AN ALTERNATE SYNTHESIS OF A 2,8-DIOXO-1,7-CYCLOERYTHRINAN, A KEY INTERMEDIATE TO ERYTHRINAN ALKALOIDS OF DIENOID-TYPE[1,2]

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Starting from homoveratrylamine, 15,16-dimethoxy-2,8-dioxo-1,7-cycloerythrinan 1a, a key intermediate to erythrinan alkaloids of dienoid-type, was synthesized in 35% overall yield by 10 steps reactions including deethoxycarbonylation of a 6-ethoxycarbonylerythrinan derivative.

In 1978, Ito et al.[3] reported an intriguing route to erysotramidine 2a, the oxo-erythrinan alkaloid of Erythrina arborescens Roxb., through a 2,8-dioxo-1,7-cycloerythrinan 1a which was prepared by a concerted intermolecular alkylation of the 7β-mesylate 4. Since the reported route from 1a to 2a must be safely applicable of synthesizing erythrinan alkaloids of dienoid type, synthesis of the intermediate 1 thus become crucial when erythraline 3b and coccuvinine 3c are attemped to be prepared.[4] The reported method for 1a has a disadvantage for that purpose because it includes Birch reduction.[5]

We present here an alternate method that is widely applicable of synthesizing 2,8-dioxo-1,7-cycloerythrinans. The method is based on an unexpected finding that

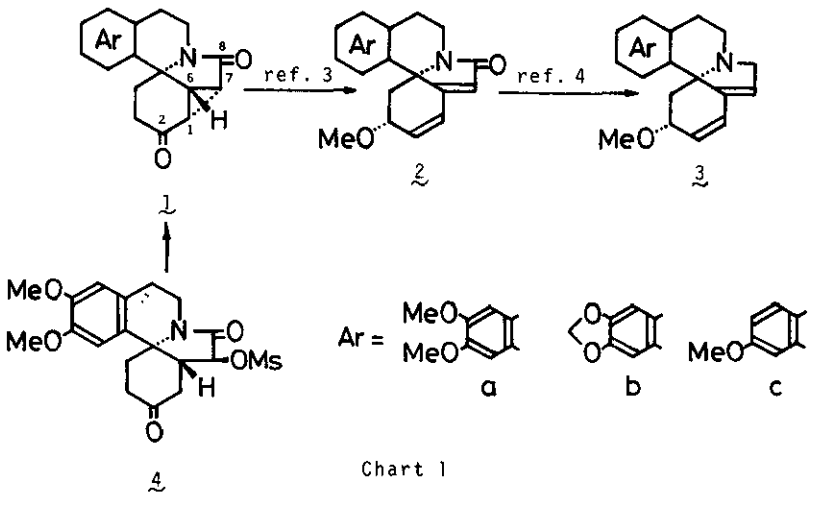
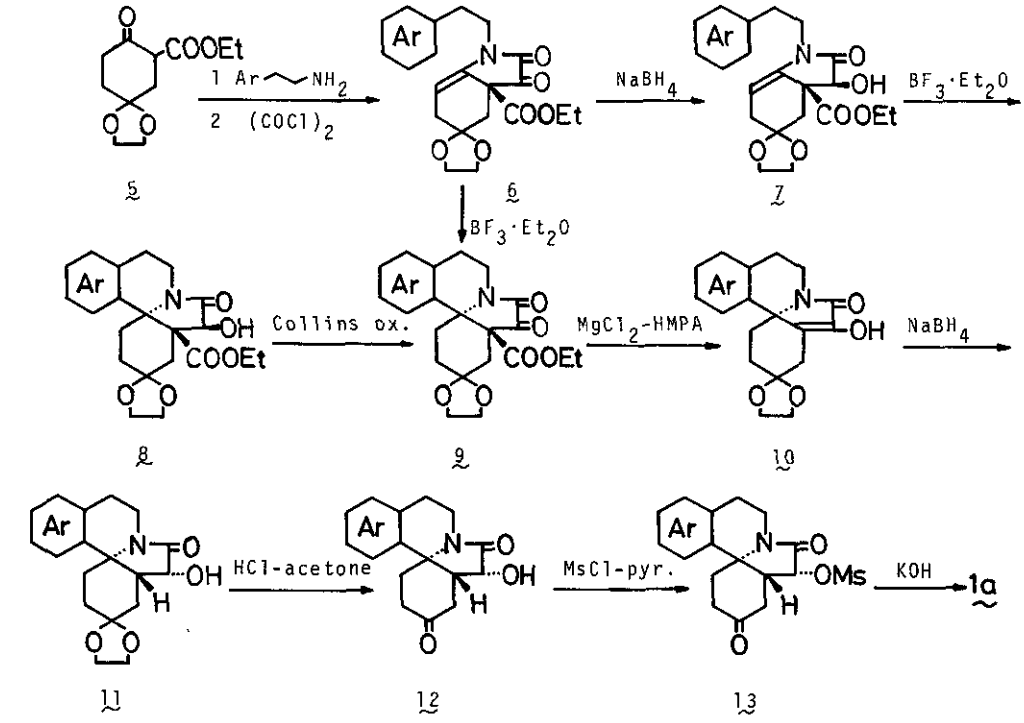


Chart 1

the 7α-mesylate 13, equally to the 7β-mesylate 4[3], gives the 1,7-cycloerythrinan 1a on base treatment. This finding opened the following route to 1 starting from β-arylethylamines.

As reported already, condensation of homoveratrylamine and 2-ethoxycarbonyl-4,4-ethylenedioxycyclohexanone 5 followed by oxidation and cyclization of the resulting product 6 with BF_3-Et_2O in CH_2Cl_2 (reflux, 40 min) gave the 6-ethoxycarbonyl-7,8-dioxoerythrinan 9 in 35% yield with two other by-products.[2] More efficacious preparation of 9 has now been achieved by the following modification. Reduction of 6 with 1/4 mol eq. of $NaBH_4$ in EtOH (0°, 40 min, 90% yield) resulted in a single alcohol 7, mp. 135-136°[6], which cyclized under milder condition (BF_3-Et_2O in CH_2Cl_2, r.t., 2 hr) than did 6 to give 8, mp. 173-174° in quantitative yield.[7] Thus starting from homoveratrylamine and the keto-ester 5, four sequential reactions gave 8 in 75% yield without isolation of the intermediates. Collins oxidation of 8 afforded 9 in 70% yield.



Ar = MeO, MeO for 6 and 7. MeO, MeO for the other compounds.

Chart 2

Heating of 9 with $MgCl_2$-HMPA[8] (145°, 2 hr) smoothly gave the deethoxycarbonylated product 10[9], mp.213-215°, in 98% yield. On $NaBH_4$ reduction 10 yielded the 7α-alcohol 11, gum, as a sole product. Deacetalization of 11 with 1% HCl-acetone (60°, 15 min) and mesylation with CH_3SO_2Cl and pyridine (r.t., 2 hr) of the resulting keto-alcohol 12, mp. 239-241°, gave the 7α-mesylate 13 (95% yield from 10), mp. 209-210°. The 7α-configuration of those compounds were confirmed by their non-identity with the corresponding 7β-derivatives.[10] On heating with 10% KOH-MeOH (reflux, 1.5 hr), the 7α-mesylate 13 afforded the 2,8-dioxo-1,7-cycloerythrinan 1a, mp. 216-217°, in 71% yield. No olefinic product was found in the reaction mixture[11]. The identity of this with 15,16-dimethoxy-2,8-dioxo-1,7-cycloerythrinan (lit. mp. 205-207°) was established by direct comparison with the authentic sample.[12] This indicates that 7α-OMs group in 13 would have been epimerized to the 7β orientation before cyclization under the reaction condition.

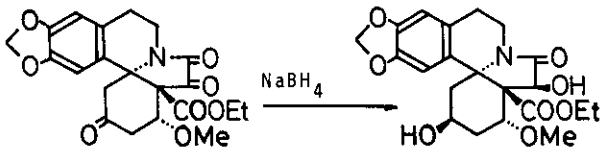
Since 6-ethoxycarbonyl-7,8-dioxoerythrinans (compounds of the structure 9) are readily available from β-arylethylamines by the method reported already[2,13] or by the above described modification, the present transformation of 9 to 1a will provide a general method of synthesizing 2,8-dioxo-1,7-cycloerythrinans 1, hence of erythrinan alkaloids of dienoid type.

Acknowledgment. The authors thanks Dr. Haruna, Meijo University, for providing us the sample of 15,16-dimethoxy-2,8-dioxo-1,7-cycloerythrinan and some spectral data. A part of this work was supported by Grant-in-Aid for Special Project Research from Ministry of Education, Science and Culture, Chemical Research in Development and Utilization of Nitrogen-Organic Resources, and Naito Research Grant, for which we are grateful.

References and Notes

1. Dioxopyrrolines XX. Part XIX: T. Sano, Y. Horiguchi, S. Kambe, J. Toda, J. Taga, and Y. Tsuda, Heterocycles, 16, in press.
2. Syntheses of Erythrina and Related Alkaloid (3). Part (2): Y. Tsuda, Y. Sakai, and T. Sano, Heterocycles, 15, 1097 (1981).
3. K. Ito, F. Suzuki, and M. Haruna, J. C. S. Chem. Comm., 1978, 733.
4. An effective method of removing the oxo-group from 2 to yield 3 was recently expoited (AlH_3 in ether). (T. Sano, J. Toda, and Y. Tsuda, to be published)
5. M. Haruna and K. Ito, J. C. S. Chem. Comm., 1976, 345.

6. The stereochemistry of 7 was evidenced as follows. $NaBH_4$ reduction of 9 yielded a single product identical with 8. The similar $NaBH_4$ reduction of the analogous compound 14 gave stereoselectively a single 7β-alcohol 15, whose structure was established by X-ray analysis of the derived diacetate. (T. Sano, J. Toda, N. Kashiwaba, Y. Tsuda, and Y. Iitaka, to be published)



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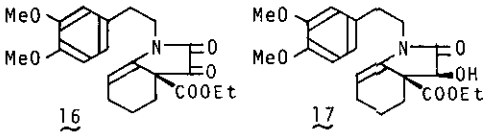
7. The following model experiments clearly showed that cyclization of a dioxopyrroline 16 is greatly accelerated by reducing its carbonyl group to the alcohol 17.

Reagent and reaction condition to yield 100% cyclization		
	PPE	BF_3-Et_2O
16	90°, 1.5 hr	r.t., 3 hr
17	85°, 35 min	r.t., 30 min



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8. For this new dealkoxycarbonylation method, see Y. Tsuda and Y. Sakai, Synthesis, 1981, 118.

9. Cf. ref. 5. Dr. Haruna informed us that the compound 10 prepared in ref. 5 was a gum, a 2:5 mixture of the keto and enol forms. The spectral data provided by him were identical with those of our 10.

10. Spectral Data: 11; IR($CHCl_3$): 3370, 1690 cm^{-1}. NMR ($CDCl_3$): δ 6.76, 6.51 (each 1H, s, Ar-H). 12; IR(KBr): 3320, 1715, 1655 cm^{-1}. NMR ($CDCl_3$): δ 6.71, 6.57 (each 1H, s, Ar-H), 4.38 (1H, d, J=9 Hz, 7β-H). 13; IR(KBr): 1710, 1690 cm^{-1}. NMR($CDCl_3$): δ 6.71, 6.61 (each 1H, s, Ar-H), 5.19 (1H, d, J=9 Hz, 7β-H). The spectral data of 7β-compounds for comparisons were provided by Dr. Haruna.

11. Usually base treatment of a sulfonate of 7α-hydroxy-8-oxo-cis-erythrinan affords a Δ^6-compound exclusively, cf. A. Mondon, K. F. Hansen, K. Bochme, H. P. Faro, H. J. Nestler, H. G. Vilhauber, and K. Döttcher, Chem. Ber., 103, 615 (1970).

12. The authentic sample of 15,16-dimethoxy-2,8-dioxo-1,7-cycloerythrinan 1a provided by Dr. Haruna showed mp. 215-216° on our mp apparatus.

13. Y. Tsuda, Y. Sakai, M. Kaneko, Y. Ishiguro, K. Isobe, J. Taga, and T. Sano, Heterocycles, 15, 431 (1981).

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