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Pachysandra Alkaloids.XI.[1] Syntheses of Pachysandrines and Epipachysandrine-A from Ergosterol[2]

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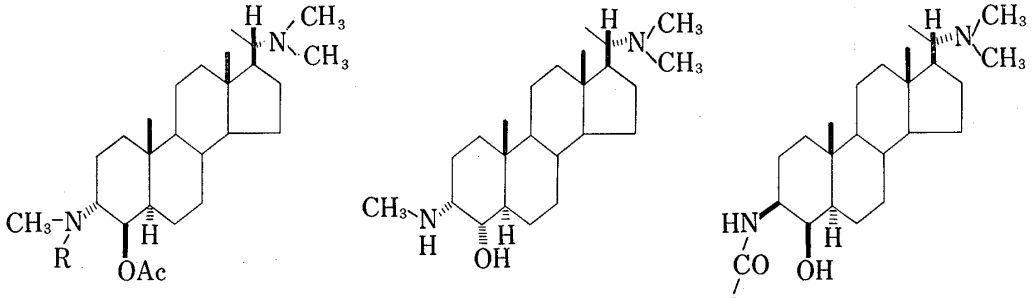
Pachysandrine-A (Ia), -B (Ib), -C (II) and epipachysandrine-A (III), steroidal alkaloids of *Pachysandra terminalis* Sieb. et Zucc. (Buxaceae), were formally synthesized from ergosterol.

A number of new aklaloids have been isolated in our laboratory from *Pachysandra terminalis* Sieb. et Zucc. (Japanese name: Fukki-so)(Buxaceae)[4] and their structures established. Among them, pachysandrine-A (Ia),[5] -B (Ib), -C (II)[6] and epipachysandrine-A (III)[1] are first examples of 4-hydroxy-3,20-diaminopregnane type alkaloids isolated from the natural source. Therefore we were interested in their syntheses which have been successfully performed.[7]



Ia : R=COC_6H_5
Ib : R=$COCH=C(CH_3)_2$

II

III

Chart 1

For the starting material to this program we chose 3β,4β-dihydroxy-20α-dimethylamino-5α-pregnane (VIIa),[8] since this compound was readily accessible by sodium borohydride reduction of the 3,4-diosphenol (V), which had previously been synthesized from ergosterol (IV) and, more conveniently, could be derived from pachysandrines by way of the amino-ketone (VI).[5]

1) Part X: T. Kikuchi, S. Uyeo, Jr., and T. Nishinaga, *Chem. Pharm. Bull.* (Tokyo), **15**, 577 (1967).
2) Preliminary accounts of this work were reported in *Tetrahedron Letters*, **1969**, 1679.
3) Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*
4) M. Tomita, T. Kikuchi, S. Uyeo, Jr., T. Nishinaga, M. Yasunishi (née Ando), and A. Yamamoto, *Yakugaku Zasshi*, **87**, 215 (1967).
5) M. Tomita, S. Uyeo, Jr., and T. Kikuchi, *Tetrahedron Letters*, **1964**, 1053; *idem*, *Chem. Pharm. Bull.* (Tokyo), **15**, 193 (1967).
6) T. Kikuchi, S. Uyeo, Jr., M. Ando, and A. Yamamoto, *Tetrahedron Letters*, **1964**, 1817; T. Kikuchi, and S. Uyeo, Jr., *Chem. Pharm. Bull.* (Tokyo), **15**, 207 (1967).
7) It should be noted in this connection that recently Goutarel *et al.* reported the syntheses of four stereoisomeric 3-dimethylamino-4-hydroxypregnanes from progesterone; see P. Longevialle and R. Goutarel, *Bull. Soc. Chim. France*, **1965**, 3225.
8) T. Kikuchi, S. Uyeo, Jr., and T. Nishinaga, *Tetrahedron Letters*, **1965**, 1993; *idem*, *Chem. Pharm. Bull.* (Tokyo), **15**, 316 (1967).

Initially we wish to describe the synthesis of pachysandrine-A (Ia), one of the major alkaloids obtained from the weakly basic fraction.[9]

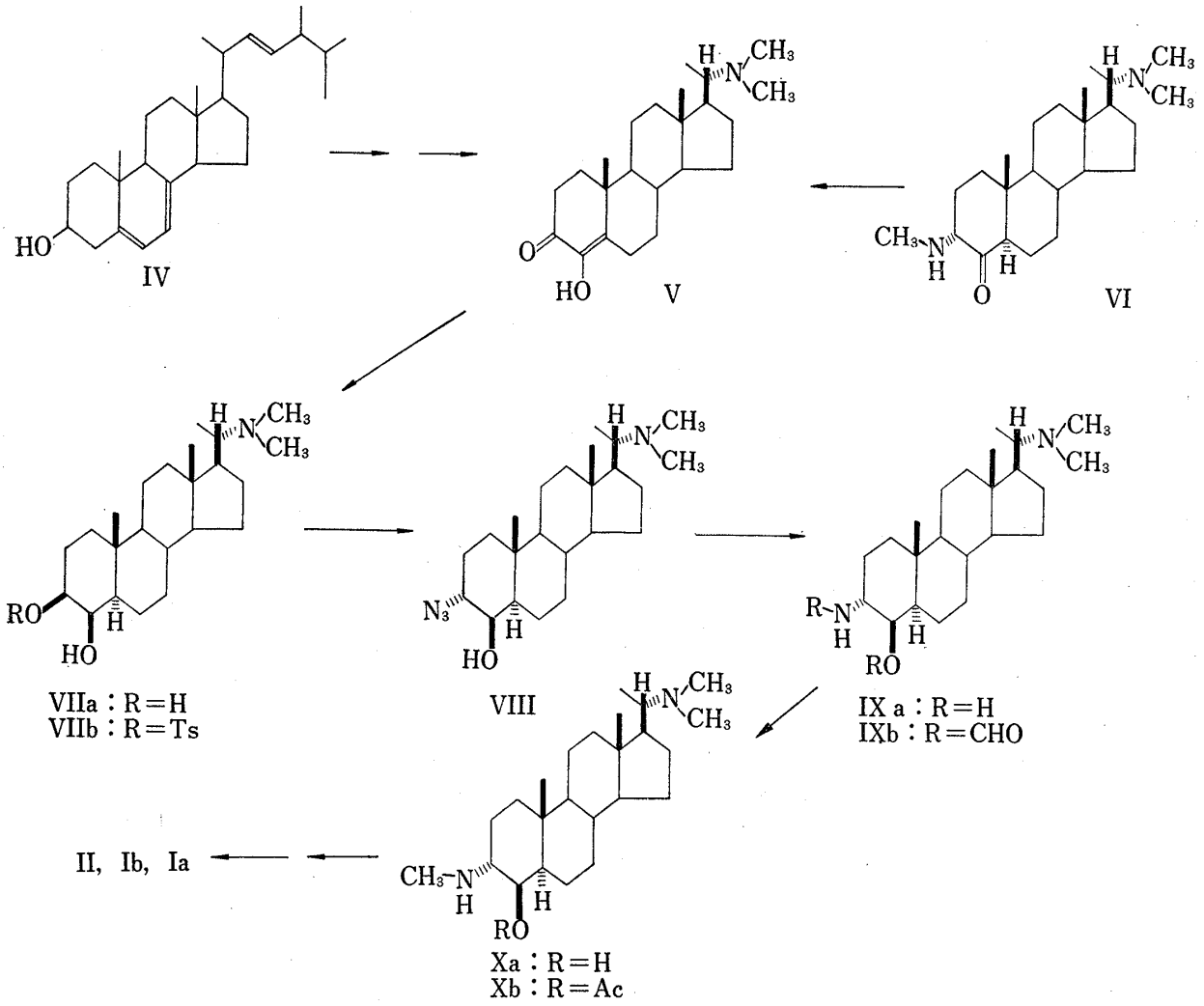


Chart 2

It seemed that the most promising method for the introduction of the 3α-amino substituent in pachysandrine-A is the nucleophilic displacement reaction of the 3β-mono-tosylate (VIIb) with sodium azide followed by metal hydride reduction.[10]

Thus the treatment of the 3β,4β-dihydroxy compound (VIIa) with *p*-toluenesulfonyl chloride in pyridine at room temperature gave a mono-tosylate (VIIb), $C_{30}H_{47}O_4NS$, mp 211—213°, in an excellent yield. The infrared (IR) spectrum[11] of VIIb showed a clear hydroxyl absorption at 3550 cm^{-1} together with strong absorptions associated with a tosyloxy function (1170, 1100, 925, 868, 810 cm^{-1}) and the nuclear magnetic resonance (NMR) spectrum[11] revealed a broad signal assignable to the axially oriented C_3-hydrogen at 5.3—5.8 τ

9) The "weakly basic alkaloid" refers to the one which remains in the chloroform layer when the alkaloid is partitioned between chloroform (or methylene chloride) and 3% HCl (or 5% aq. citric acid), and the "strongly basic alkaloid" refers to the one which moves into the acidic aqueous layer.

10) A.K. Bose, J.F. Kistner, and L. Farber, *J. Org. Chem.*, **27**, 2925 (1962); R. Goutarel, A. Cave, L. Tan, and M. Leboeuf, *Bull. Soc. Chim. France*, **1962**, 646; M.-M. Janot, M^{me} F. Khuong-Huu-Laine, and R. Goutarel, *ibid.*, **1963**, 641; see also reference 14).

11) IR spectra were measured in chloroform solutions unless otherwise stated and NMR spectra in deuterated chloroform using tetramethylsilane as the internal reference.

and a multiplet ($W^{1/2}$ about 6 cps) due to the equatorial C_4-hydrogen at 6.15 τ, indicating that the tosylation had taken place only at the C_3-hydroxyl group as expected from the view point of steric hindrance.

Reaction of this mono-tosylate (VIIb) with sodium azide was then examined in various solvents and the best result was obtained when the reaction was run in N-methyl-2-pyrrolidone at 130—140°.[12]

The crude azide (VIII), which showed an azide absorption at 2100 cm^{-1}, was immediately used for the reduction with lithium aluminum hydride in refluxing ether-tetrahydrofuran. The amino-alcohol (IXa), thereby obtained as a strongly basic product, was in turn treated with formic acid-acetic anhydride and the resulting N-formate (IXb) was submitted to lithium aluminum hydride reduction to afford the corresponding N-methyl derivative (Xa). Alumina chromatography of this compound and further purification through recrystallizations of its picrate gave rise to a pure sample Xa, $C_{24}H_{44}ON_2$, mp 214—215°, $[\alpha]_D$+28° ($CHCl_3$), which was identified in all respects with a natural sample of O,N-desacylpachysandrine-A (Xa)[5] by direct comparison.

We then used the natural Xa for further elaboration. The first step attempted was the selective O-acetylation, which may be realized by acetylation at the presence of an acid catalyst. In fact, treatment of Xa with a mixture of acetic anhydride, *p*-toluenesulfonic acid and acetic acid yielded an O-acetate (Xb), mp 182—183°, in almost quantitative yield. The NMR spectrum of this product exhibited a signal for an acetyl group at 7.94 τ and the IR spectrum an ester band at 1720 cm^{-1}. Subsequent benzoylation of this compound (Xb) gave pachysandrine-A (Ia), $C_{33}H_{50}O_3N_2$, mp 237—238°, $[\alpha]_D$+90° ($CHCl_3$). Identity was completely established by direct comparison with the natural sample (Ia).

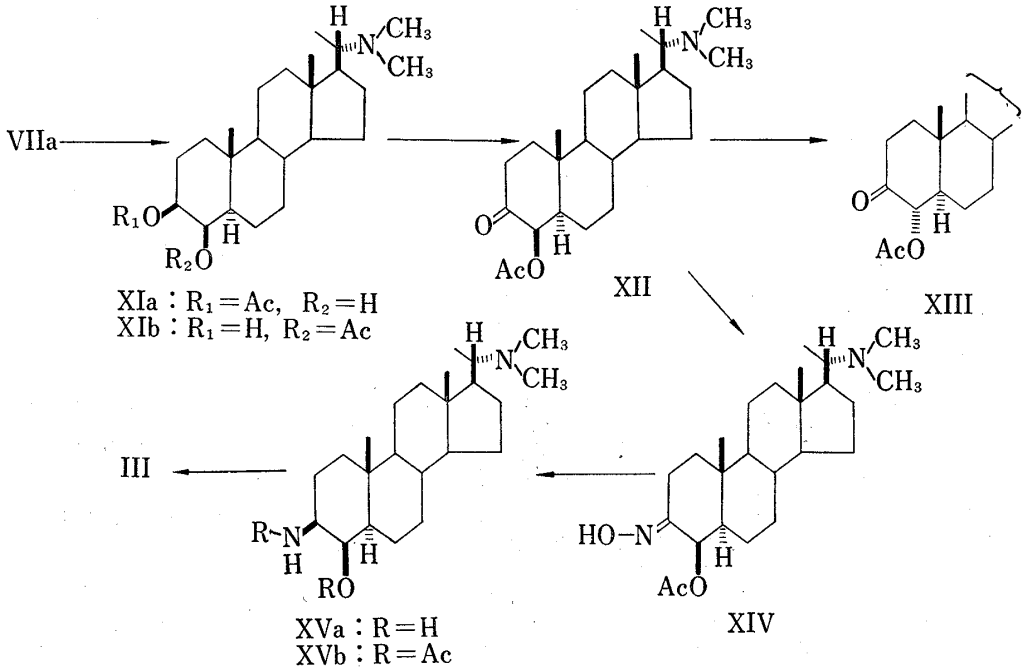


Chart 3

As reported previously, we already transformed pachysandrine-A (Ia) into pachysandrine-B (Ib) and -C (II).[6] Hence the present work also means the syntheses of the latter two alkaloids.

The next alkaloid, epipachysandrine-A (III), is a minor alkaloid which has the 3β,4β-configuration. The synthesis of this alkaloid was initiated by the partial acetylation of VIIa.

12) H.B. Henbest and W.R. Jackson, *J. Chem. Soc.*, **1962**, 954.

Reaction of the diol (VIIa) with acetic anhydride-pyridine in the analogous manner as described by Kupchan, *et al.*[13] furnished a 3-mono-acetate (XIa), $C_{25}H_{43}O_3N$, mp 212—213°, in a fairly good yield. The selective acetylation at the C_3-equatorial hydroxyl group of XIa was evidently proved by its NMR spectrum which showed a broad signal ($W^{1/2}$ about 15 cps) for the C_3-axial proton at 5.27 τ and a multiplet ($W^{1/2}$ about 6 cps) for the C_4-equatorial one at 6.17τ. Treatment of XIa with neutral alumina led to the O→O acyl migration,[13] yielding a 4-mono-acetate (XIb), mp 206—208°, which exhibited NMR signals at 6.37 and 4.90τ associated with the C_3-axial and C_4-equatorial protons, respectively.

When the 4-acetate (XIb) was oxidized with chromium trioxide in acetic acid, a ketol acetate (XII), $C_{25}H_{41}O_3N$, mp 185—187°, was isolated as a sole product. In this procedure the β-configuration of the C_4-acetoxyl group would be retained, since the compound XII underwent facile epimerization on acid treatment to give a more stable isomer (XIII), $C_{25}H_{41}O_3N$, mp 185—188°. This chemical conversion was clearly evidenced by a reasonable change of the spin-spin coupling constant of the C_4-hydrogen (XII: 5.02 τ, doublet, J=3 cps; XIII: 4.92 τ, doubelt, J=11 cps).

The above ketol acetate (XII) was converted to the corresponding oxime (XIV), mp 205—207°, and then stereospecifically reduced by lithium aluminum hydride[14] to produce a crystalline amino-alcohol (XVa) as an essentially single product. The latter was characterized as its O,N-diacetate (XVb), mp 220—225°, and identified with an authentic specimen of 3β-acetamido-20α-dimethylamino-4β-acetoxypregnane.[15]

Finally, Schotten-Baumann condensation of XVa and benzoyl chloride yielded an N-benzoyl compound (III), $C_{30}H_{46}O_2N_2 \cdot 1/2H_2O$, mp 290—293°, $[\alpha]_D$+19°. This compound was shown to be identical with natural epipachysandrine-A (III) in all respects.

Thus the formal syntheses of pachysandrine-A, -B, -C, and epipachysandrine-A from ergosterol were accomplished.

Experimental[16]

Preparation of 3β,4β-Dihydroxy-20α-dimethylamino-5α-pregnane (VIIa)——To a solution of 3α-methylamino-20α-dimethylamino-4-oxo-5α-pregnane (VI) (400 mg), derived from pachysandrine-A, in abs. *tert*-butanol (20 ml) was added potassium *tert*-butoxide (200 mg) and the mixture was stirred for 14 hr at room temperature.[17] Thereafter the mixture was poured into ice–water, acidified with acetic acid, and then basified again with NH_4OH. The product was taken up in CH_2Cl_2, washed successively with 3% acetic acid and dil. Na_2CO_3, and dried. Evaporation of the solvent gave a crystalline residue (277 mg) (*ca.* 70%), which was recrystallized once from acetone to yield the diosphenol (V), needles, mp 194—196° (150 mg). This was reduced with $NaBH_4$ (150 mg) in MeOH (18 ml)–CH_2Cl_2 (4 ml) for 4 hr at room temperature. Usual working up gave a crystalline product (145 mg). Recrystallization from acetone gave the diol (VIIa) (100 mg), mp 218—223°, which was pure enough for the synthetic purpose.

Tosylation of 3β,4β-Dihydroxy-20α-dimethylamino-5α-pregnane (VIIa)——To a solution of the 3β, 4β-dihydroxy compound (VIIa) (45 mg) in pyridine (3 ml) was added *p*-toluenesulfonyl chloride (100 mg) at room temperature and the mixture was allowed to stand for 3 days. After dilution with dil. Na_2CO_3, the product was extracted with CH_2Cl_2, washed successively with 3% acetic acid, dil. Na_2CO_3 and water, dried, and evaporated. The crystalline residue (45 mg) was recrystallized from acetone to give 3β-monotosylate (VIIb) (38 mg) as small needles, mp 211—213°, $[\alpha]_D^{26}$ −3° (c=1.0). *Anal.* Calcd. for $C_{30}H_{47}O_4NS$: C, 69.59; H, 9.15. Found: C, 69.88; H, 9.09. IR ν_{max} cm^{-1}: 3550 (OH), 1600, 1170, 1100, 925, 868,810 (tosylate). NMR τ: 2.22, 2.70 (4H, A_2B_2 quartet, J=8 cps, aromatic protons), 5.58 (1H, broad, C$\underline{H}$-OTs),

13) S.M. Kupchan, P. Slade, R.J. Young, and G.W.A. Milne, *Tetrahedron*, **18**, 499 (1962).
14) P.-L. Chien, W.E. McEwen, A.W. Burgstahler, and N.T. Iyer, *J. Org. Chem.*, **29**, 315 (1964) and references cited therein.
15) T. Kikuchi and S. Uyeo, Jr., *Chem. Pharm. Bull.* (Tokyo), **15**, 549 (1967).
16) All the melting points were determined on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. The optical rotations were taken in chloroform solutions unless otherwise specified. For drying the solutions of bases, anhydrous potassium carbonate was used unless any comment was added.
17) Treatment of the amino-ketone (VI) with 5% KOH–MeOH as reported in the previous paper[5] gave the crude diosphenol (V) in varying amounts. Instead, the reaction with potassium *tert*-butoxide in *tert*-butanol gave better yield.

6.15 (1H, multiplet, $W^{1/2}$ 7 cps; C<u>H</u>-OH), 7.56 (3H, aryl CH_3), 7.82 (6H, N-$(CH_3)_2$), 9.00, 9.38 (6H, two *tert*-CH_3), 9.13 (3H, doublet, $J=6$ cps; *sec*-CH_3). From the acidic wash solutions (3% acetic acid) was recovered a small amount of the starting material (4 mg).

Synthesis of O,N-Bisdeacylpachysandrine-A (Xa)——i) Treatment of the 3β-Mono-tosylate (VIIb) with Sodium Azide: A stirred solution of 3β-mono-tosylate (VIIb) (548 mg) and sodium azide (83 mg) in N-methyl-2-pyrrolidone (54 ml) was heated in an oil bath at 130—140° for 3 hr. The reaction mixture was poured into ice–water, basified with dil. Na_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried (anhyd. $MgSO_4$) and evaporated to give an oily product (VIII) (548 mg), IR ν_{max} cm^{-1}: 3400 (OH), 2100 (N_3) (It showed 3 spots on TLC[18] roughly in the ratio of 6:2:1).

ii) Lithium Aluminum Hydride Reduction of the Crude Azide (VIII) and the Subsequent N-Monomethylation: A suspension of the above crude azide (VIII) (548 mg) and excess $LiAlH_4$ in ether (60 ml) and tetrahydrofuran (20 ml) was refluxed for 3 hr. After the excess reagent was decomposed with aqueous ether, the insoluble material was removed by filtration and washed thoroughly with $CHCl_3$. The filtrate and the washings were combined and evaporated under reduced pressure. The residue was taken in 3% HCl, washed with CH_2Cl_2 in order to remove the weakly basic impurity, the acidic solution being basified with NH_4OH and extracted with CH_2Cl_2. After drying, evaporation of the solvent gave a crystalline product (IXa) (200 mg), which was directly used for the N-methylation.

The above product was dissolved in a formylation reagent (20 ml), which had been prepared by heating a 1:1 mixture of formic acid and acetic anhydride at 70° for 1 hr, and left standing for 21 hr at room temperature. The reaction mixture was poured into ice–water, basified with NH_4OH, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed successively with 3% HCl and dil. Na_2CO_3, dried, and evaporated to afford a weakly basic substance (crude O,N-diformate, IXb) (150 mg). This was subsequently reduced with $LiAlH_4$ and worked up in analogous manner as described above. A crystalline material (120 mg), obtained as a strongly basic fraction, was recrystallized from acetone to give needles (Xa) (40 mg), melting at about 190—200°. This compound was chromatographed over alumina (0.6×5 cm) from $CHCl_3$ and the eluate (30 mg) was then converted into a picrate in the usual manner. Recrystallizations from $CHCl_3$ gave yellow prisms, mp 244—247° (decomp.) (30 mg). The free base, recovered from the above picrate, was recrystallized from acetone to give a pure sample (Xa), mp 214—215°, $[\alpha]_D^{16}+28°$ ($c=0.5$). *Anal.* Calcd. for $C_{24}H_{44}ON_2\cdot 1/4H_2O$: C, 75.63; H, 11.77. Found: C, 75.48; H, 11.66. Mass Spectrum *m/e*: 376 (M^+, $C_{24}H_{44}ON_2$). IR (KBr), NMR, and mass spectra of this compound were identical with those of O,N-bisdeacylpachysandrine-A (Xa) and the mixed melting point did not depress.

O-Acetylation of O,N-Bisdeacylpachysandrine-A (Xa)——To a solution of O,N-bisdeacylpachysandrine-A (Xa) (71 mg) in acetic acid (2 ml) and acetic anhydride (2 ml) was added *p*-toluenesulfonic acid (130 mg) and the mixture was kept at room temperature for 20 hr. The reaction mixture was poured into ice-water, made alkaline with NH_4OH, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was again extracted with 3% HCl and the acidic extract was basified with NH_4OH, extracted with CH_2Cl_2, dried, and evaporated. Crystallization of the residue (72 mg, TLC: single spot) from acetone gave plates (Xb) (60 mg), mp 180—182°. After further recrystallization from the same solvent, the product showed mp 182—183°, $[\alpha]_D^{32}+12°$ ($c=1.0$). *Anal.* Calcd. for $C_{26}H_{46}O_2N_2$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.34; H, 11.00; N, 6.46. IR ν_{max} cm^{-1}: 1720, 1250 (O-Ac). NMR τ: 5.21 (1H, multiplet, $W^{1/2}$ 6 cps; C<u>H</u>-OAc), 7.53 (3H, N-CH_3), 7.83 (6H, N-$(CH_3)_2$), 7.94 (3H, O-Ac), 9.00, 9.35 (6H, two *tert*-CH_3), 9.12 (3H, doublet, $J=6$ cps, *sec*-CH_3).

Benzoylation of the O-Acetate (Xb)——A solution of the O-acetate (40 mg) in ether (10 ml) and CH_2Cl_2 (1.5 ml) was superposed on 10% aqueous Na_2CO_3 solution (7 ml) and cooled in an ice–water bath. To this mixture was added benzoyl chloride (0.1 ml) with mechanical stirring and the stirring continued for 1 hr. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic layer was then extracted with 3% acetic acid and the acidic aqueous solution was again extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with dil. Na_2CO_3, dried, and evaporated to give a weakly basic product (43 mg) which was recrystallized from acetone, affording colorless prisms (Ia) (30 mg), mp 235—237°. Further recrystallizations raised the melting point to 237—238°. $[\alpha]_D^{31}+90°$ ($c=1.0$). *Anal.* Calcd. for $C_{33}H_{50}O_3N_2$: C, 75.82; H, 9.64. Found: C, 75.79; H, 9.77. The IR (KBr) spectrum of this compound was superimposable on that of pachysandrine-A (Ia) and the mixed melting point did not depress.

Partial Acetylation of 3β,4β-Dihydroxy-20α-dimethylamino-5α-pregnane (VIIa)——A solution of 3β,4β-dihydroxy-20α-dimethylamino-5α-pregnane (VIIa) (70 mg) in pyridine (3 ml) and acetic anhydride (0.05 ml) was left stand for 18 hr at room temperature. After the reaction mixture was poured into an aqueous Na_2CO_3 solution, the product was taken up in CH_2Cl_2, and the CH_2Cl_2 solution was shaken with 3% acetic acid in order to separate the weakly basic and the strongly basic products. The weakly basic fraction obtained from the CH_2Cl_2 phase (XIa, 60 mg) crystallized from acetone in colorless prisms melting at 205° (40 mg). After recrystallization from the same solvent it showed mp 212—213°, $[\alpha]_D^{33}+16°$ ($c=1.0$). *Anal.* Calcd. for $C_{25}H_{43}O_3N$: C, 74.03; H, 10.69; N, 3.45. Found: C, 74.12; H, 10.68; N, 3.34. IR ν_{max}

18) Thin-layer chromatography: Aluminum oxide G acc. to Stahl (Merck) was employed. Developing solvent: Chloroform or chloroform–acetone. Coloring reagent: Iodine vapor or Dragendorff reagent.

cm^{-1}: 3550 (OH), 1728, 1250 (OAc). NMR τ: 5.27 (1H, broad, $W^{1/2}$ about 20 cps; CH-OAc), 6.17 (1H, multiplet, $W^{1/2}$ 6 cps, CH-OH), 7.82 (6H, N-$(CH_3)_2$), 7.92 (3H, OAc), 8.94, 9.34 (6H, two *tert*-CH_3), 9.12 (3H, doublet, $J=6$ cps, *sec*-CH_3).

The strongly basic fraction (30 mg), obtained from the 3% acetic acid phase, exhibited two spots on TLC roughly in a ratio of 1:1 corresponding to XIa and the starting material, respectively.

Alumina Catalyzed O→O Acyl Migration of the 3-Monoacetate (XIa)——The 3-mono-acetate (XIa) (70 mg) in benzene–$CHCl_3$ (1:1, 10 ml) was adsorbed onto alumina ("Woelm" neutral alumina, grade I) (10 g, column length: 1.0×14.5 cm). After standing for 14 hr at room temperature, elution was commenced and a small amount of impure substance was eluted with benzene (70 ml). Subsequent elution with ether–MeOH (4:1) (50 ml) gave a migrated product (XIb) (57 mg), which on trituration with acetone crystallized in prisms (50 mg) melting at 203—205°. Several recrystallizations from the same solvent gave an analytical sample, mp 206—208°, $[\alpha]_D^{32}+18°$ ($c=1.0$). *Anal.* Calcd. for $C_{25}H_{43}O_3N$: C, 74.03; H, 10.69; N, 3.45. Found: C, 73.88; H, 10.74; N, 3.64. IR ν_{max} cm^{-1}: 3480 (OH), 1725, 1260 (-OAc). NMR τ: 4.90 (1H, multiplet, $W^{1/2}$ 6 cps; CH-OAc), 6.37 (1H, broad, CH-OH), 7.82 (6H, N-$(CH_3)_2$), 7.90 (3H, OA-c), 9.01, 9.34 (6H, two *tert*-CH_3), 9.12 (3H, doublet, $J=6$ cps, *sec*-CH_3).

Chromium Trioxide Oxidation of the 4-Acetate (XIb)——To an ice-cooled solution of the 4-acetate (XIb) (50 mg) in acetic acid (2 ml) was added dropwise with mechanical agitation a solution of chromium trioxide (60 mg) in water (few drops) and acetic acid (2 ml) over a period of 30 min. After the agitation was continued for additional 4.5 hr under cooling, the reaction mixture was diluted with ice–water, made alkaline with dil. Na_2CO_3, and extracted with CH_2Cl_2. The extract was washed with water, dried (anhyd. $MgSO_4$), and evaporated to leave a crystalline residue (35 mg). Recrystallization from acetone gave a pure ketol acetate (XII) (15 mg) as colorless plates, mp 185—187°. $[\alpha]_D^{30}+89°$ ($c=1.0$). *Anal.* Calcd. for $C_{25}H_{41}O_3N$: C, 74.40; H, 10.24. Found: C, 74.50; H, 10.30. IR ν_{max} cm^{-1}: 1740, 1725, 1230 (CO and -OAc). NMR τ: 5.02 (1H, broad doublet, $J=3$ cps; CH-OAc), 7.48 (2H, CH_2-CO), 7.82 (6H, N-$(CH_3)_2$), 7.91 (3H, O-Ac), 8.87, 9.32 (6H, two *tert*-CH_3), 9.12 (3H, doublet, $J=6$ cps, *sec*-CH_3).

Epimerization of the 3-Keto-4-ol Acetate (XII)——To a solution of the compound (XII) (80 mg) in acetic acid (4 ml) was added 30% solution of HBr in acetic acid (0.2 ml) and the mixture was allowed to stand for 14 hr at room temperature. After dilution with cold water, the mixture was basified with NH_4OH and extracted with CH_2Cl_2. A viscous oil thereby obtained was dissolved in benzene and chromatographed over florisil (0.6×4.5 cm). Elution with benzene (eluate: 54 mg) and recrystallizations from hexane gave colorless prisms (XIII) (13 mg), mp 185—188°, $[\alpha]_D^{30}+5°$ ($c=1.0$). *Anal.* Calcd. for $C_{25}H_{41}O_3N\cdot1/4H_2O$: C, 73.57; H, 10.25. Found: C, 73.81; H, 10.35. IR ν_{max} cm^{-1}: 1740, 1725, 1235 (CO and O-Ac). NMR τ: 4.92 (1H, broad doublet, $J=11$ cps; CH-OAc), 7.81 (6H, N-$(CH_3)_2$), 7.86 (3H, O-Ac), 8.87, 9.31 (6H, two *tert*-CH_3), 9.12 (3H, doublet, $J=6$ cps, *sec*-CH_3).

Formation of the Oxime (XIV) from the Ketol Acetate (XII)——A mixture of hydroxylamine hydrochloride (325 mg), sodium acetate (208 mg), and MeOH (20 ml) was refluxed for 15 min. The 3-keto-4-ol acetate (XII) (73 mg) was then added to this mixture and refluxed for 3 hr. After cooling, the reaction mixture was poured into ice–water, made alkaline by addition of dil. Na_2CO_3, and extracted thoroughly with CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated to leave a crystalline mass (72 mg), which was dissolved in $CHCl_3$ and filtered through an alumina column (0.5×8 cm). Removal of the solvent *in vacuo* (residue: 60 mg) and crystallization from acetone afforded an oxime (XIV) as colorless prisms, mp 204—206°. An analytical sample was prepared by further recrystallizations from the same solvent, mp 205—207°, $[\alpha]_D^{30}-7°$ ($c=1.0$). *Anal.* Calcd. for $C_{25}H_{42}O_3N_2$: C, 71.73; H, 10.11. Found: C, 71.24; H, 10.17. IR ν_{max} cm^{-1}: 3280 (OH), 1734, 1230 (O-Ac), 1655 (C=N). NMR τ: 4.61 (1H, multiplet, $W^{1/2}$ 4 cps; CH-OAc), 7.82 (6H, N-$(CH_3)_2$), 7.98 (3H, O-Ac), 8.90, 9.33 (6H, two *tert*-CH_3), 9.11 (3H, doublet, $J=6$ cps; *sec*-CH_3).

Lithium Aluminum Hydride Reduction of the Oxime (XIV)——The above oxime (XIV) (97 mg) was reduced with excess lithium aluminum hydride (130 mg) in boiling ether (40 ml) for 3 hr. Usual working up gave a crystalline amino-alcohol (XVa) (52 mg) as a strongly basic product.

O,N-Diacetate (XVb)——A 30 mg portion of this product (XVa) was acetylated with acetic anhydride (2 ml) in pyridine (2 ml) at room temperature for 17 hr. After removal of the excess reagent *in vacuo*, the residue was worked up in the usual manner to yield an oily product (27 mg), which was essentially homogenous on TLC. This was chromatographed over alumina (0.4×6 cm) and eluted with ether–benzene mixture in the order of increasing polarity. Elution with ether–benzene (1:9, 20 ml) gave a less pure substance (XVb) (9 mg) and successive elution with ether–benzene (3:7, 20 ml) afforded a crystalline solid (XVb) (12 mg) which showed completely single spot on TLC. Recrystallization of the latter from acetone gave 3β-acetamido-20α-dimethylamino-4β-acetoxy-5α-pregnane (XVb), colorless plates, mp 220—225°, whose identity was confirmed by direct comparison with an authentic sample[15] (mixed fusion, IR (KBr) and NMR comparison).

Benzoylation of the Amino-alcohol (XVa)——The Schotten–Baumann condensation between the above crude amino-alcohol (XVa) (22 mg) and benzoyl chloride (0.2 ml) was performed for 1 hr in the same manner as given for Xb. As the reaction proceeded, a crystalline substance deposited in the reaction mixture, which was collected by filtration and washed with ether. This was dissolved again in $CHCl_3$, washed

with water, dried and evaporated *in vacuo* to give a crystalline residue (16 mg), showing a single spot on TLC. Chromatography over alumina (0.6×4 cm) from $CHCl_3$ and recrystallizations from acetone gave colorless leaves (III), mp 290—293°, $[\alpha]_D^{28}+19°$ ($CHCl_3$–MeOH (1:1), $c=0.375$). *Anal.* Calcd. for $C_{30}H_{46}O_2N_2 \cdot 1/2H_2O$: C, 75.74; H, 9.96. Found: C, 75.43; H, 9.87. This compound was shown to be identical with natural epipachysandrine-A (III) by mixed melting point determination and IR (KBr) comparison.

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