CONFORMATIONAL DIFFERENCE BETWEEN ERYTHRINAN- AND HOMOERYTHRINAN-3-ONES: TOTAL SYNTHESIS OF (±)-SCHELHAMMERIDINE AND (±)-3-EPISCHELHAMMERIDINE[1]

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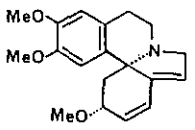
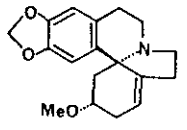
Abstract - Erythrinan- and homoerythrinan-3-ones behave differently toward hydride reductions suggesting their conformational difference: for example, Δ^1-erythrinan-3-one gives 3α-alcohol and Δ^1-homoerythrinan-3-one gives 3β-alcohol stereoselectively on reduction with $NaBH_4$-$CeCl_3$ in methanol. Based on these observations, total syntheses of homoerythrinan alkaloids, schelhammeridine and 3-epischelhammeridine, and an erythrinan alkaloid, 8-oxoerysotrine, were accomplished.

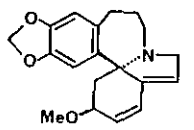
Most erythrinan alkaloids have an oxygenated function of 3α configuration (e.g. erysotrine **1a** and erythramine **2a**), while many homoerythrinan alkaloids have that of 3β configuration (e.g. schelhammeridine **3b** and schelhammericine **4b**).[2] Stereocontrolled synthesis of these alkaloids therefore requires, in many cases, stereoselective reduction of the 3-ketones, which was now found to proceed differently in erythrinan and homoerythrinan series. This suggests that the 3-ketones in erythrinan and homoerythrinan series exist in different conformations.



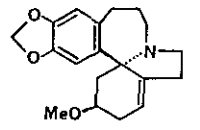
1a



2a



3b



4b

Table I shows the results of hydride reduction of various erythrinan- and homoerythrinan-3- ones with two reagents, $NaBH_4$-$CeCl_3$ (method A) and Bu_4NBH_4 (method B): the former reagent is known to produce equatorial alcohol preferentially[3] and the latter reagent attacks the ketone from the less hindered face of the molecule.

This paper is dedicated to the late Professor Tetsuji Kametani.

The $\Delta^{1(6)}$-3-ones, **5**[4] and **6**[5], gave stereoselectively 3α-alcohols, **11a** and **12a**, by method A, and 3β- alcohols, **11b** and **12b**, by method B, respectively, suggesting that they have the same conformation in erythrinan and homoerythrinan series. In fact, the molecular model shows that only one conformation ($^{3}\underline{H}_{4}$) is possible for the $\Delta^{1(6)}$- 3-ones. Axial attack of the hydride producing the equatorial 3α-alcohols by $NaBH_4$- $CeCl_3$ and attack of the hydride from the less hindered face (i.e. opposite side of the aromatic group) by the bulky Bu_4NBH_4 leading to the axial 3β-alcohols are thus well explained.

However, reductions of Δ^{1}-3-ones gave reversed results in erythrinan and homoerythrinan series. The major products by method A were the 3α-alcohol **13a** in erythrinan (**7**)[4] and 3β-alcohol **14b** in homoerythrinan series (**8**)[6], and those by method B were the 3β-alcohol **13b** in erythrinan and the 3α-alcohol **14a** in homoerythrinan series with regard to the 1,2-reduction products, though appreciable amounts of 1,4-reduction products were produced by method B. These results can only be explained by considering that the reductions took place through the different conformations in erythrinan and homoerythrinan series: a $^{5}\underline{H}_{4}$ conformation for Δ^{1}-erythrinan-3-ones[7] and a $^{4}\underline{H}_{5}$ conformation for Δ^{1}-homoerythrinan-3-ones.

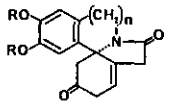
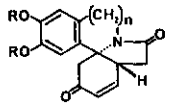
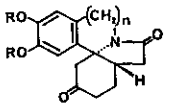
Reductions of saturated ketones, **9** and **10**, with method A gave preferentially the 3α-alcohol **15a** and the 3β-alcohol **16b**, respectively, again suggesting conformational difference between erythrinan- and homoerythrinan-3-ones. Reduction of **10** by method B gave the 3α-alcohol **16a** with the selectivity of 3/1. However, similar reduction of **9** unexpectedly gave the 3α-alcohol **15a** with the selectivity of 2.5/1.

An X-ray analysis of 8-oxohomoerythrinan-3-one **10** revealed that ring A of this compound is of a twist ($\underline{T}_{3}$) conformation. We therefore conclude that homoerythrinan-3-ones are reduced mainly through $\underline{T}_{3}$ (or $^{4}\underline{C}_{1}$) conformation, while erythrinan-3-ones are reduced through a conformation $^{1}\underline{C}_{4}$ by method A and they are reduced probably through $\underline{T}_{3}$ conformation when the bulky reducing agent was used, though the reason of this exceptional result is not clear at present.

As suggested from the low selectivities of the hydride reductions, the differences of conformational energies between $^{5}\underline{H}_{4}$ and $^{4}\underline{H}_{5}$ or $^{4}\underline{C}_{1}$ and $\underline{T}_{3}$ are so small that they are able to interconvert depending on the configuration of a substituent at ring A.

Table II shows ring A conformations of 3-OR derivatives of Δ^{1}-erythrinan and homoerythrinan. In 8-oxo-Δ^{1}-erythrinans either 3α or 3β hydroxyl group adopts quasi-equatorial orientation. On the other hand, in 8-oxo-Δ^{1}-homoerythrinans **17**, the 3α and 3β methoxyl groups are quasi-axial and quasi-equatorial, respectively, indicating

Table I Hydride Reduction of Erythrinan and Homoerythrinan (in methanol at 0 °C)[12]

3-ones			$NaBH_4$-$CeCl_3$(1:2) 1,2-reduction α : β	$n\text{-}Bu_4NBH_4$ 1,2-reduction α : β	$n\text{-}Bu_4NBH_4$ 1,4-reduction α : β
	5	n=2	4.5 : 1 (11a) (11b)	1 : >10 (11a) (11b)	
	6	n=3	5 : 1 [a] (12a) (12b)	1 : 6 [a] (12a) (12b)	
	7	n=2	2.1 : 1 (13a) (13b)	1 : 2.1 (13a) (13b)	5.3 : 2.1 (15a) (15b)
	8	n=3	1 : 2 [b] (14a) (14b)	1 : -- (14a)	2 : 1 (16a) (16b)
	9	n=2	3 : 1 (15a) (15b)	2.5 : 1 (15a) (15b)	
	10	n=3	1 : 1.5 (16a) (16b)	3 : 1 (16a) (16b)	

R=OMe for n=2 , R-R= $-CH_2-$ for n=3

a) ref.5 b) ref.6 The ratio was determined by hplc on TSK-Gel Si60 ($CHCl_3$:MeOH=19:1)

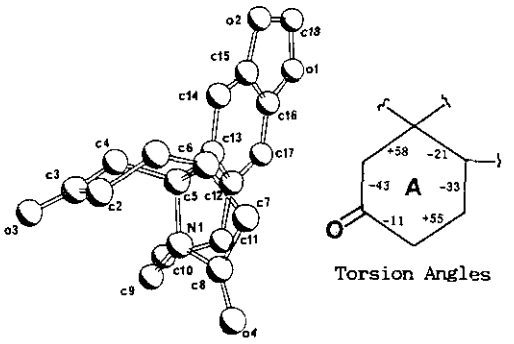
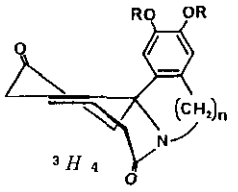
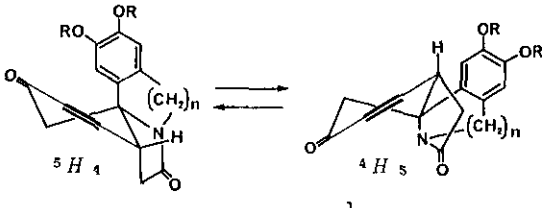


Fig.1 Crystal Structure of the 3,8-Dioxohomo-erythrinan **10**
Monoclinic, a=10.863(4), b=12.664(5),
c=10.747(6)Å, β=90.05(4), U=1478(1)Å^3
Z=4, Dc=1.41g/cm^3, Space group $P2_1$,
1790 reflections, R=0.055.

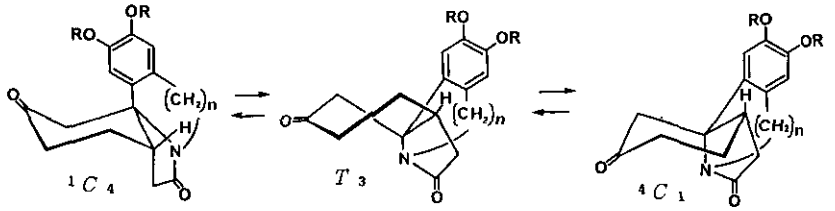
Torsion Angles



Conformation of $\Delta^{1(6)}$-3-ones



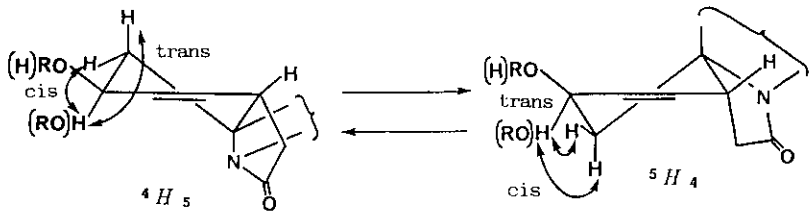
Conformation of Δ^{1}-3-ones



Conformation of Saturated Ketones

that both the **17a** and **17b** are in the conformer $^{4}\underline{H}_{5}$. However, the corresponding amines **18** take $^{5}\underline{H}_{4}$ for 3α-OMe (comosine)[8] and $^{4}\underline{H}_{5}$ for 3β-OMe (alkaloid A).[9]

Table II ^{1}H-Nmr(400M Hz) of Erythrinan and Homoerythrinan Derivatives

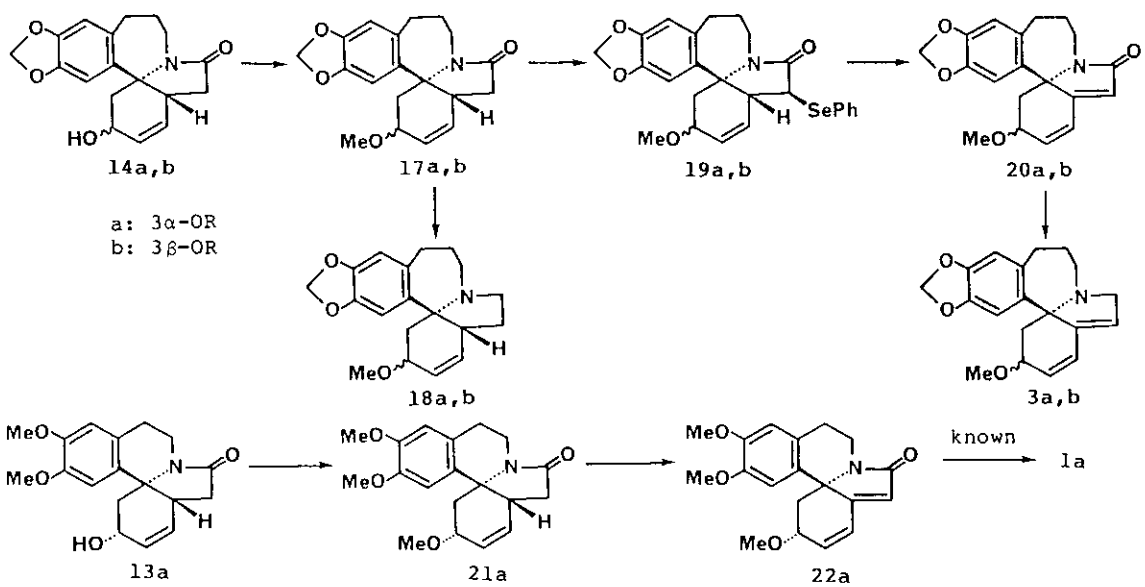


Compd		3α-OR J trans	J cis	Assigned conformation		3β-OR J trans	J cis	Assigned conformation
8-Oxo [a]	**13a**	10	5	$^{5}H_{4}$	**13b**	9.5	5	$^{4}H_{5}$
8-Oxohomo [a]	**17a**	3	5.8	$^{4}H_{5}$	**17b**	10.5	5	$^{4}H_{5}$
Homo [b]	**18a**	11.5	5	$^{5}H_{4}$	**18b**	9.8	5.4	$^{4}H_{5}$

Solvent: a) $CDCl_3$, b) C_6D_6. *J*'s are given in Hz.

Stereochemical assignments of the above reduction products are done by correlations of each other by hydrogenations and finally by leading them to the natural alkaloids, whose structures have been determined already.

Schelhammeridine **3b** and 3-epischelhammeridine **3a** were synthesized as follows. The



Syntheses of Schelhammeridine, 3-Epischelhammeridine, and 8-Oxoerysotrine

3β-alcohol **14b** was methylated by MeI/NaH in the presence of a phase transfer catalyst to the O-methyl derivative **17b**.[6] Generation of an anion by action of n-BuLi on **17b** followed by phenylselenenylation with $(PhSe)_2$ gave the 7β-phenylselenenyl derivative **19b**. syn-Elimination of the phenylselenenyl group from **19b** through oxidation with $NaIO_4$ gave the dienoid lactam **20b**, whose ^{1}H-nmr spectrum was superimposable on that of alkaloid K (8-oxoschelhammeridine) reported by Johns et al.[10] $LiAlH_4$-$AlCl_3$ (1:1) reduction[11] of **20b** furnished the amine **3b**, whose ^{1}H-nmr spectrum was identical with that reported for schelhammeridine.[10]

Similarly, the 3α-alcohol **14a** was methylated and converted to the dienoid lactam **20a**, then to the amine **3a**, whose ^{1}H-nmr spectrum was identical with that reported for 3-epischelhammeridine.[10]

In a similar manner, the 3α-alcohol **13a** was methylated and converted to the dienoid lactam **22a** through phenylselenenylation. The product was identical with (±)-erysotramidine (8-oxoerysotrine) reported previously.[11]

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12. Data of new compounds. **10**: mp 217-219°C. Ir($CHCl_3$):1720, 1680. **11a**: mp 245- 246°C. Ir($CHCl_3$):3450, 1680. δ5.82(1H, bs). **11b**: mp 171-172°C. Ir($CHCl_3$):3350, 1680. δ5.84(1H, bs). **13a**: mp 286-287°C. Ir(KBr):3426, 1658. δ 6.05(2H, bs). **13b**: mp 178-179°C. Ir($CHCl_3$):3424, 1680. δ 5.76(1H, ddd, J=10, 4, 2 Hz, C_1-H), 5.95(1H, dd, J=10, 1 Hz, C_2-H). **14a**: mp 236-237°C. δ 5.72(1H, ddd, J=10, 3, 1 Hz, C_1-H), 6.02(1H, dd, J=10, 4 Hz, C_2-H). **14b**: not purified [cf. **17a**[6]: mp 236-237°C. Ir(KBr):1690. δ 5.71(1H, ddd, J=10, 3, 1 Hz, C_1-H), 6.00(1H, ddd, J=10, 4.5, 1.5 Hz, C_2-H). **17b**[6]: mp 175- 176°C. Ir(KBr):1690. δ 5.57(1H, ddd, J=10.5, 3, 1 Hz, C_1- H), 5.95(1H, ddd, J=10.5, 3, 1.5 Hz, C_2-H)]. **15a**: mp 241-243°C. Ir($CHCl_3$):3360, 1674. **15b**: Ir($CHCl_3$):3450, 1680. **16a** and **16b**: not separated [cf. O-methyl derivatives[6]: 3α-OMe, mp 175-176°C. 3β-OMe, mp 149-150°C]. **20a**: δ 6.80(1H, dd, J=10, 2 Hz, C_1-H), 6.18(1H, d, J=10 Hz, C_2-H), 6.04(1H, s, C_7-H). **20b**: mp 212- 213°C. Ir(CCl_4):1690. δ 6.83(1H, d, J=10 Hz, C_1-H), 6.14(1H, dd, J=10, 5 Hz, C_2-H), 6.02(1H, s, C_7-H). **21a**: mp 149-151°C. δ 6.09(2H, bs, C_1- and C_2-H).

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