Tetrahedron Vol. 36, pp. 965 to 968
© Pergamon Press Ltd., 1980. Printed in Great Britain

0040-4020/80/0401-0965/$02.00/0

QUINOLIZIDINES—IV[1]

TOTAL SYNTHESES OF (±)-ANKORINE AND (±)-11-METHOXYPROTOEMETINOL

TOZO FUJII,* SHIGEYUKI YOSHIFUJI and KOICHIRO YAMADA
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

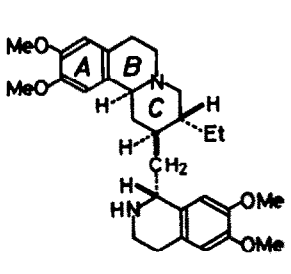
(*Received in Japan* 23 *May* 1979)

Abstract—The first total synthesis of ankorine (**4**), an *Alangium lamarckii* alkaloid, has been accomplished in the form of a recemic modification by means of an initial condensation of 2-benzyloxy-3,4-dimethoxyphenacyl bromide with the lactim ether **6**, derived from ethyl (±)-*trans*-5-ethyl-2-oxo-4-piperidineacetate (**5**), and succeeding steps proceeding through the intermediates **7a**, **8a**, **9a**, **10a** (X = Cl), **11a**, and **12a**. A parallel synthetic route starting with 3,4,5-trimethoxyphenacyl bromide and **6** gave (±)-11-methoxyprotoemetinol (**12c**) *via* the intermediates **7c**, **8c**, **9c**, **10c** (X = I, ClO_4), and **11c**. The trimethyl ether **12c** did not match the O-Me derivative (type **12e**) of natural ankorine. Thus, the formula **4** defines the structure and relative stereochemistry of ankorine.

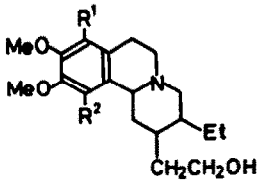
Alangium lamarckii Thw. (family *Alangiaceae*), a medicinal plant indiginous to India, produces a number of fused quinolizidine alkaloids structurally related to the Ipecac alkaloids, e.g. emetine (**1**).[2] Ankorine[3,4] is among them and was assigned the gross structure **2** by Battersby *et al.*[4] largely on the basis of physical measurements. However, the exact location of the phenolic OH group and the stereochemistry of this alkaloid remained to be determined. Szántay *et al.*[5] suggested that the phenolic function of ankorine must be placed at an alternative position, as in the structure **3**, because none of the four possible racemic stereoisomers of **2** that they synthesized matched natural ankorine. In this paper, we record the details of our own synthetic research, which have proved that the structure **4** is a complete expression for ankorine, apart from its absolute configuration. A brief account of the results described here has been published in a preliminary form.[6]

At the inception of the present study, we assumed that ankorine possesses the same stereochemistry in the benzoquinolizidine part as that of emetine (**1**), which also occurs in *A. lamarckii*.[7] Consequently, the target molecule **4** was selected for synthesis with a view to establishing the structure of ankorine. An appropriate form of one of the synthons for the synthesis of (±)-**4** would be ethyl (±)-*trans*-5-ethyl-2-oxo-4-piperidineacetate (**5**), since it already carries the necessary side chains lying trans to each other and the method for its preparation through a highly stereoselective, efficient synthetic route has been established in this laboratory.[8] Yet another advantage of this starting material (**5**) is that its conversion into the key intermediate **9a** would be easily feasible by the "lactim ether method",[9] a helpful device for introducing the phenethyl carbon skeleton onto the nitrogen of a lactam.

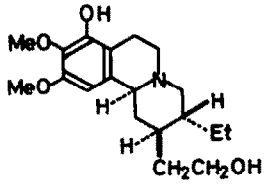
Thus, the lactim ether **6**, obtained from **5** by a method given in the literature,[10,11] was treated with 2-benzyloxy-3,4-dimethoxyphenacyl bromide[12] to give the lactam ketone **7a** in 90% yield. Reduction of **7a** with $NaBH_4$ and hydrogenolysis of the resulting diastereoisomeric mixture of the lactam alcohol **8a** using hydrogen activated on Pd-C catalyst furnished the phenolic lactam **9d** in 94% overall yield. The lactam **9d** was then benzylated with benzyl bromide in boiling acetone in the presence of anhydrous K_2CO_3 and the resulting O-benzyl derivative **9a** (99% yield) was cyclized to **10a** (X = Cl) by the action of $POCl_3$. On catalytic reduction using hydrogen and Adams catalyst, **10a** (X = Cl) afforded the tricycle **11a** in 51% overall yield (from **9a**). That all the chemical operations proceeding from **5** did not affect the stereochemical relationship already established in this starting material and the correctness of the configuration at C-11b in **11a** were supported by the recently reported[11] adaptation of the above reaction sequence to a formal synthesis of (±)-emetine [(±)-**1**] whose stereochemistry has been unequivocally established.[2] This adaptation has been accomplished by means of an initial condensation of **6** with 3,4-dimethoxyphenacyl bromide instead of z-benzyloxy-



1

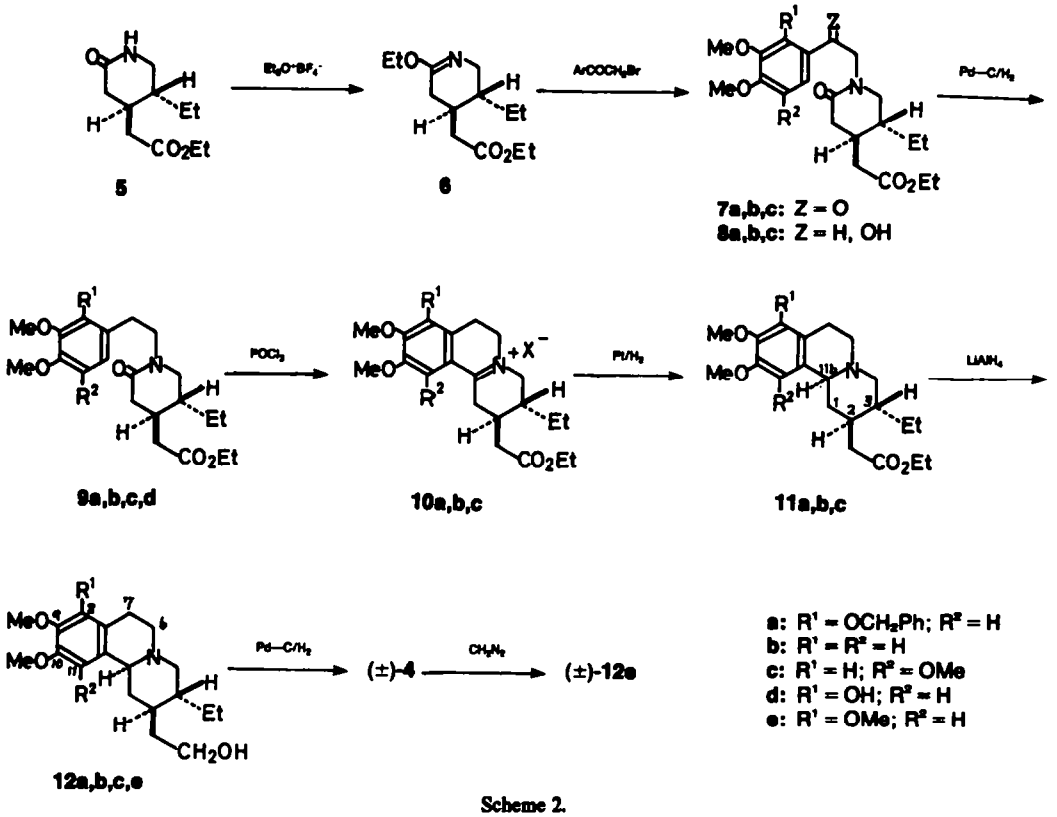


2: R^1 = H; R^2 = OH
3: R^1 = OH; R^2 = H



4

Scheme 1.



Scheme 2.

3,4-dimethoxyphenacyl bromide and succeeding steps proceeding through **7b**, **8b**, **9b**, **10b** (X = ClO_4), and **11b**.[11] The stereochemical outcome and synthetic generality of the "lactim ether method" have also been checked by the recent syntheses of structurally parallel indoloquinolizidine alkaloids[13] and stereoisomers of (±)-2,3-*cis*-emetine.[1]

Conversion of the tricyclic ester **11a** into the alcohol **12a** was effected with LAH in boiling ether. The final step was the debenzylation of **12a** using hydrogen and Pd-C as a catalyst, and the target compound (±)-**4** was obtained in 93% overall yield (from **11a**). The UV, IR (in $CHCl_3$), NMR, and mass spectra and tlc behavior of this compound were identical with those of natural ankorine.[4] The O-Me derivatives (type **12e**) of both samples, prepared by the methylation of the phenols with diazomethane, were also spectroscopically and chromatographically undistinguishable.

On the other hand, a parallel synthetic route (Scheme 2) proceeding from the lactim ether **6** and 3,4,5-trimethoxyphenacyl bromide[12] produced (±)-11-methoxyprotoemetinol [(±)-**12c**] in 34% overall yield (from **6**) *via* **7c**, **8c**, **9c**, **10c** (X = I, ClO_4), and **11c**. The solution ($CHCl_3$) IR and mass spectra and chromatographic behavior of (±)-**12c** did not conform with those of O-methylankorine[4] (type **12e**) derived from natural ankorine.

The results described above have thus identified the structure and relative stereochemistry of ankorine as **4**. Interestingly, ankorine has turned out to be the 8-hydroxy congener of protoemetinol (dihydroprotoemetine) (**12b**), apart from its absolute stereochemistry,[14] which also occurs in *A. lamarckii*.[2,4] After our preliminary communication[6] describing the results of this investigation had been published, the same conclusion followed from another synthetic elaboration of the Hungarian group,[15] whereby (±)-**4** and one of its three possible racemic stereoisomers were prepared.

In conclusion, the present snytheses of (±)-ankorine [(±)-**4**] and (±)-11-methoxyprotoemetinol [(±)-**12c**] have extended the scope of the "lactim ether method" for synthesis of benzo[*a*]quinolizidines to include the highly ring-A-oxygenated analogues. The same synthetic strategy has worked out equally well in the syntheses[16,17] of yet other phenolic *A. lamarckii* alkaloids, alangicine[18] and alangimarckine,[4] and the details will be reported elsewhere at a later date.

EXPERIMENTAL

General. All m.ps are corrected. Unless otherwise stated, the organic solutions obtained after extraction were dried over anhyd Na_2SO_4 and evaporated under reduced pressure. Spectra reported herein were measured with a Hitachi 323 UV spectrophotometer, a JASCO IRA-2 IR spectrophotometer, a JEOL JMS-01SG mass spectrometer, or a JEOL JNM-PS-100 NMR spectrometer at 23° using tetramethylsilane as an internal standard.

Ethyl trans - 1 - (2 - *benzyloxy* - 3,4 - *dimethoxyphenacyl*) - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetate* (**7a**). A soln of **6**[11] (20.4 g, 84.5 mmol) and 2 - benzyloxy - 3,4 - dimethoxyphenacyl bromide[12] (34.0 g, 93.1 mmol) in $HCONMe_2$ (20 ml) was stirred at 60° for 6 hr. For removal of the excess bromide, the mixture was then stirred with pyridine (20 ml) at room temp for 20 hr and evaporated *in vacuo*. 5% HCl aq (160 ml) was added to the oily residue and the mixture was extracted with benzene. The combined benzene extracts were washed successively with 5% HCl aq and H_2O, dried, and evaporated to leave **7a** (37.9 g, 90%) as a pale brown oil, shown to be virtually pure on tlc analysis. A portion of the oil was purified by column chromatography (Al_2O_3, AcOEt–hexane) to give a pale yellow oil, MS *m/e*: 497 (M^+); IR ($CHCl_3$): 1727 (ester C=O), 1679 (C=O), 1633 cm^{-1} (lactam C=O);

NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7 Hz, CCH_2CH_3), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 3.87 and 3.92 (3H each, s, two OMe's), 4.12 (2H, q, J = 7 Hz, OCH_2CH_3), 4.52 and 4.60 (2H, AB type d's, J = 18 Hz, NCH_2COAr), 5.18 (2H, s, OCH_2Ph), 6.77 (1H, d, J = 9 Hz, 5'–H), 7.30–7.60 (5H, m, Ph), 7.59 (1H, d, J = 9 Hz, 6'–H).

Ethyl trans - 1 - (*3,4,5 - trimethoxyphenacyl*) - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetate* (**7c**). A stirred soln of **6**[11] (2.75 g, 11.4 mmol) and 3,4,5 - trimethoxyphenacyl bromide[12] (4.34 g, 15 mmol) in $HCONMe_2$ (2 ml) was kept at 60° for 6 hr. After cooling, the mixture was worked up as described above for **7a**, yielding **7c** (4.55 g, 95%) as a yellowish solid, m.p. 60–66°. Recrystallization from AcOEt–hexane (1:3, v/v) afforded an analytical sample as colorless scales, m.p. 74–75.5° (Found: C, 62.35; H, 7.13; N, 3.21. $C_{22}H_{31}NO_7$ requires: C, 62.69; H, 7.41; N, 3.32%); MS *m/e*: 421 (M^+); IR ($CHCl_3$): 1723 (ester C=O), 1688 (C=O), 1633 cm^{-1} (lactam C=O); NMR ($CDCl_3$) δ: 0.94 (3H, t, J = 7 Hz, CCH_2CH_3), 1.28 (3H, t, J = 7 Hz, OCH_2CH_3), 3.94 (3H, s, OMe), 3.96 (6H, s, two OMe's), 4.18 (2H, q, J = 7 Hz, OCH_2CH_3), 4.76 and 4.86 (2H, AB type d's, J = 18 Hz, NCH_2COAr), 7.32 (2H, s, Ar–H's).

Ethyl trans - 1 - [2 - (2 - *benzyloxy* - 3,4 - *dimethoxyphenyl*) - 2 - *hydroxyethyl*] - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetate* (**8a**). A soln of **7a** (2.75 g, 5.53 mmol) in EtOH (40 ml) was stirred under ice-cooling, and $NaBH_4$ (210 mg, 5.55 mmol) was added portionwise. After stirring was continued at 0° for 3.5 hr, acetone (5 ml) was added and the mixture was concentrated *in vacuo*. Water (20 ml) was added to the residue and the aqueous mixture was extracted with benzene. The benzene soln was washed with H_2O, dried, and evaporated to leave **8a** (2.66 g, 96%) as a colorless solid, m.p. 90–92°, which was presumed to be a mixture of the two possible diastereoisomeric alcohols. Two recrystallizations of the solid from isopropyl ether provided an analytical sample, but of unknown stereochemical purity, as colorless minute needles, m.p. 92–93° (Found: C, 67.49; H, 7.49; N, 2.79. $C_{28}H_{37}NO_7$ requires: C, 67.31; H, 7.47; N, 2.80%); MS *m/e*: 499 (M^+); IR ($CHCl_3$): 3320 (OH), 1726 (ester C=O), 1613 cm^{-1} (lactam C=O); NMR ($CDCl_3$) δ: 0.72 (3H, t, J = 7 Hz, CCH_2CH_3), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 3.91 (6H, s, two OMe's), 4.14 (2H, q, J = 7 Hz, OCH_2CH_3), 4.98 and 5.28 (2H, AB type d's, J = 11 Hz, OCH_2Ph), 5.00–5.20 [2H, m, $CH(OH)Ar$], 6.75 (1H, d, J = 9 Hz, 5'–H), 7.20–7.60 (6H, m, Ph and 6'–H).

Ethyl trans - 1 - [2 - (3,4,5 - *trimethoxyphenyl*) - 2 - *hydroxyethyl*] - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetate* (**8c**). To a stirred, ice-cooled soln of **7c** (2.17 g, 5.15 mmol) in EtOH (30 ml) was added portionwise $NaBH_4$ (195 mg, 5.16 mmol). After stirring at room temp for 1.5 hr, the mixture was worked up as described above for **8a**, giving **8c** (2.18 g, 100%) as a pale yellow, thick oil, MS *m/e*: 423 (M^+); IR ($CHCl_3$): 3320 (OH), 1727 (ester C=O), 1619 cm^{-1} (lactam C=O); NMR ($CDCl_3$) δ: 0.74–0.96 (3H, m, CCH_2CH_3), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 3.84 (3H, s, OMe), 3.89 (6H, s, two OMe's), 4.14 (2H, q, J = 7 Hz, OCH_2CH_3), 4.82–5.06 [1H, m, $CH(OH)Ar$], 6.64 (2H, s, Ar–H's). Although the oil showed a single spot on tlc analysis, it was presumed to be a diastereoisomeric mixture.

Ethyl trans - 1 - (2 - *hydroxy* - 3,4 - *dimethoxyphenethyl*) - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetate* (**9d**). A soln of **8a** (26.0 g, 52 mmol) in EtOH (200 ml) containing 70% $HClO_4$ aq (5.2 ml) was hydrogenated over 10% Pd–C (5.0 g) at atm press and 28° for 4.5 hr. The catalyst was removed by filtration and washed with EtOH. The filtrate and washings were combined and evaporated *in vacuo* to leave a jelly. The residue was partitioned by extraction with a mixture of $CHCl_3$ (300 ml) and H_2O (50 ml). The $CHCl_3$ extracts were washed successively with H_2O, sat $NaHCO_3$ aq, and H_2O, dried, and evaporated to furnish **9d** (20.0 g, 98%) as a colorless solid, m.p. 88–89°, which was recrystallized from AcOEt–hexane (1:2, v/v) to colorless prisms, m.p. 90–91° (Found: C, 64.25; H, 7.99; N, 3.81. $C_{21}H_{31}NO_6$ requires: C, 64.10; H, 7.94; N, 3.56%); MS *m/e*: 393 (M^+); IR ($CHCl_3$): 3535 (OH), 1727 (ester C=O), 1626 cm^{-1} (lactam C=O); NMR ($CDCl_3$) δ: 0.85 (3H, t, J = 6.5 Hz, CCH_2CH_3), 1.27 (3H, t, J = 7 Hz, OCH_2CH_3), 3.84 and 3.90 (3H each, s, two OMe's), 4.14 (2H, q, J = 7 Hz, OCH_2CH_3), 6.41 (1H, d, J = 8.5 Hz, 5'–H), 6.50 (1H, br s, OH), 6.82 (1H, d, J = 8.5 Hz, 6'–H).

Ethyl trans - 1 - (3,4,5 - *trimethoxyphenethyl*) - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetate* (**9c**). A soln of **8c** (2.10 g, 5 mmol) in EtOH (80 ml) containing 70% $HClO_4$ aq (0.8 ml) was hydrogenated over 10% Pd–C (1.5 g) at 4 atm and 50° for 20 hr. The workup of the mixture was carried out in a manner similar to that described above for **9d**. Crude **9c** (1.51 g) thus obtained was then purified by column chromatography [Al_2O_3 (70 g), AcOEt–hexane (3:2, v/v)] to a colorless oil (1.37 g, 68%), MS *m/e*: 407 (M^+); IR ($CHCl_3$): 1726 (ester C=O), 1629 cm^{-1} (lactam C=O); NMR ($CDCl_3$) δ: 0.84 (3H, t, J = 7 Hz, CCH_2CH_3), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 3.83 (3H, s, OMe), 3.88 (6H, s, two OMe's), 4.15 (2H, q, J = 7 Hz, OCH_2CH_3), 6.45 (2H, s, Ar–H's).

Ethyl trans - 1 - (2 - *benzyloxy* - 3,4 - *dimethoxyphenethyl*) - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetate* (**9a**). A stirred mixture of **9d** (5.28 g, 13.4 mmol) and benzyl bromide (2.57 g, 15 mmol) in acetone (60 ml) containing anhyd K_2CO_3 (2.07 g, 15 mmol) was heated under reflux for 18 hr. The solvent was removed by vacuum distillation and the residue was partitioned by extraction with a mixture of benzene (150 ml) and H_2O (30 ml). The benzene extracts were washed with H_2O, dried, and evaporated to leave a thick oil, which was dissolved in pyridine (20 ml). The pyridine soln was heated at 65° for 2 hr and then concentrated *in vacuo*. The residual oil was partitioned by extraction with a mixture of benzene (150 ml) and 3% HCl aq (30 ml). The benzene extracts were washed successively with 3% HCl aq, H_2O, 5% K_2CO_3 aq, and H_2O, dried, and evaporated to leave **9a** (6.43 g, 99%) as a pale yellowish, thick oil, MS *m/e*: 483 (M^+); IR (film): 1728 (ester C=O), 1641 cm^{-1} (lactam C=O); NMR ($CDCl_3$) δ: 0.77 (3H, t, J = 6.5 Hz, CCH_2CH_3), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 3.87 and 3.90 (3H each, s, two OMe's), 4.14 (2H, q, J = 7 Hz, OCH_2CH_3), 5.09 (2H, s, OCH_2Ph), 6.64 (1H, d, J = 8.5 Hz, 5'–H), 6.90 (1H, d, J = 8.5 Hz, 6'–H), 7.24–7.60 (5H, m, Ph).

trans - 8 - *Benzyloxy* - 2 - *ethoxycarbonylmethyl* - 3 - *ethyl* - 1,2,3,4,6,7 - *hexahydro* - 9,10 - *dimethoxybenzo*[a]*quinolizinium chloride* (**10a**: X = Cl). A soln of **9a** (15.5 g, 32 mmol) and $POCl_3$ (24.5 g) in dry toluene (70 ml) was heated at reflux for 2 hr. After cooling, the solvent and $POCl_3$ were removed by vacuum distillation, and the residue was partitioned by extraction with a mixture of $CHCl_3$ (150 ml) and H_2O (50 ml). The $CHCl_3$ extracts were washed with H_2O, dried, and evaporated to leave crude **10a** (X = Cl) (17.8 g) as a dark brown, thick oil. The oil was used directly in the next hydrogenation step without further purification.

trans - 2 - *Ethoxycarbonylmethyl* - 3 - *ethyl* - 1,2,3,4,6,7 - *hexahydro* - 9,10,11 - *trimethoxybenzo*[a]*quinolizinium salt* (**10c**). A soln of **9c** (1.08 g, 2.65 mmol) and $POCl_3$ (2.0 g) in dry toluene (10 ml) was refluxed for 1.5 hr. The solvent and $POCl_3$ were distilled off, and the residue was dissolved in H_2O. The aqueous soln was washed with benzene and then extracted, after addition of KI (8 g), with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated to leave crude **10c** (X = I) (1.33 g, 97%) as a reddish solid, which was recrystallized from AcOEt–EtOH (18:1, v/v) to pale yellow needles, m.p. 106–107° (dec) (Found: C, 50.95; H, 6.38; N, 2.71. $C_{22}H_{32}INO_5$ requires: C, 51.07; H, 6.23; N, 2.71%); UV λ_{max}^{EtOH} 246 nm (shoulder) (log ϵ 4.11), 318 (4.28). The iodide salt was dissolved in hot EtOH and 1 molar equiv of $AgClO_4$ was added. The ppt (AgI) that resulted was filtered off and the filtrate was evaporated *in vacuo* to give **10c** (X = ClO_4) (92% yield) as a brownish solid. Recrystallization of the solid from AcOEt yielded pale yellow needles, m.p. 84–85° (Found: C, 53.71; H, 6.69; N, 3.00. $C_{22}H_{32}ClNO_9$ requires: C, 53.93; H, 6.58; N, 2.86%); UV λ_{max}^{EtOH} 246.5 nm (log ϵ 4.03), 319 (4.22).

Ethyl (±) - 8 - *benzyloxy* - 3*α* - *ethyl* - 1,3,4,6,7,11b*α* - *hexahydro* - 9,10 - *dimethoxy* - 2H - *benzo*[a]*quinolizine* - 2*β* - acetate (**11a**). The total amount of crude **10a** (X = Cl) described above was dissolved in EtOH (100 ml) and the soln was hydrogenated over Adams catalyst (250 mg) at atm press and 20° for 2 hr. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to leave a reddish brown oil, to which cold 5% NaOH aq (80 ml) was added. The mixture was extracted with benzene and the benzene extracts were washed with H_2O, dried over anhyd K_2CO_3 for 2 hr, and evaporated to leave a dark red oil (13.1 g). The oil was purified, without delay, by column chromatography [Al_2O_3, AcOEt–hexane (3:1, 2:1, v/v)] to produce **11a** (7.58 g, 51% yield from **9a**) as an unstable orange oil, IR ($CHCl_3$):

2804, 2760 (*trans* - quinolizidine ring[19]), 1726 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ: 0.92 (3H, t, J = 6.5 Hz, CCH_2CH_3), 1.30 (3H, t, J = 7 Hz, OCH_2CH_3), 3.84 and 3.88 (3H each, s, two OMe's), 4.18 (2H, q, J = 7 Hz, OCH_2CH_3), 5.00 (2H, s, OCH_2Ph), 6.53 (1H, s, 11-H), 7.20–7.60 (5H, m, Ph). When exposed to air, the oil became dark red within several hr, producing a resinous substance insoluble in ether.

Ethyl (±) - 3α - *ethyl* - 1,3,4,6,7,11bα - *hexahydro* - 9,10,11 - *trimethoxy* - 2H - *benzo*[a]*quinolizine* - 2β - *acetate* (11c). A soln of 10c (X = ClO_4) (1.09 g, 2.2 mmol) in EtOH (50 ml) was hydrogenated over Adams catalyst (200 mg) at atm press and 15° for 3 hr. The mixture was worked up in a manner similar to that described above for 11a, giving 11c [570 mg, 66% yield from 10c (X = ClO_4)] as a yellow oil, MS *m/e*: 391 (M^+); IR ($CHCl_3$): 2840, 2760 (*trans* - quinolizidine[19]), 1721 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 6.5 Hz, CCH_2CH_3), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 3.85 (6H, s, two OMe's), 3.89 (3H, s, OMe), 4.16 (2H, q, J = 7 Hz, OCH_2CH_3), 6.40 (1H, s, 8-H). The oil turned red on exposure to air.

(±) - 8 - *Benzyloxy* - 3α - *ethyl* - 1,3,4,6,7,11bα - *hexahydro* - 9,10 - *dimethoxy* - 2H - *benzo*[a]*quinolizine* - 2β - *ethanol* (12a). To a stirred, ice-cooled suspension of LAH (293 mg, 7.72 mmol) in dry ether (20 ml) was added dropwise a soln of 11a (1.80 g, 3.85 mmol) in dry ether (20 ml) over a period of 30 min. After the mixture had been heated under reflux for 4 hr, H_2O (0.3 ml), 10% NaOH aq (0.3 ml), and H_2O were successively added under ice-cooling. The supernatant ethereal soln was separated from the resulting insoluble inorganic materials by decantation, dried over K_2CO_3, and evaporated *in vacuo* to leave 12a (1.56 g, 95%) as a pale yellow oil, MS *m/e*: 425 (M^+); IR ($CHCl_3$): 3636 (OH), 2812, 2760 cm^{-1} (*trans* - quinolizidine); NMR ($CDCl_3$) δ: 0.91 (3H, t, J = 6.5 Hz, CH_2CH_3), 1.83 (1H, s, OH), 3.87 (6H, s, two OMe's), 3.64–3.91 (2H, m, CH_2CH_2OH), 5.01 (2H, s, OCH_2Ph), 6.56 (1H, s, 11-H), 7.20–7.60 (5H, m, Ph). The oil gradually became red on exposure to air.

(±) - 3α - *Ethyl* - 1,3,4,6,7,11bα - *hexahydro* - 9,10,11 - *trimethoxy* - 2H - *benzo*[a]*quinolizine* - 2β - *ethanol* [(±) - 11 - *methoxyprotoemetinol*] (12c). The ester 11c was reduced with LAH as described above for 12a, and 12c was obtained in 90% yield as a pale yellow, thick oil, MS *m/e* (rel. int.): 349 (M^+) (100), 348 (58), 334 (11), 320 (15), 318 (15), 304 (18), 302 (6), 276 (88), 235 (97), 221 (61), 206 (15); IR ($CHCl_3$): 3630 (OH), 2832, 2800, 2750 cm^{-1} (*trans*-quinolizidine); NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.5 Hz, CH_2CH_3), 2.06 (OH), 3.84 (6H, s, two OMe's), 3.88 (3H, s, OMe), 6.40 (1H, s, 8-H). The IR ($CHCl_3$), NMR, and mass spectra and tlc behavior of this sample did not match those of O - methylankorine (see below).

(±) - 3α - *Ethyl* - 1,3,4,6,7,11bα - *hexahydro* - 8 - *hydroxy* - 9,10 - *dimethoxy* - 2H - *benzo*[a]*quinolizine* - 2β - *ethanol* [(±) - *ankorine*] (4). A soln of 12a (1.44 g, 3.38 mmol) in EtOH (40 ml) was hydrogenated over 10% Pd–C (500 mg) at atm press and 20° for 35 min. Removal of the catalyst, concentration of the filtrate gave (±) - 4 (1.11 g, 98%) as a colorless solid, m.p. 198–201°, which was recrystallized from acetone to colorless prisms, m.p. 200–202° (lit.[15] m.p. 192.5°) (Found: C, 68.04; H, 8.84; N, 4.30. $C_{19}H_{29}NO_4$ requires: C, 68.03; H, 8.71; N, 4.18%); IR ($CHCl_3$): 3630, 3530 (OH), 2800, 2750 cm^{-1} (*trans*-quinolizidine); UV λ_{max}^{EtOH} 273 nm (log ε 2.98); $\lambda_{max}^{H_2O}$ (pH 13) 287 (3.36); NMR ($CDCl_3$) δ: 0.91 (3H, t, J = 6.5 Hz, CH_2CH_3), 3.84 and 3.87 (3H each, s, two OMe's), 5.90 (br, OH's), 6.33 (1H, s, 11-H); MS *m/e* (rel. int.): 335 (M^+) (79), 334 (100), 320 (32), 318 (43), 306 (10), 304 (8), 290 (15), 278 (14), 262 (65), 248 (9), 221 (54), 207 (53). The UV, IR ($CHCl_3$), NMR, and mass spectra and tlc behavior of this sample were identical with those of a natural sample of ankorine (m.p. 175–177°) kindly provided by Professor Battersby.[4]

(±) - 3α - *Ethyl* - 1,3,4,6,7,11bα - *hexahydro* - 8,9,10 - *trimethoxy* - 2H - *benzo*[a]*quinolizine* - 2β - *ethanol* [(±) - O - *methylankorine*] (12e). To a soln of (±) - 4 (5.0 mg, 0.015 mmol) in MeOH (1 ml) was added an ethereal soln (*ca* 0.1 M, 10 ml) of diazomethane, and the mixture was kept at room temp for 18 hr. After the excess of diazomethane had been destroyed by addition of AcOH, the soln was evaporated *in vacuo*. To the residue was added 5% NaOH aq (5 ml) and the mixture was extracted with ether. The ether extracts were washed with H_2O, dried, and evaporated to leave a yellow oil (4.3 mg), which was chromatographed on a 5-g silica gel column using $CHCl_3$ as eluent. Evaporation of the eluate afforded (±) - 12e (3.6 mg, 68%) as an unstable, yellow oil, IR ($CHCl_3$): 3630 (OH), 2756 cm^{-1} (*trans*-quinolizidine); MS *m/e* (rel. int.): 349 (M^+) (75), 348 (100), 334 (21), 320 (10), 318 (70), 304 (18), 302 (24), 276 (51), 235 (48), 221 (48), 206 (26). The IR ($CHCl_3$) and mass spectra and tlc behavior of this specimen were identical with those of O-methylankorine prepared from natural (−) - ankorine[4] in a similar manner.

Acknowledgments—We are grateful to Professor A. R. Battersby and Dr. R. S. Kapil (Cambridge) for a valuable supply of ankorine, to Professors S. Sugasawa (Tokyo) and Y. Ban (Sapporo) for their interest and encouragement, and to the Ministry of Education, Science and Culture, Japan, for financial support in the form of a Grant-in-Aid for Special Project Research.

REFERENCES

[1]Paper III in this series, T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* **27**, 2497 (1979).

[2]For reviews, see [a]H. T. Openshaw, *Chemistry of the Alkaloids* (Edited by S. W. Pelletier), pp. 85–115. Van Nostrand, New York (1970); [b]A. Brossi, S. Teitel and G. V. Parry, *The Alkaloids* (Edited by R. H. F. Manske), Vol. XIII, pp. 189–212. Academic Press, New York (1971).

[3]B. Dasgupta, *J. Pharm. Sci.* **54**, 481 (1965).

[4]A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant and S. S. Salgar, *Tetrahedron Letters* 4695 (1966).

[5]C. Szántay, E. Szentirmay and L. Szabó, *Ibid.* 3725 (1974).

[6]T. Fujii, S. Yoshifuji and K. Yamada, *Ibid.* 1527 (1975).

[7]H. Budzikiewicz, S. C. Pakrashi and H. Vorbrüggen, *Tetrahedron* **20**, 399 (1964).

[8]T. Fujii, S. Yoshifuji and M. Ohba, *Chem. Pharm. Bull.* **26**, 645 (1978), and earlier refs cited.

[9a]T. Fujii, S. Yoshifuji and K. Yamada, *Chem. & Ind.* 177 (1975); [b]*Chem. Pharm. Bull.* **26**, 2071 (1978).

[10]M. Uskoković, C. Reese, H. L. Lee, G. Grethe and J. Gutzwiller, *J. Am. Chem. Soc.* **93**, 5902 (1971).

[11]T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* **27**, 1486 (1979).

[12]T. Fujii, S. Yoshifuji and M. Ohba, *Ibid.* **26**, 3218 (1978).

[13]T. Fujii, S. Yoshifuji and H. Ito, *Heterocycles* **7**, 149 (1977).

[14]For the absolute configuration of ankorine, see S. Yoshifuji and T. Fujii, *Tetrahedron Letters* 1965 (1975).

[15]C. Szántay, E. Szentirmay, L. Szabó and J. Tamás, *Chem. Ber.* **109**, 3420 (1976).

[16]T. Fujii, K. Yamada, S. Yoshifuji, S. C. Parkrashi and E. Ali, *Tetrahedron Letters* 2553 (1976).

[17]T. Fujii, S. Yoshifuji and H. Kogen, *Ibid.* 3477 (1977).

[18]S. C. Pakrashi and E. Ali, *Ibid.* 2143 (1967).

[19a]F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958); [b]E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.* **78**, 6417 (1956).