

AN ALTERNATE SYNTHESIS OF A 2,8-DIOXO-1,7-CYCLOERYTHRINAN, A KEY INTERMEDIATE  
TO ERYTHRINAN ALKALOIDS OF DIENOID-TYPE<sup>1,2</sup>

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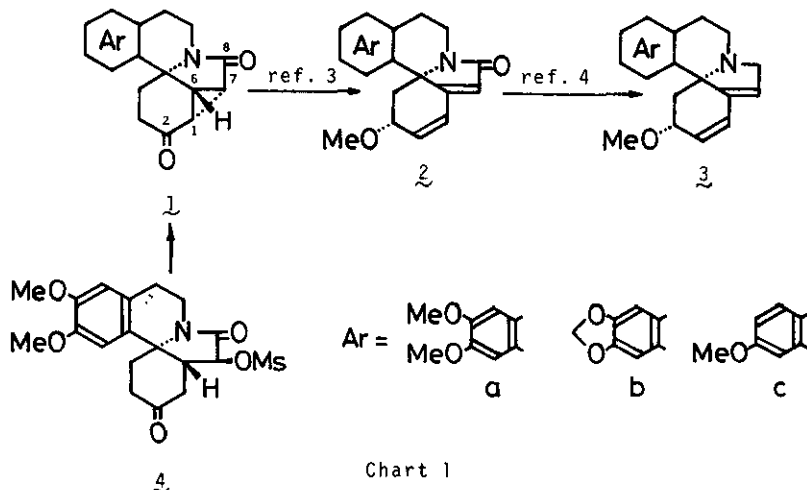
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Starting from homoveratrylamine, 15,16-dimethoxy-2,8-dioxo-1,7-cycloerythrinan **1a**, a key intermediate to erythrinan alkaloids of dienoid-type, was synthesized in 35% overall yield by 10 steps reactions including deethoxycarbonylation of a 6-ethoxycarbonylerythrinan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

In 1978, Ito et al.<sup>3</sup> 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 7 $\beta$ -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 coccupinine **3c** are attempted to be prepared.<sup>4</sup> The reported method for **1a** has a disadvantage for that purpose because it includes Birch reduction.<sup>5</sup>

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



the 7 $\alpha$ -mesylate 13, equally to the 7 $\beta$ -mesylate 4<sup>3</sup>, gives the 1,7-cycloerythrinan 1a on base treatment. This finding opened the following route to 1 starting from  $\beta$ -arylethylamines.

As reported already, condensation of homoveratrylamine and 2-ethoxycarbonyl-4,4-ethylenedioxcyclohexanone 5 followed by oxidation and cyclization of the resulting product 6 with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$  (reflux, 40 min) gave the 6-ethoxycarbonyl-7,8-dioxoerythrinan 9 in 35% yield with two other by-products.<sup>2</sup> More efficacious preparation of 9 has now been achieved by the following modification. Reduction of 6 with 1/4 mol eq. of  $\text{NaBH}_4$  in EtOH (0°, 40 min, 90% yield) resulted in a single alcohol 7, mp. 135-136°<sup>6</sup>, which cyclized under milder condition ( $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$ , r.t., 2 hr) than did 6 to give 8, mp. 173-174° in quantitative yield.<sup>7</sup> 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.

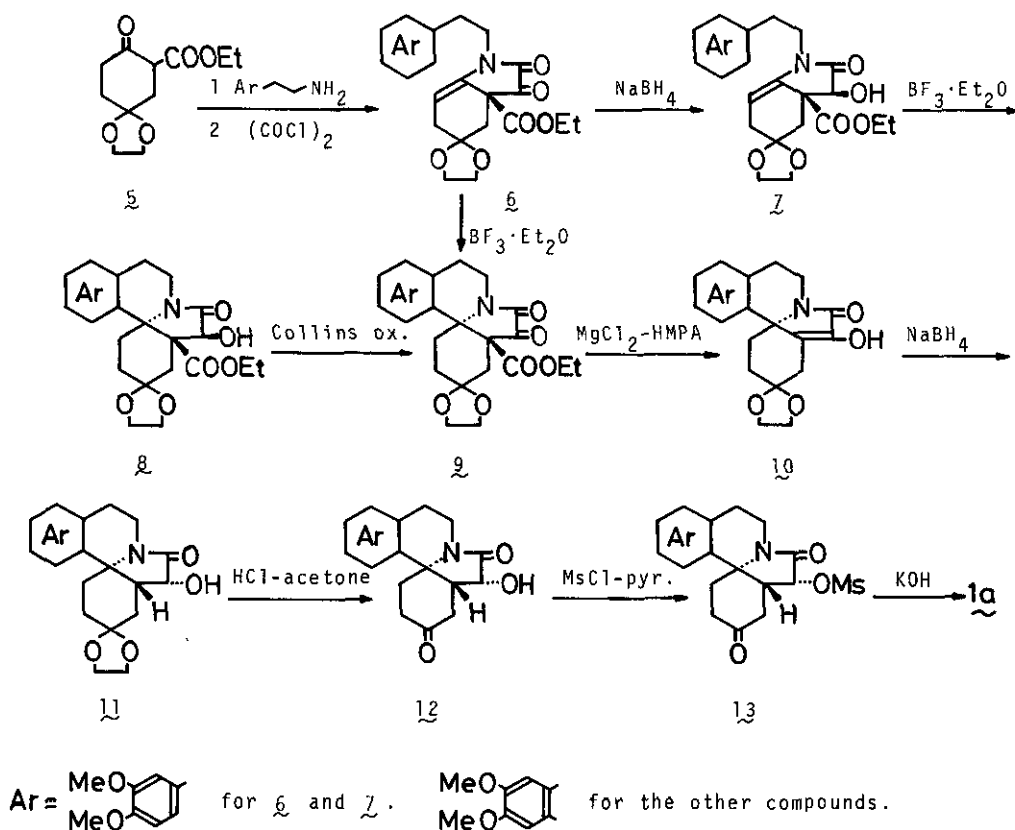


Chart 2

Heating of 9 with  $MgCl_2$ -HMPA<sup>8</sup> (145°, 2 hr) smoothly gave the deethoxycarbonylated product 10<sup>9</sup>, mp. 213-215°, in 98% yield. On  $NaBH_4$  reduction 10 yielded the 7 $\alpha$ -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 7 $\alpha$ -mesylate 13 (95% yield from 10), mp. 209-210°. The 7 $\alpha$ -configuration of those compounds were confirmed by their non-identity with the corresponding 7 $\beta$ -derivatives.<sup>10</sup> On heating with 10% KOH-MeOH (reflux, 1.5 hr), the 7 $\alpha$ -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<sup>11</sup>. 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.<sup>12</sup> This indicates that 7 $\alpha$ -OMS group in 13 would have been epimerized to the 7 $\beta$  orientation before cyclization under the reaction condition.

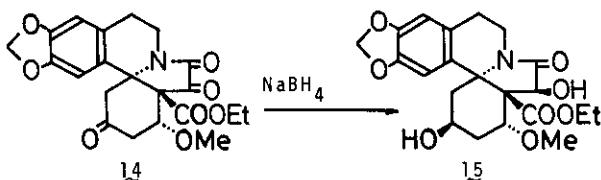
Since 6-ethoxycarbonyl-7,8-dioxoerythrinans (compounds of the structure 9) are readily available from  $\beta$ -arylethylamines by the method reported already<sup>2,13</sup> or by the above described modification, the present transformation of 9 to 1a will provide a general method of synthesizing 2,8-dioxo-1,7-cycloerythrinans 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

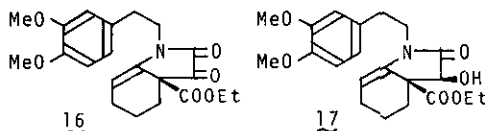
1. Dioxopyrrolines XX. Part XIX: T. Sano, Y. Horiguchi, S. Kambe, J. Toda, J. Taga, and Y. Tsuda, Heterocycles, 16, in press.
2. Syntheses of Erythrina and Related Alkaloid (3). Part (2): Y. Tsuda, Y. Sakai, and T. Sano, Heterocycles, 15, 1097 (1981).
3. K. Ito, F. Suzuki, and M. Haruna, J. C. S. Chem. Comm., 1978, 733.
4. An effective method of removing the oxo-group from 2 to yield 3 was recently exploited ( $AlH_3$  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.  $\text{NaBH}_4$  reduction of 2 yielded a single product identical with 8. The similar  $\text{NaBH}_4$  reduction of the analogous compound 14 gave stereoselectively a single 7 $\beta$ -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)



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

| Reagent and reaction condition to yield 100% cyclization |             |   |  |
|--|-------------|---|--|
|  | PPE         | $\text{BF}_3 \cdot \text{Et}_2\text{O}$ |  |
| <u>16</u>  | 90°, 1.5 hr | r. t., 3 hr                             |  |
| <u>17</u>  | 85°, 35 min | r. t., 30 min                           |  |



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( $\text{CHCl}_3$ ): 3370, 1690  $\text{cm}^{-1}$ . NMR ( $\text{CDCl}_3$ ):  $\delta$  6.76, 6.51 (each 1H, s, Ar-H). 12; IR(KBr): 3320, 1715, 1655  $\text{cm}^{-1}$ . NMR ( $\text{CDCl}_3$ ):  $\delta$  6.71, 6.57 (each 1H, s, Ar-H), 4.38 (1H, d, J=9 Hz, 7 $\beta$ -H). 13; IR(KBr): 1710, 1690  $\text{cm}^{-1}$ . NMR( $\text{CDCl}_3$ ):  $\delta$  6.71, 6.61 (each 1H, s, Ar-H), 5.19 (1H, d, J=9 Hz, 7 $\beta$ -H). The spectral data of 7 $\beta$ -compounds for comparisons were provided by Dr. Haruna.
11. Usually base treatment of a sulfonate of 7 $\alpha$ -hydroxy-8-oxo-*cis*-erythrinan affords a  $\Delta^6$ -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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