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Pachysandra Alkaloids. XII.[1] Transformation of Epipachysandrine-A into Pachystermine-A and -B[2]

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Pachystermine-A (I) and -B (II), isolated from *Pachysandra terminalis* Sieb. et Zucc. (Buxaceae), are novel type alkaloids having a β-lactam ring system in the molecule. These were synthesized from epipachysandrine-A (III) which was obtained as a minor component from the same source.

Among the pregnane-type alkaloids isolated so far from *Pachysandra terminalis* Sieb. et Zucc. (Japanese name: Fukki-so) (Buxaceae),[4] pachystermine-A (I) and -B (II)[5] are unique in the structural feature having a four-membered lactam (β-lactam).[6] Much attention has recently been focussed on the synthesis of β-lactam system and various methods have been developed.[7] We were also interested in the syntheses of these novel type alkaloids from other *pachysandra* alkaloid with more simple structure. Present paper deals with the formal syntheses of pachystermine-A (I) and -B (II) starting from epipachysandrine-A (III),[8] a minor alkaloid having the $3\beta,4\beta$-configuration in the ring-A.

For elaboration of the β-lactam ring, a key step in the synthesis, a feasible approach appeared to be the cyclization[9] of an appropriate amino acid (VII or its analogue) which may be prepared through oxidation of pachystermine-diol (IV). As previously described,[5] pachystermine-diol (IV) is readily available by lithium aluminum hydride reduction of pachystermine-A (I) or -B (II) and therefore our effort was initially made on the transformation of IV into pachystermine-A and -B.

Several attempts at the direct oxidation of pachystermine-diol (IV) with chromium trioxide or dimethylsulfoxide[10] were unsatisfactory, leading only to intractable mixtures in poor yields or recovery of the starting material. An alternative approach was then undertaken as outlined in Chart 1.

Treatment of the diol (IV) with acetic anhydride and acetic acid in the presence of *p*-toluenesulfonic acid yielded an O,O-diacetate (V), $C_{33}H_{58}O_4N_2$, mp 131—134°, which demonstrated infrared (IR) bands[11] for O-acetyls (1725 and 1250 cm^{-1}) and no amide band.

1) Part XI: T. Kikuchi, T. Nishinaga, and Y. Yoshimura, *Chem. Pharm. Bull.* (Tokyo), **19**, 1886 (1971).
2) Preliminary account of this work appeared in *Tetrahedron Letters*, **1968**, 909.
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) T. Kikuchi and S. Uyeo, Jr., *Chem. Pharm. Bull.* (Tokyo), **15**, 549 (1967).
6) The occurrence of β-lactam system in nature had been limited only to the antibiotics penicillins and cephalosporin C.
7) W.A. Bolhofer, J.C. Sheehan, and E.L.A. Abrams, *J. Am. Chem. Soc.*, **82**, 3437 (1960); A.K. Bose, B. Anjaneyulu, S.K. Bhattacharya, and M.S. Manhas, *Tetrahedron*, **23**, 4769 (1967); A.K. Bose and I. Kugajevsky, *ibid.*, **23**, 957 (1967) and references cited therein.
8) T. Kikuchi, S. Uyeo, Jr., and T. Nishinaga, *Chem. Pharm. Bull.* (Tokyo), **15**, 577 (1967).
9) J.C. Sheehan and K.R. Henery-Logan, *J. Am. Chem. Soc.*, **81**, 3089 (1959).
10) K.E. Pfitzner and J.G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963); V.J. Traynelis and W.L. Hergenrother, *ibid.*, **86**, 298 (1964); J.B. Jones and D.C. Wigfield, *Canad. J. Chem.*, **44**, 2517 (1966).
11) All the IR spectra were determined in chloroform solutions unless otherwise stated.

When the latter compound (V) was heated with hydrochloric acid in acetic acid, it underwent selective hydrolysis to generate a mono-acetate (VI) in good yield, mp 165—168°. The structure was proved by its nuclear magnetic resonance (NMR) spectrum[12] which showed a singlet for the acetyl group (7.91 τ), a broad doublet attributable to the carbinol methylene at 6.32 τ and a multiplet for the C_4-hydrogen at 4.73 τ.

Oxidation of the mono-acetate (VI) was achieved smoothly with chromium trioxide in acetic acid containing a few drops of sulfuric acid[13] to give the desired amino-acid (VII), showing IR absorptions at 3300, 2700—2200, and 1580 cm^{-1}. On treatment with diazomethane, VII gave the corresponding methyl ester (VIII) as a sole product, mp 186—188°, which was correctly analyzed for $C_{32}H_{56}O_4N_2$ and showed $[\alpha]_D+2°$ ($CHCl_3$).

However, the configuration of 3′-position of this amino-acid (VII) was still ambiguous, since the possibility of epimerization during the oxidation could not completely be excluded. Therefore the clear-cut assignment had to be made at this stage.

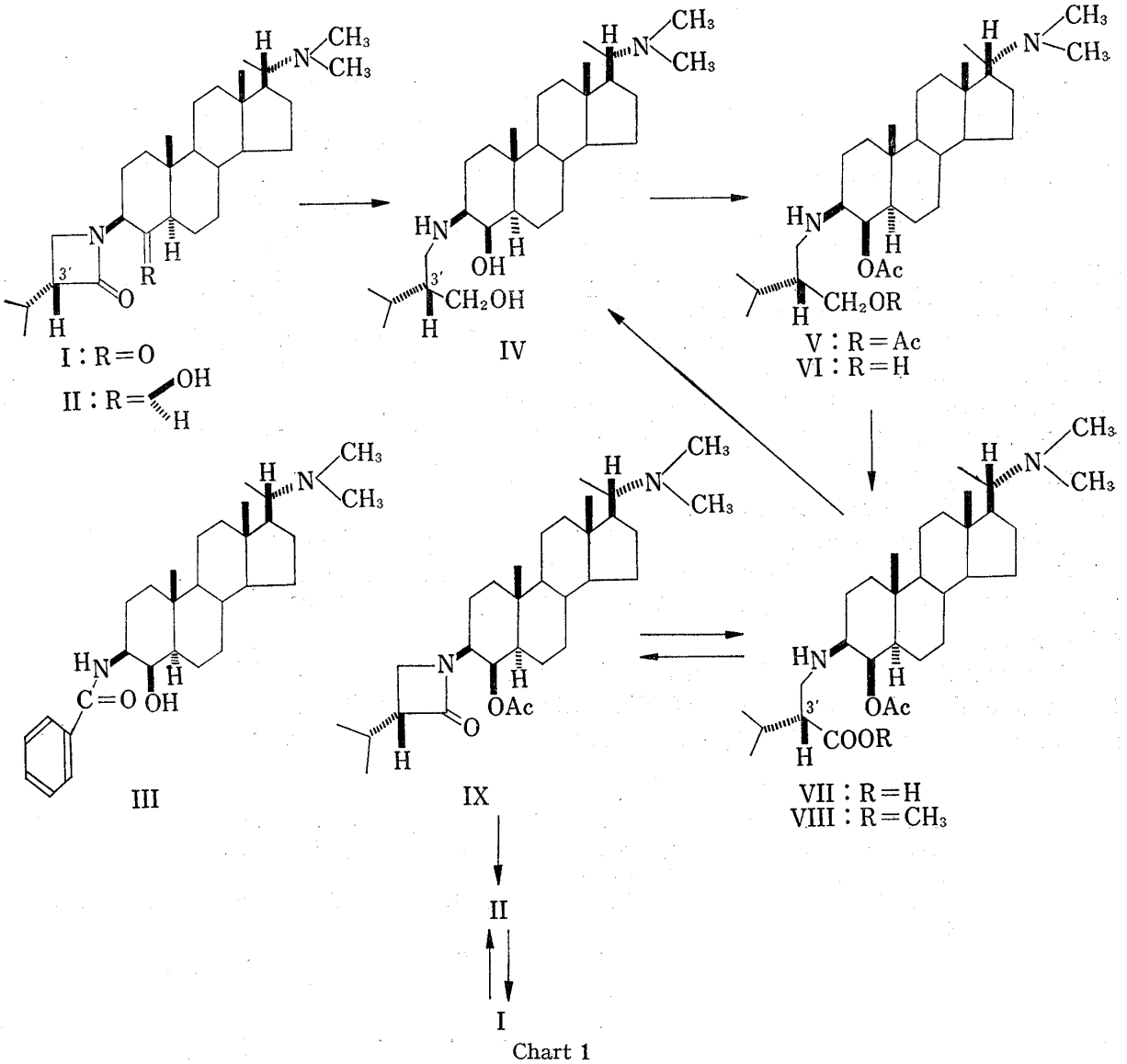

Chart 1

12) NMR spectra were measured on a Varian Associates A-60 High-Resolution NMR Spectrometer in deuterated chloroform using tetramethylsilane as the internal reference and chemical shifts are reported in τ values.

13) W.S. Johnson, J.A. Marshall, J.F.W. Keana, R.W. Franck, D.G. Martin, and V.J. Bauer, *Tetrahedron, Supplement*, No. **8** (Part II), 541 (1966).

Hydrolysis of pachystermine-B acetate (IX)[5] with hydrochloric acid in warm acetic acid resulted in the ring opening of the β-lactam system, affording solely an amino-acid (VII) which in turn was esterified with diazomethane to yield a methyl ester (VIII). This compound crystallized in needles, mp 188—190°, and showed $[\alpha]_D$+6° ($CHCl_3$). Reduction of this ester (VIII) with lithium aluminum hydride followed by N-methylation by formalin-sodium borohydride procedure gave 3′-normal N-methylpachystermine-diol (XVIa) exclusively and no trace of the corresponding 3′-isomer (XVIb) could be detected upon thin-layer chromatography (TLC).[14,15] Accordingly it followed that the configuration at 3′-position was kept unchanged in the acidic hydrolysis of pachystermine-B acetate (IX), in contrary to the result observed in alkaline hydrolysis which gave a mixture of 3′-epimeric pair.[5]

The two methyl esters (VIII) described above were proved to be identical with each other by IR comparison (KBr), thus confirming the 3′-normal stereochemistry in the amino-acid (VII) prepared by oxidation of the mono-acetate (VI).

Lactam cyclization of the crude amino-acid (VII) was effected with dicyclohexylcarbodiimide in methylene chloride at room temperature,[9] the β-lactam (IX) being isolated from the weakly basic fraction [16] in approximately 25% yield. This compound, mp 242—245°, $[\alpha]_D$−20° ($CHCl_3$), was correctly analyzed for $C_{31}H_{52}O_3N_2$ and identified as pachystermine-B acetate (IX) by direct comparison (mixed fusion and IR (KBr)).

The next problem is the conversion of IX to pachystermine-B (II). As described above, the β-lactam linkage is comparatively sensitive to acidic or basic hydrolysis and hence the selective hydrolysis of O-acetyl group in IX would not be possible in such conditions. Alternatively, our attention was turned to the general finding that the reduction of ester grouping with lithium aluminum hydride is preferred to that of amide grouping. Indeed, brief treatment of the compound (IX) with lithium aluminum hydride in tetrahydrofuran at−10— −20° gave an alcohol (II), mp 258—259°, $[\alpha]_D$−28° ($CHCl_3$), in 50% yield, which was identified with pachystermine-B (II) in all respects.

Pachystermine-B (II) can be easily transformed into pachystermine-A (I) by chromium trioxide oxidation as reported previously.[5]

Having accomplished the conversion of pachystermine-diol (IV) into pachystermine-A and -B, we next examined the transformation of epipachysandrine-A (III) into IV. In the course of structure elucidation of pachystermine-A and -B, we have synthesized a mixture of 3′-epimeric diols (XIII) by a sequence of reactions (XV→O,N-diacyl compound→XIII) starting from the amino-alcohol (XV).[5]

In analogous manner, we carried out the Schotten-Baumann reaction of an amino-ester (X),[8] an acyl-migration product of epipachysandrine-A (III), with the acid chloride (XI) of ethyl isopropylmalonate and the resulting product(XII)was reduced with lithium aluminum hydride in refluxing tetrahydrofuran to afford a mixture of diols (XIII), mp 200—205°, whose IR spectrum ($CHCl_3$) and behavior on TLC were identical with those of pachystermine-diol (IV) and of the above 3′-epimeric mixture (XIII). However all the attempts to isolate each diastereomer (IV and 3′-isomer) at this stage, even through several salts or acyl derivatives, resulted in failure.

Therefore, we turned our attention next to the utilization of N-methylpachystermine-diol (XVIa) for the present purpose, since N-methyl-diol (XVIa) could be separated from the mixture of 3′-stereoisomers (XVIa and XVIb) by careful alumina chromatography as already

14) Aluminum oxide G acc. to Stahl (Merck) was employed. Developing solvent: chloroform or chloroform–acetone. Coloring reagent: iodine vapor or Dragendorff reagent.

15) Both 3′-normal pachystermine-diol and its 3′-iso stereomer have the same *Rf* value on TLC, while their corresponding N-methyl compounds have different ones.

16) The term "weakly basic alkaloid" refers to the one which remains in chloroform (or methylene chloride) phase when the alkaloid is partitioned between chloroform (or methylene chloride) and 3% HCl (or 5% citric acid).

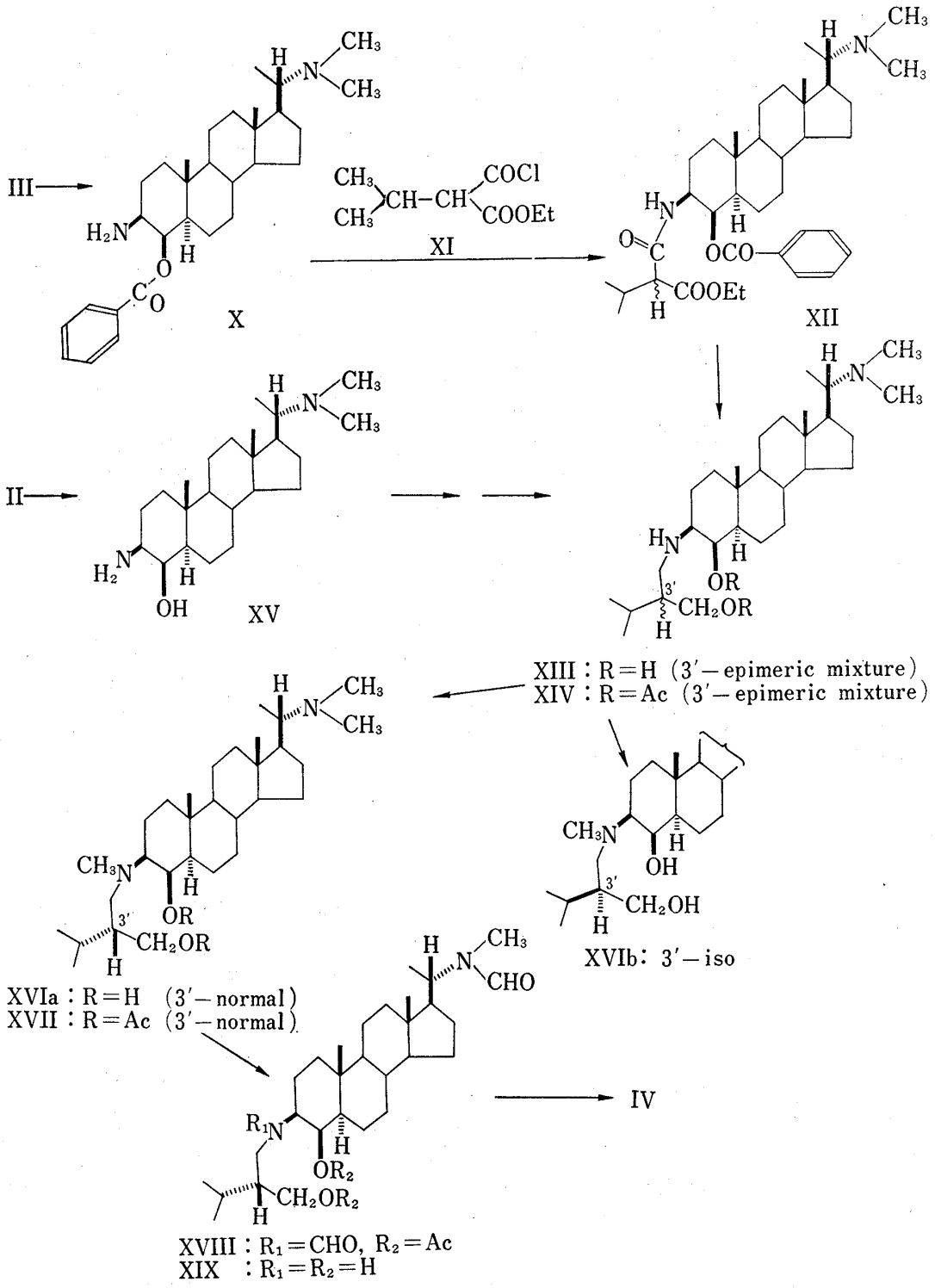

Chart 2

reported.[5] Initially we attempted the selective von Braun degradation in the hope that the preferential demethylation at the C_3-N-methyl group would occur, but it gave only an intractable mixture.

Finally we examined the CrO_3-pyridine oxidation of O,O-diacetyl-N-methylpachystermine-diol (XVII), mp 130—132°, whereupon was obtained a neutral diformate (XVIII) as an oily product. The structure of this product was supported by the intense amide absorption band at 1660 cm^{-1} and NMR signals at 1.73 (1H, $N(CH_2R)$-C<u>H</u>O), 1.92, 2.04 (1H, two peaks,

$N(CH_3)$-CHO), 7.21, 7.27 τ (3H, two peaks, amide N-CH_3).[17] On hydrolysis with potassium hydroxide in refluxing methanol, XVIII furnished a mono-formate (XIX), $C_{29}H_{52}O_3N_2$, mp 192—195°, which was then reduced with lithium aluminum hydride to give a diamine (IV), $C_{29}H_{54}O_2N_2$, mp 196—198°, $[\alpha]_D$ −6° ($CHCl_3$). This compound was found to be identical with pachystermine-diol (IV) by mixed fusion and IR (KBr) comparison.

Thus the transformation of epipachysandrine-A(III) into pachystermine-A (I) and B (II) was formally completed. Since the former (III) has been derived from ergosterol,[1] the present work also means the syntheses of pachystermine-A and -B from ergosterol.

Experimental[18]

O,O-Diacetylpachystermine-diol (V)——To a solution of pachystermine-diol (IV) (100 mg) in acetic acid (2 ml) and acetic anhydride (2 ml) was added *p*-toluenesulfonic acid (160 mg) and the mixture was kept at room temperature for 2 days. The mixture was poured into ice–water, made alkaline with NH_4OH and the product was taken up in CH_2Cl_2, washed with water, dried (K_2CO_3), and evaporated. Crystallization of the residue from hexane gave the O,O-diacetate (V) (70 mg) as colorless prisms, mp 125—130°. Further recrystallizations from CH_2Cl_2–acetone gave a pure sample, mp 131—134°, $[\alpha]_D^{29}$ +6° (c=1.0). *Anal.* Calcd. for $C_{33}H_{58}O_4N_2$: C, 72.48; H, 10.69; N, 5.12. Found: C, 72.29; H, 10.93; N, 5.03. IR ν_{max} cm^{-1}: 1725, 1250 (O-Ac). NMR τ: 4.77 (1H, multiplet, CH-OAc), 5.91 (2H, doublet, J=5 cps, CH_2-OAc), 7.42 (2H, CH_2-N), 7.83 (6H, N-$(CH_3)_2$), 7.93, 7.97 (6H, two O-Ac), 9.05, 9.36 (6H, two *tert*-CH_3), 9.10 (6H, dobulet, J=6 cps, two *sec*-CH_3), 9.13 (3H, doublet, J=6 cps, *sec*-CH_3).

Acid Hydrolysis of O,O-Diacetylpachystermine-diol (V)——A solution of V (100 mg) in acetic acid (2 ml) and 15% HCl (2 ml) was heated on steam bath for 7.5 hr. Thereafter, water was added to the reaction mixture, basified with NH_4OH, and extracted with CH_2Cl_2. The extract was washed with water, dried (K_2CO_3), and evaporated to yield a viscous oil (VI) (95 mg), which was chromatographed on alumina (0.6 ×2 cm). Two recrystallizations of the benzene eluate (72 mg) from acetone afforded a mono-acetate (VI) as colorless prisms, mp 165—168°, $[\alpha]_D^{30}$ −4° (c=1.0). *Anal.* Calcd. for $C_{31}H_{56}O_3N_2$: C, 73.76; H, 11.18; N, 5.55. Found: C, 73.81; H, 11.10; N, 5.50. IR ν_{max} cm^{-1}: 3200 (OH), 1726, 1250 (O-Ac). NMR τ: 4.73 (1H, multiplet, CH-OAc), 6.32 (2H, broad doublet, J=5 cps, CH_2-OH), 7.17 (2H, CH_2-N), 7.83 (6H, N-$(CH_3)_2$), 7.91 (3H, O-Ac), 9.04, 9.36 (6H, two *tert*-CH_3), 9.12 (6H, doublet, J=6 cps, two *sec*-CH_3), 9.13 (3H, doublet, J=6 cps, *sec*-CH_3). The CH_2Cl_2 eluate (23 mg) of the above alumina chromatography gave the diol (IV), mp 196—198°.

Chromium Trioxide Oxidation of the Mono-acetate (VI) (Formation of the Amino Acid (VII))——To an ice-cooled solution of the mono-acetate (VI) (35 mg) and conc. sulfuric acid (one drop) in acetic acid (2 ml) was added dropwise with mechanical stirring a solution of chromium trioxide (35 mg) in water (1.4 ml) and conc. sulfuric acid (0.1 ml) and the stirring continued for 5 hr under cooling. The reaction mixture was then poured into ice–water, made alkaline by the addition of dil. NH_4OH, and extracted thoroughly with a large amount of $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$) and evaporated *in vacuo* and the residue was washed with hexane. The insoluble amino acid (VII) (24 mg) was obtained as a slightly brown solid. IR ν_{max} cm^{-1}: 3300—2200, 1580 (amino-acid), 1730, 1230 (O–Ac).

Methylation of the Amino Acid (VII) with Diazomethane——The above amino acid (VII) (24 mg) was dissolved in MeOH–$CHCl_3$ and converted to its hydrochloride by the addition of conc. HCl (*ca.* 0.1 ml). To this solution was added an etherial diazomethane and the mixture was allowed to stand at room temperature for several hours. After removal of the solvents, the product was taken up in CH_2Cl_2, washed with dil. Na_2CO_3, dried (K_2CO_3), and evaporated to give a crude methyl ester (VIII). Recrystallization from acetone afforded a pure sample (10 mg), mp 186—188°, $[\alpha]_D^{29}$ +2° (c=1.0). *Anal.* Calcd. for $C_{32}H_{56}O_4N_2$: C, 72.13; H, 10.59. Found: C, 72.18; H, 10.35. This compound (VIII) showed no melting point depression upon admixture with the sample (VIII) derived from pachystermine-B acetate (IX) (see below) and their IR (KBr) spectra were superimposable.

Acid Hydrolysis of Pachystermine-B Acetate (IX) and Subsequent Esterification——A mixture of pachystermine-B acetate (IX) (100 mg), acetic acid (4 ml), and conc. HCl (1 ml) was heated on a steam bath for 1 hr and then diluted with water, washed with CH_2Cl_2 to remove the weakly basic substance. Basification of the aqueous layer and extraction with $CHCl_3$ gave a crude amino-acid (VII) (100 mg) whose IR spectrum ($CHCl_3$) was almost identical with the above amino-acid (VII) synthesized from VI. Treatment of this amino-acid with diazomethane in the same manner as above yielded a methyl ester (VIII) (100 mg) which

17) 20-N-Acyl derivatives of various pachysandra alkaloids show complicated patterns in the NMR spectrum probably owing to restricted rotations.

18) All the melting points were determined on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. All the specific rotations were measured in chloroform solution unless otherwise specified.

crystallized from acetone in colorless prisms, melting at 186—188°. An analytical sample, prepared by further recrystallization from the same solvent, showed mp 188—190°, $[\alpha]_D^{15}+6°$ ($c=1.0$). *Anal.* Calcd. for $C_{32}H_{56}O_4N_2$: C, 72.13; H, 10.59. Found: C, 72.02; H, 10.84. IR ν_{max} cm^{-1}: 1725, 1250 ($COOCH_3$ and O-Ac). NMR τ: 4.77 (1H, multiplet, C<u>H</u>–OAc), 6.32 (3H, $COOCH_3$), 7.83 (6H, N-$(CH_3)_2$), 7.90 (3H, O-Ac), 9.05, 9.36 (6H, two *tert*-CH_3), 9.09 (6H, doublet, $J=6$ cps, two *sec*-CH_3), 9.14 (3H, doublet, $J=6$ cps, *sec*-CH_3).

Lithium Aluminum Hydride Reduction of the Methyl Ester (VIII) and Subsequent N-Methylation——The methyl ester (VIII) (50 mg) was treated with excess $LiAlH_4$ (50 mg) in boiling ether (20 ml) for 3.5 hr. Excess reagent was then decomposed with water, the inorganic precipitate being filtered off and washed thoroughly with $CHCl_3$. The filtrate and the washings were combined and evaporated to give a diol (IV) (25 mg). Two recrystallizations from acetone afforded a pure sample (10 mg), needles, mp 193—196°, which was identified with pachystermine-diol (IV) by mixed melting point determination and IR (KBr) and NMR comparisons.

The mother liquor of the diol (IV) (15 mg) was dissolved in MeOH (10 ml) and treated with 37% formalin (0.4 ml) at room temperature for 1 hr. To this mixture was added portionwise excess $NaBH_4$ and stirred for 1 hr. After removal of the solvent *in vacuo*, the mixture was diluted with water, extracted with CH_2Cl_2, dried (K_2CO_3), and evaporated to give a crystalline product (XVIa), showing only a single spot on TLC (the spot of 3′-iso-N-methyl pachystermine-diol (XVIb) could not be observed at all). Recrystallization of this product from acetone gave colorless plates, mp 193—195°, which was proved to be identical with N-methylpachystermine-diol (XVIa) by mixed fusion and IR (KBr) comparison.

β-Lactam Ring Closure of the Amino Acid (VII)——A mixture of the amino acid (VII) (200 mg), dicyclohexylcarbodiimide (1 g) and CH_2Cl_2 (60 ml) was allowed to stand at room temperature for 5 days. After washing the mixture with 3% HCl and dil. Na_2CO_3 successively, the organic layer was dried (K_2CO_3) and evaporated. The residue was then partitioned between ether and 3% HCl, the acidic aqueous phase being separated and filtered to remove some insoluble material. Basification of the filtrate with Na_2CO_3 and extraction with CH_2Cl_2 gave a weakly basic product which was chromatographed over alumina (0.7 $\times$ 17 cm). Elution with benzene and ether–benzene (1:19) furnished an oily substance (60 mg) and subsequent elution with ether–benzene (1:9), ether, and CH_2Cl_2 gave a crystalline base (50 mg). Two recrystallizations of the latter from acetone–CH_2Cl_2 gave the β-lactam (IX) as colorless prisms (30 mg), mp 242—245°, $[\alpha]_D^{28}-20°$ ($c=1.0$). This was identified with an authentic sample of pachystermine-B acetate (IX) by mixed melting point determination and IR (KBr) comparison. *Anal.* Calcd. for $C_{31}H_{52}O_3N_2$: C, 74.35; H, 10.47. Found: C, 74.18; H, 10.76.

Controlled Reduction of Pachystermine-B Acetate (IX) with Lithium Aluminum Hydride——To a chilled suspension (−10——15°) of $LiAlH_4$ (70 mg) in tetrahydrofuran (9 ml) was added a chilled solution of IX (50 mg) in tetrahydrofuran (50 ml) under vigorous stirring and the reaction was monitored by TLC. After about ten minutes, a new spot corresponding to pachystermine-diol (IV) appeared on TLC.[19] At this point, the reaction was stopped by the careful addition of aqueous tetrahydrofuran and worked up as usual. The weakly basic product thereby obtained was chromatographed over alumina (0.7 $\times$ 5 cm) and the eluate (35 mg) with CH_2Cl_2 was recrystallized from acetone to give colorless prisms (23 mg), mp 258—259°, $[\alpha]_D^{27}-28°$ ($c=1.0$). This substance was found to be completely identical with natural pachystermine-B (II) (mixed fusion and IR (KBr)). *Anal.* Calcd. for $C_{29}H_{50}O_2N_2$: C, 75.93; H, 10.99. Found: C, 76.19; H, 11.26.

Transformation of Epipachysandrine-A (III) into 3′-Isomeric Pachystermine-diols (XIII)——i) Acyl Migration of Epipachysandrine-A (III): As previously described,[8] treatment of epipachysandrine-A (III) (100 mg) with HCl in warm acetic acid gave the benzoyl ester (X) (95 mg).

ii) Schotten–Baumann Condensation of X with the Acid Chloride (XI): A solution of the compound (X) (95 mg) in $CHCl_3$ (5 ml) and ether (30 ml) was superposed on 10% aqueous Na_2CO_3 solution (10 ml) and the mixture was cooled in an ice–bath. To this mixture was added dropwise with stirring the acid chloride (XI) which had been prepared by treating ethyl isopropylmalonate (1.05 g) with thionyl chloride (1 ml). After the stirring continued for 1 hr, the orgaic layer was separated from the aqueous layer which was further extracted with CH_2Cl_2. The combined organic layers were evaporated *in vacuo* and the residue was dissolved in 3% acetic acid, washed with ether, and then extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with dil. Na_2CO_3, dried (K_2CO_3), and evaporated to leave an oily substance (XII) (150 mg), which was used directly for the $LiAlH_4$ reduction.

iii) Lithium Aluminum Hydride Reduction of XII: The above substance (XII) (150 mg) was refluxed with excess $LiAlH_4$ (300 mg) in tetrahydrofuran (20 ml) for 13 hr.[20] The product (60 mg) thereby obtained could not be induced to crystallize at this stage. Therefore it was converted into the O,O-diacetate (XIV)

19) Since pachystermine-B (II) and its acetate (IX) are indistinguishable on TLC, the end point of reaction was recognized based on the appearance of pachystermine-diol in the reaction mixture.

20) This reduction was initially run in ether (20 ml)-tetrahydrofuran (10 ml) whereupon was obtained an N-acyl compound, mp 267—270°. An enforced condition was required for the complete reduction of the amide group.

by the same procedure as described for V. The crude O,O-diacetate (XIV) (30 mg), IR ν_{max} cm^{-1}: 1725 and 1250, was isolated as a strongly basic product by the usual working up. This was then submitted to the reductive hydrolysis using excess $LiAlH_4$ in ether, affording a crystalline amino-alcohol (XIII) (20 mg), which on recrystalization from acetone showed mp 200—205°. This product was indistinguishable from the 3′-isomeric mixture of pachystermine-diol (XIII) on TLC and also their IR spectra were superimposable.

N-Methylpachystermine-diol O,O-Diacetate (XVII)——A mixture of N-methylpachystermine-diol (XVIa) (467 mg), *p*-toluenesulfonic acid (700 mg), acetic anhydride (5 ml), and acetic acid (5 ml) was allowed to stand at room temperature. The product (530 mg), isolated in the usual manner, was recrystallized from acetone–CH_2Cl_2 to afford the O,O-diacetate (XVII) (323 mg) as long needles, mp 130—132°, $[\alpha]_D^{33}$ −5° (c=1.0). *Anal.* Calcd. for $C_{34}H_{60}O_4N_2 \cdot H_2O$: C, 70.54; H, 10.80; N, 4.84. Found: C, 70.91; H, 10.64; N, 4.91. IR ν_{max} cm^{-1}: 1730, 1250 (O-Ac). NMRτ: 4.63 (1H, multiplet, C<u>H</u>-OAc), 5.94 (2H, doublet, J=5.5 cps, C<u>H</u>$_2$-OAc), 7.72 (3H, N-CH_3), 7.84 (6H, N-$(CH_3)_2$), 7.99 (6H, two O-Ac), 9.03, 9.37 (6H, two *tert*-CH_3), 9.12 (6H, doublet, J=6 cps, two *sec*-CH_3), 9.15 (3H, doublet, J=6 cps, *sec*-CH_3).

Oxidation of N-Methylpachystermine-diol O,O-Diacetate (XVII) with Chromium Trioxide-Pyridine——A solution of the O,O-diacetate (XVII) (60 mg) in pyridine (1.5 ml) was added to a mixture of chromium trioxide (100 mg) and pyridine (3 ml), and the mixture was allowed to stand at room temperature for two days. The reaction mixture was poured into an aqueous Na_2CO_3 solution and extracted with ether. The etherial extract was washed successively with 3% HCl and dil. Na_2CO_3, dried ($MgSO_4$), and evaporated to give a colorless oil (XVIII) (40 mg), which showed a single spot on TLC. All the attempts to crystallize this product resulted in failure. IR ν_{max} cm^{-1}: 1733, 1230 (O-Ac), 1660 (N-CHO). NMRτ: 1.73 (1H, singlet, N(CH_2R)-C<u>H</u>O), 1.92, 2.04 (1H, two peaks, N(CH_3)-C<u>H</u>O), 4.80 (1H, multiplet, C<u>H</u>-OAc), 5.98 (2H, doublet, J=5 cps, C<u>H</u>$_2$-OAc), 7.21, 7.27 (3H, two peaks, amide N-CH_3), 7.97 (6H, two O-Ac).

Hydrolysis of the N,N-Diformate (XVIII)——A solution of the N,N-diformate (XVIII) (85 mg) in 1% KOH–MeOH (16 ml) was refluxed for 1 hr. After evaporation of the solvent *in vacuo* and dilution with water, the reaction mixture was extracted with ether. The etherial solution was then shaken with 3% HCl, whereupon was deposited a sparingly soluble substance (hydrochloride of mono-formate (XIX)), which was separated by filtration. This precipitate was suspended in dil. Na_2CO_3, extracted with CH_2Cl_2, dried (K_2CO_3), and evaporated to give the N-formyl compound (XIX) (50 mg), which crystallized from acetone in prisms, mp 185—190°. Further recrystallization from hexane gave a pure sample, mp 192—195°. $[\alpha]_D^{33}$ +2° (c=0.53). *Anal.* Calcd. for $C_{29}H_{52}O_3N_2$: C, 73.06; H, 11.00; N, 5.88. Found: C, 72.77; H, 10.80; N, 5.68. IR ν_{max} cm^{-1}: 3400 (OH), 1660 (N-CHO). NMRτ: 1.92, 2.04 (1H, two peaks, N(CH_3)-C<u>H</u>O), 6.27 (3H, C<u>H</u>$_2$OH and C<u>H</u>-OH), 7.21, 7.27 (3H, two peaks, amide N-CH_3).

Lithium Aluminum Hydride Reduction of the N-Formyl Compound (XIX)——The compound (XIX) (30 mg) was refluxed with excess $LiAlH_4$ in ether (15 ml) and tetrahydrofuran (5 ml) for 4 hr. The strongly basic product (25 mg), obtained in the usual way, was recrystallized from acetone to yield IV (11 mg) as colorless needles, mp 196—198°, $[\alpha]_D^{34}$ −6° (c=0.5). *Anal.* Calcd. for $C_{29}H_{54}O_2N_2$: C, 75.27; H, 11.76. Found: C, 75.05; H, 12.01. This was identified in all respects with pachystermine-diol (IV).

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