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Syntheses of Hexahydroindole-2,6-diones and 15,16-Dimethoxyerythrinane-3,8-dione*

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Hydrolytic cyclization of 2-acyl-(2-cyanoethyl)succinates (Ib, c) was found to give 2,3,3a,4,5,6-hexahydroindole-2,6-diones (IIb, c), which readily yielded 6-hydroxyoxindoles (III) by dehydrogenation. Four-step synthesis of the erythrinane skeleton from methyl acetoacetate *via* IIb is also described.

In the preceding papers,[2] one of us described that hydrolytic cyclization of 3-(2-cyanoethyl)-3-(3,4-dimethoxyphenyl) levulinate (Ia) in 65% H_2SO_4 gave 3a-(3,4-dimethoxyphenyl)-2,3,3a,4,5,6-hexahydroindole-2,6-dione (IIa). The alternative structure (IIIa) was excluded by conversion of the product into *dl*-mesembrane (IVa) and *dl*-mesembrine (IVb). The mechanism of formation of IIa was also presented there.

In continuation of the above study, we now wish to report a similar cyclization of 2-acyl-2-(2-cyanoethyl) succinates (Ib, c), which also gave hexahydroindole-2,6-diones (IIb, c), but none of the alternative compounds (IIIb, c). When dehydrogenated with palladium on carbon (Pd–C), they smoothly gave rise to pharmacologically interesting 6-hydroxyoxindoles (V and VI),[3] and moreover IIb is a key intermediate of a four-step synthesis of the erythrinane skeleton[4] from methyl acetoacetate as is shown later.

The starting materials, Ib and Ic, were readily prepared by alkylation of the corresponding acetoacetates with methyl or ethyl bromoacetate[5] followed by Michael reaction with acrylonitrile.

Brief heating with 65% H_2SO_4 (H_2SO_4: H_2O=1: 1 v/v) was proved to be best for hydrolytic cyclization of Ia, which, however, was untenable in the present case (Ib, c), causing complete hydrolysis to give water soluble dicarboxylic acids. Higher concentration of H_2SO_4 was found favorable for the proposed cyclization. Also was found how the cyclization yields are greatly influenced by acid concentration as is shown in Table I.

Spectral properties only (Table I) were not enough to support the structure of cyclization products to discriminate from IIIb,c. Thus IIb,c were converted into 6-hydroxyoxindoles (Vb,c) and 6-methoxyoxidoles (VIb,c), which were readily indentified mainly by nuclear magnetic resonance (NMR) spectroscopy. The spectral data (infrared (IR), ultraviolet (UV) and NMR) of Vb and VIb were coincident with those reported in the literatures.[6]

Success in synthesizing IIb in moderate yield prompted us to attempt the synthetic approach to Erythrina alkaloids. Synthesis of the erythrinane skeleton by acid catalyzed cy-

* Dedicated to the memory of Prof. Eiji Ochiai.

1) Location: *2-2-50, Kawagishi, Toda, Saitama.*

2) *a*) T. Oh-ishi and H. Kugita, *Tetrahedron Letters*, **1968**, 5445; *b*) T. Oh-ishi and H. Kugita, *Chem. Pharm. Bull.* (Tokyo), **18**, 291 (1970); *c*) T. Oh-ishi and H. Kugita, *ibid.*, **18**, 299 (1970).

3) By our preliminary screenings, these compounds have an antiplatelet aggregating activity.

4) Various kinds of syntheses of the erythrinane skeleton were reviewed by R.K. Hill, "The Alkaloids," Vol. IX, ed. by R.H.F. Manske, Academic Press, New York and London, 1967, Chapter 12.

5) H. Adkins, N. Isbell, and B. Wojicik, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York and London, 1963, p. 262.

6) *a*) A.H. Beckett, R.W. Daisley, and J. Walker, *Tetrahedron*, **24**, 6093 (1968); *b*) T. Wieland and O. Unger, *Chem. Ber.*, **96**, 253 (1963).

Table I. Hydrolytic Cyclization Reaction of Ib, c

Products	Yield (%) in 80% H_2SO_4	Yield (%) in 88% H_2SO_4	mp (°C)	UV λ_{max}^{EtOH} mμ (ε)	IR ν_{max}^{Nujol} cm^{-1}
IIb	14	64.1	158—159	272—273 (39200)	1738, 1630[a], 1590
IIc	41.4	14.9	195—197	285—287 (26000)	1740[a], 1730, 1710, 1618, 1590

a) shoulder

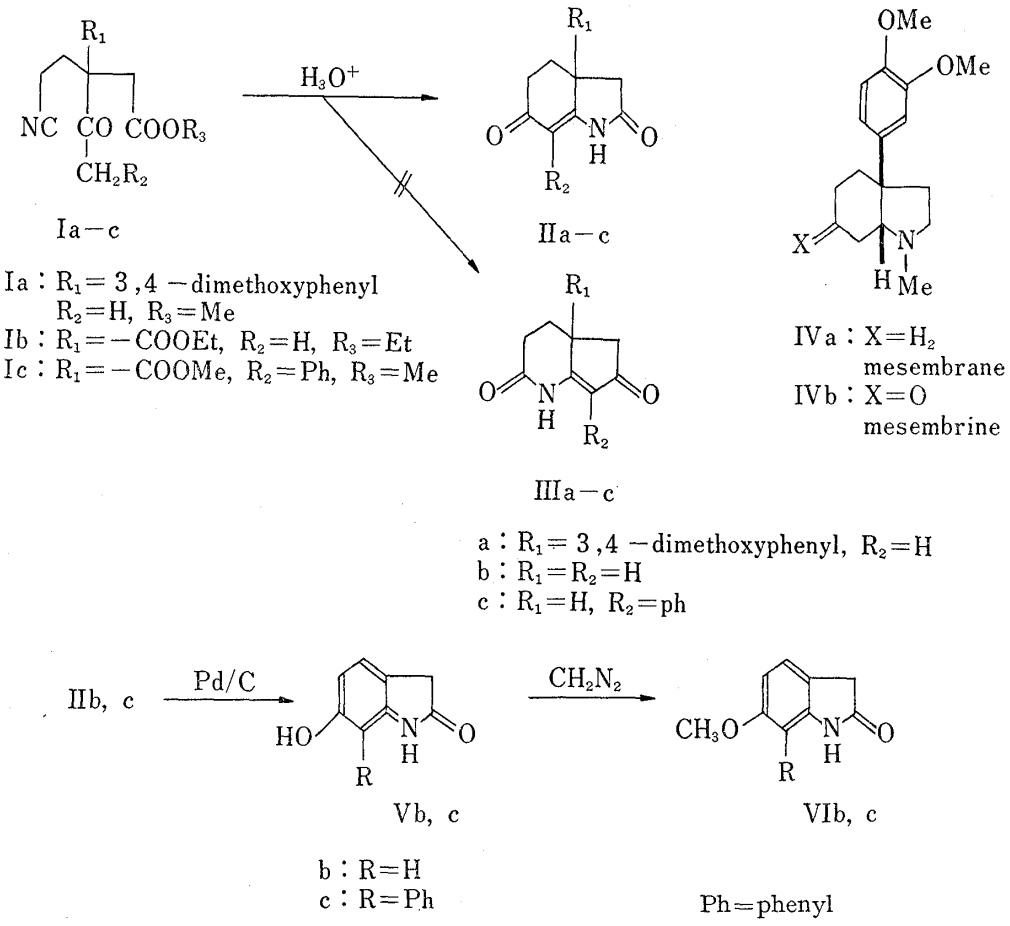

Chart 1

clization of XI and, more recently, of XII has been achieved by Mondon, *et al.*[7] They also predicted that 1-[β-(3,4-dimethoxyphenyl)ethyl]-2,3,3a,4,5,6-hexahydroindole-2,6-dione (VII) might cyclize to 15,16-dimethoxyerythrinane-3,8-dione (VIII), which has an oxygen function at C-3, the site of the methoxyl group in the alkaloids.

We now prepared VII in good yield by alkylating IIb with 3,4-dimethoxyphenethyl bromide in the presence of sodium methyl sulfinyl methide in dimethyl sulfoxide (DMSO). Cyclization of VII to VIII was examined under a variety of conditions. Although heating in 85% H_3PO_4 at 100° for 3 hr, as described for XII, was unfavorable, heating VII with HCOOH gave VIII in 32% yield with 19.6% recovery of VII. The prediction made by Mondon has now been verified by the present synthesis. The IR spectrum of VIII (Fig. 1) had two peaks in the carbonyl region for a ketone (1720 cm^{-1}) and a lactam (1680 cm^{-1}), and the NMR spectrum had two singlets at 6.58 ppm (1H) and 6.65 ppm (1H) ascribable to protons at C-14 and C-17 of the erythrinane skeleton. Ketalization of VIII and successive reduction with lithium

7) *a*) A. Mondon, *Chem. Ber.*, **92**, 1472 (1959); *b*) A. Mondon and K. Böttcher, *ibid.*, **103**, 1512 (1970).

aluminum hydride (LAH) followed by treatment with 5% HCl gave known 15,16-dimethoxyerythrinan-3-one (IX). The melting points of IX and its picrate were coincident with those reported in the literatures.[8] The IR spectrum is shown in Fig. 2. Further proof for the erythrinane skeleton was provided after conversion of VIII into isomeric alcohols, Xa and Xb, by LAH reduction, whose structures and stereochemistry had been already established by Prelog, *et al.*[8a] The IR (KBr) spectrum of Xa is superimposable to the chart of Hydroxy-Base A (the 3β-OH isomer) presented in the Prelog's report. As to Xb, direct comparison of IR chart with the authentic one (KBr) could not be made, because our sample is still an oil. However, its UV absorption maxima (283 mμ, ε 3780; 287 mμ, ε 3780) and melting points of the picrate and the perchlorate are identical with those of their Hydroxy-Base B (the 3α-OH isomer). The IR charts of our Xa (KBr) and Xb (CCl_4) are shown in Fig. 3 and 4.

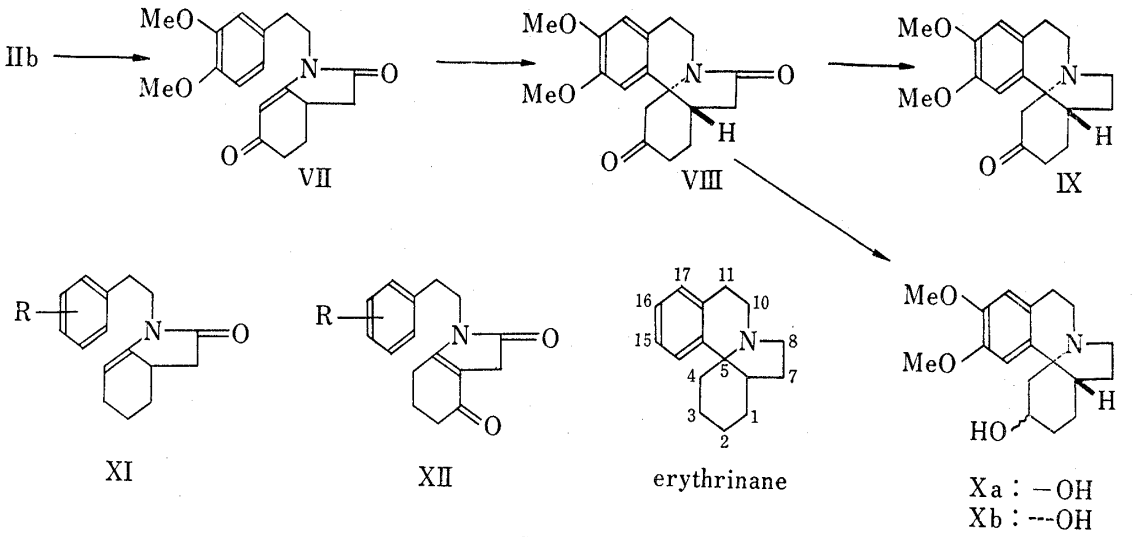

Chart 2

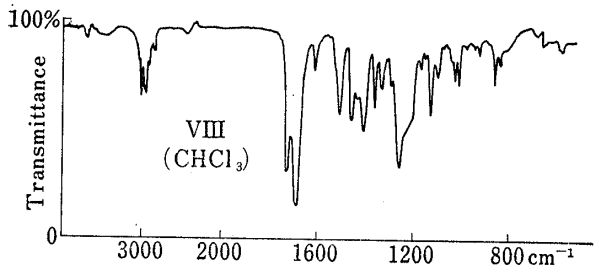

Fig. 1. IR spectrum of 15,16-Dimethoxyerythrinane-3,8-dione (VIII) measured on Hitachi EPI-G21 Spectrophotometer

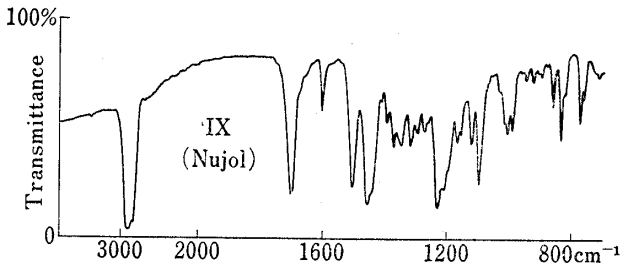

Fig. 2. IR spectrum of 15,16-Dimethoxyerythrinan-3-one (IX) measured on Nippon Bunko Model IR-E Spectrophotometer

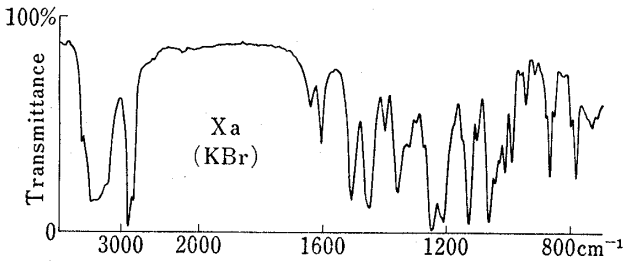

Fig. 3. IR spectrum of 15,16-Dimethoxyerythrinan-3β-ol (Xa) measured on Nippon Bunko Model IR-E Spectrophotometer

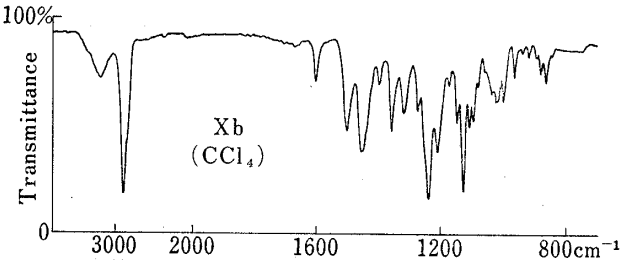

Fig. 4. IR spectrum of 15,16-Dimethoxyerythrinan-3α-ol (Xb) measured on Nippon Bunko Model IR-E Spectrophotometer

8) *a*) V. Prelog, A. Langemann, O. Rodig, and M. Ternbah, *Helv. Chim. Acta*, **42**, 1301 (1959); *b*) R.V. Stevens and M.P. Wentland, *Chem. Comm.*, **1968**, 1104.

Experimental

Melting points were measured on a Yamato Scientific Co. melting point apparatus and uncorrected. IR spectra were measured on a Nippon Bunko Model IR-S or IR-E spectrophotometer. UV spectra were measured on Hitachi recording spectrophotometer M-323. NMR spectra were measured on a Japan Electron Optics Co. JNM C-60 spectrometer with tetramethylsilane as an internal standard.

Methyl Phenylacetylsuccinate——Methyl 4-phenylacetoacetate (37.5 g) was added to a stirred solution of MeONa in MeOH (Na 4.5 g, MeOH 90 ml) at room temperature. To this was added methyl bromoacetate (30 g) under cooling. The mixture was stirred at room temperature and then refluxed for 1 hr. MeOH was removed *in vacuo*. The residue was taken up in AcOEt, washed with water and dried over Na_2SO_4. Distillation twice gave a colorless oil (33.1 g, 64.3%), bp 143—146° (1.0 mmHg). IR ν_{max}^{liq} cm^{-1}: 1710—1730 (broad). NMR ($CDCl_3$) δ: 2.88 (2H, d, $J=7$ Hz), 3.62 (3H, s), 3.70 (3H, s), 3.96 (2H, s), 4.11 (1H, t, $J=7$ Hz), 7.25 (5H, s). *Anal.* Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.72; H, 6.03.

Ethyl 2-Acetyl-2-(2-cyanoethyl)succinate (Ib)——To a mixture of ethyl acetylsuccinate[5] (66.9 g) and EtONa (Na, 0.36 g; EtOH, 10 ml) was dropwise added acrylonitrile (23 g) below 60°. Stirring was continued for 1 hr at room temperature. The mixture was acidified with AcOH, diluted with ether, washed with water and dried over Na_2SO_4. Evaporation of the solvent and distillation gave an oil (Ib), (57.3 g, 69%), bp 139—144° (2 mmHg). IR ν_{max}^{liq} cm^{-1}: 2245, 1730. NMR ($CDCl_3$) δ: 1.26 (3H, t, $J=7$ Hz), 1.30 (3H, t, $J=7$ Hz), 2.27 (3H, s), 2.45 (4H, m), 2.96 (2H, s), 4.16 (2H, q, $J=7$ Hz), 4.30 (2H, q, $J=7$ Hz). *Anal.* Calcd. for $C_{13}H_{19}O_5N$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.84; H, 7.09; N, 5.07.

Methyl 2-(2-Cyanoethyl)-2-phenylacetylsuccinate (Ic)——To a stirred mixture of methyl phenylacetylsuccinate (10 g), Triton B (40% MeOH solution, 1 ml) and dioxane (10 ml) was added acrylonitrile (5.2 ml) below 40°. After stirring for 2.5 hr at room temperature the mixture was acidified with AcOH and diluted with benzene. The benzene was washed with water, dried over Na_2SO_4 and evaporated. Distillation of the residue gave an oil (Ic), (9.4 g, 78.3%), bp 193—199° (1.0 mmHg). IR ν_{max}^{liq} cm^{-1}: 2280, 1730, 1710. NMR ($CDCl_3$) δ: 2.2—2.6 (4H, m), 3.05 (2H, s), 3.78 (3H, s), 3.70 (3H, s), 3.96 (2H, s), 6.9—7.6 (5H). *Anal.* Calcd. for $C_{17}H_{19}O_5N$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.11; H, 5.99; N, 4.71.

2,3,3a,4,5,6-Hexahydroindole-2,6-dione (IIb)——Ib (10 g) was dissolved in 88% H_2SO_4 (H_2SO_4: H_2O= 4: 1 v/v) (50 ml) and heated at 140—150° for 10 min. After cooling the mixture was poured into ice-water and neutralized with $BaCO_3$. $BaSO_4$ was removed by filtration and washed well with hot EtOH. The filtrate and EtOH washings were combined and evaporated to dryness. The residue was recrystallized from EtOH to give prisms (IIb), (3.6 g, 64.1%), mp 158—159°. IR ν_{max}^{Nujol} cm^{-1}: 1738, 1630 (shoulder), 1590. UV λ_{max}^{EtOH} $m\mu$ (ε): 272—273 (39200). NMR ($CDCl_3$) δ: 5.63 (1H, d, $J=1.5$ Hz). *Anal.* Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.59; H, 6.28; N, 9.22.

When the reaction was carried out in 80% H_2SO_4 (H_2SO_4: H_2O=2: 1 v/v), Ib gave IIb only in 14% yield.

7-Phenyl-2,3,3a,4,5,6-hexahydroindole-2,6-dione (IIc)——A mixture of Ic (11.2 g) and 80% H_2SO_4 (66 ml) was heated at 140—150° for 10 min, poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with sat.$NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated to give crystals. Recrystallization from EtOH gave needles (IIc), (3.32 g, 41.4%), mp 196—198°. IR ν_{max}^{Nujol} cm^{-1}: 3080, 1740 (shoulder), 1730, 1710, 1618, 1590. UV λ_{max}^{EtOH} $m\mu$ (ε): 232—233 (12700), 282—285 (26000). *Anal.* Calcd. for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.71; N, 6.16. Found: C, 74.13; H, 5.82; N, 6.23.

The reaction of Ic in 88% H_2SO_4 gave IIc in 15% yield. Contrary to the case of Ib, 80% H_2SO_4 was better for Ic than 88% H_2SO_4.

6-Hydroxyoxindole (Vb)——IIb (5.0 g) in *p*-cymene (5 ml) was heated to reflux with 10% Pd-C (0.30 g) for 25 min under N_2. The mixture was diluted with EtOH, filtered and evaporated to give a solid, which was recrystallized from EtOH to give needles (Vb), (3.37 g, 68.3%), mp 264—267° (decomp.). The literature[6a] reported mp 244—246° (decomp.) for Vb. IR ν_{max}^{Nujol} cm^{-1}: 3140, 1680 (shoulder), 1660, 1625, 1610. NMR (DMSO-d_6) δ: 3.40 (2H, s, C-3 methylene), 6.6—6.4 (2H, m, aromatic protons), 7.25—7.05 (1H, m, aromatic proton), 9.3H (1H, s, OH), 10.24 (1H, broad s, NH). *Anal.* Calcd. for $C_8H_7O_2N$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.35; H, 4.74; N, 9.41.

6-Hydroxy-7-phenyl-oxindole (Vc)——IIc (1.0 g) in *p*-cymene (10 ml) was heated to reflux with 10% Pd-C (0.5 g) for 25 min under N_2. Work-up as described for Vb and recrystallization from EtOH gave prisms (Vc), (0.77 g, 77.5%), which melted once at 113°, solidified again and decomposed at 177—178°. IR ν_{max}^{Nujol} cm^{-1}: 3160, 1665, 1620. NMR (DMSO-d_6) δ: 3.48 (2H, s, C-3 methylene), 6.65 (1H, d, $J=8$ Hz, C-4 or C-5 aromatic proton), 7.10 (1H, d, $J=8$ Hz, C-4 or C-5 aromatic proton), 7.47 (5H, 7-phenyl protons), 9.37 (1H, s, OH), 9.85 (1H, broad s, NH). *Anal.* Calcd. for $C_{14}H_{11}O_2N \cdot 1/4\ H_2O$: C, 73.17; H, 5.05; N, 6.14. Found: C, 73.33; H, 5.30; N, 6.05.

6-Methoxyoxindole (VIb)——Vb (80 mg) in EtOH (5 ml) was treated with excess ethereal CH_2N_2 and stored overnight in a cold room. Evaporation of the solvents and recrystallization of the residue from EtOH gave plates (VIb), (55 mg, 63.2%), mp 155—158° (lit.,[6a] mp 161—162°; lit.,[6b] mp 158°). IR ν_{max}^{Nujol} cm^{-1}: 3140, 1700, 1650, 1625. UV λ_{max}^{MeOH} $m\mu$ (ε): 258 (4900), 288 (3200), 292 (2760). NMR ($CDCl_3$) δ: 3.48 (2H, s, C-3 methylene), 3.75 (3H, s, $-OCH_3$), 6.4—6.65 (2H, m, aromatic protons), 7.0—7.2 (1H, m, aromatic proton), 9.59 (1H, broad s, NH).

6-Methoxy-7-phenyl-oxidole (VIc)——Vc (270 mg) in EtOH (10 ml) was methylated with CH_2N_2 as described for Vb. Recrystallization from EtOH gave VIc (150 mg, 52.3%), mp 201—202°. IR ν_{max}^{Nujol} cm^{-1}: 3140, 1690, 1615. NMR ($CDCl_3$) δ: 3.46 (2H, d, J=*ca.* 1.0 Hz, C-3 methylene), 3.70 (3H, s, $-OCH_3$), 6.57 (2H, d, J=8 Hz, C-4 or C-5 proton), 7.1 (2H, d, J=8 Hz, C-4 or C-5 proton), 7.35 (5H, s, 7-phenyl protons), 7.5 (1H, broad s, NH). *Anal.* Calcd. for $C_{15}H_{13}O_2N$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.53; H, 5.62; N, 5.98.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-2,3,3a,4,5,6-hexahydroindole-2,6-dione (VII)——IIb (0.50 g) in DMSO (5 ml) was added to a solution of sodium methylsulfinyl methide prepared from NaH (95 mg) and DMSO (5 ml) under N_2 and stirred for 30 min at room temperature. To this was added 2-(3,4-dimethoxyphenyl)-ethylbromide (1.0 g) in DMSO (5 ml). The mixture was warmed at 45—50° for 3.5 hr under stirring and poured into ice-water. Extraction with $CHCl_3$, washing with water and evaporateon gave a residue, which was recrystallized from EtOH to give VII (0.93 g, 89%), mp 167—168°. IR ν_{max}^{Nujol} cm^{-1}: 1735, 1640 (shoulder), 1610, 1600 (shoulder). UV λ_{max}^{EtOH} mμ (ε): 231—233 (11800), 277—279 (30800). NMR ($CDCl_3$) δ: 5.53 (1H, d, J=1.5 Hz, an olefinic proton). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 7.61; N, 4.44. Found: C, 68.84; H, 6.81; N, 4.41.

15,16-Dimethoxyerythrinane-3,8-dione (VIII)——Suspended VII (5.0 g) in HCOOH (35 ml) was stirred at 95—100° for 16 hr under N_2. Most of HCOOH was evaporated *in vacuo*. The residue was taken up in $CHCl_3$, washed with 10% HCl, saturated $NaHCO_3$ and water, successively, and dried over Na_2SO_4. Evaporation of the solvent gave an amorphous powder (4.9 g), which was chromatographed on alumina (80 g). From early parts of the eluate with benzene, VII (1.12 g, 22.4%) was recovered. Further elution with benzene and benzene–MeOH (95: 5) and recrystallization from EtOH gave VIII (1.60 g, 32%), mp 155—156°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680. UV λ_{max}^{EtOH} mμ (ε): 285—289° (4650). NMR ($CDCl_3$) δ: 6.58 (1H, s, C-14 or C-17 aromatic proton), 6.65 (1H, s, C-14 or C-17 aromatic proton). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.32; H, 6.57; N, 4.36.

15,16-Dimethoxyerythrinan-3-one (IX)——A mixture of VIII (0.40 g), 2-ethyl-2-methyl-1,3-dioxolane (8 ml) and a trace of *p*-toluenesulfonic acid was heated to reflux for 3 hr. Work-up gave a ketal of VIII (0.39 g), mp 183—185°, IR ν_{max}^{Nujol} cm^{-1}: 1660 (lactam). The ketal (0.29 g) was reduced with LAH (0.30 g) in 40 ml of refluxing tetrahydrofuran (20 hr). After decomposition of excess LAH, the mixture was filtered. Evaporation of the solvent gave a colorless oil, which was dissolved in 5% HCl, warmed at 60—65° for 1.5 hr, and made alkaline with K_2CO_3. A separated oil was extracted with $CHCl_3$, dried over K_2CO_3 and evaporated to give a residue. Recrystallization from isopropyl ether gave needles (IX) (90 mg), mp 142.5—143.5°, (lit.,[8b] mp 143—144°). IR ν_{max}^{Nujol}: 1720 (ketone). *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.56, H, 7.66; N, 4.66. The picrate, mp 144—147°, (lit.,[8a] mp 144—146°).

15,16-Dimethoxyerythrinan-3β-ol (Xa) and 15,16-Dimethoxyerythrinan-3α-ol (Xb)——VIII (200 mg) was reduced with LAH (300 mg) in 50 ml of refluxing tetrahydrofuran (22 hr). After the usual work-up, a resultant oil was separated by preparative thin-layer chromatography on silica gel using $CHCl_3$–EtOH (9: 1 v/v) as eluent. From a band with high *Rf* value, Xb was obtained as an oil (60 mg). IR ($CHCl_3$) spectrum (Fig. 4). UV λ_{max}^{EtOH} mμ (ε): 283—288 (3780). The picrate (yellow needles from EtOH), mp 170—172°, (lit.,[8a] mp 168—170°). *Anal.* Calcd. for $C_{24}H_{28}O_{10}N_4$ (picrate): C, 54.13; H, 5.30; N, 10.52. Found: C, 53.80; H, 5.30; N, 10.16. The perchlorate of Xb decomposed at 215—217°, (lit.,[8a] mp 218—222° (decomp.)).

Xa was obtained as crystals from a band with lower *Rf* value. Recrystallization from MeOH–H_2O gave needles (56 mg), mp 97—98°, (lit.,[8a] mp 101—105°). IR (KBr) spectrum (Fig. 3). UV ν_{max}^{EtOH} mμ (ε): 283—288 (4480). *Anal.* Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31; N, 4.62. Found: C, 70.83: H, 8.27; N, 4.34.

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