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Application of INDOR and NOE Techniques to Determination of the Substitution Pattern on an Aromatic Ring of Erythrinan Alkaloids

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The utility of the INDOR and NOE techniques for the determination of the substitution pattern on the aromatic ring of erythrinan alkaloids is demonstrated.

Synthesis of 3α,16-dimethoxyerythrinan-1(6)-ene (III) was accomplished by a route similar to that developed by Mondon, *et al.*

Keywords——substitution pattern on aromatic ring; INDOR; NOE; Erythrinan alkaloid; synthesis of 3α,16-dimethoxyerythrinan-1(6)-ene

In the course of the investigation of alkaloid constituents of *Cocculus* species (Menispermaceae), we isolated two 'abnormal' type aromatic erythrinan alkaloids, *i.e.* a known alkaloid, cocculine (Ia)[2] and a new alkaloid named coccutrine (II)[3] from *Cocculus trilobus* DC. In spite of the Barton's biogenetic view of erythrinan alkaloids[4] that aromatic erythrinan alkaloids should most likely bear oxygen function at the C(16) position, both compounds (Ia) and (II) lack O-function at C(16) but possess hydroxyl group at C(15) position. In this sense, this type of erythrinan alkaloids are called 'abnormal'.[5] The unusual aromatic substitution pattern offered a difficulty in the course of structure elucidation of the alkaloids of this type. The only affirmative proof has been given by X-ray analyses.[2,3]

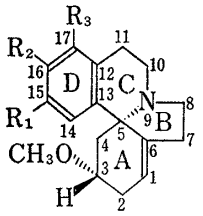
In order to explore a new technique which can be simply employed for determination of the substituent pattern on an aromatic ring of erythrinan alkaloids, 3α, 16-dimethoxyerythrinan-1(6)-ene (III), an isomer of natural cocculidine (O-methylcocculine) (Ib) with regard to the aromatic methoxyl orientation, was synthesized and an application of nuclear magnetic double resonance (NMDR) techniques (homonuclear internuclear double resonance (INDOR), nuclear Overhauser effect (NOE)) on III and other alkaloids was conducted and in this paper a full detail of the experiments is described.

Synthesis of 3α, 16-Dimethoxyerythrinan-1(6)-ene

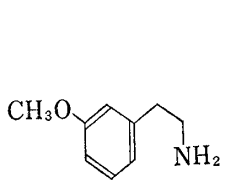
A few synthetic routes of aromatic erythrinan alkaloids containing the carbon-carbon double bond in ring A have been reported. The compound (III) was synthesized by a route similar to the method developed by Mondon, *et al.*[6]

1) Location: *a) Edagawa-cho, Nishinomiya, Hyogo 663, Japan; b) Igawadani, Tarumi-ku, Kobe 673, Japan; c) Yagoto, Tempaku-ku, Nagoya 468, Japan.*
2) R. Razakov, S.Y. Yunusov, S.M. Nasyrov, A.N. Chekhlov, V.G. Andrianov, and Y.T. Struchkov, *Chem. Commun.*, **1974**, 150.
3) A.T. McPhail, K.D. Onan, H. Furukawa, M. Ju-ichi, *Tetrahedron Lett.*, **1976**, 485.
4) D.H.R. Barton, R.B. Boar, and D.A. Widdowson, *J. Chem. Soc.* (*C*), **1970**, 1208; D.H.R. Barton, R. James, G.W. Kirby, D.W. Turner, and D.A. Widdowson, *J. Chem. Soc.* (*C*), **1968**, 1529.
5) D.S. Bhakuni, H. Uprety, D.A. Widdowson, *Phytochemistry*, **15**, 739 (1976); H. Pande, N.K. Saxena, D.S. Bhakuni, *Ind. J. Chem.*, **14B**, 366 (1976); A.N. Singh, H. Pande, D.S. Bhakuni, *Experientia*, **32**, 1368 (1976).
6) A. Mondon, K.F. Hansen, K. Boeme, H.P. Faro, H.J. Nestler, H.G. Vilhuber, K. Boettcher, *Chem. Ber.*, **103**, 615 (1970).

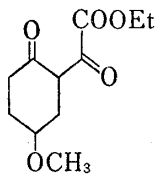
Condensation of 3-methoxyphenylethylamine (IV)[7] with ethyl 4-methoxycyclohexanone-2-glyoxylate (V)[8] gave an oily intermediate (VI)[6] which, without isolation, was treated with 85% phosphoric acid to result in the compound (VII)[9] possessing the erythrinan skeleton. The NMR spectrum of the compound (VII) in $CDCl_3$ showed the existence of the keto-enol (VII⇄VIII) equilibrium in the ratio of 3 to 2 (calculated from the ratio of the methoxyl



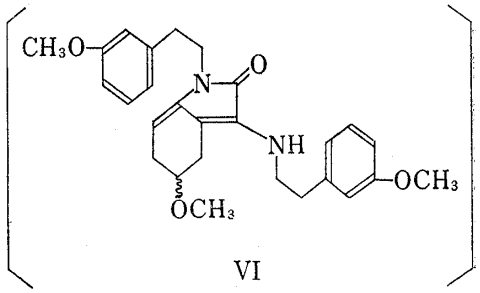
Ia : R_1=OH, R_2=R_3=H
Ib : R_1=OCH_3, R_2=R_3=H
II : R_1=OH, R_2=H, R_3=OCH_3
III : R_1=R_3=H, R_2=OCH_3



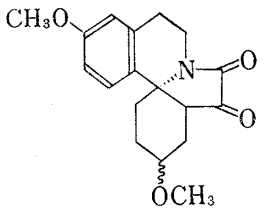
IV



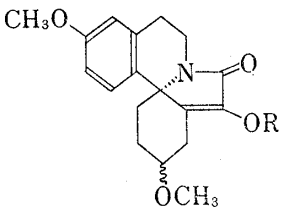
V



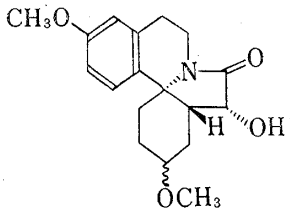
VI



VII

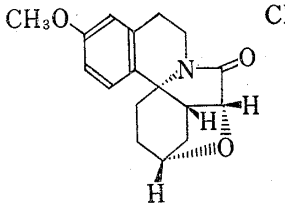


VIII : R=H
IX : R=$COCH_3$

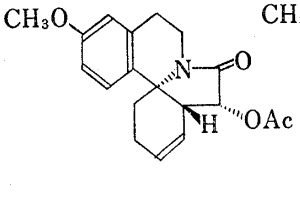


X

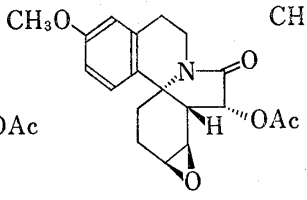
Chart 1



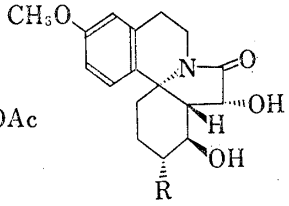
XI



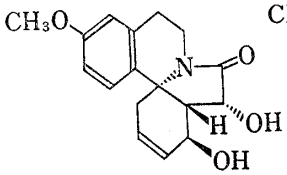
XII



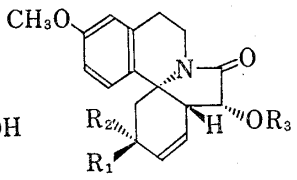
XIII



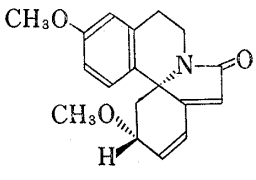
XIV : R=$N(CH_3)_2$
XV : R=$N(CH_3)_2$
O



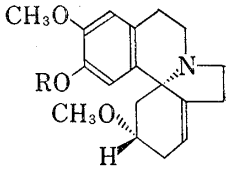
XVI



XVII : R_1=H, R_2=OCH_3, R_3=H
XVIII : R_1=OCH_3, R_2=R_3=H
XIX : R_1=H, R_2=OCH_3, R_3=Ts



XX



XXI : R=CH_3
XXII : R=H

Chart 2

7) A. Marchant, A.R. Pinder, *J. Chem. Soc.*, **1956**, 327.
8) F. Hunziker, F.X. Mueller, H. Schaltegger, *Helv. Chim. Acta.*, **38**, 1943 (1955).
9) The racemic modification was expressed by one enantiomer as shown in the Chart 1.

proton signals). The presence of the keto–enol equilibrium was confirmed by the fact that treatment of VII with acetic anhydride in pyridine gave the enol-acetate (IX) as the sole product. Reduction of VII with sodium borohydride afforded the hydroxy-lactam (X) in which the α configuration of a hydroxyl group was assumed from the preferential attack of the hydride from the less hindered β side. Compound (X) was best converted into the oxide-lactam (XI) by treating with the mixture of conc. sulfuric acid and dimethylformamide (1: 1). The compound (XI) was refluxed with *p*-toluenesulfonic acid in acetic anhydride to give an oily mixture which was chromatographed over silica gel column to yield the acetoxy-lactam (XII) in a pure state. Formation of the double bond isomer of XII was anticipated in this reaction, but no further examination to isolate the isomer was made. Allylic oxidation of XII with selenium dioxide, *tert*-butyl chromate, N-bromosuccinimide and sodium chromate was tried with the intention of introducing an oxygen function at the C(3) position, but no fruitful result was obtained. This functionalization was accomplished as follows: Epoxidation of XII with *m*-chloroperbenzoic acid gave the epoxide (XIII). The β configuration of the oxide ring was inferred from the preferential attack of the reagent from the less hindered side of the molecule. Treatment of XIII with dimethylamine caused the oxide ring fission to give an N,N-dimethylamino compound (XIV) which was then oxidized with *m*-chloroperbenzoic acid to give the N-oxide (XV). The solution of XV in N,N-dimethylformamide was heated under nitrogen atmosphere to afford the Cope type elimination[10] product (XVI). Allylic rearrangement of XVI was performed with 6N hydrochloric acid in methanol to give two kinds of the products (XVII and XVIII). These two compounds were assumed to be epimeric due to a newly introduced methoxyl group at the C(3) position and the structures were determined by the INDOR and NOE technique which is described in the following section.

The compound (XVII) which has the same α configuration of the methoxyl group at the C(3) position as that of natural product was tosylated and detosylation of the tosylate (XIX) with 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) provided the α,β-γ,δ-dienone lactam (XX). Reduction of this compound (XX) with lithium aluminum hydride, followed by catalytic hydrogenation gave the aimed compound (III)[11] as an oily substance.

Application of INDOR and NOE Techniques to Determination of the Substitution Pattern on an Aromatic Ring of Erythrinan Alkaloids

The assignments of aromatic protons of erythrinan alkaloids have been reported by Bhakuni, *et al.*[5] on the basis of the long-range coupling between the C(17) aromatic proton and the C(11) benzylic protons by means of the NMDR technique.

However, during our synthetic investigation of aromatic erythrinan alkaloids described above, the NOE between the 3β proton and the C(14) proton was found useful and convenient tool for the assignment of substitution pattern on the aromatic ring.

The configuration of the allylic rearrangement reaction products (XVII and XVIII) has been determined as follows: In the INDOR experiments of the compound (XVII), the peaks were observed at δ 2.37 and 3.93 (C(4)-H_{eq}, C(3)-H_{ax}) by monitoring the signal at δ 1.96 (C(4)-H_{ax}) and the results were also confirmed by monitoring the signals of C(4)-H_{eq} and C(3)-H_{ax}, respectively, and allowed the identification of the coupled protons. (Fig. 1). In the NOE measurement of XVII, the increment (12.5%) was observed at the signals with *ortho* coupling constants (J=9.0 Hz) of aromatic region upon irradiation at C(3) proton. These facts and examination of the Dreiding model of the molecule led us to conclude that the aromatic proton which showed the increments in the NMDR experiments was assigned to the proton at C(14) position situated spacially near to the β oriented proton at C(3) position. On the other hand, the same technique was applied to the compound (XVIII), but no incre-

10) P.F. Beal, M.A. Rebenstorf, J.E. Pike, *J. Am. Chem. Soc.*, **81**, 1231 (1959).
11) This hydrogenetic 1,4-addition reaction is already known for erythrinan diene alkaloids. cf. V. Prelog, K. Wiesner, H.G. Khorana, G.W. Kenner, *Helv. Chim. Acta.*, **32**, 453 (1949).

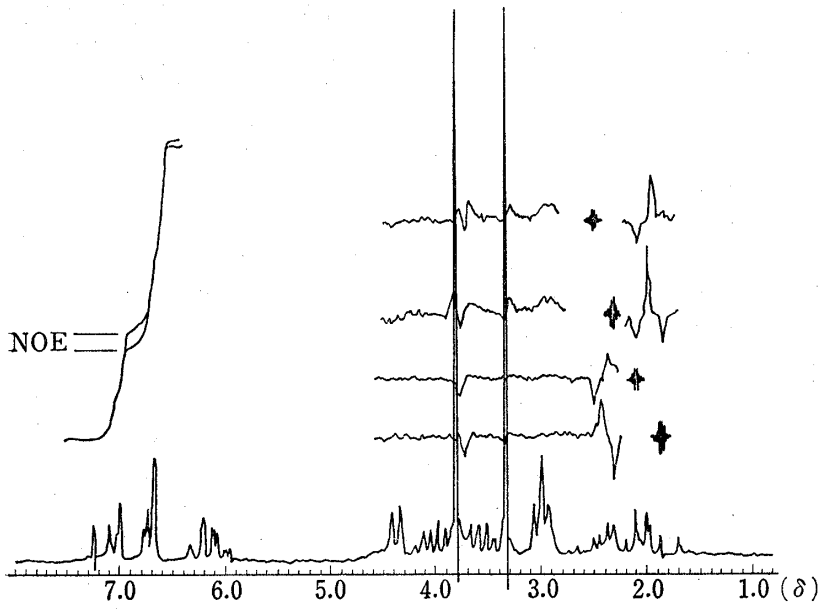


Fig. 1. 90 MHz INDOR and NOE Spectrum of 3α, 16-Dimethoxy Compound (XVII) in $CDCl_3$

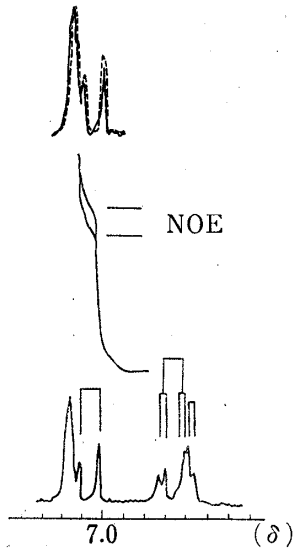


Fig. 2. NOE Spectrum of Aromatic region of 3α, 16-Dimethoxyerythrinan-1(6)-ene (III), irradiated at 3.89δ

ment was noticed in NOE spectrum between any aromatic proton and the proton at C(3) position. From these NMR analyses, the configuration of the C(3) methoxyl groups of the compounds (XVII) and (XVIII) are α and β, respectively.

Next, this technique was applied to 3α, 16-dimethoxyerythrinan-1(6)-ene (III). Irradiating the signal of the proton at C(3) position at δ 3.89, the increment (about 8—10%) of the signals of aromatic region was observed only at the signals with *ortho* coupling constants (J=8.5 Hz). The effected proton should be situated at C(14) position and the signals for the other two aromatic protons at C(15) and C(17) were not affected by the C(3)-H irradiation, and the coupling constants were consistent with the assignments. (Fig. 2).

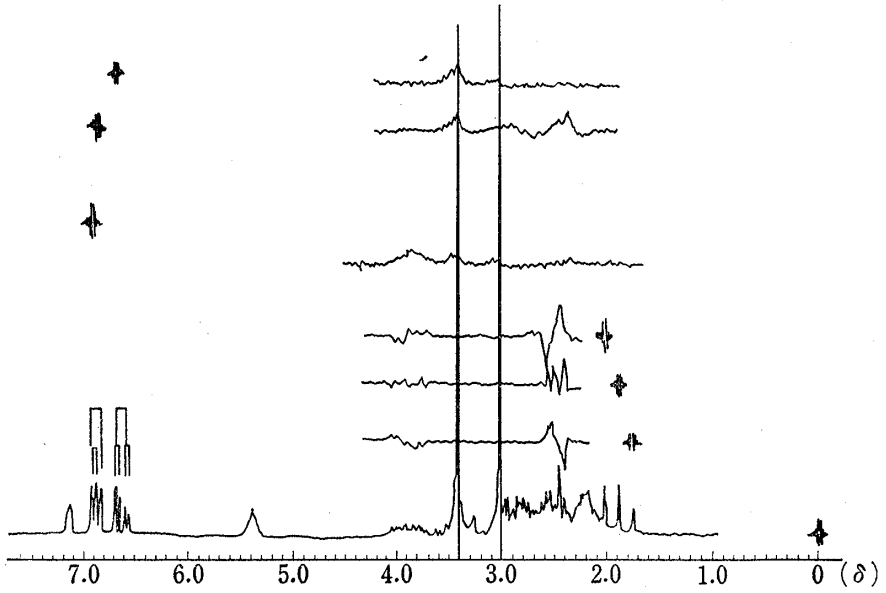


Fig. 3. 90 MHz INDOR Spectrum of Cocculidine (Ib) in C_6D_6

The INDOR spectrum of cocculidine (Ib) is shown in the Fig. 3. In order to split the overlapped methoxyl signal attached to the aromatic ring and the proton signal of C(3) position, the solvent was changed from $CDCl_3$ to benzene-d_6. By monitoring the character-

istic high field triplet of the axial proton at C(4), peaks appeared at δ 2.53 and 3.87 and the chemical shifts corresponded to a geminal proton at C(4) and a vicinal proton attached to the C(3) with aliphatic methoxyl group, respectively. The assignment of the multiplet signals for C(3)-H was thus reconfirmed. Monitoring the aromatic proton at δ 6.93 (J=2.5 Hz), peaks appeared at δ 3.87 (CH_3O–$\underset{|}{C}$–$\underline{H}$) and 3.40 (aromatic CH_3O). When signals at δ 6.90 (J=8.5 Hz) were monitored, peaks emerged at δ 3.40 (aromatic CH_3O), 2.92 and 2.41 (benzylic protons). In contrast, by monitoring δ 6.65 (J=8.5, 2.5 Hz), appearance of the peak was observed only at δ 3.40. These results show that the aromatic proton with J value of 2.5 Hz at δ 6.93 is spacially near to the proton at C(3) position. These INDOR measurements allowed the assignments of signals with the spacial arrangement of aromatic protons and other protons situated close to them. In order to reconfirm the above INDOR results, the NOE experiments were performed. Irradiating the signal at δ 2.41, the heights of the C(17) proton signals increased but the half-band width of them decreased at the same time. This phenomenon was assumed to result mainly from decoupling effect because the integration trace was found to be unchanged. On the other hand, irradiation at δ 2.92 induced a few percent increments on the signals of C(17) proton by NOE. Furthermore, irradiation of the proton at C(3) at δ 3.87 resulted in the NOE (increment *ca.* 16%) only at C(14) proton, and no variation was noticed on the other aromatic protons. The results of the above NMDR technique on cocculidine (Ib) proved the applicability of the method to the 'abnormally' substituted aromatic erythrinan alkaloids.

The example of the application of this technique to normal type aromatic erythrinan alkaloid, *i.e.*, dihydroerysotrine (XXI), whose structure is already known to possess the aromatic methoxyl groups at C(15) and C(16) positions, is shown. In this case, the protons at C(14) and C(17) positions are observed as two singlets. Irradiating the signal of the proton at C(3) position, the increment of about 10% was observed at low field signal at δ 6.80. Therefore, this low field signal was assigned to C(14) proton.

Recently, we have isolated a new aromatic erythrinan alkaloid named dihydroerysovine (XXII)[12] from *Cocculus trilobus* DC. The absolute structure of XXII was determined except for the positions of methoxyl and hydroxyl groups on an aromatic ring by the fact that methylation of XXII with diazomethane gave dihydroerysotrine (XXI). The INDOR experiment showed a response of the proton at δ 3.89 (C(3)-H_{ax}) by monitoring the signal of the C(14) aromatic proton at δ 6.99. Irradiating the signal at δ 3.89, the NOE increment of about 15% was observed at the δ 6.99. These results indicate the spacially close relationship between the $C_{3\beta}$ axial proton and C(14) aromatic proton. Moreover, monitoring the aromatic proton signal at δ 6.30, obvious response due to NOE (15.4% increment) and decoupling effect of the aromatic methoxyl signal at δ 3.27 was observed, but the irradiation of the signal at δ 6.99 gave no response at δ 3.27. From these results, the aromatic methoxyl and hydroxyl groups were determined easily to locate at C(16) and C(15), respectively.

In conclusion, the INDOR and NOE techniques are proved to be useful and convenient for the determination of substitution pattern on an aromatic ring of erythrinan alkaloids.

Experimental

All melting points were measured on Yanagimoto Melting Point Apparatus and were uncorrected. IR spectra were measured for solutions in chloroform with a Jasco IR-G Spectrometer. NMR spectra were measured on Varian A-60 and/or Hitachi R22 High Resolution Spectrometer in $CDCl_3$ or C_6D_6 with TMS as an internal standard and chemical shifts were given in δ values. Mass spectra were taken on Hitachi Mass Spectrometer Model RMU-6MG. TLC were performed on silica gel (Kieselgel G nach Stahl) or alumina (Aluminium Oxyd G nach Stahl) using acetone–chloroform or acetone–methanol as a developing solvent.

12) M. Ju-ichi, Y. Ando, Y. Yoshida, J. Kunitomo, T. Shingu, and H. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **25**, 533 (1977).

2,16-Dimethoxyerythrinan-7,8-dione (VII)——A solution of 73 g of 3-methoxyphenylethylamine (IV)[7] and 55.7 g of ethyl 4-methoxycyclohexanone-2-glyoxylate (V)[8] in 1000 ml of dry benzene was refluxed on an oil bath for 10 hr while water, distilled off as an azeotropic mixture with benzene, was separated with a Dean-Stark type apparatus. After removal of benzene *in vacuo*, the residue was dissolved in 1000 ml of MeOH and 1000 ml of 85% H_3PO_4 and the mixture was refluxed for 20 hr under N_2 atmospheric condition. After cooling, the reaction mixture was poured into ice water and extracted with CH_2Cl_2. The extract was shaken with 5% NaOH solution and enolizable substance dissolved in aqueous layer. The aqueous layer was made acidic with concd. HCl and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, dried over $MgSO_4$ and evaporated to give an oily compound, which was chromatographed over silica gel in CH_2Cl_2 and elution with the same solvent gave colorless oily compound. Recrystallization from MeOH gave 30.89 g of the dione (VII) as colorless cubes, mp 182—183°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (C=O), 1705 (lactam). NMR ($CDCl_3$, δ): 3.18, 3.32, 3.77, 3.79 (s, OCH_3), 6.52—7.48 (m, aromatic protons). MS *m/e*: 315 (M^+). *Anal.* Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.02; H, 6.74; N, 4.41. The keto-enol (VII⇄VIII) equilibrium was presumed by the ratio of methoxyl groups and was confirmed by transformation to its enol-acetate (IX).

Enol-acetate (IX)——To a solution of 50 mg of above keto-enol equilibrium mixture (VII and VIII) in 5 ml of pyridine was added 5 ml of acetic anhydride and the mixture was allowed to stand overnight at room temperature. The solvent was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$ and evaporated to give an oily compound, which was chromatographed over silica gel. Elution with acetone gave 46 mg of colorless oily compound (IX). TLC 1 spot. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 ($OCOCH_3$), 1680 (lactam). NMR ($CDCl_3$, δ): 2.27 (3H, s, $OCOCH_3$), 3.27, 3.75 (each 3H, s, OCH_3), 6.73 (1H, d.d, J=2.5, 9.5 Hz), 6.80 (1H, s), 7.33 (1H, d, J=9.5 Hz). MS *m/e*: 357 (M^+).

Hydroxy-lactam (X)——To a solution of 22.69 g of the above equilibrium mixture (VII and VIII) in 200 ml of MeOH and 15 ml of water was added 4.13 g of sodium borohydride in portions with ice cooling, and the mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$ and evaporated to yield an oily compound. Trituration with 95% EtOH afforded crystalline solid. Recrystallization from the same solvent gave the hydroxy-lactam (X) as colorless fine needles, mp 92—94°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH), 1670 (lactam). NMR ($CDCl_3$, δ): 7.15 (1H, d, J=8.5 Hz), 6.75 (1H, d.d, J=8.5, 2.5 Hz), 6.60 (1H, d, J=2.5 Hz), 4.30—3.95 (2H, m), 3.75, 3.37 (each 3H, s, OCH_3). *Anal.* Calcd. for $C_{18}H_{23}NO_4 \cdot H_2O$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.17; H, 7.55; N, 4.14.

2,7-Oxide-lactam (XI)——To 71.34 g of hydroxy-lactam (X) were added 400 ml of mixture of concd. H_2SO_4 and N,N-dimethylformamide (DMF) (1:1) and the reaction mixture was warmed at 40—50° for 2 days on an oil bath. After cooling, the mixture was poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water thoroughly, dried over $MgSO_4$ and evaporated to give 66.51 g of an oily compound which was chromatographed over silica gel column. Elution with CH_2Cl_2 afforded the 2,7-oxide-lactam (XI) as crystalline solid. Recrystallization from acetone gave 25.23 g of colorless needles, mp 158—160°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (lactam). NMR ($CDCl_3$, δ): 7.23 (1H, d, J=8.5 Hz), 6.83 (1H, d.d, J=8.5, 2.5 Hz), 6.63 (1H, d, J=2.5 Hz), 4.51 (1H, m), 4.25 (1H, d, J=6.0 Hz), 3.78 (3H, s, OCH_3). *Anal.* Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.46; H, 6.75; N, 4.86.

Reaction of Oxide-lactam (XI) with *p*-Toluenesulfonic Acid in Acetic Anhydride (Acetoxy-lactam (XII))——A solution of 261.5 mg of the oxide-lactam (XI) in 20 ml of acetic anhydride was added 190 mg of *p*-toluenesulfonic acid and the reaction mixture was refluxed for 1.5 hr. The mixture was poured into ice water and allowed to stand at room temperature until the excess of acetic anhydride is decomposed. The aqueous layer was extracted with CH_2Cl_2. The extract was washed with water, 2% sodium bicarbonate solution, and water, successively, then dried over $MgSO_4$ and evaporated. The residual oil was chromatographed on silica gel in CH_2Cl_2. Elution with 5% acetone–CH_2Cl_2 gave a crystalline solid. Recrystallization from 95% EtOH afforded 165 mg of acetoxy-lactam (XIII) as colorless cubes, mp 138°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 ($OCOCH_3$), 1685 (lactam). NMR ($CDCl_3$, δ): 7.13 (1H, d, J=9.0 Hz), 6.77 (1H, d. d, J=9.0, 2.5 Hz), 6.71 (1H, d, J=2.5 Hz), 6.20, 5.80 (each 1H, m), 5.43 (1H, d, J=7.5 Hz), 3.78 (3H, s, OCH_3), 2.10 (3H, s, $OCOCH_3$). MS *m/e*: 327 (M^+). *Anal.* Calcd. for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.27; H, 6.49; N, 4.15.

Epoxidation of Acetoxy-lactam (XII)——To a solution of 226 mg of acetoxy-lactam (XII) in 50 ml of $CHCl_3$ was added 484 mg of *m*-chloroperbenzoic acid in portions with ice cooling, and the mixture was allowed to stand in the dark at room temperature for 2 days. The reaction mixture was diluted with $CHCl_3$ and water. The organic layer was washed with saturated sodium thiosulfate solution to decompose the excess peracid, then with 1% sodium bicarbonate solution, and water, dried over $MgSO_4$ and evaporated to give 200 mg of an oily compound which was dissolved in CH_2Cl_2 and chromatographed over silica gel. Elution with 5% acetone–CH_2Cl_2 gave 86 mg of colorless oily epoxide (XIII). TLC 1 spot. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 ($OCOCH_3$), 1705 (lactam). NMR ($CDCl_3$, δ): 7.18 (1H, d, J=8.5 Hz), 6.77 (1H, d.d, J=8.5, 3.0 Hz), 6.59 (1H, d, J=3.0 Hz), 5.38 (1H, d, J=8.0 Hz), 4.25 (1H, m), 3.73 (3H, s, OCH_3), 2.15 (3H, s, $OCOCH_3$). MS *m/e*: 343 (M^+).

N,N-Dimethylamino-diol-lactam (XIV)——A mixture of 1 g of epoxide (XIII) and 10 ml of 40% dimethylamine solution was heated in a sealed tube at 85—95° for 15 hr. The mixture was cooled, made acidic with

concd. HCl and extracted with CH_2Cl_2 to remove neutral compound. The aqueous layer was then made alkaline with 28% NH_4OH and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$ and evaporated to give 320 mg of an oily compound which was dissolved in CH_2Cl_2 and chromatographed over silica gel.

Elution with MeOH gave 81 mg of the compound (XIV) as yellow oil. TLC 1 spot. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1680 (lactam). NMR ($CDCl_3$, δ): 7.22 (1H, d, J=8.5 Hz), 6.77 (1H, d.d, J=8.5, 2.5 Hz), 6.57 (1H, d, J=2.5 Hz), 4.20 (2H, br.s, 2×OH, disappeared with D_2O), 4.17 (1H, d, J=7.5 Hz), 3.77 (3H, s, OCH_3), 2.32 (6H, s, $-N(CH_3)_2$). MS m/e: 346 (M^+).

Cope Elimination of N,N-Dimethylamino Compound (XIV)——To a solution of 953 mg of the N,N-dimethylamino compound (XIV) in 10 ml of $CHCl_3$ was added 953 mg of *m*-chloroperbenzoic acid in portions with ice cooling and stirred in the dark for 1 hr. Then, absolute ether was added to precipitate the N-oxidized compound (XV), which was filtered off. The filtered N-oxide (XV) was dissolved in 100 ml of DMF and refluxed for 6 hr under N_2 atmosphere. The solvent was removed *in vacuo* and the residue was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated to give 707 mg of brown oil, which was separated by silica gel column chromatography. Elution with 20% acetone–CH_2Cl_2 gave a crystalline solid. Recrystallization from acetone gave 204 mg of the diol-lactam (XVI) as colorless cubes, mp 156—158°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH), 1675 (lactam). NMR ($CDCl_3$, δ): 7.28 (1H, d, J=8.5 Hz), 6.73 (1H, d.d, J=8.5, 2.5 Hz), 6.61 (1H, d, J=2.5 Hz), 6.25 (1H, m), 5.83 (1H, m), 4.72 (1H, m), 4.52 (1H, d, J=8.0 Hz), 3.78 (3H, s, OCH_3). *Anal.* Calcd. for $C_{17}H_{19}NO_4 \cdot H_2O$: C, 63.93; H, 6.63; N, 4.39. Found: C, 64.06; H, 6.18; N, 4.29.

Allylic Rearrangement of Diol-lactam (XVI)——To a solution of 88 mg of diol-lactam (XVI) in 90 ml of MeOH was added 10 ml of 6 N hydrochloric acid and refluxed for 20 hr. After cooling, the solvent was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$ and evaporated to give 66 mg of an oily compound which was chromatographed over silica gel. Elution with 10% acetone–CH_2Cl_2 gave two compounds; the 3β,16-dimethoxy compound (XVIII) (11%) in the earlier eluate and the 3α,16-dimethoxy compound (XVII) (10%) in the following eluate. The 3β,16-dimethoxy compound (XVIII): Recrystallization from acetone gave colorless cubes, mp 162—164°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH), 1680 (lactam). NMR (90 MHz, $CDCl_3$, δ): 7.12 (1H, d, J=8.5 Hz), 6.73 (1H, d.d, J=8.5, 2.5 Hz), 6.57 (1H, d, J=2.5 Hz), 6.08 (1H, br.d, J=11.0 Hz), 5.90 (1H, d.q, J=11.0, 1.5 Hz), 4.47 (1H, d, J=8.0 Hz), 4.22 (1H, m), 3.76, 3.31 (each 3H, s, OCH_3), 2.47 (1H, d.d, J=13.5, 5.0 Hz), 1.75 (1H, d.d, J=13.5 Hz). *Anal.* Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.58; H, 6.83; N, 4.39. The 3α,16-dimethoxy compound (XVII): colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH), 1670 (lactam). NMR (90 MHz, $CDCl_3$, δ): 7.06 (1H, d, J=9.0 Hz), 6.71 (1H, d.d, J=9.0, 2.5 Hz), 6.68 (1H, d, J=2.5 Hz), 6.27 (1H, br.d, J=11.0 Hz), 6.04 (1H, d.q, J=11.0, 2.0 Hz), 4.36 (1H, d, J=8.0 Hz), 3.78, 3.29 (each 3H, s, OCH_3), 3.93 (1H, sextet, J=6.5 Hz), 2.37 (1H, d.d, J=5.0, 12.0 Hz), 1.96 (1H, d.d, J=12.0 Hz). MS m/e: 315 (M^+).

Tosylation of 3α,16-Dimethoxy Compound (XVII)——To a solution of 80 mg of the 3α-methoxy compound (XVII) in 20 ml of dry pyridine was added 160 mg of *p*-toluenesulfonyl chloride and the reaction mixture was allowed to stand for 2 days in a refrigerator. The mixture was poured into ice water and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated to give an oily residue, CH_2Cl_2 solution of which was passed through a silica gel column. Elution with 5% acetone–CH_2Cl_2 afforded the tosylate (XIX) as colorless oil. TLC 1 spot. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695 (lactam). NMR ($CDCl_3$, δ): 7.89 (2H, d, J=8.5 Hz), 7.33 (2H, d, J=8.5 Hz), 7.06 (1H, d, J=9.0 Hz), 6.75 (1H, d.d, J=9.0, 3.0 Hz), 6.68 (1H, d, J=3.0 Hz), 6.32 (1H, q, J=11.0, 1.0 Hz), 6.02 (1H, d.q, J=11.0, 2.0 Hz), 5.08 (1H, d, J=7.5 Hz), 3.78, 3.30 (each 3H, s, OCH_3), 2.45 (3H, s, CH_3).

Detosylation of XIX with DBU——To a solution of 55 mg of the tosylate (XIX) in 10 ml of dry benzene was added a solution of 100 mg of DBU in 10 ml of dry benzene and the reaction mixture was refluxed for 3 hr. After cooling, 5% hydrochloric acid was added and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to give an oily compound, which was chromatographed over silica gel column and on elution with acetone, 29 mg of dienone (XX) was afforded as colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (lactam). NMR ($CDCl_3$, δ): 7.17 (1H, d, J=8.5 Hz), 6.90 (1H, d.d, J=2.5, 8.5 Hz), 6.78 (1H, d, J=2.5 Hz), 6.67 (1H, d.d, J=2.5, 10.0 Hz), 6.32 (1H, br.d, J=10.0 Hz), 6.03 (1H, s), 3.78, 3.35 (each 3H, s, OCH_3). MS m/e: 297 (M^+).

3α,16-Dimethoxyerythrinan-1(6)-ene (III)——To a solution of 141 mg of the dienone (XX) in 30 ml of dry ether was added 200 mg of $LiAlH_4$, and the reaction mixture was refluxed for 6 hr with stirring. After cooling, excess $LiAlH_4$ was decomposed with water and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated to give 129 mg of oily compound. IR ($CHCl_3$): no carbonyl band. Because of its difficulty to separate, this oily mixture was used for the next stage reaction without purification. The above reduction product was dissolved in 30 ml of MeOH and hydrogenated over 200 mg of 5% Pd–C under atmospheric pressure. After absorption ceased, catalyst was filtered off and the filtrate was evaporated *in vacuo*, and the residue was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated to give an oily compound, CH_2Cl_2 solution of which was chromatographed over silica gel. Elution with acetone gave 24 mg of 3α,16-dimethoxyerythrinan-1(6)-ene (III) as colorless oil. TLC 1 spot. NMR (90

MHz, C_6D_6, δ): 7.06 (1H, d, J=8.5 Hz), 6.67 (1H, d.d, J=8.5, 2.5 Hz), 6.57 (1H, d, J=2.5 Hz), 5.42 (1H, m, olefinic H), 3.89 (1H, m), 3.37, 3.04 (each 3H, s, OCH_3), 2.46 (1H, d.d, J=11.0, 4.5 Hz), 1.92 (1H, d.d, J=11.0 Hz). MS *m/e*: 285 (M^+).

Cocculidine (O-Methylcocculine) (Ib)——To a solution of 20 mg of cocculine (I)[3] in 20 ml of MeOH was added a solution of diazomethane, prepared from nitrosomethylurea (3 g), in ether. The mixture was allowed to stand overnight at room temperature. Working up as usual way afforded an oily product. Purification of the product by silica gel column chromatography gave the cocculidine (Ib) (18 mg). Crystallization from petroleum ether afforded colorless cubes, mp 93—95° (lit.[2] mp 84—86°). MS *m/e*: 285 (M^+). NMR (90 MHz, C_6D_6, δ): 6.93 (1H, d, J=2.5 Hz), 6.90 (1H, d, J=8.5 Hz), 6.65 (1H, d.d, J=8.5, 2.5 Hz), 5.41 (1H, m, olefinic H), 3.01, 3.40 (each 3H, s, OCH_3), 3.87 (1H, m, CH_3O–$\underset{|}{C}$–H), 2.53 (1H, m), 1.89 (1H, t, J=12.0 Hz).

Dihydroerysotrine (XXI)——O-Methylation of dihydroerysovine (XXII)[12] with diazomethane afforded an oily product, which was purified by silica gel column chromatography to give dihydroerysotrine (XXI) as an oil. TLC 1 spot. The IR, NMR spectra and TLC behavior of the product were identical with those of an authentic sample. NMR (90 MHz, C_6D_6, δ): 1.93 (1H, t, J=11.5 Hz), 2.54 (1H, m), 3.07, 3.43, 3.51 (each 3H, s, OCH_3), 3.90 (1H, m, CH_3O–$\underset{|}{C}$–H), 5.42 (1H, m, olefinic H), 6.42, 6.80 (each 1H, s, aromatic H).

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