SYNTHESES OF ERYTHRINA AND RELATED ALKALOIDS (6)
TOTAL SYNTHESIS OF ERYSOTRINE AND ERYTHRALINE[1]

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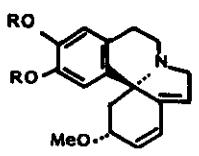
Abstract----- An efficiently stereocontrolled synthesis of the erythrina alkaloids, erysotrine and erythraline was described.

A Δ^2-pyrroline-4,5-dione has been demonstrated to be a potential synthon for hydroindole synthesis[2]. We recently reported the short step synthesis of ring D functionalized erythrinans (3 or 4) via Diels-Alder reaction of the isoquinolinopyrrolinediones (2) with 1,3-bis(trimethylsilyloxy)butadiene or 1-methoxy-3-trimethylsilyloxybutadiene[3]. The reaction proceeded with control of regio- and stereochemistry to result in what one might envisage to constitute the dienoid type erythrina alkaloids such as erysotrine (1a)[4] or erythraline (1b)[5]. In this communication we describe the stereocontrolled transformation of the Diels-Alder adducts (3 and 4) into these alkaloids.



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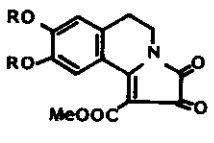

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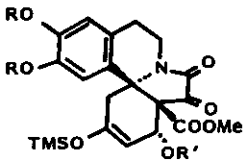


3 R'=TMS
4 R'=Me

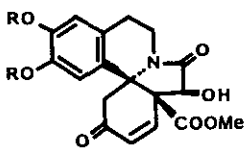
a: R=Me , b: R-R=-CH_2-

Partial reduction of 3a and 3b with a stoichiometric amount of $LiBH_4$ under mild condition (in THF, -60°, 20 min.), followed by acid treatment of the resulting products (5%HCl-THF (1:1), reflux, 1 hr) afforded the unsaturated ketone (5a and 5b) in ca. 80% yield, respectively, 5a, mp.216-218°, [νmax (Nujol): 1730, 1690, and 1670 cm^{-1}] and 5b, mp.229-231°, [νmax (Nujol): 1730, 1690 and 1670 cm^{-1}].

Similar treatment of 4a and 4b also afforded the ketone (5a and 5b) in comparative yields (ca. 80%). Appearance of a set of clean doublet (J=10 Hz) at δ 6.42(1H) and 7.53(1H) in the ^{1}H n.m.r. spectrum of 5a corroborated the structure. The assignment of C_7-hydroxyl group as β is based on the result of analogous reduction.[3] Demethoxycarbonylation of 5a and 5b with $MgCl_2$ in DMSO[6] (140°, 1 hr) gave, with concomitant dehydration, the dienone (6a)(40%), mp.193-195°, [ν max (Nujol): 1690 cm^{-1}, λ max (EtOH): 276(14,200) nm] and (6b)(42%), mp.193-196°, [νmax (Nujol): 1690 cm^{-1}, UV: 278(14,600) nm], respectively. Three olefinic proton signals, one singlet (δ 6.36) and a pair of doublet (δ 6.40 and 7.73, J=10 Hz), appeared in the ^{1}H n.m.r. spectrum of 6a, confirming the structure. Stereoselective reduction of 6a and 6b to the alcohol 7a and 7b of the same configuration as that of the natural alkaloids was achieved in good yield by Meerwein-Pondorf reduction. The epimeric alcohol 8a and 8b were the major product when the reduction of 6a and 6b was carried out with $NaBH_4$, which also gave the undesired 1,4-reduction product 9a and 9b, respectively. The results on reductions of 6 under various conditions are assembled in the Table.

Methylation of 7a and 7b with CH_3I catalysed by KOH-Et_4NBr[8] furnished (±)-erysotramidine (10a), gum (84%) and (±)-8-oxoerythraline (10b), gum (86%), respectively. Identity of 10a with erysotramidine, a natural non-basic alkaloid, was confirmed by comparisons of the ^{1}H n.m.r. and IR($CHCl_3$) spectra[9]. Similar methylation of the C_3-epimer (8a and 8b) gave (±)-3-epierysotramidine (11a)(83%), mp.168-170°, [^{1}H n.m.r.($CDCl_3$): δ 5.94(1H, s, C_7-H), 6,35(1H, dd, J=5 and 10 Hz, C_1-H), 6.29(1H, d, J=10 Hz, C_2-H), 3.18(3H, s, C_3-OMe)] and (±)-3-epi-8-oxo-erythraline (11b)(60%), mp.161-165°, [^{1}H n.m.r.($CDCl_3$): δ 5.96(1H, s, C_7-H), 6.30 (1H, dd, J=5 and 10 Hz, C_1-H), 6.89(1H, d, J=10 Hz, C_2-H), 3.12(3H, s, C_3-OMe)], respectively.

Reduction of 10a and 10b with $LiAlH_4$-$AlCl_3$ (1:1)[10] (THF, r.t., 2 hr) afforded (±)-erysotrine (1a)(62%)[picrate: mp.194-196°(lit.[11]197-198°)] and (±)-erythraline (1b)(71%)(picrate: mp.196-199°), respectively, whose identity with natural erysotrine and erythraline was confirmed by NMR and IR($CHCl_3$) comparisons.



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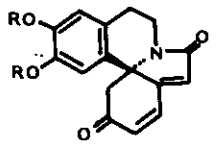

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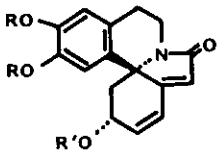
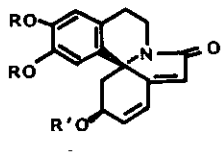
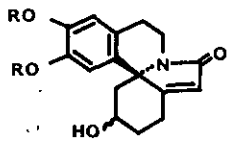


7 R'=H
10 R'=Me



8 R'=H
11 R'=Me



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a : R=Me , b : R-R=-CH_2-

Table Reductions of the dienones (6)

	Reagent	Solvent	Temp.	Time	Yield(%) 7	8	9
6a	$NaBH_4$	EtOH	0°	1 hr	15	42	35
6a	$n\text{-}Bu_4NBH_4$	MeOH	0°	5 min	10	52	13
6a	$Zn(BH_4)_2$	THF-Et_2O	r.t.	24 hr	52	30	-
6a	$NaBH_4$-$CeCl_3$[7]	MeOH	0°	10 min	60	30	-
6a	$(i\text{-}PrO)_3Al$	iPrOH	reflux	24 hr	70	25	-
6b	$NaBH_4$	EtOH	0°	1 hr	23	40	15
6b	$(i\text{-}PrO)_3Al$	iPrOH	reflux	24 hr	58	20	-

7a: mp.232-235°, ^1H n.m.r.($CDCl_3$): δ 6.20(1H, s), 6.29(1H, d, J=10 Hz), 6.81 (1H, dd, J=2.5 and 10 Hz).

7b: mp.122-125°, ^1H n.m.r.($CDCl_3$): δ 5.96(1H, s), 6.29(1H, d, J=10 Hz), 6.81 (1H, dd, J=2.5 and 10 Hz).

8a: mp.181-183°, ^1H n.m.r.($CDCl_3$): δ 5.98(1H, s, 6.31(1H, dd, J=4.5 and 10 Hz), 6.93(1H, d, J=10 Hz).

8b: mp.205-207°, ^1H n.m.r.($CDCl_3$): δ 5.98(1H, s), 6.26(1H, dd, J=5 and 10 Hz), 6.88(1H, d, J=10 Hz).

9a: mp.193-194°, ^1H n.m.r.($CDCl_3$): δ 5.91(1H, d, J=1.5 Hz).

9b: mp.245-247°, ^1H n.m.r.($CDCl_3$): δ 5.96(1H, d, J=1.5 Hz).

Acknowledgement

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References

1. Dioxopyrrolines XXIII. Part XXII: T. Sano, J. Toda, Y. Horiguchi, K. Imafuku, and Y. Tsuda, Heterocycles, 1981, 16, 1463.
2. a. Y. Tsuda, K. Isobe, and A. Ukai, Chem. Comm., 1971, 1554.
   b. Y. Tsuda, Y. Horiguchi, and T. Sano, Heterocycles, 1976, 4, 1355.
   c. T. Sano and Y. Tsuda, Heterocycles, 1976, 4, 1361.
3. T. Sano, J. Toda, K. Kashiwaba, Y. Tsuda, and Y. Iitaka, Heterocycles, 1981, 16, 1151.
4. R. M. Letcher, J. Chem. Soc., (C), 1971, 652.
5. K. Folkers and F. Koniuszy, J. Am. Chem. Soc., 1940, 62, 436.
6. Y. Tsuda and Y. Sakai, Synthesis, 1981, 118.
7. J. L. Luche, L. Rodriguez-Hahn, and P. Crabbé, J. C. S. Chem. Comm., 1978, 601.
8. D. Reushling, H. Piatsch, and A. Linkies, Tetrahedron Lett., 1978, 615.
9. K. Ito, F. Suzuki, and M. Haruna, J. C. S. Chem. Comm., 1978, 733.
10. $LiAlH_4$ reduction gave complex mixture. C.f. A. Mondon, J. Zander, and H-U, Menz, Ann. Chem., 1963, 667, 126, and A. Mondon, Liebigs Ann. Chem., 1959, 628, 123.
11. A. Mondon and H. J. Nestler, Chem. Ber., 1979, 112, 1329.

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