was concentrated *in vacuo*. The residue was recrystallized from proper solvent to give the corresponding pure product (IVa—e).

4,6-Dimethyl-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (V)——A suspension of IVa (0.283 g, 0.001 mole) in HCOOH (5 ml) was refluxed for 10 hr. The solution was evaporated to dryness *in vacuo* and the residue was recrystallized from H_2O to give the product (V) (0.12 g, 67%), mp 254—257°, identified with an authentic sample.[8]

1,3-Dimethyl-6-phenyl-7-azalumazine (3-Phenylfervenulin) (X)——Method A: A mixture of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (VIII)[10] (0.398 g, 0.002 mole) and acetophenone (0.216 g, 0.002 mole) in EtOH (10 ml) was refluxed for 10 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was triturated with EtOH and the insoluble solid was filtered. Recrystallization from EtOH afforded the pure product (X) (0.06 g, 11%), mp 267—270°, which is identical in all respects with the authentic sample.[11]

Method B: A mixture of 6-benzylidenehydrazino-1,3-dimethyluracil (IX)[12] (0.77 g, 0.003 mole), NDA (0.44 g, 0.006 mole) and $POCl_3$ (0.94 g, 0.006 mole) was heated at 90° for 15 min. The reaction mixture was triturated with H_2O and the insoluble solid was recrystallized from EtOH to give the product (X) (0.27 g, 35%) which is identical in all respects with the compound prepared by Method A.

[Chem. Pharm. Bull. 24(8)1921—1925(1976)]

UDC 547.833.9.04 : 546.819.04

Studies on Tetrahydroisoquinolines. XII.[1] An Alternative Synthesis of (±)-Bracteoline, (±)-Isoboldine, (±)-N-Methyllaurotetanine, and Their Related Aporphines

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By the treatment of the *p*-quinol acetate (Xa) and (Xb) with trifluoroacetic acid, (±)-10-benzyloxy-1-hydroxy-2,9-dimethoxyaporphine (XIa) and (±)-9-benzyloxy-1-hydroxy-2,10-dimethoxyaporphine (XIb) were given in good yield, respectively. Furthermore, XIa and XIb were converted to (±)-bracteoline (XIIa) and (±)-isoboldine (XIIb) by catalytic debenzylation, or to (±)-10-hydroxy-1,2,9-trimethoxyaporphine (XIVa) and (±)-N-methyllaurotetanine (XIVb) by methylation and successive debenzylation, respectively.

Previously, a simple synthesis[1] *via* a *p*-quinol acetate of aporphines having alkoxyl groups in the D ring, such as (±)-thaliporphine (I), (±)-domesticine (II), and (±)-1-hydroxy-2,9,10,-11-tetramethoxyaporphine (III), has been achieved in our laboratory.

As an extension of the method, synthesis of aporphines having a hydroxyl group in the D ring was undertaken and we report here an improved synthesis of (±)-bracteoline (XIIa),[3] (±)-isoboldine (XIIb),[4] and (±)-N-methyllaurotetanine (XIVb).[5]

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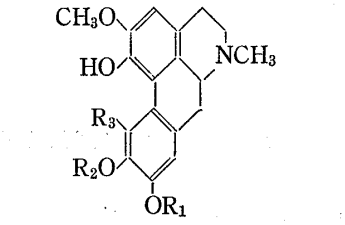
1) Part XI: H. Hara, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **24**, 262 (1976).
2) Location: *12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*
3) *a*) T. Kametani, S. Shibuya, H. Sugi, O. Kusama, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 2446; T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Tetrahedron*, **27**, 5375 (1971); *b*) P. Kerekes, K. Délenk-Heydenreich, and S. Pfeifer, *Chem. Ber.*, **105**, 609 (1972).
4) *a*) B. Franck, G. Dunkelmann, and H.J. Lubs, *Angew. Chem. Internat. Edit.*, **6**, 1075 (1967); W.W-C. Chan and P. Maitland, *J. Chem. Soc.* (*C*), **1966**, 753; T. Kametani, K. Fukumoto, A. Kozuka, H. Yagi, and M. Koizumi, *ibid.* (*C*), **1969**, 2034; T. Kametani, A. Kozuka, and K. Fukumoto, *ibid.*, (*C*), **1971**, 1021; A.R. Battersby, A.K. Bhatnager, P. Hackett, C.W. Thornber, and J. Stauton, *Chem. Commun.*, **1968**, 1214; *b*) A.H. Jackson and J.A. Martin, *J. Chem. Soc.* (*C*), **1966**, 2061; T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *Tetrahedron*, **25**, 3667 (1969); *c*) S.M. Kupchan and P.F. O'Brien, *J.C.S. Chem. Commun.*, **1973**, 915.
5) *a*) I. Kikkawa, *Yakugaku Zasshi*, **79**, 83 (1959); *b*) T. Kametani, K. Fukumoto, S. Shibuya, H. Nemoto, T. Nakano, T. Sugahara, T. Takahashi, Y. Aizawa, and M. Toriyama, *J. Chem. Soc. Perkin I*, **1972**, 1435.

Our general plan was to cyclize the 7-phenolic tetrahydroisoquinolines having the protected hydroxyl group in the C ring and to adopt the standard method (successive deprotection or methylation followed by deprotection).

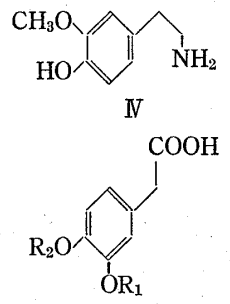
We chose the benzyl group for the protection, because the protecting group must be effective enough to bring about the cyclization and sufficiently stable to the cyclizing agent, such as trifluoroacetic acid (CF_3CO_2H), at least for several hours.[6]

The starting 7-phenolic tetrahydroisoquinolines (IXa, b) were prepared essentially according to the method of Brossi, *et al.*,[7] as follows.

Bishler-Napieralski reaction of the amide (VIa, b) with phosphoryl chloride ($POCl_3$) in methylene chloride (CH_2Cl_2)[8] gave the dihydro bases (VIIa, b), sodium borohydride ($NaBH_4$) reduction of which afforded the tetrahydro bases (VIIIa, b). Subsequent methylation (formalin, $NaBH_4$) led to IXa, b.

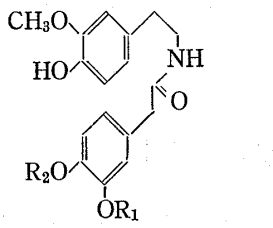


I : $R_1=R_2=CH_3$, $R_3=H$
II : $R_1=R_2=CH_2$, $R_3=H$
III : $R_1=R_2=CH_3$, $R_3=OCH_3$

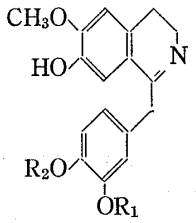


IV

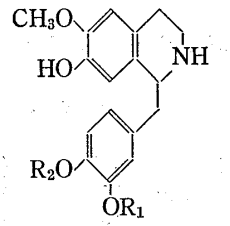
Va : $R_1=CH_3$, $R_2=C_7H_7$
Vb : $R_1=C_7H_7$, $R_2=CH_3$



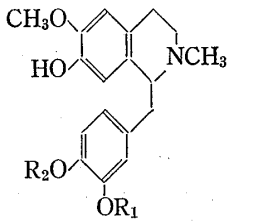
VIa : $R_1=CH_3$, $R_2=C_7H_7$
VIb : $R_1=C_7H_7$, $R_2=CH_3$



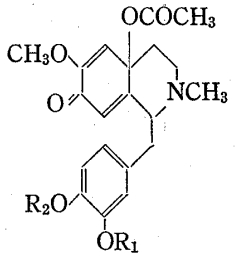
VIIa : $R_1=CH_3$, $R_2=C_7H_7$
VIIb : $R_1=C_7H_7$, $R_2=CH_3$



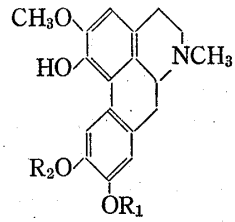
VIIIa : $R_1=CH_3$, $R_2=C_7H_7$
VIIIb : $R_1=C_7H_7$, $R_2=CH_3$



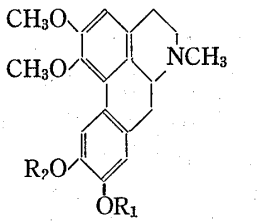
IXa : $R_1=CH_3$, $R_2=C_7H_7$
IXb : $R_1=C_7H_7$, $R_2=CH_3$



Xa : $R_1=CH_3$, $R_2=C_7H_7$
Xb : $R_1=C_7H_7$, $R_2=CH_3$



XIa : $R_1=CH_3$, $R_2=C_7H_7$
XIb : $R_1=C_7H_7$, $R_2=CH_3$
XIIa : $R_1=CH_3$, $R_2=H$
XIIb : $R_1=H$, $R_2=CH_3$



XIIIa : $R_1=CH_3$, $R_2=C_7H_7$
XIIIb : $R_1=C_7H_7$, $R_2=CH_3$
XIVa : $R_1=CH_3$, $R_2=H$
XIVb : $R_1=H$, $R_2=CH_3$

Chart 1

Lead tetraacetate [$Pb(OAc)_4$] oxidation of IXa in acetic acid gave the expected *p*-quinol acetate (Xa), the structure of which was ascertained by infrared (IR) spectral measurement.

6) Benzyl group has been hydrolysed with CF_3CO_2H at room tempt. for 10[b] or 18[a] hr; *a*) J.P. Marsh, Jr. and L. Goodman, *J. Org. Chem.*, **30**, 2491 (1965); *b*) E. Kotani and S. Tobinaga, *Tetrahedron Letters*, **1973**, 4759.

7) *a*) A. Brossi, J. van Burik, and S. Teitel, *Helv. Chim. Acta*, **51**, 1965 (1968); *b*) S. Teitel and A. Brossi, *J. Heterocyclic Chem.*, **5**, 825 (1968).

8) Brossi, *et al.* have used chloroform[7a] or acetonitrile[7b] as a solvent.

The crude Xa was treated with CF_3CO_2H in CH_2Cl_2 to give, after purification on preparative thin layer chromatography, (±)-10-benzyloxy-1-hydroxy-2,9-dimethoxyaporphine (XIa), mp 74—76°, in 48% yield. The structure was quite reasonable on the basis of spectral data including in nuclear magnetic resonance (NMR) the presence of three singlets due to aromatic protons, one of which appearing at δ 8.12 diagnostic for aporphines.

Similarly, the phenolic base (IXb) gave (±)-9-benzyloxy-1-hydroxy-2,10-dimethoxyaporphine (XIb), mp 155.5—157°, in 44% yield.

Catalytic debenzylation (palladium on carbon, methanol) of XIa and XIb afforded (±)-bracteoline (XIIa),[3] mp 209—211° (dec.) and (±)-isoboldine (XIIb),[4] mp 208—209° (dec.) in 60% and 88% yield.

Furtheremore, methylation with diazomethane of XIa and XIb gave (±)-10-benzyloxy-1,2,9-trimethoxy-(XIIIa),[9] mp 153—154°, and (±)-9-benzyloxy-1,2,10-trimethoxy-aporphine (XIIIb),[5a] mp 130—132°, respectively, in each quantitative yield. Successive debenzylation of XIIIa and XIIIb afforded (±)-hydroxy-1, 2,9-trimethoxyaporphine (XIVa),[9] mp 184.5—185.5°, and (±)-N-methyllaurotetanine (XIVb),[5] mp 144—145°[10] in 88% and quantitative yield, respectively.

Experimental[11]

N-β-(4-Hydroxy-3-methoxyphenyl)ethyl-4′-benzyloxy-3′-methoxyphenylacetamide (VIa) and N-β-(4-Hydroxy-3-methoxyphenyl)ethyl-3′-benzyloxy-4′-methoxyphenylacetamide (VIb)——VIa: Amine (IV)[7a] (3.02 g) and phenylacetic acid (Va)[12,13] (4.90 g) were heated at 180—190° (bath tempt.) for 4 hr. On cooling, usual work-up gave a dark brown oily compound (7.52 g), which was crystallized from ether yielding colorless needles (VIa) (5.90 g, 78%), mp 87—88°. An analytical sample had mp 87—88° (ether). IR[14] ν_{max}^{KBr} cm^{-1}: 3375 (NH), 1640 (CONH). NMR δ: 3.42 (2H, s, $COCH_2Ar$), 3.78, 3.81 (each 3H, s, $2\times OCH_3$), 5.11 (2H, s, $OCH_2C_6H_5$). *Anal.* Calcd. for $C_{25}H_{27}O_5N$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.13; H, 6.68; N, 3.31. VIb: IV (3.1 g) and phenylacetic acid (Vb)[13,15] (5.0 g) were heated at 170° (bath tempt.) for 4 hr. On cooling, usual work-up gave colorless crystals (VIb) (7.0 g, 90%), mp 122—123°. An analytical sample had mp 125—126° (iso-C_3H_7OH). IR[14] ν_{max}^{KBr} cm^{-1}: 3260 (OH), 1625 (CONH). NMR δ: 2.60 (2H, t, $ArCH_2CH_2$-NH), 3.40 (2H, s, $COCH_2Ar$), 3.77, 3.84 (each 3H, s, $2\times OCH_3$), 5.09 (2H, s, $OCH_2C_6H_5$). *Anal.* Calcd. for $C_{25}H_{27}O_5N\cdot 1/4H_2O$: C, 70.49; H, 6.51; N, 3.29. Found: C, 70.61; H, 6.48; N, 3.28.

(±)-1-(4′-Benzyloxy-3′-methoxybenzyl)-1,2,3,4-tetrahydto-7-hydroxy-6-methoxyisoquinoline (VIIIa)——The amide (VIa) (421 mg) and $POCl_3$ (1 ml) in anhydrous CH_2Cl_2 (5 ml) were refluxed for 4 hr with stirring. Removal of the solvent under reduced pressure gave a viscous oil, which was washed well with petr. benzine. To this oily compound was added ice water and the whole was carefully basified with $NaHCO_3$ (powder). The product was taken up in $CHCl_3$. Usual work-up gave an oil (VIIa) (460 mg) [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH), 1660 (C=N)], which was treated with $NaBH_4$ (80 mg) in CH_3OH (40 ml) at room tempt. for 1 hr. Removal of the solvent under reduced pressure gave an oily residue, to which was added water and NH_4Cl (powder), and the product was taken up in $CHCl_3$. Usual work-up gave an amorphous mass (408 mg), which was chromatographed on silica gel.[16] Elution with C_6H_6–CH_3OH (100:1—100:2) gave colorless sands (VIIIa) (268 mg, 66%), mp 160—164°. An analytical sample had mp 166—167° (CH_3OH-iso-C_3H_7OH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH). NMR δ: 3.72, 3.78 (each 3H, s, $2\times OCH_3$), 5.09 (2H, s, $OCH_2C_6H_5$). *Anal.* Calcd. for $C_{25}H_{27}O_4N$: C, 74.05; H, 6.71; N, 3.45. Found: C, 73.89; H, 7.02; N, 3.52.

(±)-1-(4′-Benzyloxy-3′-methoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (IXa)——To a stirred solution of VIIIa (55 mg) in CH_3OH (3 ml) was added 37% HCHO (0.05 ml), and stir-

9) W.H. Baarshers and R.R. Arndt, *Tetrahedron*, **21**, 2155 (1965).
10) So far, the base has been known as an oil.
11) All melting points were uncorrected and measured on a Buchi melting point measuring apparatus. NMR spectra were taken with a JEOL Model JNR-4H-100 spectrometer (100 NHz) in $CDCl_3$ solution (5—10%) by using $(CH_3)_4Si$ as internal standard, unless otherwise noted. Following abbreviations were used; s: singlet; t: triplet; q: quartet. IR spectra were run on a Hitachi Model 215 spectrometer, unless otherwise noted. Preparative thin-layer chromatographies were performed over Silica gel GF_{254} (Merck).
12) R.L. Douglas and J.M. Gulland, *J. Chem. Soc.*, **1931**, 2893.
13) M. Tomita and J. Kunitomo, *Yakugaku Zasshi*, **80**, 1238 (1960).
14) A Hitachi Model 225 spectrometer was used.
15) K.W. Gopinath, T.R. Govindachari, and N. Viswanathan, *Chem. Ber.*, **92**, 1657 (1957).
16) Silica gel (Kanto Chemical Co., Inc.).

ring was continued at room tempt. for 30 min. The mixture was treated with $NaBH_4$ (53 mg) at room tempt. for 1 hr and usual work-up gave an oily compound (IXa) (50 mg, 88%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH). NMR δ: 2.43 (3H, s, NCH_3), 3.73, 3.77 (each 3H, s, $2\times OCH_3$), 5.07 (2H, s, $OCH_2C_6H_5$). Picrolonate; yellow prisms, mp 117—119° (CH_3OH–iso-C_3H_7OH). *Anal.* Calcd. for $C_{36}H_{37}O_9N_5\cdot H_2O$: C, 61.61; H, 5.60; N, 9.98. Found: C, 61.62; H, 5.32; N, 10.23.

(±)-1-(3′-Benzyloxy-4′-methoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (VIIIb)——The amide (VIb) (2 g) and $POCl_3$ (7.5 ml) in anhydrous CH_2Cl_2 (100 ml) were refluxed for 8 hr. Work-up as usual gave a brownish yellow oil (VIIb) (2.35 g) [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH), 1660 (C=N)], which was treated with $NaBH_4$ (600 mg) in CH_3OH (60 ml) at room tempt. for 30 min. Usual work-up gave a brownish yellow viscous oil (2.15 g), which was crystallized from CH_3OH to give colorless prisms (VIIIb) (1.5 g, 78%), mp 154—156°. An analytical sample had mp 170—171° (transition at 156—158°) (CH_3OH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH). NMR δ: 3.70, 3.78 (each 3H, s, $2\times OCH_3$), 5.04 (2H, s, $OCH_2C_6H_5$). *Anal.* Calcd. for $C_{25}H_{27}O_4N$: C, 74.05; H, 6.71; N, 3.45. Found: C, 73.93; H, 6.73; N, 3.62.

(±)-1-(3′-Benzyloxy-4′-methoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (IXb)——VIIIb (1.4 g) in CH_3OH (120 ml) was treated with 37% HCHO (5 ml) and $NaBH_4$ (2.5 g) according to the procedure given for IXa to afford an oily compound (IXb) (1.5 g, quantitative). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH). NMR δ: 2.39 (3H, s, NCH_3), 3.77, 3.79 (each 3H, s, $2\times OCH_3$), 5.03 (2H, s, $OCH_2C_6H_5$). Methiodide; colorless prisms, mp 224—225° (CH_3OH–iso-C_3H_7OH). *Anal.* Calcd. for $C_{27}H_{32}O_4NI$: C, 57.76; H, 5.75; N, 2.49. Found: C, 57.74; H, 5.81; N, 2.46.

(±)-10-Benzyloxy-1-hydroxy-2,9-dimethoxyaporphine (XIa)——To a stirred solution of the phenolic isoquinoline (IXa) (81 mg, 0.193 mmole) in AcOH (2 ml) was added $Pb(OAc)_4$ (103 mg, 0.232 mmole) in one portion and stirring was continued at room tempt. for 30 min. The same treatment as described previously[1] gave an oily *p*-quinol acetate (Xa) (90 mg) [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 ($OCOCH_3$), 1670, 1640, 1620 (dienone)], which was treated with CF_3CO_2H (0.5 ml) in CH_2Cl_2 (10 ml) at room tempt. for 2 hr. Usual work-up gave a brown amorphous mass (76 mg), which was purified on preparative TLC ($CHCl_3$: CH_3OH=20: 1) to afford an oily compound (XIa) (39 mg, 48%). Trituration with ether gave pale yellow crystals, mp 68—70°. An analytical sample had mp 74—76° (ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520 (OH). NMR δ: 2.50 (3H, s, NCH_3), 3.80, 3.85 (each 3H, s, $2\times OCH_3$), 5.17 (2H, s, $OCH_2C_6H_5$), 6.48 (1H, s, 3-H), 6.78 (1H, s, 8-H), 8.12 (1H, s, 11-H), 1.17 (6H, t, J=6.3 Hz, $2\times OCH_2C\underline{H}_3$), 3.45 (4H, q, J=6.3 Hz, $2\times OC\underline{H}_2CH_3$). *Anal.* Calcd. for $C_{26}H_{27}O_4H\cdot C_2H_5OC_2H_5$: C, 73.09; H, 7.59; N, 2.85. Found: C, 73.09; H, 7.44; N, 2.99.

(±)-9-Benzyloxy-1-hydroxy-2,10-dimethoxyaporphine (XIb)——The same treatment as noted above of IXb (147 mg, 0.35 mmole) in AcOH (4 ml) with $Pb(OAc)_4$ (186 mg, 0.42 mmole) gave an oily *p*-quinol acetate (Xb) (221 mg) [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 ($OCOCH_3$), 1670, 1640, 1620 (dienone)], which was treated with CF_3CO_2H (0.75 ml) in CH_2Cl_2 (15 ml) at room tempt. for 2 hr. Work-up as usual gave a dark brown amorphous mass, which was purified on preparative TLC ($CHCl_3$: CH_3OH: NH_4OH=450: 60: 1) to give pale brown crystals (XIb) (64.3 mg, 44%), mp 113—120°. An analytical sample had mp 155.5—157° (ether–acetone). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3510 (OH). NMR (d_6-DMSO) δ: 2.38 (3H, s, NCH_3), 3.72, 3.75 (each 3H, s, $2\times OCH_3$), 5.10 (2H, s, $OCH_2C_6H_5$), 6.62 (1H, s, 3-H), 7.02 (1H, s, 8-H), 8.07 (1H, s, 11-H). *Anal.* Calcd. for $C_{26}H_{27}O_4N$: C, 74.80; H, 6.52; N, 3.36. Found: C, 74.83; H, 6.54; N, 3.33.

(±)-10-Benzyloxy-1,2,9-trimethoxyaporphine (XIIIa)——XIa (50 mg) in CH_3OH (2 ml) was treated with diazomethane–ether (excess) at room tempt. for 2 days to give colorless crystals (XIIIa) (50 mg, quantitative), mp 153—154°. An analytical sample had mp 153—154° (iso-C_3H_7OH) (lit.[9] mp 148—150°). NMR δ: 2.50 (3H, s, NCH_3), 3.38, 3.81, 3.89 (each 3H, s, $3\times OCH_3$), 5.21 (2H, s, $OCH_2C_6H_5$), 6.56 (1H, s, 3-H), 6.81 (1H, s, 8-H), 8.12 (1H, s, 11-H). *Anal.* Calcd. for $C_{27}H_{29}O_4N$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.01; H, 6.82; N, 3.37. The NMR data was consistent with that reported in the literature.[9]

(±)-9-Benzyloxy-1,2,10-trimethoxyaporphine (XIIIb)——XIb (20 mg) in CH_3OH (2 ml) was treated with diazomethane–ether (excess) at room tempt. for 5 days to give a colorless viscous oil (29 mg), which was purified on preparative TLC ($CHCl_3$: CH_3OH=15: 1) to give pale yellow crystals (XIIIb) (20 mg, quantitative), mp 111—116°. An analytical sample had mp 130—132° (ether–*n*-hexane) (lit.[5a] mp 119—121°). NMR δ: 2.53 (3H, s, NCH_3), 3.63, 3.83, 3.87 (each 3H, s, $3\times OCH_3$), 5.18 (2H, s, $OCH_2C_6H_5$), 6.58 (1H, s, 3-H), 6.73 (1H, s, 8-H), 8.13 (1H, s, 11-H). *Anal.* Calcd. for $C_{27}H_{29}O_4N$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.43; H, 6.76; N, 3.21.

(±)-Bracteoline (XIIa)——A mixture of XIa (45 mg), 2% $PdCl_2$ (1 ml), and active carbon (30 mg) in CH_3OH (10 ml) was shaken in atmosphere of H_2 at room tempt., until uptake of H_2 ceased. Work-up as usual afforded pale greenish yellow sands (XIIa) (21 mg, 60%), mp 116—125°. Recrystallization from ether–CH_3OH gave pale yellow needles (7 mg, 20%), mp 209—211° (decomp.) (transition at 138—142°) (lit. mp 208—210°,[3b] 210—211°[3a]). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH). NMR (d_6-DMSO) δ: 2.44 (3H, s, NCH_3), 3.79 (6H, s, $2\times OCH_3$), 6.52 (1H, s, 3-H), 6.75 (1H, s, 8-H), 7.87 (1H, s, 11-H). The NMR data was well consistent with that reported in the literature.[3b]

(±)-Isoboldine (XIIb)——XIb (107 mg) was treated with 2% $PdCl_2$ (1 ml) and active carbon (50 mg) in CH_3OH (15 ml) according to the procedure given for XIIa to afford pale brown crystals (XIIb) (74.4 mg 88%), mp 208—209° (decomp.). Recrystallization from acetone gave colorless prisms (40 mg, 49%), mp 208—209° (decomp.) (lit.[4c] mp 207—208°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3510 (OH). NMR δ: 2.51 (3H, s, NCH_3), 3.85 (6H, s, $2\times$

OCH_3), 6.52 (1H, s, 3-H), 6.79 (1H, s, 8-H), 8.02 (1H, s, 11-H). The NMR data was well consistent with that reported in the literature.[4b]

(±)-10-Hydroxy-1,2,9-trimethoxyaporphine (XIVa)——XIIIa (72 mg) was treated with 2% $PdCl_2$ (1 ml) and active carbon (50 mg) in CH_3OH (15 ml) according to the procedure given for XIIa to afford colorless crystals (XIVa) (50 mg, 88%), mp 180—182° (decomp.). An analytical sample had mp 184.5—185.5° (ether–acetone) (lit.[9] mp 140—145°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH). NMR δ: 2.55 (3H, s, NCH_3), 3.64, 3.82, 3.86 (each 3H, $3\times OCH_3$), 6.58 (1H, s, 3-H), 6.77 (1H, s, 8-H), 8.03 (1H, s, 11-H). *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.05; H, 6.78; N, 4.13. The NMR data was consistent with that reported in the literature.[9]

(±)-N-Methyllaurotetanine (XIVb)——XIIIb (540 mg) was reduced with 2% $PdCl_2$ (5 ml) and active carbon (250 mg) in CH_3OH (100 ml) according to the procedure given for XIIa to afford colorless crystals (XIVb) (quantitative), mp 138—142°, which were recrystallized from ether–acetone to give colorless prisms (278 mg, 65%), mp 142—144°. Further recrystallization from acetone yielded colorless prisms, mp 144—145° (lit.[5] oil or powder). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH). NMR δ: 2.37 (3H, s, NCH_3), 3.62 (3H, s, OCH_3), 3.83 (6H, s, $2\times OCH_3$), 6.57 (1H, s, 3-H), 6.78 (1H, s, 8-H), 8.06 (1H, s, 11-H). *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.05; H, 6.84; N, 4.00. Oxalate; colorless prisms, mp 201—203° (decomp.) (acetone–CH_3OH) (lit. mp 212° (decomp.),[5a] 199—202° (decomp.)[5b]). The NMR data was consistent with that reported in the literature.[5b]

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Synthesis of Stereoisomeric Alanine Containing Peptide Derivatives[1]

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As analogues of D-cycloserine, the part structure of penicillin and D–D carboxypeptidase substrate of peptidoglycan of bacterial cell wall, D-alanine derivatives and their stereoisomers and D-alanyl-D-alanine derivatives and their stereoisomers (R_1-Ala-R_2, R_1-Ala-Ala-R_2: R_1=Z, H; R_2=$NHNH_2$, $NHCH_3$, $NHCH_2CH_2OH$) were synthesized. All compounds obtained did not show any antibacterial activity against *Staphylococcus aureus*, *Sarcina lutea*, *Pseudomonas aeruginosa* and *Escherichia coli*.

Some antibiotics inhibit the growth of bacteria due to interfering the synthesis of peptidoglycan of the cell walls.[3] It is well known that the structure of D-cycloserine is similar to that of D-alanine[4] and the highly reactive CO–N bond in the β-lactam ring of penicillin is the analogue of the CO–N bond in the peptide, D-alanyl-D-alanine.[5,6]

Our studies were directed to the synthesis of D-alanyl-D-alanine analogues which are analogues not only of D-cycloserine and penicillin but also of the substrates of D-D carboxypepti-

1) Abbreviations used are those recommended by IUPAC-IUB Commission on Biochemical Nomenclature: *Biochemistry*, **5**, 3485 (1966); *ibid.*, **6**, 362 (1967); *ibid.*, **11**, 1726 (1972). Z=benzyloxycarbonyl.
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