidwillii*. Their structures were elucidated by spectroscopic analyses and chemical evidence. 8-Oxoerythraline epoxide is the first erythrinan alkaloid possessing an epoxy ring.

The genus *Erythrina* is widely distributed in tropical and subtropical regions of the world and has been occasionally used as indigenous folk medicines.[1] In flowers, seeds and bark of the genus *Erythrina*, there have been found erythrinan alkaloids, some of which have curare-like and hypnotic actions.[1,2] *Erythrina* x *bidwillii* is a shrub with colorful flowers and has been planted as an ornamental plant in southern area of Japan. We previously reported the isolation of a new erythrinan alkaloid, erythbidin B (**2**) along with three known erythrinan alkaloids, erythrinine (**4**), erythraline (**6**) and erysodine (**7**) from the methanol extract of *E.* x *bidwillii* flowers.[3] Further studies of the acetone extract of this plant flowers led to isolation of two new erythrinan alkaloids, 10,11-dioxoerythraline (**1**) and 8-oxoerythraline epoxide (**5**) together with three known erythrinan alkaloids, 8-oxoerythraline (**3**),[4-6] crystamidine (**8**)[7] and 8-oxoerythrinine (**9**).[8] In this note, we wish to describe the isolation and structural elucidation of the two new erythrinan alkaloids (**1** and **5**).

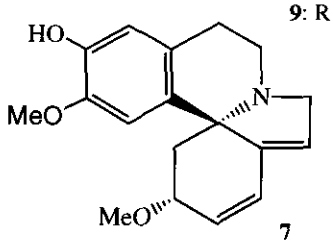
10,11-Dioxoerythraline (**1**) was obtained as an amorphous solid and the IR spectrum showed the presence of carbonyl groups (1680 and 1710 cm^{-1}). The molecular formula was determined to be $C_{18}H_{15}NO_5$ by the HRMS (*m/z* 325.0964). The MS spectrum displayed a molecular ion peak at *m/z* 325 and the characteristic 1, 6-diene system fragments at *m/z* 310 $[M-Me]^+$, 294 $[M-OMe]^+$ and 292 $[M-H-MeOH]^+$.[9]



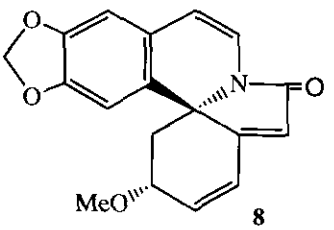
1: $R_1 = R_2 = O$, $X = H_2$
2: $R_1 = O$, $R_2 = \beta$-OH, $X = H_2$
3: $R_1 = R_2 = H_2$, $X = O$
4: $R1 = \beta$-OH, $R_2 = X = H_2$
6: $R_1 = R_2 = X = H_2$
9: $R_1 = \beta$-OH, $R_2 = H_2$, $X = O$



5



7



8

The ^{1}H NMR spectrum exhibited signals of the dienoid protons (δ 5.84, 5.97 and 6.68), a methylenedioxy group (δ 6.07 and 6.10), three aliphatic protons in A ring (δ 2.25-2.31 and 3.63), two geminal aliphatic protons in B ring (δ 4.61), a methoxyl group (δ 3.24) and two singlet aromatic protons (δ 7.12 and 7.41). The ^{13}C NMR spectrum revealed the presence of two carbonyl carbons (δ 159.3 and 181.5)(Table 1).[10] From these data, **1** was thought to be 10-oxo analogue of **2** whose absolute structure was known. The carbonyl carbon at δ 181.5 was assigned to C-11 by the HMBC spectrum which showed correlation between C-11 and H-17 (δ 7.41). In order to confirm the structure of **1** including absolute stereochemistry, **2** was converted to **1** with MnO_2. Synthetic compound (**1**) was virtually coincided with the natural compound. Thus, the structure was represented as structure (**1**) and the absolute configurations at C-3 and C-5 were assigned as 3*R* and 5*S*, respectively.

8-Oxoerythraline epoxide (**5**) was obtained as colorless oil and the IR spectrum showed the presence of carbonyl group (1680 cm^{-1}). The molecular formula was determined to be $C_{18}H_{17}NO_5$ by the HRMS (*m/z* 327.1098). The ^{1}H NMR spectrum displayed signals of an olefinic proton (δ 6.49), a methylenedioxy group (δ 5.94 and 5.98), AX_2-type protons in A ring (δ 1.59, 2.36 and 3.64), four aliphatic protons in C ring (δ 2.93, 3.09, 3.57 and 3.83), a methoxyl group (δ 3.41) and two singlet aromatic protons (δ 6.55 and 6.72) which were closely similar to those of **3**. The ^{1}H NMR (δ 4.24 and 3.83) and ^{13}C NMR (δ 48.7 and 52.9) signals indicated the presence of an epoxy ring between C-1 and C-2, and the structure was elucidated as **5**. The relative stereochemistry of **5** was confirmed from the NOESY spectrum as shown in Figure 1. The observation of NOEs between H-14 / H-1, H-14 / H-2, H-14 / H-3 and H-4e / H-11a

revealed that the methoxyl and epoxy groups have the same orientation and the relation between the epoxy ring and C(5)-N bond is *cis*. Biogenetic consideration of erythrinan alkaloids[1,2] and the positive optical rotation value[11] of **5** suggested that **5** has the same absolute configurations at C-3 and C-5 with those of **1** and **3**. From these results, the structure was represented as structure (**5**). This is the first isolation of an erythrinan alkaloid possessing an epoxy group.

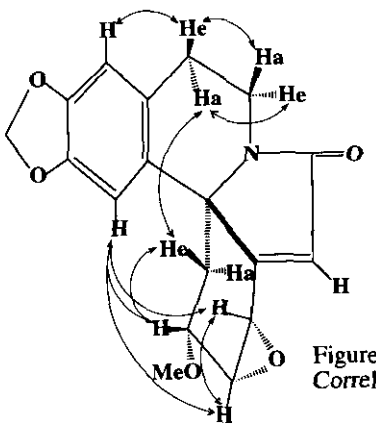


Figure 1. The NOESY Correlations of Compound (**5**).

Table 1. ^{13}C NMR spectral data of **1**, **3** and **5** in $CDCl_3$

C	1	3	5
1	124.2	123.9	48.7
2	132.2	136.3	52.9
3	75.5	74.9	74.6
4	49.6	41.2	32.9
5	70.5	66.8	67.4
6	137.5	157.0	155.0
7	120.6	120.3	129.7
8	54.2	171.1	170.2
10	159.3	37.8	37.4
11	181.5	27.4	27.5
12	125.8	127.8	128.0
13	143.5	130.0	130.0
14	104.1	105.0	105.7
15	148.0*	147.0*	147.2*
16	152.0*	146.0*	146.0*
17	108.6	109.4	109.8
OCH_2O	102.4	101.1	101.3
OMe	56.5	56.4	56.6

* Assignments may be interchanged.

EXPERIMENTAL

General. The instruments used for this study were as follows: a JASCO DIP-370 digital polarimeter (for specific rotation, measured at 23° C); a JASCO IR-810 spectrophotometer (for IR spectra); a Shimadzu UV-2100 spectrophotometer (for UV spectra); a JEOL JMS-D 300 spectrometer (for MS and HRMS); a JEOL JNM-A 600 spectrometer (for NMR spectra using tetramethylsilane as an internal standard). Column chromatography was carried out with silica gel 60 (230-400 mesh: MERCK). Spots on TLC were detected under UV light (254 nm) or by spraying with Dragendorff's reagent.

Plant material. Flowers of *E.* x *bidwillii* were collected at Kagoshima Prefecture, Japan, in May, 1998. A voucher specimen is deposited at the Department of Natural Product Chemistry in the Faculty of Pharmacy, Meijo University.

Extraction and isolation. Flowers (11.2 kg) were extracted with acetone (36 L) at 23°C for 72 h and evaporated to give a dark green residue (46.6 g). The residue was divided into *n*-hexane-, CH_2Cl_2-, and EtOAc-soluble fractions. The CH_2Cl_2-soluble fraction (16.2 g) was chromatographed on silica gel eluting with a gradient of $CHCl_3$-acetone and subsequently $CHCl_3$-MeOH (10:1) to give 24 fractions (each fraction; 200 mL, Column A). The fraction A4 was rechromatographed on silica gel eluting with benzene-EtOAc (1:1)(frs. B1-38)(each fraction; 30 mL, Column B) to afford **2** (58 mg)(frs. B31-33) and **1** (51 mg)(frs. B36-37). The fraction A20 were rechromatographed by silica gel column chromatography [benzene-EtOAc (3:1)(frs. D1-5) and benzene-EtOAc (1:1)(frs. D6-31)(each fraction; 10 mL, Column D)] to afford **8** (58 mg)(fr. D3), **5** (7.2 mg)(fr. D22), **3** (127 mg)(fr. D24) and **9** (21 mg)(fr. D30). The fraction A24 underwent silica gel column chromatography [$CHCl_3$-MeOH (20:1)(frs. E1-32)(each fraction; 10 mL, Column E]] to yield **6** (762 mg)(frs. E25-26). The EtOAc-soluble fraction (4 g) was subjected to column chromatography on silica gel eluting with $CHCl_3$-acetone (1:1) (frs. F1-42) and subsequently $CHCl_3$-MeOH (1:1) (frs. F43-56)(each fraction; 30 mL, Column F) to give **4** (202 mg)(frs. F42-43) and **7** (29 mg)(frs. F 44-45). Identification of **3**,[4-6] **8**[7] and **9**[8] was made by comparison of the physical and spectral data with those published in the literature.

8-Oxoerythraline (3). Colorless oil. $[\alpha]_D$ +135° (*c* 0.1, $CHCl_3$). IR ($CHCl_3$) ν_{max} cm^{-1}: 1670. UV λ_{max} nm (MeOH)(log ε): 205 (4.57), 248 (4.12), 294 (3.66 *sh*). MS *m/z*: 311 ($[M]^+$, 100), 296 (44), 280 (61), 279 (43), 278 (89), 268 (18), 266 (13), 250 (38), 238 (10). HRMS *m/z* 311.1143 (M^+, calcd for $C_{18}H_{17}NO_4$: 311.1157). ^1H NMR ($CDCl_3$): δ 1.70 (1H, *t*-like, *J*=11.0 Hz, H-4a), 2.79 (1H, *dd*, *J*=11.0, 5.1 Hz, H-4e), 2.96 (1H, *ddd*, *J*=16.1, 7.3, 3.7 Hz, H-11e), 3.12 (1H, *ddd*, *J*=16.1, 9.5, 7.3, H-11a), 3.35 (3H, *s*, OMe), 3.64 (1H, *ddd*, *J*=12.5, 7.3, 3.7 Hz, H-10e), 3.78 (1H, *m*, H-3), 3.89 (1H, *ddd*, *J*=12.5, 9.5, 7.3 Hz, H-10a), 5.90 (1H, *s*, OCH_2O), 5.94 (1H, *s*, OCH_2O), 6.02 (1H, *s*, H-7), 6.31 (1H, *d*, *J*=10.3 Hz, H-2), 6.71 (1H, *s*, H-17), 6.74 (1H, *s*, H-14), 6.86 (1H, *dd*, *J*=10.3, 2.2 Hz, H-1). ^{13}C NMR: see Table 1. The erroneous assignments (C-4 and C-10) of ^{13}C NMR spectrum in literature[4] were corrected by the HSQC and HMBC

experiment.

10,11-Dioxoerythraline (1). Colorless amorphous solid. $[\alpha]_D$ +254° (*c* 0.1, $CHCl_3$). IR ($CHCl_3$) ν_{max} cm^{-1}: 1710, 1680, 1650, 1610. UV λ_{max} nm (MeOH)(log ε): 204 (4.32), 247 (4.17), 292 (3.62 *sh*), 351 (3.53). MS *m/z*: 325 ([M]$^+$, 100), 310 (12), 294 (46), 292 (34), 282 (37), 266 (83), 264 (63), 254 (11), 252 (15), 240 (27), 226 (26), 213 (18), 209 (21), 165 (13), 152 (22). HRMS *m/z* 325.0964 (M^+, calcd for $C_{18}H_{15}NO_5$: 325.0949). ^{1}H NMR ($CDCl_3$): δ 2.25-2.31 (2H, *m*, H-4), 3.24 (3H, *s*, OMe), 3.63 (1H, *m*, H-3), 4.61 (2H, *br s*, H-8), 5.84 (1H, *br s*, H-7), 5.97 (1H, *d*, *J*=10.3 Hz, H-2), 6.07 (1H, *d*, *J*=1.5 Hz, OCH_2O), 6.10 (1H, *d*, *J*=1.5 Hz, OCH_2O), 6.68 (1H, *dd*, *J*=10.3, 2.2 Hz, H-1), 7.12 (1H, *s*, H-14), 7.41 (1H, *s*, H-17). ^{13}C NMR: see Table 1.

8-Oxoerythraline epoxide (5). Colorless oil. $[\alpha]_D$ +94° (*c* 0.1, $CHCl_3$). CD (EtOH; *c* 3.07 x 10^{-5}): Δε +3.51 (292), -17.31 (228), +20.76 (202). IR ($CHCl_3$) ν_{max} cm^{-1}: 1680. UV λ_{max} nm (EtOH)(log ε): 205 (4.59), 289 (3.78). MS *m/z*: 327 ([M]$^+$, 53), 311 (14), 298 (30), 296 (22), 278 (14), 266 (14), 241 (100) 212 (43). HRMS *m/z* 327.1098 (M^+, calcd for $C_{18}H_{17}NO_5$: 327.1106). ^{1}H NMR ($CDCl_3$): δ 1.59 (1H, *t*-like, *J*=11.7 Hz, H-4a), 2.36 (1H, *dd*, *J*=11.7, 5.1 Hz, H-4e), 2.93 (1H, *ddd*, *J*=16.1, 7.3, 3.7 Hz, H-11e), 3.09 (1H, *ddd*, *J*=16.1, 9.5, 7.3, H-11a), 3.41 (3H, *s*, OMe), 3.57 (1H, *ddd*, *J*=12.5, 7.3, 3.7 Hz, H-10e), 3.64 (1H, *m*, H-3), 3.83 (1H, *ddd*, *J*=12.5, 9.5, 7.3 Hz, H-10a), 3.83 (1H, *d*, *J*=4.0 Hz, H-2), 4.24 (1H, *d*, *J*=4.0 Hz, H-1), 5.94 (1H, *d*, *J*=1.5 Hz, OCH_2O), 5.98 (1H, *d*, *J*=1.5 Hz, OCH_2O), 6.49 (1H, *s*, H-7), 6.55 (1H, *s*, H-14), 6.72 (1H, *s*, H-17). ^{13}C NMR: see Table 1.

Reduction of 2 with AlH_3. A solution of excess AlH_3, prepared from $LiAlH_4$: $AlCl_3$ = 3:1, in anhydrous Et_2O (5 mL) was added to a solution of **2** (7 mg) in anhydrous THF (5 mL) and the mixture was stirred at rt for 2 h. After decomposition of excess hydride with ice water, the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with EtOAc-MeOH (10:1) to give **4**[6, 12] (4 mg, 60%) as colorless solid. This compound was identical with the natural sample in every respect ($[\alpha]_D$, IR, ^{1}H NMR and TLC behavior).

Oxidation of 2 with MnO_2. A mixture of **2** (26 mg) and activated MnO_2 (20 mg) in $CHCl_3$ (5 mL) was stirred at rt overnight. The reaction mixture was filtered off and the filtrate was evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with benzene-EtOAc (3:1) to afford **1** (21 mg, 81%) as a colorless oil, identical with the natural sample in every respect ($[\alpha]_D$, IR, ^{1}H NMR and TLC behavior).

REFERENCES AND NOTES

1. S. F. Dyke and S. N. Quessy, "The Alkaloids", Vol. 18, p.1, ed. by R. G. A. Rodrigo, Academic press, New York, 1981.

2. Y. Tsuda and T. Sano, "The Alkaloids", Vol. 48, p. 249, ed. by G. A. Cordell, Academic Press, San Diego, 1996.
3. H. Tanaka, T. Tanaka, and H. Etoh, *Phytochemistry,* 1998, **48,** 1461.
4. A. S. Chawla, S. Chunchatprasert, and A. H. Jackson, *Org. Magn. Reson.,* 1983, **21**, 39.
5. P. G. Mantle, I. Laws, and D. A. Widdowson, *Phytochemistry,* 1984, **23,** 1336.
6. Y. Tsuda, S. Hosoi. T. Sano, H. Suzuki, and J. Toda, *Heterocycles*, 1993, **36,** 655.
7. K. Ito, M. Haruna, Y. Jinno, and H. Furukawa, *Chem. Pharm. Bull.,* 1976, **24,** 52.
8. E. Dagne and W. Steglich, *Phytochemistry,* 1984, **23,** 449.
9. R. B. Boar and D. A. Widdowson, *J. Chem. Soc. (B),* 1970, 1591.
10. The unambiguous assignment of the ^{1}H NMR and ^{13}C NMR signals of **1**, **3** and **5** was accomplished by analyses of the ^{1}H-^{1}H COSY, HSQC and HMBC spectra.
11. M. M. El-Olemy, A. A. Ali, and M. A. El-Mottaleb, *Lioydia,* 1978, **41**, 342.
12. K. Ito, H. Furukawa, and H. Tanaka, *J. Chem. Soc., Chem. Comm.,* 1970, 1076.

Received, 1st July, 1999