Synthesis of Highly Dehydrogenated Oxoerythrinan Alkaloids, Erytharbine and Crystamidine[1,2)]

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2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of 3,8-dioxoerythrinan-1(6)-enes in dioxane gave the ring B dehydrogenated products, the 1,6-dienones, while oxidation in benzene gave the fully dehydrogenated products, the 1,6,10-trienones. The same trienones were obtained by DDQ oxidation of the 1,6-dienones in bezene. On the contrary, oxidation of the isomeric enone, 3,8-dioxoerythrinan-1-ene, in either dioxane or benzene gave the ring C dehydrogenated product, the 1,10-dienone. The 1,6,10-trienones were transformed to the highly dehydrogenated 8-oxoerythrinan alkaloids, erytharbine and crystamidine, in racemic forms.

Keywords DDQ; dehydrogenation; *Erythrina* alkaloid; erytharbine; crystamidine; total synthesis

Erytharbine (**1a**) and crystamidine (**1b**) are two of the neutral *Erythrina* alkaloids isolated from *E. arborescens* ROXB.[3)] and *E. crysta-galli* L.,[4)] respectively. They are characteristic in having a highly dehydrogenated aromatic erythrinan skeleton and a lactam group in the molecule, suggesting that they are derived from the corresponding dihydro derivatives, 8-oxoerysotrine (erysotramidine **2a**) and 8-oxoerythraline (**2b**). Since the latter compounds were synthesized in the course of our total synthesis of erysotrine and erythraline,[5,6)] we planned to synthesize **1a** and **1b** by dehydrogenation of appropriate precursors.

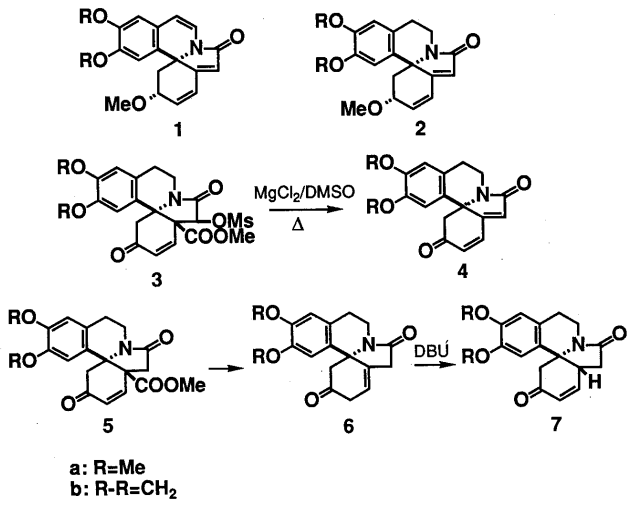


Chart 1

We picked the dienone (**4**) as the preferred precursor for dehydrogenation; it is preparable by decarbomethoxylation of **3** with $MgCl_2$ in dimethyl sulfoxide.[5)] Similarly, decarbomethoxylation of **5** gave the enone (**6**) which was quantitatively isomerized to the conjugated enone (**7**).[6)] These enones are also plausible precursors. In this paper, we describe the synthesis of the title alkaloids in racemic forms by the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of those enones (**5**, **7**) and dienones (**4**). The reactions exhibited interesting solvent and structure dependencies.

The dienones (**4a** and **4b**) were oxidized in benzene with 10 mol eq of DDQ at 130—140 °C for 12 h to give the expected trienones (**8a** and **8b**) in 35 and 25% yields, repectively. In other solvents, such as methanol, dioxane, and dichloromethane, the oxidation was slower and the yield was lower.

Treatment of the enone (**6a**) with 7 mol eq of DDQ in dioxane at 110 °C for 5 h gave the dienone (**4a**) in 29% yield together with the trienone (**8a**, 15%), as reported previously.[6)] On the other hand, similar oxidation of **6a** in benzene at 130 °C for 3 h gave the trienone (**8a**) as a major product (35%) together with a minute amount of the dienone (**4a**, 7%). It should be noted that, in the oxidation

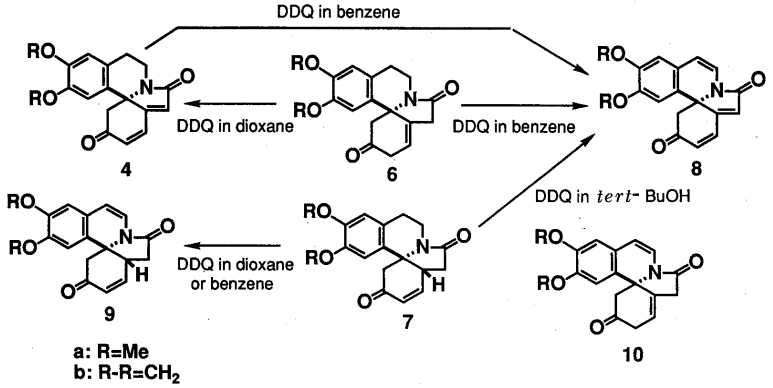
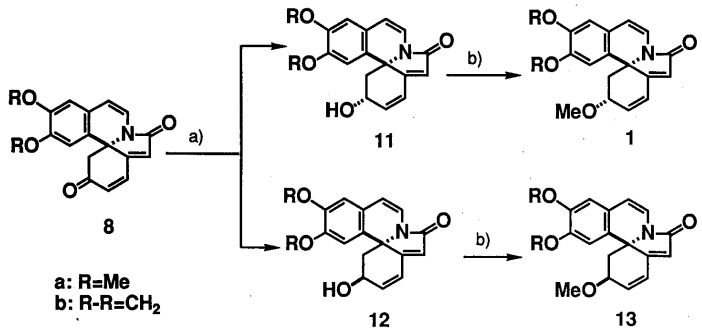


Chart 2



a) Al(iso-PrO)$_3$ in iso-PrOH. b) MeI/KOH/Et$_4$NBr

Chart 3

of **6a** in benzene, the trienone (**8a**) was always formed predominantly even under conditions that left the starting material (**6a**) partially unreacted. This result suggests that oxidation of **6** to **8** in benzene proceeds not only through the intermediacy of the dienone (**4**) but also, as a major course, through a different intermediate such as **10**.

DDQ oxidation of the isomeric enone (**7**) gave different results. The enone (**7a**) gave, on oxidation with 7 mol eq of DDQ either in benzene or dioxane at 110 °C for 1.5 h, the dienone with a different structure (**9a**), having the newly formed double bond at the 10 (11) position, in 59 or 45% yield, with recovery of the starting material (**7a**, 20 or 2%). Oxidation of **7a** in *tert*-BuOH at 110 °C for 2 h directly produced the trienone (**8a**) as the only characterizable product, but the yield was very low (5%). The structures of the above dienone (**9a**) and trienones (**8a** and **8b**) were established on the basis of their ^{1}H-NMR spectra.[7]

The trienones (**8a** and **8b**) obtained above were respectively converted to (±)-erytharbine (**1a**) and (±)-crystamidine (**1b**), as follows.

Meerwein–Ponndorf–Verley reduction of the trienones (**8a** and **8b**) with aluminum isopropoxide in isopropanol gave the 3α-alcohols (**11a** and **11b**) as major and the 3β-alcohols (**12a** and **12b**) as minor products in the ratios of 7 : 4 and 7 : 2, respectively. Methylation of the 3α-alcohols (**11a** and **11b**) with iodomethane and KOH using a phase-transfer catalyst (Et_4NBr) gave the corresponding methyl ethers (**1a** and **1b**) whose spectral data were identical with those of (+)-erytharbine and (+)-crystamidine,[8] respectively.

Similarly, methylation of the 3β-alcohols (**12a** and **12b**) afforded (±)-3-epierytharbine (**13a**) and (±)-3-epicrystamidine (**13b**), respectively.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage melting point apparatus and are uncorrected. IR spectra were taken in chloroform solution and are given in cm^{-1}. UV spectra were recorded in ethanol solution and are given in λ_{max} nm (ε). ^{1}H-NMR (100 MHz) spectra were taken in $CDCl_3$ solution with tetramethylsilane as an internal standard and are given in δ. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-D300 mass spectrometer. For column chromatography, Wakogel C-200 (silica gel) was used. Preparative thin-layer chromatography (PTLC) was performed on a Merck precoated plate of 0.5 mm thickness. Medium-pressure liquid chromatography (MPLC) was performed on a Kusano CIG prepacked silica gel column. Identities were confirmed by comparisons of melting point (for crystalline compounds), and TLC and spectral (IR and NMR) behavior.

DDQ Oxidation of the Dienones (4a and 4b) (1) A solution of **4a** (10 mg) and DDQ (77 mg, 10 mol eq) in benzene (5 ml) was heated at 140 °C for 12 h in a sealed tube with stirring. Two batches of the reaction mixture were combined and concentrated *in vacuo*. The residue was partially purified by passing it through a short column of Al_2O_3 with CH_2Cl_2. The eluate was purified by MPLC (AcOEt : hexane = 4 : 1) to afford the trienone **8a** (7 mg, 35%), as orange prisms from AcOEt–Et_2O, mp 171—173 °C. IR (Nujol): 1695, 1680 sh. UV: 213 (24400), 242 (20200), 272 (22400), 418 (1500). ^{1}H-NMR: 2.43, 3.19 (each 1H, d, J = 14 Hz, H-4), 3.76, 3.86 (each 3H, s, OMe), 6.18, 6.93 (each 1H, d, J = 7 Hz, H-10, 11), 6.39 (1H, d, J = 10 Hz, H-2), 6.47 (1H, s, H-7), 6.63, 6.76 (each 1H, s, ArH), 7.86 (1H, d, J = 10 Hz, H-1). HRMS: Calcd for $C_{18}H_{15}NO_4$ (M^+): 309.0998. Found: 309.0988.

(2) A solution of **4b** (10 mg) and DDQ (77 mg, 10 mol eq) in benzene (10 ml) was heated at 130 °C for 12 h in a sealed tube with stirring. Eleven batches of the reaction mixture were combined and treated as described above. The crude product was purified by MPLC (AcOEt) to affod the trienone **8b** (27 mg, 25%), as orange prisms from CH_2Cl_2–MeOH, mp 192—192.5 °C. IR (Nujol): 1700, 1670. UV: 246 (19400), 276 (20600), 418 (1700). ^{1}H-NMR: 2.43, 3.21 (each 1H, d, J = 14 Hz, H-4), 5.93 (2H, s, OCH_2O), 6.13, 6.90 (each 1H, d, J = 7 Hz, H-10, 11), 6.36 (1H, d, J = 10 Hz, H-2), 6.46 (1H, s, H-7), 6.66, 6.71 (each 1H, s, ArH), 7.83 (1H, d, J = 10 Hz, H-1). HRMS: Calcd for $C_{17}H_{11}NO_4$ (M^+): 293.0543. Found: 293.0528.

DDQ Oxidation of the Enone (6a) (1) In dioxane[6]: A solution of **6a** (57 mg) and DDQ (288 mg, 7 mol eq) in dioxane (4 ml) was heated at 110 °C for 5 h in a sealed tube with stirring to give, after chromatography of the product, the dienone **4a** (16 mg, 29%) and the trienone **8a** (8 mg, 15%).

(2) In benzene: A solution of **6a** (4.3 mg) and DDQ (20 mg, 7 mol eq) in benzene (1 ml) was heated at 130 °C for 3 h in a sealed tube with stirring. The mixture was poured onto a silica gel column and eluted with benzene–acetate (2 : 1) to afford the dienone **4a** (0.3 mg, 7%) and the trienone **8a** (1.5 mg, 35%).

DDQ Oxidation of the Conjugated Enone (7a) (1) In dioxane: A solution of **7a** (24.5 mg) and DDQ (126 mg, 7 mol eq) in dioxane (3 ml) was heated at 110 °C for 1.5 h in a sealed tube with stirring and worked up as described for **6a**. Chromatography of the product eluted with CH_2Cl_2–AcOEt (5 : 1) gave the starting material **7a** (5.6 mg, 20%) and the dienone **9a** (14.3 mg, 59%), as yellow prisms from MeOH, mp 242.5—247 °C. IR (KBr): 1710, 1690. ^{1}H-NMR: 3.86, 3.75 (each 3H, s, OMe), 6.02, 6.85 (each 1H, d, J = 8 Hz, H-10, 11), 6.29 (1H, br d, J = 10 Hz, H-2), 6.66, 6.62 (each 1H, s, ArH), 7.20 (1H, dd, J = 10, 5 Hz, H-1). *Anal.* Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.10; H, 5.41; N; 4.11.

(2) In benzene: A solution of **7a** (21.6 mg) and DDQ (110 mg, 7 mol eq) in benzene (3 ml) was heated at 110 °C for 1.5 h in a sealed tube with stirring. The mixture was concentrated *in vacuo*. Chromatography of the residue on alumina with CH_2Cl_2 gave the dienone **9a** (9.6 mg, 45%) and the starting material **7a** (0.5 mg, 2%).

(3) In *tert*-BuOH: A solution of **7a** (192 mg) and DDQ (978 mg, 7 mol eq) in *tert*-BuOH (6 ml) was heated at 110 °C for 2 h in a sealed tube with stirring. The mixture was concentrated *in vacuo* and the residue was purified by MPLC ($CHCl_3$: acetone = 9 : 1) to afford the trienone **8a** (9.5 mg, 5%) together with intractable products.

Meerwein–Ponndorf–Verley Reduction of the Trienones (8a and 8b) (1) An argon-purged mixture of **8a** (20 mg) and Al(iso-PrO)$_3$ (132 mg, 10 mol eq) in iso-PrOH (15 ml) was heated under reflux for 5 h with stirring. After cooling, the mixture was diluted with CH_2Cl_2, washed with water, and concentrated *in vacuo*. The residue was purified by PTLC ($CHCl_3$: acetone = 4 : 1) to afford the 3α-alcohol (**11a**) (7 mg, 35%) from a less mobile fraction and the 3β-alcohol (**12a**) (5 mg, 23%) from a more

mobile fraction.

The 3α-Alcohol (**11a**): Pale yellow prisms from $CHCl_3$, mp 257—259 °C. IR: 1690. UV: 267 (29900), 360 (2200). ^{1}H-NMR[7]: 1.43 (1H, dd, J=12, 10 Hz, H-4), 2.69 (1H, dd, J=12, 2 Hz, H-4), 3.78, 3.88 (each 3H, s, OMe), 4.0—4.2 (1H, m, H-3), 6.09 (1H, s, H-7), 6.16, 6.91 (each 1H, d, J=7 Hz, H-10, 11), 6.32 (1H, br d, J=10 Hz, H-2), 6.67, 6.76 (each 1H, s, ArH), 6.98 (1H, dd, J=10, 2 Hz, H-1). *Anal.* Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.37; H, 5.43; N, 4.50.

The 3β-Alcohol (**12a**): Pale yellow gum. IR: 1690. ^{1}H-NMR: 1.80 (1H, dd, J=14, 5 Hz, H-4), 2.69 (1H, br d, J=14 Hz, H-4), 3.84, 3.89 (each 3H, s, OMe), 4.46 (1H, m, H-3), 6.04 (1H, s, H-7), 6.13, 6.88 (each 1H, d, J=7 Hz, H-10, 11), 6.32 (1H, dd, J=10, 5 Hz, H-2), 6.77, 6.88 (each 1H, s, ArH), 6.97 (1H, d, J=10 Hz, H-1). HRMS: Calcd for $C_{18}H_{17}NO_4$ (M^+): 311.1157. Found: 311.1180.

(2) An argon-purged mixture of **8b** (10 mg) and Al(iso-PrO)$_3$ (70 mg, 10 mol eq) in iso-PrOH (10 ml) was heated under reflux for 4 h with stirring. After cooling, the mixture was worked up as described above. PTLC ($CHCl_3$: acetone = 4 : 1) of the product afforded the 3α-alcohol (**11b**) (7 mg, 70%) and the 3β-alcohol (**12b**) (2 mg, 20%).

The 3α-Alcohol (**11b**): Colorless prisms from CH_2Cl_2, mp 219.5—220 °C. IR (Nujol): 3300, 1650. UV: 212 (22200), 228 (22400), 265 (23800), 360 (2700). ^{1}H-NMR:[7] 1.41 (1H, dd, J=11, 10 Hz, H-4), 2.69 (1H, dd, J=11, 5 Hz, H-4), 4.1—4.2 (1H, m, H-3), 5.94 (2H, dd, J=3, 1 Hz, OCH_2O), 6.07 (1H, s, H-7), 6.10, 6.88 (each 1H, d, J=7 Hz, H-10, 11), 6.29 (1H, br d, J=10 Hz, H-2), 6.68, 6.71 (each 1H, s, ArH), 6.91 (1H, dd, J=10, 2 Hz, H-1). HRMS: Calcd for $C_{17}H_{13}NO_4$ (M^+): 295.0843. Found: 295.0833.

The 3β-Alcohol (**12b**): Colorless gum. IR: 3350, 1680. ^{1}H-NMR: 1.78 (1H, dd, J=14, 5 Hz, H-4), 2.70 (1H, br d, J=14 Hz, H-4), 5.96 (2H, s, OCH_2O), 6.02 (1H, s, H-7), 6.08, 6.85 (each 1H, d, J=7 Hz, H-10, 11), 6.28 (1H, dd, J=10, 5 Hz, H-2), 6.72, 6.88 (each 1H, s, ArH), 6.93 (1H, d, J=10 Hz, H-1). HRMS: Calcd for $C_{17}H_{13}NO_4$ (M^+): 295.0843. Found: 295.0826.

(±)-Erythrabine (1a) KOH (85%, 2 mg), Et_4NBr (1 mg), and CH_3I (20 mg) were added to an ice-cooled solution of **11a** (6 mg) in tetrahydrofuran (THF, 8 ml) with stirring and the mixture was stirred at room temperature for 40 h. The mixture was diluted with $CHCl_3$, washed with water, and concentrated *in vacuo*. The residue was purified by PTLC ($CHCl_3$: acetone = 4 : 1) to afford the *O*-methyl derivative (**1a**) (3 mg, 41%) as a pale yellow gum. IR: 1685. UV: 225 (20700), 266 (20700), 355 (1800). ^{1}H-NMR:[7] 1.40 (1H, dd, J=11, 10 Hz, H-4), 2.70 (1H, dd, J=11, 2 Hz, H-4), 3.7—3.9 (1H, m, H-3), 3.27, 3.78, 3.88 (each 3H, s, OMe), 6.07 (1H, s, H-7), 6.14, 6.90 (each 1H, d, J=8 Hz, H-10, 11), 6.32 (1H, br d, J=10 Hz, H-2), 6.66, 6.75 (each 1H, s, ArH), 6.95 (1H, dd, J=10, 2 Hz, H-1). HRMS: Calcd for $C_{19}H_{19}NO_4$ (M^+): 325.1309. Found: 325.1316. The IR and ^{1}H-NMR spectra were identical with those of (+)-erythrabine.[8]

(±)-Crystamidine (1b) KOH (85%, 2 mg), Et_4NBr (1 mg), and CH_3I (4 mg) were added to an ice-cooled solution of **11b** (8 mg) in THF (5 ml) with stirring. The mixture was stirred at room temperature for 21 h and worked up as described above to afford the *O*-methyl derivative (**1b**) (6 mg, 71%) as a pale yellow gum. IR: 1680. UV: 228 (19000), 264 (26400), 357 (2200). ^{1}H-NMR[7]: 1.40 (1H, dd, J=11, 10 Hz, H-4), 2.71 (1H, dd, J=11, 5 Hz, H-4), 3.28 (3H, s, OMe), 3.6—3.8 (1H, m, H-3), 5.94 (2H, dd, J=5, 1 Hz, OCH_2O), 6.06 (1H, s, H-7), 6.10, 6.89 (each 1H, d, J=7 Hz, H-10, 11), 6.31 (1H, br d, J=10 Hz, H-2), 6.69, 6.72 (each 1H, s, ArH), 6.91 (1H, dd, J=10, 2 Hz, H-1). HRMS: Calcd for $C_{18}H_{15}NO_4$ (M^+): 309.0999. Found: 309.0989. The IR and ^{1}H-NMR spectra were identical with those of (+)-crystamidine.[8]

(±)-3-Epierytharbine (13a) The 3β-alcohol **12a** (3 mg) in THF (3 ml) was methylated with 5% KOH (1 mg), Et_4NBr (1 mg), and CH_3I (40 mg) for 88 h and worked up as described above. The product was purified by PTLC ($CHCl_3$: acetone = 4 : 1) to afford (±)-3-epierytharbine (**13a**) (0.6 mg, 19%) as a colorless gum. IR: 1690. UV: 230 (18600), 255 (13300), 370 (800). ^{1}H-NMR: 1.58 (1H, dd, J=13, 5 Hz, H-4), 2.75 (1H, d, J=13 Hz, H-4), 2.96 3.78, 3.84 (each 3H, s, OMe), 4.02 (1H, t, J=5 Hz, H-3), 6.00 (1H, s, H-7), 6.09, 6.82 (each 1H, d, J=8 Hz, H-10, 11), 6.30 (1H, dd, J=10, 5 Hz, H-2), 6.65, 6.87 (each 1H, s, ArH), 6.95 (1H, d, J=10 Hz, H-1), HRMS: Calcd for $C_{19}H_{19}NO_4$ (M^+): 325.1309. Found. 325.1313.

(±)-3-Epicrystamidine (13b) The 3β-alcohol **12b** (8 mg) in THF (5 ml) was methylated with 85% KOH (2 mg), Et_4NBr (1 mg), and CH_3I (4 mg) for 48 h and worked up as described above. The product was purified by MPLC (AcOEt : hexane = 4 : 1) to afford (±)-3-epicrystamidine (**13b**) (4 mg, 48%) as a colorless gum. IR: 1690, 1480. UV: 225 (23500), 250 (17800), 368 (1900). ^{1}H-NMR: 1.55 (1H, dd, J=13, 5 Hz, H-4), 2.82 (1H, d, J=13 Hz, H-4), 3.02 (3H, s, OMe), 4.05 (1H, t, J=5 Hz, H-3), 5.92 (2H, d, J=2 Hz, OCH_2O), 6.01 (1H, s, H-7), 6.07, 6.82 (each 1H, d, J=7 Hz, H-10, 11), 6.28 (1H, dd, J=10, 5 Hz, H-2), 6.64, 6.87 (each 1H, s, ArH), 6.94 (1H, d, J=10 Hz, H-1). HRMS: Calcd for $C_{18}H_{15}NO_4$ (M^+): 309.0999. Found: 309.1019.

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References and Notes

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7) For the assignment, see Part XXXVIII.[1]
8) The spectra were provided by Prof. H. Furukawa, Meijo University.