Chem. Pharm. Bull. 23(9)2048—2053(1975) UDC 547.94.057 : 547.833.04

Studies on Tetrahydroisoquinolines. IX.[1] The Synthesis of (±)-Domesticine and a Related (±)-Homoaporphine *via* *p*-Quinol Acetates

Osamu Hoshino, Hiroshi Hara, Nobuaki Serizawa, and Bunsuke Umezawa

Faculty of Pharmaceutical Sciences, Science University of Tokyo[2]

(Received January 25, 1975)

Acid (conc. H_2SO_4–Ac_2O) treatment of the *p*-quinol acetate derived from (±)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methyl-1-(3′,4′-methylenedioxy-benzyl or -phenethyl)-isoquinoline (VIII or IX) gave the corresponding 1-monoacetoxy- and 1,4-diacetoxy-aporphine (XIX, XXa, and XXb) or -homoaporphine (XXIII and XXIV), respectively. Hydrolysis of XIX afforded (±)-domesticine (VI).

Previously, we described that the lead tetraacetate [$Pb(OAc)_4$] oxidation followed by acid (conc. H_2SO_4–Ac_2O) treatment of (±)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (I, II or III) bearing an activated benzyl or phenethyl group at the 1-position of the isoquinoline afforded readily an aporphine[3] or homoaporphine,[4] and that the novel synthesis of (±)-thaliporphine (IV)[5] or (±)-kreysigine (V)[6] was achieved. In these cases, the benzyl or phenethyl group was activated by methoxyl. For exploring the scope of the reaction, hence, we turned our attention to the activating effect of methylenedioxy instead of methoxyl group. Accordingly, we chose (±)-domesticine (VI)[7,8,9] and a related (±)-homoaporphine (VII) as the target and accomplished the synthesis of VI and VII.

The starting material, (±)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methyl-1-(3′,4′-methylenedioxy-benzyl or -phenethyl)isoquinoline (VIII or IX) was prepared as follows. For the synthesis of the former (VIII), the cyclization (Bischler-Napieralski reaction) of N-β-(4-benzyloxy-3-methoxyphenyl)ethyl-3′,4′-methylenedioxyphenylacetamide (X) derived from the phenethylamine and methyl 3,4-methylenedioxyphenylacetate[10] afforded the 3,4-dihydroisoquinoline hydrochloride (XI·HCl), mp 208.5—210°, whose neutralization followed by its methylation with methyl iodide gave a methiodide (XII), mp 186—188°. Sodium borohydride ($NaBH_4$) reduction of the methiodide (XII) yielded a (±)-tetrahydroisoquinoline

---

1) Part VIII: O. Hoshino, K. Ohyama, M. Taga, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 2587 (1974).

2) Location: *12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*

3) O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Commun.*, **1971**, 1533; *idem*, *Chem. Pharm. Bull.* (Tokyo), **22**, 1302 (1974).

4) O. Hoshino, T. Toshioka, and B. Umezawa, *J. C. S. Chem. Commun.*, **1972**, 740; *idem*, *Chem. Pharm. Bull.* (Tokyo), **22**, 1307 (1974).

5) M. Shamma and W.A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967); R.J. Spangler and D.C. Boop, *Tetrahedron Letters*, **1971**, 4851; T. Kametani, S. Shibuya, and S. Kano, *J. Chem. Soc. Perkin I*, **1973**, 1212; S.M. Kupchan and P.F.O Brien, *J. C. S. Chem. Commun.*, **1973**, 915.

6) A.R. Battersby, R.B. Bradbury, R.B. Herbert, M.H.G. Munro, and R. Ramage, *Chem. Commun.*, **1967**, 450; T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc.*, (*C*), **1971**, 1923; T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **36**, 3733 (1971).

7) T. Kametani, K. Fukumoto, and T. Sugahara, *Tetrahedron Letters*, **1968**, 5459; *idem*, *J. Chem. Soc.*, (*C*), **1969**, 801; S.V. Kessar, S. Batra, and S.S. Gandhi, *Indian J. Chem.*, **1970**, 468.

8) T. Kametani, S. Shibuya, H. Sugi, O. Kusama, and K. Fukumoto, *J. Chem. Soc.*, (*C*), **1971**, 2446; T. Kametani, S. Shibuya, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Chem. Soc.*, (*C*), **1971**, 2712.

9) S.M. Kupchan and A.J. Liepa, *J. Amer. Chem. Soc.*, **95**, 4062 (1973).

10) F.W. Semmler and K. Bartelt, *Ber.*, **41**, 2752 (1908).

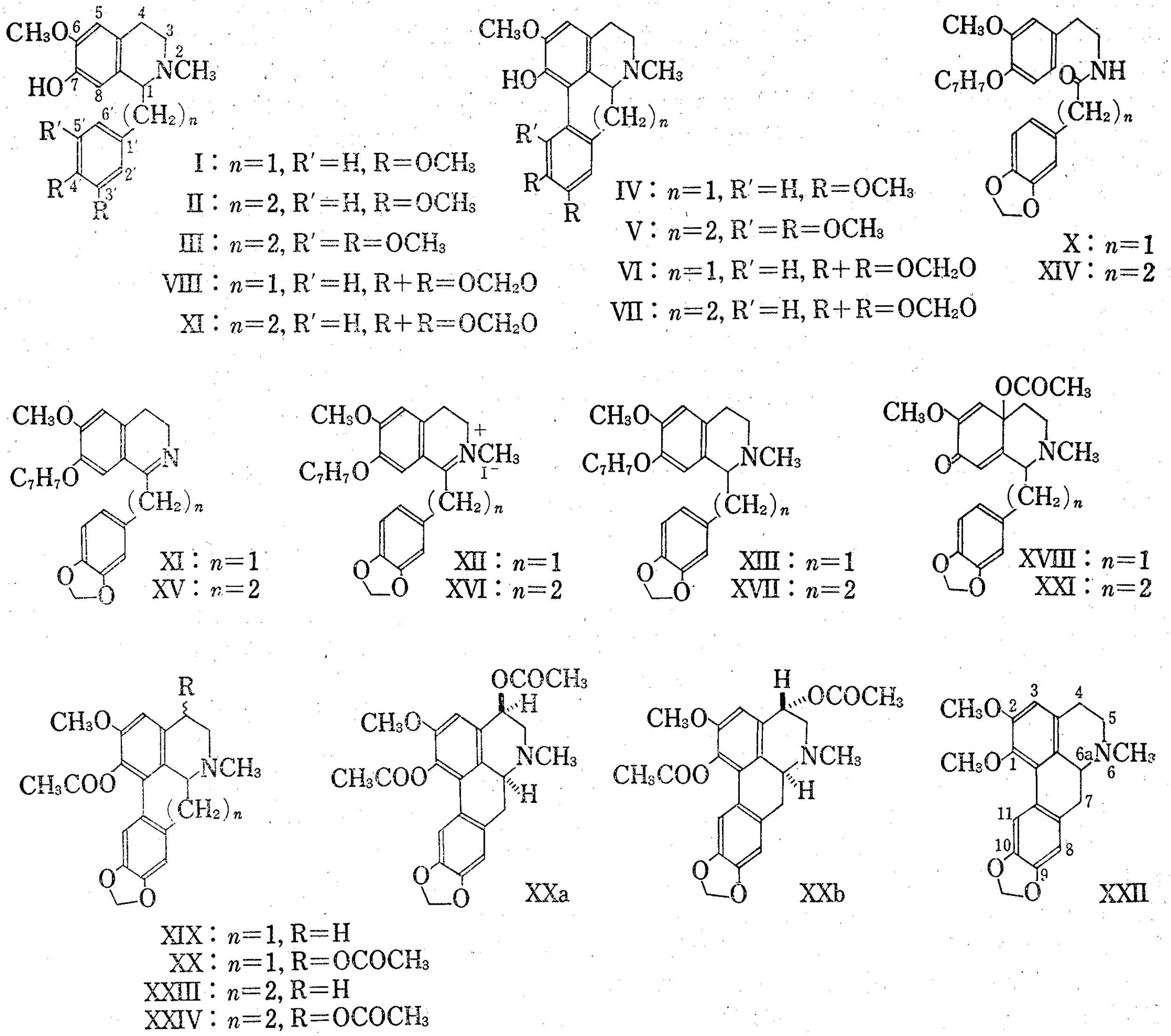

Chart 1

(XIII) as an oil, whose debenzylation by catalytic hydrogenolysis produced the phenolic (±)-tetrahydroisoquinoline (VIII), mp 116—117°.

As to the formation of the latter (IX), the similar sequence of reaction of N-β-(4-benzyloxy-3-methoxyphenyl)ethyl-3',4'-methylenedioxyphenylpropionamide (XIV) derived from the amine and the methyl propionate[11] was carried out yielding the phenolic (±)-tetrahydroisoquinoline (IX) as an oil.

A solution of the phenolic (±)-base (VIII) in acetic acid (AcOH) was treated with 2.1 eq of Pb(OAc)$_4$ at room temperature for 20 min and usual work-up of the reaction mixture gave a p-quinol acetate (XVIII), whose infrared (IR) spectrum showed characteristic absorption bands due to an acetoxyl group at 1740 cm^{-1} and to a dienone grouping at 1680, 1650 and 1630 cm^{-1}. Subsequent treatment of the crude p-quinol acetate (XVIII) with conc. H$_2$SO$_4$–Ac$_2$O at room temperature for 1 hr gave, after purification of the reaction mixture by preparative thin-layer chromatography (TLC) over silica gel, three kinds of products (A, B and C).

---

[11] Reduction of 3,4-methylenedioxycinnamic acid with Raney nickel in 10% aq. NaOH at 23—26° afforded the corresponding phenylpropionic acid in good yield, while the similar reaction at 80—88° produced m-hydrophenylpropionic acid (*cf.* E. Schwenk and D. Papa, *J. Org. Chem.*, **10**, 232 (1945)].

IR spectrum of the product (A), mp 157—158°, isolated from the most polar part, showed an absorption band due to an aromatic acetoxyl group at 1760 cm^{-1} and its nuclear magnetic resonance (NMR) spectrum exhibited three aromatic protons at δ 6.58, 6.69 and 7.39. Hence, the structure of the product (A) was proved to be (±)-1-acetoxy-2-methoxy-6-methyl-9,10-methylenedioxyaporphine (XIX) on the basis of the spectral data as noted above and elemental analysis.

The product (B), mp 197—197.5°, and (C), mp 204—206°, which were isolated from the less and the least polar part, respectively, had the same molecular formula ($C_{23}H_{23}O_7N$) as supported by their mass spectra [*m/e*: 425 (M^+)] and elemental analyses. Their IR spectra showed absorption bands due to an aromatic acetoxyl group at 1770 cm^{-1} and an aliphatic acetoxyl at 1735 or 1740 cm^{-1}. Accordingly, structures of the product (B) and (C) appeared to be diasteromeric (±)-1,4-diacetoxy-2-methoxy-6-methyl-9,10-methylenedioxyaporphines (XX). The product (A), (B) and (C) were obtained in 18, 4.7 and 5.5% yield, respectively.

The stereochemical feature of the last two product (B) and (C) was confirmed as follows. Namely, NMR spectrum of the former (B) exhibited one proton broad triplet$^{12)}$ (a half-band width of 5.0 Hz) at δ 5.93 for the 4-hydrogen, while that of the latter (C) showed one proton double doublets (J=6.25, 10 Hz) centered at δ 6.13 for the 4-hydrogen. From the spectral data and by inspection of a Dreiding model, it was deduced that in the former the 4- and 6a-hydrogens were *cis*, while in the latter *trans*. Accordingly, the stereochemical structures of the product (B) and (C) were assigned to be XXa and XXb, respectively, provided that the 6a-hydrogen in aporphine skeleton was α oriented.

Hydrolysis of the (±)-1-acetoxyaporphine (IXX) with 4N HCl in dioxane afforded (±)-domesticine (VI), mp 186—187°, which was identical with an authentic sample$^{8)}$ by comparison of each NMR spectrum. Furthermore, methylation of (±)-domesticine (VI) with diazomethane in methanol (CH_3OH) produced (±)-nantenine (XXII),$^{13)}$ mp 140—142°.

Analogously, the treatment of the phenolic (±)-1-phenethylisoquinoline (IX) with 2 eq of the oxidant in AcOH at room temperature for 25 min furnished an oily *p*-quinol acetate (XXI) as revealed by its IR spectrum (1740, 1665, 1645 and 1630 cm^{-1}). Immediate treatment of the crude *p*-quinol acetate (XXI) with conc. H_2SO_4–Ac_2O under ice-cooling gave an oily product, which was subjected to column chromatography over silica gel. The first eluate with benzene (C_6H_6)–CH_3OH (100: 1) afforded a brown oil, which was purified on a preparative TLC producing a diastereomeric mixture of (±)-1,4-diacetoxyhomoaporphine (XXIV), mp 180—192°, in 0.8% yield. The structure of XXIV was confirmed by its IR spectrum [1770 (aromatic-$OCOCH_3$) and 1730 cm^{-1} (aliphatic-$OCOCH_3$)] and elemental analysis. The second eluate with C_6H_6–CH_3OH (100: 1)–(20: 1) furnished an amorphous mass, which was recrystallized from *n*-hexane to give (±)-1-acetoxyhomoaporphine (XXIII), mp 137—140°, in 15.6% yield. Its structure was supported by the spectral data (IR and NMR) and elemental analysis.

Thus, it was proved that a homoaporphine (XXIII) was formed readily.

Hydrolysis of (±)-1-acetoxyhomoaporphine (XXIII) with 5% aq. potassium carbonate in CH_3OH produced (±)-1-hydroxy-2-methoxy-6-methyl-10,11-methylenedioxyhomoaporphine (VII), mp 139—141°, in 80% yield.

Thus, it was found that the activation of benzyl or phenethyl by methylenedioxy group was powerful enough to bring about the desired ring-closure and that the group suffered practically no change in the reaction. Therefore, the present reaction would be a useful supplement for synthesizing aporphine or homoaporphine alkaloids. Mechanistic pathway on formation of XXa, XXb and XXIV was obscure.

---

12) *Cf.* I. Ribas, J. Sueiras, and L. Castedo, *Tetrahedron Letters*, **1972**, 2033.
13) Z. Kitasato and H. Shishido, *Ann.*, **527**, 176 (1937).

Experimental[14)]

N-β-(4-Benzyloxy-3-methoxyphenyl)ethyl-3′,4′-methylenedioxyphenylacetamide (X)——A mixture of the phenethylamine (11.7 g) [freed from its oxalate (15 g)] and methyl 3,4-methylenedioxyphenylacetate[10)] (8.9 g) was heated under slightly reduced pressure (water aspirator) at 160° (bath tempt.) for 5 hr. On cooling, the resultant crystalline mass was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 5% HCl and brine, and dried over $MgSO_4$. Removal of the solvent gave an amide (X) (12.9 g, 71.3%), mp 127—129°, which was recrystallized from CH_3OH to give colorless prisms, mp 130—131°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3420 (=NH), 1660 (CONH–). *Anal.* Calcd. for $C_{25}H_{25}O_5N$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.73; H, 6.00; N, 3.28.

7-Benzyloxy-3,4-dihydro-6-methoxy-1-(3′,4′-methylenedioxybenzyl)isoquinoline Hydrochloride (XI·HCl)——A mixture of the amide (X) (5 g) and $POCl_3$ (5 ml) in anhydrous $CHCl_3$ (50 ml) was gently refluxed for 2 hr. Removal of the solvent under reduced pressure gave a crystalline mass, which was washed well with petr. ether to afford the crude 3,4-dihydroisoquinoline hydrochloride (XI·HCl) (4.6 g, 88%), mp 205—207°. Recrystallization from CH_3OH furnished pale yellow needles, mp 208.5—210°. IR[15)] $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1640 ($\mathrm{C{=}\overset{+}{N}H-}$). *Anal.* Calcd. for $C_{25}H_{24}O_4NCl$: C, 68.56; H, 5.52; N, 3.20. Found: C, 68.75; H, 5.51; N, 3.01.

7-Benzyloxy-3,4-dihydro-6-methoxy-2-methyl-1-(3′,4′-methylenedioxybenzyl)isoquinolinium Iodide (XII)——A solution of the 3,4-dihydroisoquinoline (XI) (4.6 g) [freed from the hydrochloride (XI·HCl) (5 g)] and CH_3I (40 ml) in CH_3OH (150 ml) was gently refluxed for 2 hr. The reaction mixture was condensed under reduced pressure giving a methiodide (XII) (5.3 g, 85%), mp 184—187°, which was recrystallized from CH_3OH to give yellow prisms, mp 186—188°. *Anal.* Calcd. for $C_{26}H_{26}O_4NI$: C, 57.40; H, 4.79; N, 2.54. Found: C, 57.69; H, 4.84; N, 2.68.

(±)-7-Benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-(3′,4′-methylenedioxybenzyl)isoquinoline (XIII)——To an ice-cooled, stirred suspension of the methiodide (XII) (4.17 g) in CH_3OH (80 ml) was added $NaBH_4$ (1.6 g) over a period of 1.5 hr. The reaction mixture gradually became clear as the metal hydride was added. After 2.5 hr's stirring at room tempt. the reaction mixture was gently refluxed for 1 hr. To the residue obtained on removal of the solvent under reduced pressure was added H_2O and the product was taken up in ether. The ether extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave an oil (XIII) (2.7 g, 89%). NMR δ: 2.49 (3H, s, NCH_3), 3.81 (3H, s, OCH_3), 4.85 (2H, s, $OCH_2C_6H_6$), 5.87 (2H, s, OCH_2O). Methiodide, mp 209—211° (CH_3OH–iso-C_3H_7OH). *Anal.* Calcd. for $C_{27}H_{30}O_4NI$: C, 57.96; H, 5.40; N, 2.53. Found: C, 57.81; H, 5.30; N, 2.54.

(±)-1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-methyl-1-(3′,4′-methylenedioxybenzyl)isoquinoline (VIII)——A mixture of the benzyloxyisoquinoline (XIII) (3.39 g), 2% aq. $PdCl_2$ (10 ml) and active carbon (1.5 g) in CH_3OH (300 ml) was shaken in an atmosphere of H_2 at room tempt., until uptake of H_2 ceased. After filtration of the catalyst, removal of the solvent under reduced pressure afforded an oil, which was dissolved in 10% aq NaOH. The alkaline solution was washed with ether and treated with NH_4Cl (solid) to give the phenolic base. The product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over K_2CO_3. Removal of the solvent furnished an oil (2.7 g), which was recrystallized from ether yielding colorless prisms (VIII) (2.1 g, 78.9%), mp 115—116°, and an analytical sample had mp 116—117°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3530 (–OH). NMR δ: 2.40 (3H, s, NCH_3), 3.61 (1H, t, $J=6.25$ Hz, 1-H), 3.78 (3H, s, OCH_3), 5.84 (2H, s, OCH_2O), 6.37 (1H, s, arom. H), 6.50—6.70 (4H, m, arom. H). *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.48; H, 6.49; N, 4.35.

Methyl 3,4-Methylenedioxyphenylpropionate——To a stirred solution of 3,4-methylenedioxycinnamic acid[16)] (10 g) in 5% aq. NaOH (1.65 liters) was added at 23—26° Raney nickel (10 g) over a period of 2 hr. The mixture was stirred at room tempt. for 1 hr. The filtrate obtained on filtration of Raney nickel was acidified with conc. HCl. The product was taken up in ether (2.5 liters). The ether extract was washed with brine and dried over $MgSO_4$. Removal of the solvent gave an acid (6.9 g, 69%) as colorless needles, mp 82—85° (lit.[17)] mp 87—88°). A solution of the acid (6.7 g) and conc. H_2SO_4 (1.3 ml) in anhydrous CH_3OH was refluxed for 4 hr. The mixture was condensed under reduced pressure and poured into ice-water. The product was taken up in ether. The ether extract was washed with 5% aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of

---

[14)] All melting points were uncorrected and measured on a Büchi melting point measuring apparatus. NMR spectra were taken with a JEOL Model JNR-4H-100 spectrometer (100 MHz) in $CDCl_3$ solution (5—10%) by using $(CH_3)_4Si$ as internal standard. Following abbreviations were used; s: singlet; dd: double doublets; t: triplet; bs: broad singlet; bt: broad triplet; m: multiplet. IR spectra were run on a Hitachi Model 215 spectrometer, unless otherwise noted. Mass spectra were measured with a Hitachi Model RMU-6E mass spectrometer, unless otherwise noted. Preparative thin-layer chromatographies were performed over Silica gel GF_{254} (Merck) with C_6H_6–CH_3OH–$CH_3COOC_2H_5$ (6: 1: 0.5) as developing solvent.

[15)] A. Hitachi Model 225 spectrometer was used.

[16)] R.D. Hawarth, W.H. Perkin, Jr., and J. Rankin, *J. Chem. Soc.*, **125**, 1693 (1924).

[17)] W.H. Perkin, Jr. and R. Robinson, *J. Chem. Soc.*, **91**, 1084 (1907).

the solvent gave an oil (6.0 g), which was fractionally distilled under reduced pressure to give the ester (5.62 g, 79%), bp 114—126° (3 mmHg). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1740 ($-COOCH_3$).

N-β-(4-Benzyloxy-3-methoxyphenyl)ethyl-3′,4′-methylenedioxyphenylpropionamide (XIV)——A mixture of the phenethylamine (8.7 g) [freed from its oxalate (12 g)] and the ester (7.6 g) was heated under slightly reduced pressure (water aspirator) for 6 hr. After cooling, the reaction mixture was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 5% HCl and brine, and dried over $MgSO_4$. Removal of the solvent gave an amide (XIV) (14.2 g, 97%), mp 123—126°, which was recrystallized fron CH_3OH to furnish colorless prisms, mp 134—135°, and an analytical sample had the same mp. IR15) $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3290 (=NH), 1630 (CONH–). *Anal.* Calcd. for $C_{26}H_{27}O_5N$: C, 72.04; H, 6.28; N, 3.23. Found: C, 71.94; H, 6.28; N, 3.16.

7-Benzyloxy-3,4-dihydro-6-methoxy-2-methyl-1-(3′,4′-methylenedioxyphenethyl)isoquinolinium Iodide (XVI)——A solution of the amide (XIV) (5 g) and $POCl_3$ (5 ml) in anhydrous $CHCl_3$ (50 ml) was refluxed for 3 hr. Removal of the solvent under reduced pressure gave an oil, which was washed well with petr. ether to afford an hydrochloride (XV·HCl) (5 g. 96%), mp 104—114°. Repeated recrystallization from CH_3OH–iso–C_3H_7-OH gave yellow needles, mp 170—171.5°. *Anal.* Calcd. for $C_{26}H_{26}O_4NCl$: C, 69.09; H, 5.80; N, 3.12. Found: C, 69.17; H, 5.69; N, 2.88. A solution of the free base (XV) (2.6 g) [freed from the hydrochloride (XV·HCl) (3.2 g)] and CH_3I (5.2 ml) in CH_3OH (20 ml) was heated at 60° for 3 hr. Removal of the solvent under reduced pressure gave an amorphous mass (3 g), which was recrystallized from CH_3OH–iso-C_3H_7OH to produce a methiodide (XVI) (2 g, 57.3% from XV), mp 164—167°, and an analytical sample had mp 166—167.5°. *Anal.* Calcd. for $C_{27}H_{28}O_4NI$: C, 58.17; H, 5.06; N, 2.53. Found: C, 58.45; H, 5.06; N, 2.24.

(±)-7-Benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-(3′,4′-methylenedioxyphenethyl)isoquinoline (XVII)——To an ice-cooled, stirred suspension of the methiodide (XVI) (2 g) in CH_3OH (40 ml) was added portionwise $NaBH_4$ (0.74 g) over a period of 30 min and the reaction mixture was stirred at room tempt. for 1 hr. To a residue obtained on removal of the solvent under reduced pressure was added H_2O and the product was taken up in ether. The ether extract was washed with brine and dried over K_2CO_3. Removal of the solvent gave (±)-tetrahydroisoquinoline (XVII) (1.5 g, 97%) as an oil. NMR δ: 2.44 (3H, s, NCH_3), 3.82 (3H, s, OCH_3), 5.09 (2H, s, $OCH_2C_6H_6$). Methiodide, mp 110—113° (CH_3OH–iso-C_3H_7OH). *Anal.* Calcd. for $C_{28}H_{32}O_4NI$: C, 58.64, H, 5.63; N, 2.44. Found: C, 58.21; H, 6.11; N, 2.38.

(±)-1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-methyl-1-(3′,4′-methylenedioxyphenethyl)isoquinoline (IX)——A mixture of the benzyloxyisoquinoline (XVII) (1.5 g), 2% aq. $PdCl_2$ (2.6 ml), conc. HCl (0.8 ml) and active carbon (0.21 g) in AcOH (150 ml) was shaken in an atmosphere of H_2 at room tempt. until uptake of H_2 ceased. The mixture was filtered and the filtrate was diluted with H_2O. The solution was basified with conc. NH_4OH and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over $MgSO_4$. Removal of the solvent gave a (±)-phenolic isoquinoline (IX) (1.2 g, 99%) as an oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3550 (–OH). Picrolonate, mp 205—208° (C_2H_5OH). *Anal.* Calcd. for $C_{30}H_{31}O_9N_5$: C, 59.50; H, 5.16; N, 11.57. Found: C, 59.34; H, 5.28; N, 11.34.

$Pb(OAc)_4$ Oxidation and Acid Treatment of VIII——To a water-cooled, stirred solution of the phenolic isoquinoline (VIII) (2.35 g, 7.2 mmoles) in AcOH (144 ml) was added in one portion $Pb(OAc)_4$ (6.65 g, 15 mmoles) and stirring was continued at room tempt. for 20 min. The reaction mixture was poured into crashed ice and carefully basified with $NaHCO_3$ (powder). The product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over $MgSO_4$. Removal of the solvent gave an amorphous mass (2.29 g)[IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1740 ($-OCOCH_3$), 1680, 1650, 1630 (dienone)]. To an ice-cooled, stirred solution of the crude *p*-quinol acetate (XVII) (2.29 g) in Ac_2O (14 g) was added a cold mixture of conc. H_2SO_4 (1.2 g) in Ac_2O (2.4 g) over a period of 5 min. The reaction mixture was stirred at room tempt. for 1 hr and then poured into crashed ice. The acidic solution was washed with ether and basified with $NaHCO_3$ (powder). The product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over $MgSO_4$. Removal of the solvent gave an amorphous mass (1.4 g), which was subjected to preparative TLC yielding three kinds of products. Elution of an absorbent corresponding to the most polar part with $CHCl_3$–CH_3OH (3: 1) followed by its recrystallization from C_6H_6–*n*-hexane gave (±)-1-acetoxyaporphine (XIX) (470.7 mg, 18%), 157—158°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1760 (arom.-$OCOCH_3$). NMR δ: 2.26 (3H, s, $OCOCH_3$), 2.43 (3H, s, NCH_3), 3.73 (3H, s, OCH_3), 5.87 (2H, s, OCH_2O), 6.58, 6.69 (each 1H, s, arom. H), 7.39 (1H, s, 11-H). *Anal.* Calcd. for $C_{21}H_{21}O_5N$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.35; H, 5.82; N, 3.89.

Elution of an absorbent corresponding to the less polar part with $CHCl_3$–CH_3OH (3: 1) and recrystallization of the eluate from C_6H_6–*n*-hexane afforded (±)-1,4β-diacetoxyaporphine (XXa) (144.9 mg, 4.7%), mp 195—196°, and an analytical sample had mp 197—197.5°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1770 (arom.-$OCOCH_3$), 1735 (aliph.-$OCOCH_3$). NMR δ: 2.15, 2.30 (each 3H, s, $2\times OCOCH_3$), 2.50 (3H, s, NCH_3), 3.81 (3H, s, OCH_3), 5.93 (1H, bt, half-band width 5.0 Hz, 4-H), 5.95 (2H, s, OCH_2O), 6.78, 6.88 (each 1H, s, arom. H), 7.43 (1H, s, 11-H). *Anal.* Calcd. for $C_{23}H_{23}O_7N$ (mol. wt. = 425.42): C, 64.93; H, 5.45; N, 3.29. Found: C, 64.79; H, 5.53; N, 3.33. Mass spectrum *m/e*: 425 (M^+). Elution of an absorbent corresponding to the least polar part with $CHCl_3$–CH_3OH (3: 1) followed by recrystallization from C_6H_6–*n*-hexane gave (±)-1,4α-diacetoxyaporphine (XXb) (171.2 mg, 5.5%), mp 204—205°, and an analytical sample had mp 204—206°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1770 (arom.-$OCOCH_3$), 1740 (aliph.-$OCOCH_3$). NMR δ: 2.13, 2.29 (each 3H, s, $2\times OCOCH_3$), 2.50 (3H, s, NCH_3), 3.82 (3H, s, OCH_3), 5.92 (2H, s, OCH_2O), 6.13 (1H, dd, J = 6.25, 10.0 Hz, 4-H), 6.73, 6.77 (each 1H, s, arom. H), 7.41 (1H, s, 11-H). *Anal.* Calcd. for $C_{23}H_{23}O_7N$ (mol. wt.=425.42): C, 64.93; H, 5.45; N, 3.29. Found: C, 64.98; H, 5.50; N, 3.39. Mass spectrum *m/e*: 425 (M^+).

(±)-Domesticine (VI) and (±)-Nantenine (XXII)——A solution of the 1-acetoxyaporphine (XIX) (98 mg) and 4N HCl (10 ml) in dioxane (30 ml) was heated at 85° for 3 hr. The reaction mixture was condensed under reduced pressure and basified with $NaHCO_3$ (powder). The product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over $MgSO_4$. Removal of the solvent gave an amorphous mass (VI) (72 mg, 83%), which was recrystallized from C_6H_6–*n*-hexane to produce colorless prisms, mp 186—187° (lit.8) mp 185—186°). It NMR spectral datum was consistent with that of an authentic sample.8)

A solution of (±)-domesticine (VI) (64 mg) and CH_2N_2–ether (60 ml) in CH_3OH (5 ml) was allowed to stand at room tempt. overnight. Removal of the solvent gave (±)-nantenine (XXII) (61.9 mg, 95%), which was recrystallized from *n*-hexane to give colorless prisms, mp 140—142° (lit.13) mp 142°). NMR δ: 2.53 (3H, s, NCH_3), 3.63, 3.85 (each 3H, s, $2\times OCH_3$), 5.93 (2H, s, OCH_2O), 6.53, 6.73 (each 1H, s, arom. H), 7.93 (1H, s, 11-H). Mass spectrum *m/e*: 339 (M^+).

$Pb(OAc)_4$ Oxidation and Acid Treatment of IX——To a water-cooled, stirred solution of the phenolic isoquinoline (IX) (1.71 g, 5 mmoles) was added in one portion $Pb(OAc)_4$ (4.43 g, 10 mmoles) and stirring was continued at room tempt. for 25 min. The reaction mixture was poured into crashed ice and basified with $NaHCO_3$ (powder). The product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over $MgSO_4$. Careful evaporation of the solvent (below 30°) under reduced pressure afforded an oil (2.0 g) [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 ($-OCOCH_3$), 1665, 1645, 1630 (dienone)]. To an ice-cooled, stirred solution of the crude *p*-quinol acetate (XXI) (2 g) in Ac_2O (10 g) was added dropwise a cold mixture of conc. H_2SO_4 (1 g) and Ac_2O (3 g) during 10 min and stirring was continued at the same tempt. for 10 min. The reaction mixture was poured into crashed ice. The acidic solution was washed with ether and basified with $NaHCO_3$ (powder). The product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract furnished a brown oil (1.64 g), which was subjected to column chromatography over silica gel (50 g). Elution with C_6H_6–CH_3OH (100: 1) gave a brown oil (182 mg), which was purified on a preparative TLC affording a diastereomeric mixture of (±)-1,4-diacetoxyhomoaporphine (XXIV) (18 mg, 0.8%), mp 170—190°. Recrystallization from C_6H_6–*n*-hexane furnished colorless prisms (8 mg, 0.4%), mp 174—194°, and an analytical sample had mp 180—192°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (arom.-$OCOCH_3$), 1730 (aliph.-$OCOCH_3$). NMR δ: 2.08 (6H, s, $2\times OCOCH_3$), 2.42 (3H, s, NCH_3), 3.82 (3H, s, OCH_3), 5.89 (1H, bs, 4-H), 5.95 (2H, s, OCH_2O), 6.71, 6.80 (each 1H, s, arom. H), 6.92 (1H, s, 12-H). *Anal.* Calcd. for $C_{24}H_{25}O_7N$ (mol. wt.=439.45): C, 65.59; H, 5.73; N, 3.19. Found: C, 65.28; H, 5.91; N, 3.14. Mass spectrum18) *m/e*: 439 (M^+). Elution with C_6H_6–CH_3OH (100: 1)–(20: 1) yielded an amorphous mass (506 mg), which was triturated in *n*-hexane producing (±)-1-acetoxyhomoaporphine (XXIII) (417 mg, 21.8%), mp 130—140°. Recrystallization from C_6H_6–*n*-hexane gave colorless prisms (300 mg, 15.6%), mp 135—140°, and an analytical sample had mp 137—140°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (arom.-$OCOCH_3$). NMR δ: 2.12 (3H, s, $OCOCH_3$), 2.45 (3H, s, NCH_3), 3.84 (3H, s, OCH_3), 5.96 (2H, bs, OCH_2O), 6.74 (2H, s, arom. H), 6.81 (1H, s, 12-H). *Anal.* Calcd. for $C_{22}H_{23}O_5N$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.50; H, 6.11; N, 3.94.

(±)-1-Hydroxy-2-methoxy-6-methyl-10,11-methylenedioxyhomoaporphine (VII)——A mixture of the 1-acetoxyhomoaporphine (XXIII) (470 mg) and 5% aq. K_2CO_3 (50 ml) in CH_3OH (50 ml) was refluxed for 30 min. To a residue obtained on removal of the solvent under reduced pressure was added H_2O and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave a brown syrup (360 mg), which was crystallized from C_6H_6–*n*-hexane yielding (±)-1-hydroxyhomoaporphine (VII) (332 mg, 80%), mp 136—138°. Repeated recrystallization from the same solvent gave pale yellow needles, mp 139—141°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (–OH). NMR δ: 2.38 (3H, s, NCH_3), 3.78 (3H, s, OCH_3), 5.96 (2H, s, OCH_2O), 6.62, 6.75 (each 1H, s, arom. H), 7.04 (1H, s, 12-H). *Anal.* Calcd. for $C_{20}H_{21}O_4N\cdot{}^1/_3C_6H_6$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.06, 72.07; H, 6.38, 6.66; N, 3.62, 3.46.

Acknowledgement The authors are indebted to Prof. T. Kametani of Tohoku University for the NMR spectrum of (±)-domesticine and to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for his kind supply of the starting material. Thanks are due to Sankyo Co., Ltd. for elemental analyses, Prof. S. Sakai of Chiba University for mass spectral (a Hitachi Model RMU-6E mass spectrometer), and to Miss T. Kawana and Miss S. Komatsu of this Faculty for NMR and mass spectral measurements.

---

18) A Hitachi Model RMU-7M spectrometer was used.