Conversion of Erythrinane into Erythroidine Skeleton

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Synthesis of erythroidine skeleton, containing β,γ -unsaturated- δ -lactone system derived from erythrinane skeleton was described.

Erythrina alkaloids, occurring in the seeds and plant parts of *Erythrina* species, cause the paralysis of smooth muscles similar to the effect of curare.^{1~3)} Cocculolidine has an insecticidal activity.⁴⁾ The alkaloids are derived into two groups according to their structural features; the one includes erythrinanes such as erysodine (I) and erythraline (II) which have a tetracyclic system in which D

ring is aromatic, and the other includes D-ring unsaturated δ - or γ -lactonic erythroidines (III) and cocculolidine (IV).

The synthesis of erythrina alkaloids has been investigated by many groups. Belleau and the schools of Wiesner, Prelog, Mondon, Rapoport and Scott have achieved significant successes.

Mondon succeeded in the synthesis of

FIG. A.

FIG. B.

erysotrine (O-methyl erysodine)⁵⁾ and a naturally occurring alkaloid, dihydroerysodine⁶⁾ via oxidative coupling.⁷⁾ Frank *et al.*⁸⁾ also accomplished the synthesis of erythrinadione of a biogenetic type⁹⁾ development of this field has been reviewed in details.^{10~16)}

The syntheses of erythroidines and cocculolidine have not been accomplished yet. Recently Umezawa *et al.*¹⁷⁾ reported the synthesis of an erythroidine-type compound from erythrinane. The synthesis of the erythroidine system has also been studied by our group. We wish to describe the conversion of erythrinane to the erythroidine skeleton containing a β,γ -unsaturated δ -lactone system in D-ring.

As a starting material was used 8-oxo-16-methoxy erythrinane derived from ethyl 2-oxo-cyclohexyl acetate (VI) and 2-(*m*-hydroxyphenyl) ethylamine (VII). Pyrolysis of the keto-ester (VI) with the amine (VII) in toluene gave a crude en-lactam (VIII) as an oily product which without purification was submitted to cyclization by treating with phosphoric acid in ethanol to afford a mixture of tetracyclic lactam phenols (IX, X) which can be separated by silica gel chromatography. However, without separation, the mixture was directly methylated with dimethyl sulfate and

sodium hydride to give two products in good yield separated by silica gel chromatography. First fraction contained a minor product (about 20% of the mixture), 8-oxo-14-methoxyerythrinane (XI), and a major one (80% of the mixture), the starting material (V).

The birch reduction of the lactam (V) and the subsequent hydrolysis of the resulting enol ether with methanolic hydrogen chloride gave a conjugated enone (XII) in 62~71% yield. The aldol condensation of the enone (XII) with benzaldehyde in the presence of a catalytic amount of piperidine acetate at 80°C in benzene afforded its benzylidene derivative (XIII), isolated as a sole product by silica gel chromatography in 63% yield, mp 185.5~187°C. UV and NMR data supported that a benzylidene group was introduced at C₁₅-position as expected.

Other possible structures (XVII, XVIII) were excluded by these analytical data.

FIG. D.

FIG. C.

The benzylidene derivative (XIII) was ozonized in CHCl_3 at $-20 \sim 30^\circ\text{C}$ and the resulting ozonide was oxidized with alkaline-hydrogen peroxide at $0 \sim 5^\circ\text{C}$ to a clude acid (XIV) which immediately esterified with diazomethane to afford a keto-ester (XV) as an oily product. To obtain the final product from the keto-ester (XV), Corey's method of epoxide-synthesis¹⁸⁾ was employed. The keto ester was treated with methyl oxosulfonium methylide in dimethyl sulfoxide¹⁹⁾ and successively with methanolic hydrogen chloride to afford a final product, 3-demethoxy-8-oxo-tetrahydro β -erythroidine (XVI). The structure of the final product was supported by physical data. Thus we have accomplished the synthesis of the erythroidine skeleton starting from erythrinane system. The synthesis of cocculolidine system is now under investigation.

EXPERIMENTAL

All mps were uncorrected.

14- and 16- Hydroxy-8-oxo-erythrinane (XI, X)

A mixture of *m*-hydroxyphenethylamine (6.8 g) and ethyl 2-oxo-cyclohexylacetate (9.2 g) in toluene (50 ml) was refluxed for 7 hr. The solvent was removed *in vacuo* and the resulting yellow brown oil was dissolved in 85% phosphoric acid (30 ml) and 99% ethanol (120 ml). After the mixture was refluxed for 7 hr, the solvent was removed *in vacuo* and the residual oil was poured into cold water, extracted with methylene chloride (50 ml $\times$ 5). The extract was washed with water and dried over magnesium sulfate (MgSO_4). The solvent was distilled off and the resulting oil (14.6 g) was a mixture of two products. The main product was obtained by silica gel chromatography. mp 282°C , colorless prisms. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3200, 1660, 1580. Anal. Found: C, 74.65; H, 7.47; N, 5.45. Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_2$: C, 74.68; H, 7.44; N, 5.44. The mixture of the two products was submitted to successive reactions without purification.

8-Oxo-14-methoxyerythrinane (XI) and 8-oxo-16-methoxyerythrinane (V)

To a solution of the crude lactam phenol (14.6 g) in 120 ml anhydrous DMF, 50% sodium hydride (3.6 g) was added portionwise, and to this, dimethyl sulfate (9.8 g) was added dropwise in a period of 20 min at $40 \sim 50^\circ\text{C}$. After the addition was completed, the mixture was stirred at $80 \sim 90^\circ\text{C}$ under a nitrogen atmosphere for 4 hr. The reaction mixture was cooled

to r.t., poured into cold water and extracted with CHCl_3 (50 ml $\times$ 5) successively. The extract was washed with water and dried over MgSO_4 . Evaporation of the solvent afforded a mixture of two methyl ethers as a yellowbrown oil (15.3 g). Silica gel chromatography gave two main products. The first fraction, eluted by $\text{CHCl}_3/\text{Et}_2\text{O}=9/1$, is 8-oxo-14-methoxyerythrinane (XI) mp $102 \sim 103^\circ\text{C}$, yield 1.92 g (14.2%) IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1678, 1600 (weak), 1580 (strong), 1258. NMR δ ppm: 1.20 $\sim$ 3.20 (methylene proton), 3.87 (3H, singlet, $-\text{OCH}_3$), 6.64 $\sim$ 6.80 (2H, $2 \times$ double doublet, C_{15} - and C_{17} -H), 7.06 $\sim$ 7.22 (1H, double doublet, C_{16} -H). Anal. Found: C, 75.15; H, 7.79; N, 4.98. Calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_2$: C, 75.24; H, 7.80; N, 5.16%. The major one, obtained as the second fraction in 59.3% yield (8.01 g), is 8-oxo-16-methoxyerythrinane (V), mp $106 \sim 107^\circ\text{C}$. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1678, 1605 (strong), 1575 (weak), 1500, 1240. NMR δ ppm: 1.40 $\sim$ 3.50 (methylene proton), 3.83 (3H, singlet, $-\text{OCH}_3$), 6.70 (1H, doublet, $J_{17-15}=2.5$ Hz, C_{17} -H), 6.81 (1H, double doublet, $J_{15-14}=8.5$ Hz, $J_{15-17}=2.5$ Hz, C_{15} -H) 7.34 (1H, doublet, $J_{14-15}=8.5$ Hz, $J_{14-17} \approx 0$, C_{14} -H). Anal. Found: C, 74.92; H, 7.83; N, 4.89. Calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_2$: C, 75.24; H, 7.80; N, 5.16.

8, 16-Dioxo-13, 14, 15, 16-tetrahydro erythrinane (XII)

To a stirred solution of the methyl ether (V, 10 g) and anhydrous ethanol (50 ml) in liquid ammonia (700 ml), lithium (7.8 g) was added in small pieces during a period of 30 min. After the addition was completed, the mixture was stirred for additional 15 min, and excess ammonium chloride was added to stop the reaction. Ammonia was evaporated and the residual oil was treated with methanolic HCl (5% soln.) and extracted with CHCl_3 (50 ml $\times$ 5). The extract was washed with dilute sodium bicarbonate and water and dried over MgSO_4 . The solvent was removed to give an enone (XII) in 72% yield (6.9 g), colorless prism, mp $140 \sim 140.5^\circ\text{C}$, recrystallized from *n*-propyl alcohol. UV $\lambda_{\text{max}}^{\text{EtOH}}$: 251 nm, $\epsilon=11300$ IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1680, 1665, 1610. NMR δ ppm: 6.02 (1H, singlet-(small coupling with allylic methylene) olefinic proton). Anal. Found: C, 74.18; H, 8.14; N, 5.24. Calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_2$: C, 74.10; H, 8.16; N, 5.40.

15-Benzylidene-8, 16-dioxo-13, 14, 15, 16-tetrahydro-erythrinane (XIII)

To a solution of piperidine (400 mg), acetic acid (260 mg) and the enone (XII, 2.0 g) in anhydrous benzene (80 ml), benzaldehyde (880 mg) in benzene (20 ml) was added at once, and the mixture was refluxed with stirring under a nitrogen atmosphere for 7 hr. The reaction mixture was poured into water and extracted with CHCl_3 . The extract was washed with dilute hydrochloric acid, water, a dilute sodium bicarbonate

solution and water successively and dried over MgSO_4 . The solvent was removed and ether (10 ml) was added to the residue to afford a benzylidene derivative (XIII), as yellow crystals (528 mg). Silica gel chromatography (CHCl_3 : Et_2O =15:1) of the residual oil (2.16 g) to afford another crop (795 mg). The starting material (180 mg) was recovered as a second fraction. The total yield of the benzylidene derivative was 55%. Physical data are as follows. mp $185.5\sim 186.5^\circ\text{C}$, recrystallized from *n*-ProOH. UV $\lambda_{\text{max}}^{\text{EtOH}}$: 307 nm, $\epsilon=8820$. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1680, 1675 (shoulder), 1650, 1638, 1595, 1585. NMR δ ppm: 5.84 (1H, broad singlet, olefinic proton). 7.2~7.6 (6H, aromatic proton, $\text{C}_6\text{H}_5\text{CH}-$). Anal. Found: C, 79.26; H, 7.39; N, 3.78. Calcd. for $\text{C}_{23}\text{H}_{25}\text{NO}_2$; C, 79.50; H, 7.25; N, 4.03.

3-Demethoxy- γ -oxo-tetrahydro- β -erythroidine (XVI)

The benzylidene derivative (XIII, 700 mg) in CHCl_3 (50 ml) was ozonized at $-20\sim -30^\circ\text{C}$, and the resulting ozonide was treated with alkaline hydrogen peroxide, prepared from 30% H_2O_2 (2 ml) and 5% NaOH (30 ml), at 0°C for 90 min. The aqueous layer was acidified and extracted with CHCl_3 repeatedly. The extract was dried over MgSO_4 , and was treated with excess diazomethane to give a crude product. Silica gel chromatography ($\text{CHCl}_3/\text{Et}_2\text{O}=10/1$) afforded an oily keto-ester, (XV, 246 mg), IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1735, 1720 (shoulder), 1680 cm^{-1} , NMR δ ppm: 3.86 (s, 3H, $-\text{OCH}_3$). The keto-ester (XV, 168 mg) was treated with dimethyl oxosulfonium methylide (1.5 Meq), prepared as described in reference, from trimethyl sulfoxonium iodide (197 mg) and methyl sulfinyl carbanion derived from 65% sodium hydride (36 mg) and anhydrous dimethyl sulfoxide (10 ml). The reaction was carried out under a nitrogen atmosphere at room temperature for 24 hr. The reaction mixture was poured into dilute hydrochloric acid and extracted with CHCl_3 (30 ml $\times$ 8). The extract was washed with water and dried over MgSO_4 . Evaporation of the solvent gave a crude yellowish oil. The oil was treated with methanolic hydrochloric acid (2% solution) at room temperature for 24 hr. The solvent was removed *in vacuo* and the residue was diluted with water and then extracted with CHCl_3 (50 ml $\times$ 5). The extract was washed with water and dried over MgSO_4 . The solvent was removed *in vacuo* to give a crude product. Silica gel chromatography ($\text{CHCl}_3/\text{Et}_2\text{O}=15/1$) afforded 3-demethoxy-8-oxo-tetrahydroerythroidine as colorless crystals (64 mg),

mp $155\sim 156^\circ\text{C}$ IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1725, 1685, 1620. NMR δ ppm: 4.65 (2H, singlet). Anal. Found: C, 68.89; H, 7.25; N, 5.34. Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_3$; C, 68.94; H, 7.33; N, 5.36.

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