[Chem. Pharm. Bull. 32(8)3271—3272(1984)]

A Novel Synthesis of *cis*-15,16-Dimethoxyerythrinan-3-one

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(Received December 22, 1983)

Birch reduction of a dibenzazonine base (**1**) with sodium produced the desired diene (**2**) in a good yield. The diene (**2**) was heated with 10% sulfuric acid and cyclized readily to provide the erythrina base (**3**) as a sole product, which was subsequently converted by treatment with excess diazomethane to the known base, *cis*-15,16-dimethoxyerythrinan-3-one (**4**).

Keywords——erythrina alkaloid; dibenzazonine alkaloid; Birch reduction; *cis*-15,16-dimethoxyerythrinan-3-one; acid cyclization

2,12-Dimethoxy-5,6,8,9-tetrahydro-7*H*-dibenz[*d,f*]azonine-3,11-diol plays[1] an important role *in vivo* in the synthesis of erythrina alkaloids. It is well-known[2] that most syntheses from dibenzazonine alkaloids to Erythrina alkaloids have involved the phenolic oxidation of dibenzazonine bases. Recently, we have reported[3] the synthesis of 3-demethoxyerythratidinone, which was prepared by phenolic oxidation of 2,3-dimethoxy-5,6,8,9-tetrahydro-7*H*-dibenz[*d,f*]azonin-11-ol with various oxidizing reagents.

We have now found a novel route from a dibenzazonine base (**1**) to an erythrina base (**3**). In this paper, we wish to describe the synthesis of *cis*-15,16-dimethoxyerythrinan-3-one (**4**) by Birch reduction of the dibenzazonine base (**1**). The compound (**4**) was first synthesized from homoveratrylamine and α-(3-chloro-buten-2-yl)-γ-butyrolactone by Prelog *et al.*[4] and later prepared by annelation using methyl vinyl ketone and endocyclic enamine by Stevens *et al.*[5] Finally, Oh-ishi *et al.*[6] reported that **4** was readily synthesized from 2,3,3a,4,5,6-hexahydroindole-2,6-dione and 3,4-dimethoxyphenethyl bromide.

The starting material, 2,12-dimethoxy-5,6,8,9-tetrahydro-7*H*-dibenz[*d,f*]azonin-3-ol (**1**), for our synthesis of **4** was prepared as described in the previous report.[7]

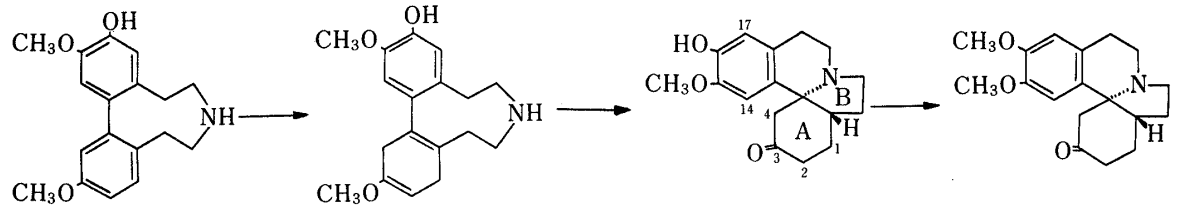

Chart 1

Treatment of **1** with sodium and methanol in liquid ammonia produced the expected diene (**2**) in 96.0% yield. The nuclear magnetic resonance (NMR) spectrum of this diene (**2**) showed a broad singlet signal due to an olefinic proton at δ 4.07 and a signal due to a methoxyl group of the enol methylether portion at δ 3.59. This compound (**2**) was heated with 10% sulfuric acid, and readily underwent hydrolysis and cyclization to give 16-hydroxy-15-

methoxyerythrinan-3-one (**3**) as a sole product in 79.4% yield. The infrared (IR) spectrum of **3** exhibited a saturated ketone absorption at 1710 cm^{-1} along with a hydroxyl group absorption at 3545 cm^{-1}. The NMR spectrum showed the disappearance of a signal in the olefinic proton region, and furthermore the observed aromatic proton signal at δ 6.54 revealed that the ring A/B of the compound (**3**) must be *cis*-fused.[8] Furthermore, methylation of **3** with excess diazomethane gave the known O-methyl product (**4**), which was identical with an authentic sample.

Thus, we achieved the synthesis of an erythrinan base (**3**) *via* the Birch reduction product (**2**) of a dibenzazonine base (**1**). This reaction seems to represent a useful route for the synthesis of Erythrina alkaloids.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. Mass spectra (MS) were recorded on a Hitachi M-52 spectrometer and high resolution MS on a JEOL JMS-D-300 spectrometer. IR spectra were obtained on a JASCO IRA-3 spectrophotometer and NMR spectra were recorded on a JEOL JNM-PS-100 NMR spectrometer with tetramethyl silane as an internal standard. Abbreviations used: s = singlet, br = broad.

Birch Reduction of 2,12-Dimethoxy-5,6,8,9-tetrahydro-7*H*-dibenz[*d*,*f*]azonin-3-ol (1)[7] (Formation of 2)——Sodium (2 g) was added during 1 h with stirring to **1**[7] (150 mg) in a mixture of methanol (4 ml), ether (2 ml), tetrahydrofuran (2 ml), and liquid ammonia (20 ml) at −60 to −70 °C. After cautious addition of ether, water, and NH_4Cl, the ammonia was allowed to evaporated off and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4, and evaporated to afford **2**.[9] Colorless oil. (145 mg) (96.0%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), NMR ($CDCl_3$) δ: 3.59, 3.83 (6H, 2 × s, 2 × OCH_3), 4.07 (1H, br s, olefinic H), 6.55, 6.67 (2H, 2 × s, 2 × arom. H). MS *m/z*: 301 [M^+], 286, 258 (100%), 239, 225. *Anal.* Calcd for $C_{18}H_{23}NO_3$: *m/z* 301.1677. Found: *m/z* 301.1671.

***cis*-16-Hydroxy-15-methoxyerythrinan-3-one (3)**——A solution of **2** (103 mg) in 10% sulfuric acid (3 ml) and dimethylformamide (2 ml) was heated with stirring at 60 °C for 2 h. After cooling of the mixture, water (20 ml) was added. The mixture was neutralized with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4, and evaporated to give **3**. The solid residue was recrystallized from EtOH and ether. Colorless needles. mp 79—80 °C (78 mg) (79.4%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3545 (OH), 1710 (CO). NMR ($CDCl_3$) δ: 3.84 (3H, s, OCH_3), 6.54 (2H, s, 2 × arom. H). MS *m/z*: 287 [M^+], 230 (100%), 228, 215, 192. *Anal.* Calcd for $C_{17}H_{21}NO_3$: *m/z* 287.1520. Found: *m/z* 287.1509.

***cis*-15,16-Dimethoxyerythrinan-3-one (4)**——An ethereal solution of excess diazomethane was added to a solution of **3** (31 mg) in methanol (10 mg), and the mixture was stirred for 6 h. The solvent was evaporated off and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated to yield **4**. The solid was recrystallized from isopropyl ether. Colorless needles. mp 140—142 °C (lit.[5] 143—144 °C) (23 mg) (70.7%). IR ν_{max}^{Nujol} cm^{-1}: 1720 (CO). NMR ($CDCl_3$) δ: 3.88 (6H, s, 2 × OCH_3), 6.49, 6.59 (2H, 2 × s, 2 × arom. H). MS *m/z*: 301 [M^+], 258, 244 (100%), 230. Its picrate; yellow needles. mp 143—146 °C (lit.[4] 144—146 °C). Spectral (IR and NMR) properties of this product were indistinguishable from those of an authentic sample.[6]

Acknowledgement The authors are grateful to Dr. T. Oh-ishi and Dr. T. Iwakuma of the Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., for providing the NMR and IR spectra of *cis*-15,16-dimethoxyerythrinan-3-one.

References and Notes

1) D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc.* (*C*), **1970**, 1213.
2) *a*) D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *J. Chem. Soc.* (*C*), **1968**, 1529; *b*) B. Franck and V. Teetz, *Angew. Chem., Int. Ed. Engl.*, **10**, 411 (1971).
3) H. Tanaka, M. Shibata, and K. Ito, *Chem. Pharm. Bull.*, **32**,1578 (1984).
4) V. Prelog, A. Langemann, O. Rodig, and M. Ternbah, *Helv. Chim. Acta*, **42**, 1301 (1959).
5) R. V. Stevens and M. P. Wentland, *J. Chem. Soc., Chem. Commun.*, **1968**, 1104.
6) T. Oh-ishi, I. Iijima, N. Itoh, and S. Sugasawa, *Chem. Pharm. Bull.*, **23**, 2573 (1975).
7) K. Ito, H. Tanaka, and M. Shibata, *Heterocycles*, **9**, 485 (1978).
8) A. Mondon and P-R. Seidel, *Chem. Ber.*, **104**, 2937 (1971).
9) This compound is unstable.