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Phenolic Cyclization. III.[1] One Step Synthesis of *cis*- and *trans*-16-Hydroxy-15-methoxyerythrinanone by Phenolic Cyclization (Studies on the Syntheses of Heterocyclic Compounds. CCLXIV[2])

Tetsuji Kametani, Hideo Agui, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University School of Medicine[3]

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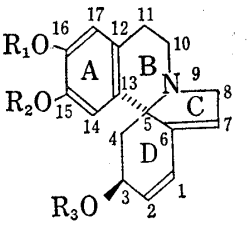
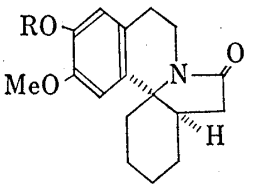
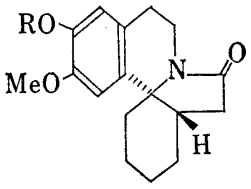
cis-(IIa) and *trans*-16-Hydroxy-15-methoxyerythrinanone (IIb) were prepared by phenolic cyclization and the former (IIa) was transformed to corresponding *cis*-erythrinane (VII) by lithium aluminum hydride and to 15,16-dimethoxyerythrinane (VI) *via* *cis*-15,16 dimethoxyerythrinanone (Va). *cis*-(Va) and *trans*-15,16-dimethoxyerythrinanone (Vb) were obtained from homoveratrylamine (VIII) and 2-carboxymethylcyclohexanone ethylene ketal (IX).

The alkaloids[4] (Ia–e) found in numerous species of the genus *Erythrina* are of wide interest because of their remarkable physiological action.[5] Approaches to the total synthesis of erythrina alkaloids have hitherto been investigated by several investigators.[6–8] In these cases, since the erythrinane skeleton has been synthesized only in acid media, it seems to be very difficult to prepare the characteristic skeleton having a labile methoxyl group at C_3-position in D-ring in acid media. Therefore, we wish to report one step synthesis of (±)-*cis*- and *trans*-16-hydroxy-15-methoxyerythrinanone (IIa and IIb) under the mild conditions without acid by application of our phenolic cyclization.[9]







Erysopine Ia : $R_1=R_2=H$; $R_3=Me$
Erysonine Ib : $R_1=R_3=H$; $R_2=Me$
Erysodine Ic : $R_1=H$; $R_2=R_3=Me$
Erysovine Id : $R_1=R_3=Me$; $R_2=H$
Erythraline Ie : $R_1=R_2=CH_2$; $R_3=Me$

IIa : R=H
Va : R=Me

IIb : R=H
Vb : R=Me

Chart 1

3-Hydroxy-4-methoxyphenethylamine (III) was heated with 2-ethoxycarbonylmethylcyclohexanone (IV) in ethanol for 3 hr in a current of nitrogen and the careful work up

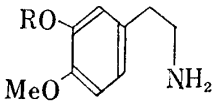
1) Part II: T. Kametani, S. Shibuya, and M. Satoh, *Chem. Pharm. Bull.* (Tokyo), **16**, 940 (1968).
2) Part CCXLII: *Yakugaku Zasshi*, **88**, 937 (1968); Part CCXLIII: *Chem. Comm.*, **1968**, 786.
3) Location: *No. 85, Kita-4-bancho, Sendai.*
4) H.G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961, p.383.
5) D. Megirlan, D.E. Leary, and I.H. Slater, *J. Pharmil. Exptl. Therap.*, **113**, 212 (1955).
6) A. Mondon, H. J. Nestler, H.G. Vilhuber, and M. Ehrhardt, *Ber.*, **98**, 46 (1965).
7) S. Sugasawa and H. Yoshikawa, *Chem. Pharm. Bull.* (Tokyo) **8**, 290 (1960).
8) A. Mondon, *Ber.*, **72**, 1472 (1959).
9) T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc.* (C), **1968**, 112.

involving silicic acid chromatography gave two compounds; the first one (IIa) from chloroform part as eluent was obtained as colorless needles, $C_{17}H_{21}O_3N$, mp 124—125°, M^+ 287, ν_{max} 3420, 1664 (in $CHCl_3$), 1654 (in KBr), NMR (τ in $CDCl_3$) 6.14 (O-methyl), 3.26 (C_{17}-H), 3.19 (C_{14}-H), and the second one (IIb) from chloroform–methanol (10:1) part as eluent was formed as colorless needles, $C_{17}H_{21}O_3N$, mp 143—144°, M^+ 287, ν_{max} 3420, 1664 (in $CHCl_3$), 1660 (in KBr), NMR (τ in $CDCl_3$) 6.17 (O-methyl), 3.27 (C_{17}-H), 3.20 (C_{14}-H). These data showed both compounds to be stereoisomers at C_5- and C_6-position each other. The former compound (IIa) was methylated with diazomethane to give (±)-*cis*-15,16-dimethoxyerythrinanone (Va), $C_{18}H_{23}O_3N$, mp 118—119°, M^+ 301, ν_{max} 1640 (in KBr), NMR (τ in $CDCl_3$) 6.20 (O-methyl 6H), 3.27 (two aromatic protons), and then reduced with lithium aluminum hydride to give (±)-*cis*-15,16-dimethoxyerythrinane (VI) as a colorless viscous oil, bp 110° (bath temperature) at 10^{-3} mmHg, whose hydrochloride showed mp 226°. The IR and NMR spectra of these compounds (Va) and (VI), were superimposable on those of authentic samples, whose stereochemistry was decided by Mondon.[10-12] Therefore, the first erythrinanone (IIa) was *cis*-configuration at C_5- and C_6-positions and the latter (IIb) should be *trans*-configuration at these positions.

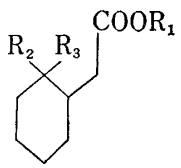
The reduction of IIa with lithium aluminum hydride gave 16-hydroxy-15-methoxyerythrinane (VII) as a colorless viscous oil, which could not be crystallized as its derivatives or salts, ν_{max} 3505 (in $CHCl_3$), NMR (τ in $CDCl_3$) 6.8—8.9 (aliphatic protons, 17H), 6.19 (O-methyl), 3.30 (C_{17}-H), 3.25(C_{14}-H).

In a synthesis of Va from 3,4-dimethoxyphenethylamine (VIII) and 2-carboxymethylcyclohexanone ethylene ketal (IX), the other erythrinanone (Vb), which had not yet been separated, $C_{18}H_{23}O_3N$, mp 110—111°, M^+ 301 [ν_{max} 1643 (in KBr), NMR (τ in $CDCl_3$) 6.15 (O-methyl, 6H), 3.24 (two aromatic protons)] was obtained. Since the spectral data of this compound are very similar to those of *cis*-compound (Va), the second compound (Vb) seems to be *trans*-15,16-dimethoxyerythrinanone.

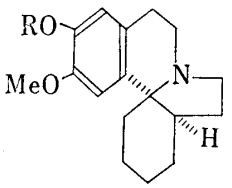
Thus, two stereoisomers (IIa and IIb) of erythrinanone were obtained by phenolic cyclization[9] as the important key intermediates for the total synthesis of erythrina alkaloids. Furthermore, two isomers of 15,16-dimethoxyerythrinanone were found to be separated.



III : R=H
VIII : R=Me



IV : R_1=Et, R_2+R_3=O
IX : R_1=H, R_2+R_3=OCH_2CH_2O



VI : R=Me
VII : R=H

Chart 2

Experimental[13]

***cis*-(IIa) and *trans*-16-Hydroxy-15-methoxyerythrinanone (IIb)**——3-Hydroxy-4-methoxyphenethylamine (III), prepared from 1.7 g of III-hydrochloride and 2.0 g of anhyd. Na_2CO_3 by usual method, was refluxed with 1.2 g of 2-ethoxycarbonylmethylcyclohexanone (IV) in 10 ml of EtOH in a current of N_2 for 3 hr. After removal of the solvent by distillation in a current of N_2, the reddish residue was chromatographed on 17.5 g of silicic acid. The $CHCl_3$ eluate gave a pale orange gum, which was triturated with *n*-hexane to

10) A. Mondon, *Ber.*, **72**, 1461 (1959).
11) A. Mondon, *Ann.*, **628**, 123 (1959).
12) A. Mondon and K.F. Hanson, *Tetrahedron Letters*, **1960**, 5.
13) All melting points and boiling points were not corrected. NMR spectra were taken on a Hitachi H-60 with Me_4Si as an internal standard. Mass spectra were taken on RMU-6D, Hitachi Mass spectrometer.

afford a solid, whose recrystallization from EtOH yielded 0.274 g of IIa as colorless needles, mp 124—125°. IR cm^{-1} $\nu_{max}^{CHCl_3}$: 3420 (OH), 1664 (>C=O); ν_{max}^{KBr}: 1654 (>C=O). NMR (τ in $CDCl_3$): 6.14 (3H, singlet, $OC\underline{H}_3$), 3.26 (1H, singlet, C_{17}–$\underline{H}$), 3.19 (1H, singlet, C_{14}–$\underline{H}$). Mass spectrum: M+287. *Anal.* Calcd. for $C_{17}H_{21}O_3N \cdot 1/4H_2O$: C, 69.96; H, 7.43; N, 4.80. Found: C, 69.71; H, 7.38; N, 4.80. Further elution with $CHCl_3$–MeOH (10:1) afforded a red gum, which was triturated with *n*–hexane to give a crystalline substance. Recrystallization from MeOH–petr. ether gave 0.57 g of IIb as colorless needles, mp 143—144°. IR cm^{-1} $\nu_{max}^{CHCl_3}$: 3420 (OH), 1664 (>C=O); ν_{max}^{KBr}: 1660 (>C=O). NMR (τ in $CDCl_3$): 6.17 (3H, singlet, $OC\underline{H}_3$), 3.27 (1H, singlet, C_{17}–$\underline{H}$), 3.20 (1H, singlet, C_{14}–$\underline{H}$). Mass spectrum: M+287. *Anal.* Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.83; H, 7.96; N, 4.76.

***cis*-(Va) and *trans*-15,16-Dimethoxyerythrinanone (Vb)**——a) A mixture of 1.7 g of 2-carboxymethylcyclohexanone ethylene ketal (IX) and 1.6 g of 3,4-dimethoxyphenethylamine (VIII) was heated at 150° for 5 hr and at 190° for further 5 hr in a current of N_2 in the presence of 0.2 g of Dowex 50, and the mixture was subjected to chromatography using 25.0 g of silicic acid. The $CHCl_3$ eluate gave 2.17 g of a pale yellow solid, which was recrystallized from MeOH–petr. ether to afford Va as colorless needles, mp 118—119°. IR cm^{-1} $\nu_{max}^{CHCl_3}$: 1657 (>C=O). NMR (τ in $CDCl_3$): 6.18 (6H, singlet $2\times OC\underline{H}_3$), 3.25 (2H, singlet, aromatic protons). *Rf* 0.86 ($CHCl_3$: MeOH=5:2, silica gel, 0.2 mm). Mass spectrum: M+301. *Anal.* Calcd. for $C_{18}H_{23}O_3N \cdot 1.5H_2O$: C, 66.65; H, 8.07; N, 4.35. Found: C, 66.51; H, 8.08; N, 4.58. This base was shown to be identical with authentic sample by direct comparison of IR ($CHCl_3$ and KBr) and NMR spectra, TLC and mixed melting point test. The final elution with $CHCl_3$–MeOH (10:1) gave 0.68 g of a dark red solid, which was recrystallized from MeOH–petr. ether to afford Vb as colorless needles, mp 110—111°. IR cm^{-1} $\nu_{max}^{CHCl_3}$: 1659 (>C=O). NMR (τ in $CDCl_3$): 6.15 (6H, singlet, $2\times OC\underline{H}_3$), 3.24 (2H, singlet, aromatic protons). *Rf* 0.66 ($CHCl_3$: MeOH=5:2, silica gel, 0.2 mm). Mass spectrum: M+301. *Anal.* Calcd. for $C_{18}H_{23}O_3N \cdot 1.5H_2O$: C, 66.65; H, 8.07. Found: C, 66.75; H, 8.24.

b) A mixture of 50 mg of *cis*–16–hydroxy–15–methoxyerythinanone (IIa) and an excess of diazomethane in 10 ml of ether was allowed to stand for 48 hr at room temperature. The usual work up gave 40 mg of Va, whose IR ($CHCl_3$ and KBr) and NMR spectra and *Rf* value were superimposable on those of the authentic sample prepared by the method a). *trans*–Isomer (IIb) (100 mg) also gave 96 mg of Vb by the same method as above.

***cis*-15,16-Dimethoxyerythrinane (VI)**——A mixture of 0.25 g of *cis*–15,16–dimethoxyerythrinanone (Va) and 0.20 g of $LiAlH_4$ in 10 ml of anhyd. tetrahydrofuran was refluxed for 4 hr in a current of N_2. The usual work up gave a dark orange viscous oil, which was distilled to give 0.1 g of VI as a colorless viscous oil, bp 110° (0.001 mmHg) (bath temp.). The hydrochloride showed mp 226°. This base was identical with the authentic sample by direct comparison of IR and NMR spectra.

***cis*-16-Hydroxy-15-methoxyerythrinane (VII)**——A solution of 0.3 g of *cis*–16–hydroxy–15–methoxyerythrinanone (IIa) in the 10 ml of anhyd. tetrahydrofuran was reduced with 0.15 g of $LiAlH_4$ under refluxing for 4 hr. The usual work up gave 0.25 g of a colorless viscous oil (VII). IR cm^{-1} $\nu_{max}^{CHCl_3}$: 3505 (OH). NMR (τ in $CDCl_3$): 6.8—8.9 (17H, aliphatic protons), 6.19 (3H, singlet, $OC\underline{H}_3$), 3.30 (1H, singlet, C_{17}–$\underline{H}$), 3.25 (1H, singlet, C_{14}–$\underline{H}$).

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