38. Tohru Kikuchi, Shoichiro Uyeo, and Toshinari Nishinaga: Pachysandra Alkaloids. V. Structure of Epipachysamine-A, -B, -C, -D, -E, and -F. (Faculty of Pharmaceutical Sciences, Kyoto University)

Structure determination of epipachysamine-A (I), -B (Ilia), -C (III), -D (IVb), -E (V), and -F (V), new alkaloids isolated from Pachysandra terminalis Sieb. et Zucc. (Buxaceae), was described herewith. Among these alkaloids, epipachysamine-B (IIia) is unique in that it has a nicotinamide grouping in the molecule.

(Received May 27, 1966)

In succession to the structure elucidation of pachysamine-A and -B, described in the preceding paper, the constitutions of another class of Pachysandra alkaloids, for which we proposed the same epipachysamine, are discussed in the present paper. Seven new alkaloids of this class, epipachysamine-A, -B, -C, -D, -E, -F, and desacyl-epipachysamine-A, have so far been isolated from Pachysandra terminalis Sieb. et Zucc. (Japanese name: Fukki-so) and they represent the stereoisomer of pachysamine type with respect to the 3-amino grouping.

Epipachysamine-A (I), $\alpha$-napthylacetate, m.p. 201~203°C, $[\alpha]_D -17^\circ$ (CHCl$_3$), was analyzed for C$_{16}$H$_{14}$On$_2$ and exhibited a tertiary amide band at 1625 cm$^{-1}$ in the infrared spectrum. The nuclear magnetic resonance (NMR) spectrum of the alkaloid gave a rather complicated pattern as illustrated in Fig. 1. This is indicative of the restricted internal rotation at the molecular part involving N-acyl grouping.

It remained unchanged upon alkaline and acidic hydrolyses under various conditions, but the treatment with phenyllithium in ether-benzene led to a desacyl compound (IIa), m.p. 96~98°C, $[\alpha]_D +20^\circ$ (CHCl$_3$). This compound gave analytical results in agreement with the empirical formula C$_{16}$H$_{14}$N$_2$1/4H$_2$O and the substitution pattern in its molecule could be demonstrated by its NMR spectrum which showed signals for one N-methyl (7.65r), one N-dimethyl (7.74r), one secondary C-methyl (8.93r, doublet, J 6 c.p.s.), and two tertiary C-methyis (9.24 and 9.33r). On acetylation, it regenerated the parent alkaloid (I), m.p. 203~205°C, $[\alpha]_D -14^\circ$ (CHCl$_3$). This confirmed the presence of an N-acyl group in epipachysamine-A (I).

Treatment of the above desacyl compound (IIa) with formalin-formic acid gave rise to an N-methyl compound (IIb), m.p. 103~106°C, $[\alpha]_D +12^\circ$ (CHCl$_3$), showing NMR signals for two N-dimethyl groups (7.73 and 7.85r). This compound was shown to be identical with an authentic sample of N,N-dimethylchonemorphine (IIb) in every respect, establishing the fundamental skeleton and stereochemistry of epipachysamine-A (I).

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* Preliminary accounts of the structure elucidation of these alkaloids appeared in a) Tetrahedron Letters, No. 27, 1817 (1964); b) Ibid., No. 24, 1993 (1965); c) Ibid., No. 36, 3169 (1965).
* Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto (栃池一 菊尾), Kyoto University.
* The infrared spectra were determined in chloroform solutions unless otherwise specified. For identification of compounds, spectra were taken in KBr discs using a Koken DS-301 Spectrometer.
* All NMR spectra were measured on a Varian Associates A-60 High-Resolution Spectrometer in deuterochloroform solutions at 60 Mc. and chemical shifts are recorded in $\tau$ values using tetramethylsilane as the internal reference.
2) A. Chatterjee, B. Das: Chem. Ind., 1445 (1959); Ibid., 1247 (1960).
Physical properties of the desacylepipachysamine-A are nearly the same as those of 3β-dimethylamino-20α-methy lamino-5α-pregnane (IIa) which had been synthesized by Corey, et al., \(^3\) although no direct comparison could be achieved.\(^{**}\)

A strong proof for the proposed structure (IIa) for desacylepipachysamine-A was provided by the mass spectrum\(^*\) which showed a very strong peak at m/e 58 (A) and moderately strong peaks at m/e 84 and 110 (B and C, respectively) (Fig. 4).\(^{**}\)

![Chart 1](image)

\(^{**}\) In this connection it is pertinent to note that the isolation and structure determination of 3β-methyl amino-20α-dimethylamino-5α-pregnane (=dictyophlebine) was recently reported by Goutarel and collaborators. The reported melting point (149\(°\)) is distinctly different from that of desacylepipachysamine-A (IIa). See Q. Khuong-Huu, X. Monseur, M. Truong-Ho, R. Kocjan, R. Goutarel: Bull. soc. chim. France, 3035 (1965); R. Goutarel: "Les Alkaloides steroidiques des Apocynacees," 66 (1964), Hermann, Paris.

\(^*\) The mass spectra were taken on a Hitachi Mass Spectrometer Model RMU-6D equipped with a direct inlet system.

\(^{**}\) The genesis of the other characteristic peaks at m/e 303 (M+−57) and 288 (M+−72) will be discussed in Part \(\text{VI}\) of this series (Yakugaku Zasshi, in press.

This behavior is in good agreement with the proposed fragmentation mechanism\(^9\) for this type of alkaloids, which can be visualized as shown in Chart 2 and evidently localized the methyamino group at the 20-position. Therefore the structure of epipachysamine–A should be represented by the formula I.\(^9\)

Epipachysamine–C (III)\(^{99}\) is a minor alkaloid which was obtained as its neutral N,N-diacetate from the acetylated product of the strongly basic alkaloid fraction of the plant.\(^9\)

The diacetate (N\(\alpha\)), m.p. 242–243\(^\circ\), \([\alpha]_D^{20} = -16^\circ\) (CHCl\(_3\)), was analyzed for C\(_{27}\)H\(_{46}\)O\(_2\)N\(_2\) and showed a strong tertiary amide band (1625 cm\(^{-1}\)) in the infrared spectrum. It should be noted that the NMR spectrum of the diacetate (N\(\alpha\)) exhibited a very complicated pattern (Fig. 2), from which, notwithstanding, the presence of two methylacetylamino and three C-methyl groups was presumed. These observations coupled with the correlation to other Pachysandra alkaloids led us to assume that the diacetate might be either 3\(\beta\),20\(\alpha\)-bismethylacetylamino-5\(\alpha\)-pregnane (N\(\alpha\)) or its 3\(\alpha\)-isomer. The former base (N\(\alpha\)) was synthesized from epipachysamine–A (I) via the intermediates, N\(\beta\) and N\(\epsilon\).

Treatment of epipachysamine–A (I) with cyanogen bromide in boiling benzene gave rise to an N–CN compound (N\(\beta\)), C\(_{27}\)H\(_{45}\)O\(_2\)N\(_2\), m.p. 234–235\(^\circ\), whose infrared spectrum clearly demonstrated the C≡N band at 2200 cm\(^{-1}\). Hydrolysis of this compound with potassium hydroxide in diethylene glycol led to an NH compound (N\(\epsilon\)), m.p. 206–207\(^\circ\), \([\alpha]_D^{20} = +5^\circ\) (CHCl\(_3\)), which, on acetylation, yielded a neutral N,N-diacetate (N\(\epsilon\)), C\(_{27}\)H\(_{46}\)O\(_2\)N\(_2\),

\(^9\) Recently Chatterjee and collaborators reported the isolation and structural elucidation of saracodine, m.p. 190–192\(^\circ\), from Sarcoceca pruniiformis Linn., and gave the same structure as epipachysamine–A (I) to saracodine. As suggested by them, it is probably identical with epipachysamine–A, although no direct comparison has achieved yet. (See A. Chatterjee, B. Das, C. P. Dutta, K. S. Mukherjee: Tetrahedron Letters, No. 1, 67 (1965)).

m.p. 243~244°, [α]D -22° (CHCl₃). The infrared spectrum (KBr) of the above compound (IIa) was shown to be identical with that of N,N-diacetylpipachysamine-C and also the mixed melting point gave no depression.

Since no amide band was observed in the infrared spectrum of the original, crude alkaloid fraction, the structure of epipachysamine-C is assigned to the formula III.*¹⁰

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*¹⁰ It should be mentioned that, after our results were published in preliminary communication, Goutarel and collaborators reported the structure elucidation of dictyodiamine isolated from Dycltyophleba lucida (K. Scopa) Pfeffer and they gave the structure III for the alkaloid. Also, they cited in a table two alkaloids obtained from Funtumia latifolia, named futudiamine-A (V) and -B (IIa), whose structures are identical with epipachysamine-F and desacylepipachysamine-A, respectively. (See, Q. Khuong-Huu, X. Monsieur, M. Truong-Ho, R. Kocjan, R. Goutarel: Bull. soc. chim. France, 3035 (1965)).
Epipachysamine-F (V) is also a minor alkaloid obtained as its N-acetate from the acetylated product of strongly basic alkaloid fraction.  

The acetate (VI), m.p. 250-253°, \([\alpha]_D +6^\circ\) (CHCl₃), showed the infrared bands (3420, 1660, and 1510 cm⁻¹) for a secondary amide group and the NMR signals for one acetyl (8.07\(\tau\)), one N-dimethyl (7.72\(\tau\)), one secondary C-methyl (8.87\(\tau\), doublet, J 6 c.p.s.), and two tertiary C-methyls (9.23 and 9.30\(\tau\)) (Fig. 3). Elemental analyses of the acetate gave results which supported the empirical formula \(C_{35}H_{44}ON_2 \cdot 1/2 H_2O\).

Mass spectrometry provided an important information about the gross structure of epipachysamine-F acetate. The intense peaks at m/e 84 (b) and 110 (c) together with the characteristic peaks at m/e 302 (d), 345 (\(M^+ - CH_3CO\)), and 373 (\(M^+ - CH_4\)) suggested strongly the structure VI for the base⁹ (except for the configuration of 3-dimethylamino group) (Fig. 5).

![Mass Spectrum of N-Acetylpachysamine-F (VI)](image)

Acid hydrolysis of the acetate (VI) and the subsequent N-methylation afforded a diamine (IIb), \(C_{35}H_{44}N_2\), m.p. 106-108°, \([\alpha]_D +28^\circ\) (CHCl₃), identified with an authentic \(N,N\)-dimethylchonemorphine (IIb).

At this stage, the experiments were made to correlate directly N-acetylpachysamine-F (VI) to epipachysamine-A (I) in the following scheme:

The acetate was reduced with lithium aluminum hydride and the resulting amine (VIIa) was submitted to N-methylation to give an \(N(CH_3)CH_2CH_3\) compound (VIIb), m.p. 105-107°, \([\alpha]_D +38^\circ\) (CHCl₃). This compound was identified by direct comparison

![NMR Spectrum of Epipachysamine-B (VIIa)](image)
### Table I.

<table>
<thead>
<tr>
<th></th>
<th>Epipachysamine-B (Ⅲa)</th>
<th>Epipachysamine-D (Ⅲb)</th>
<th>Epipachysamine-E (Ⅲc)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Natural</td>
<td>Synthetic</td>
<td>Natural</td>
</tr>
<tr>
<td>Formula</td>
<td>C_{29}H_{44}NO_{3}</td>
<td>C_{29}H_{44}NO_{3}</td>
<td>C_{29}H_{44}NO_{3}</td>
</tr>
<tr>
<td>m.p. (°C)</td>
<td>260~262</td>
<td>260~263</td>
<td>245~248</td>
</tr>
<tr>
<td>( [\alpha]_D ) (CHCl\textsubscript{3}) (°C)</td>
<td>+16</td>
<td>+38</td>
<td>+13</td>
</tr>
<tr>
<td>IR (CHCl\textsubscript{3}) (cm\textsuperscript{-1})</td>
<td>1660</td>
<td>1655</td>
<td>1630</td>
</tr>
<tr>
<td>NMR signals for the acid portion (( \tau ))</td>
<td>2.68, 1.91\textsuperscript{a}</td>
<td>Identical</td>
<td>2.1~2.7 (5H)</td>
</tr>
<tr>
<td>Other characteristic bands</td>
<td>1590</td>
<td>Identical</td>
<td>1515</td>
</tr>
<tr>
<td>(pyridine)</td>
<td>1600, 1580</td>
<td>1485 (phenyl)</td>
<td>1665 (C=C)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}) Assignments of the signals are as follows (see "NMR Spectra Catalog," Vol. 2, 453, 454 (1963), Varian Associates, Palo Alto, California):

- H\textsubscript{a} : 1.04\tau, doublet, J\textsubscript{a,b} 2 c.p.s.
- H\textsubscript{b} : 1.91\tau, sextet, J\textsubscript{b,a} 8 c.p.s., J\textsubscript{a,b,1a} 1.5~2 c.p.s.
- H\textsubscript{c} : 2.68\tau, quartet, J\textsubscript{c,a} 8 c.p.s., J\textsubscript{a,c} 5 c.p.s.
- H\textsubscript{d} : 1.33\tau, quartet, J\textsubscript{d,a} 5 c.p.s., J\textsubscript{a,d} 1.5 c.p.s.

\textsuperscript{b}) Overlapping on the N,N-dimethyl signal.

![Chart 3](image)

![Chart 4](image)
(infrared (IR) in KBr and mixed melting point) with the compound VIIb, derived from epipachysamine-A (I) by lithium aluminum hydride reduction.

The structure of epipachysamine-F was therefore proved to be V. 6

Epipachysamine-B (VIIa), -D (VIIb), and -E (VIIc) are mutually in very close relation, the first of which was isolated from the strongly basic alkaloid fraction of the plant and the latter two from the weakly basic fraction. Their properties are summarized in Table I.

The interrelationship between these three alkaloids was demonstrated by their infrared spectra (secondary amide bands), NMR spectra (signals for one N-dimethyl, one secondary C-methyl, and two tertiary C-methyl groups), and the observation that the hydrolysis with hydrochloric acid-acetic acid afforded the common desacyl base (X), m.p. 149~150 °C, [α]D +21° (CHCl3), which was identified as chonemorphone (X) by direct comparison with a synthetic sample. 7

Further characterization of this desacyl base was achieved by its transformation to the N,N-dimethyl compound (IIb), C24H34N2, m.p. 105~108 °C, [α]D +7° (CHCl3), and to the N-acetyl compound (X), C24H34O3N, m.p. 266~267 °C, [α]D +23° (CHCl3). Their identities were confirmed by direct comparison with authentic N,N-dimethylchonemorphone (IIb) and N-acetylchonemorphone (X). 2

The acid portions consisting of each amide group in epipachysamine-B (VIIa), -D (VIIb), and -E (VIIc) were considered to be nicotinic acid, benzoic acid, and β,β-dimethylacryl chloride, respectively, based mainly on inspection of their NMR and infrared spectra (Table I) and on consideration of the empirical formulas.

The confirmative evidences were presented by the condensation of chonemorphone (X) with nicotinic acid by mixed anhydride method, 4 and with benzoyl chloride and β,β-dimethylacryl chloride by Schotten-Baumann method, whereby obtained the corresponding amides whose properties are summarized in Table I. The synthesized compounds, VIIa, VIIb, and VIIc, were found to be identical with epipachysamine-B, -D, and -E, respectively, by mixed melting point determinations and infrared (KBr) comparisons.

The structure of epipachysamine-B (VIIa) is of considerable interest, because it presents a novel example of alkaloid in which a nicotinamide group consists of the partial structure. In this connection it might be pertinent to note that Cais and coworkers 7 reported recently the isolation of an alkaloid (cathidine-D) involving an O-nicotinate group from Catha edulis.

Experimental*11

Desacylepipachysamine-A (IIa) — To a solution of phenyllithium in ether (prepared from lithium (300 mg.) and bromobenzene (4.0 g.)) was added with stirring a solution of epipachysamine-A (I) (600 mg.) in benzene at room temperature and the mixture was refluxed for 3 hr. After the excess reagent was decomposed by addition of water, the organic solvent phase was separated and it was extracted with 10% acetic acid. The acidic extract was washed with CH2Cl2, made basic with NH4OH, extracted with CH2Cl2, dried over K2CO3, and evaporated. The crystalline residue (470 mg.) was dissolved in acetone and converted into crystalline hydrochloride by addition of conc. HCl. The hydrochloride was filtered and washed with acetone and then it was converted to the free base in the usual way. Recrystallizations from acetone or aqueous acetone afforded desacylepipachysamine-A (IIa) (280 mg.), m.p. 96~98 °C, as colorless plates. [α]D +20° (c=1.28). Anal. Calcd. for C24H34N2·1/2H2O: C, 78.95; H, 12.29; N, 7.68. Found: C, 78.94, 78.66; H, 12.14, 12.30; N, 7.86. NMR

*11 All the melting points were measured on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. All the optical rotations were taken in chloroform solutions.

\[
\tau : 7.65 \text{ (3H, N-CH}_3\text{), 7.74 (6H, N-(CH}_3\text{)}, 8.93 \text{ (3H, doublet), J 6 c.p.s.; sec. CH}_3\text{), 9.24, 9.33 \text{ (6H, two tert. CH}_3\text{). MS m/e : 360 (M\textsuperscript{+}), 110 (55\%), 84 (25\%), 58 (base peak).}
\]

From the CHC\textsubscript{6}H\textsubscript{5}Cl\textsubscript{2} washing solution was recovered the unchanged starting material (125 mg.), which showed m.p. 185~190\degree C (50 mg.) after recrystallization from acetone.

**Acetylation of Desacylepipaschamine-A (IIa)**—A mixture of the desacyl compound (IIa) (30 mg.), pyridine (0.2 ml.), and acetic anhydride (0.2 ml.) was heated on a water bath for 4 hr. The product (34 mg.), isolated in the usual way, was recrystallized from acetone to afford colorless plates (25 mg.), m.p. 203~205\degree C, which was identified with epipaschamine-A (I) by mixed m.p. and IR (KBr) comparison. [\(\alpha\textsubscript{D}\textsuperscript{+} = -14\degree \text{ (c=1.14).}
\]

**Acetyl. C. for C\textsubscript{2}H\textsubscript{2}H\textsubscript{2}ON\textsubscript{2} : C, 77.55; H, 11.52. Found : C, 77.84; H, 11.53. IR \nu_{\text{amide}} \text{ cm}^{-1} : 1625 (NCOCH\textsubscript{3}).

**N-Methylation of Desacylepipaschamine-A (IIa)**—A solution of the desacyl compound (IIa) (40 mg.) in formic acid (0.5 ml.) and 37\% formalin (0.5 ml.) was heated on a water bath for 4 hr. The product, isolated in the usual working up, was recrystallized from aqueous acetone to give the N-methyl compound (IIb) (37 mg.) as colorless needles, m.p. 103~106\degree C, identical with an authentic sample of N,N-dimethylchonemorphine (IIb) by mixed m.p. and IR (KBr) comparison. [\(\alpha\textsubscript{D}\textsuperscript{+} = +12\degree \text{ (c=1.14).}
\]

**Acetyl. C. for C\textsubscript{2}H\textsubscript{2}H\textsubscript{2}N\textsubscript{2} : C, 80.15; H, 12.38. Found : C, 80.18; H, 12.54. NMR \tau : 7.73, 7.85 (12H, two N-(CH}_3\text{)\textsubscript{2}H\textsubscript{2}ON\textsubscript{2} : C, 77.26; H, 11.41. Found : C, 77.40; H, 11.58. IR \nu_{\text{uvb}} \text{ cm}^{-1} : 3400, 3300 (NH), 1665, 1515 (NCOCH}_3).$$

**Acetylation of Desacylepipaschamine-B (IX)**—The crude desacyl compound (IX) (70 mg.) was acetylated by heating with acetic anhydride (1 ml.) and pyridine (1 ml.) for 1 hr on a water bath. The product, recovered with CHC\textsubscript{6}H\textsubscript{5}Cl\textsubscript{2} and dil. Na\textsubscript{2}CO\textsubscript{3}, was chromatographed over alumina (1 x 10 cm.). Elution with CHC\textsubscript{6}H\textsubscript{5}Cl\textsubscript{2} followed by recrystallization from acetone-CHC\textsubscript{6}H\textsubscript{5}Cl\textsubscript{2} gave the N-acetate (X) (40 mg.) in colorless plates, m.p. 264~266\degree C. Pure sample showed m.p. 266~267\degree C, [\(\alpha\textsubscript{D}\textsuperscript{+} = +23\degree \text{ (c=1.0).}
\]

**Acetyl. C. for C\textsubscript{2}H\textsubscript{2}H\textsubscript{2}ON\textsubscript{2} : C, 77.26; H, 11.41. Found : C, 77.40; H, 11.58. IR \nu_{\text{uvb}} \text{ cm}^{-1} : 3400, 3300 (NH), 1665, 1515 (NCOCH}_3).$$

**Preparation of Chonemorphine Nicotinate (VIIIA)**—Ethyl chloroformate (0.2 ml.) was added with stirring to a chilled solution of nicotinic acid (350 mg.) and triethylamine (0.3 ml.) in abs. dimethylsulfoxide (3 ml.) and tetrahydrofuran (2 ml.). To this mixture was added dropwise a solution of chonemorphine (V) (54 mg.) in abs. dimethylsulfoxide (1 ml.) and abs. tetrahydrofuran (3 ml.) under ice-cooling and the stirring continued for 20 minutes and then at room temperature for additional 2 hr. After decomposition of the excess reagent with water and evaporation of solvents in vacuo, the residue was diluted with dil. Na\textsubscript{2}CO\textsubscript{3}, extracted with CHC\textsubscript{6}H\textsubscript{5}Cl\textsubscript{2}, dried, and evaporated. Recrystallizations of the residue from acetone afforded the nicotinate (VIIa) (36 mg.), m.p. 256~260\degree C. Further purification by alumina chromatography followed by recrystallization gave a pure sample (25 mg.) as colorless leaves, m.p. 260~263\degree C, [\(\alpha\textsubscript{D}\textsuperscript{+} = +38\degree \text{ (c=1.10).}
\]

**Acetyl. C. for C\textsubscript{2}H\textsubscript{2}H\textsubscript{2}ON\textsubscript{2} : C, 75.49; H, 10.48; N, 10.16. Found : C, 75.76; H, 10.24; N, 10.24. IR \nu_{\text{uvb}} \text{ cm}^{-1} : 3220 (N-CN), 1625 (N-COCH\textsubscript{3}).$$

**Preparation of Chonemorphine Nicotinate (VIIIA)**—Ethyl chloroformate (0.2 ml.) was added with stirring to a chilled solution of nicotinic acid (350 mg.) and triethylamine (0.3 ml.) in abs. dimethylsulfoxide (3 ml.) and tetrahydrofuran (2 ml.). To this mixture was added dropwise a benzene solution (10 ml.) of cyanogen bromide (1.5 g.) at room temperature and stirred for 20 minutes. The mixture was then refluxed for 3 hr. The excess reagent and solvent were evaporated under reduced pressure, the residue was dissolved in CHC\textsubscript{6}H\textsubscript{5}Cl\textsubscript{2} and passed through an alumina column (1 x 10 cm.). Elution with the same solvent and recrystallization from acetone-CHC\textsubscript{6}H\textsubscript{5}Cl\textsubscript{2} gave the N-CN compound (N) (300 mg.) as needles, m.p. 234~236\degree C, [\(\alpha\textsubscript{D}\textsuperscript{+} = +22\degree \text{ (c=1.0).}
\]

**Acetyl. C. for C\textsubscript{2}H\textsubscript{2}H\textsubscript{2}ON\textsubscript{2} : C, 75.49; H, 10.48; N, 10.16. Found : C, 75.76; H, 10.24; N, 10.24. IR \nu_{\text{uvb}} \text{ cm}^{-1} : 3220 (N-CN), 1500, 1485 (pyridine). This material was identified with epipaschamine-B by IR (KBr) and NMR comparisons and mixed n.**

**Reaction of Epipaschamine-A (I) to N,N-Diacetylepipaschamine-C (IVA). i) von Braun**

**Hydrolysis of the N-CN Compound (IVb)**—In a flask fitted with an air condenser, a mixture of the N-CN compound (IVb) (250 mg.), KOH (2 g.), water (1 ml.), diethylene glycol (10 ml.), and MeOH (10 ml.) was refluxed for 4 hr in an oil bath at 150\degree C. After cooling, the mixture was diluted with water and extracted with CHC\textsubscript{6}H\textsubscript{5}Cl\textsubscript{2}. The extract was washed successively with 3\% HCl and dil. Na\textsubscript{2}CO\textsubscript{3}, dried over K\textsubscript{2}CO\textsubscript{3}, and evaporated to give a crystalline residue (230 mg.). Recrystallizations from acetone gave colorless needles (N-c) (192 mg.), m.p. 206~207\degree C, [\(\alpha\textsubscript{D}\textsuperscript{+} = +5\degree \text{ (c=1.0).}
\]

**Acetyl. C. for C\textsubscript{2}H\textsubscript{2}H\textsubscript{2}ON\textsubscript{2} : C, 75.39; H, 11.31; N, 7.15. Found : C, 76.66; H, 11.42; N, 7.12. IR \nu_{\text{uvb}} \text{ cm}^{-1} : 1625 (NCOCH\textsubscript{3}).$$

**NMR \tau : 7.21, 7.27 (3H, two peaks, N(COR)-CH\textsubscript{3}), 7.59 (3H, N-CH\textsubscript{3}), 7.88, 7.96 (3H, two peaks, N-COCH\textsubscript{3}), 9.22 (6H, broad, two tert. CH\textsubscript{3}), and about 7.85 (3H?, three peaks, sec. CH\textsubscript{3}).**
iii) Acetylation of the NH Compound (IVc) —— The compound (IVc) (50 mg.) was treated with acetic anhydride (1 ml.) and pyridine (1 ml.) at room temperature overnight. The neutral compound was used for recrystallization from ether—CH₂Cl₂ to afford the diacetate (Va) (52 mg.), colorless leaves, m.p. 243—244⁰, [α]²₅ + 22⁰ (c = 1.0). IR νᵥmax cm⁻¹: 1625 (C=OCH₃). This compound was identified with N,N-diacyethylpachyphasamine—C by mixed m.p. and IR (KBr) comparison. Anal. Calcd. for C₁₃H₁₇O₄N₇: C, 75.30; H, 10.77; N, 6.51. Found: C, 75.57; H, 10.94; N, 6.26.

Acid hydrolysis of Epipachyphasamine-D (VIIIb) —— A solution of the alkaloid (VIIb) (200 mg.) in conc. HCl (2 ml.) and acetic acid (2 ml.) was heated in a sealed tube at 150—160⁰ (bath temp.) for 5 hr. Usual working up, as described for epipachyphasamine—B, afforded the strongly basic hydrolysis product (X) (150 mg.), whose IR spectrum (CHCl₃) was identical with that of authentic chonemophine (K).

N-Methylation of Desacetyl pachyphasamine-D (IX) —— The crude desacyl base (X) (50 mg.) was heated with 37% formalin (2 ml.)—formic acid (2 ml.) for 4 hr. and worked up as usual. After recrystallization from acetone, the N,N-dimethyl compound (IX) (40 mg.) showed m.p. 105—108⁰, [α]₁₉ + 7⁰ (c = 1.0). This was identified as N,N-dimethylchonemophine. Anal. Calcd. for C₁₇H₃₄N₂: C, 81.15; H, 12.38; N, 7.48. Found: C, 79.87; H, 12.40; N, 7.51.

Acetylation of Desacetyl pachyphasamine-D (IX) —— The crude hydrolysis product (X) (60 mg.) was dissolved in pyridine (2 ml.) and acetic anhydride (2 ml.) with gentle warming and the solution was kept overnight at room temperature. The crude product (70 mg.), recovered with dil. Na₂CO₃ and CH₃CO₂H, was recrystallized from acetone to give the N-acetate (X) in colorless leaves, m.p. 267—268⁰, [α]₁₉ + 12⁰ (c = 1.06), which was identified with an authentic sample of N,N-dimethylchonemophine (X) by mixed m.p. and IR (KBr) comparison. Anal. Calcd. for C₁₇H₄₄O₄N₂: C, 77.26; H, 11.41; N, 7.21. Found: C, 77.54; H, 11.41; N, 7.08.

Preparation of Chonemophine Benzoate (VIIIb) —— Benzoy chloride (0.1 ml.) was added dropwise with mechanical stirring to a solution of chonemophine (80 mg.) in ether (10 ml.)—CH₂Cl₂ (2 ml.) placed on 10% aqueous KOH solution (3 ml.) and the stirring was continued for 1 hr. Then the organic phase was separated and the aqueous phase was extracted with ether. The combined extracts were evaporated under reduced pressure and the residue was dissolved in CH₂Cl₂, washed successively with 3% HCl and dil. Na₂CO₃, dried over K₂CO₃, and evaporated. Recrystallization of the residue from acetone gave the benzoate (VIIb) (65 mg.), colorless prisms, m.p. 243—247⁰. Further recrystallizations from the same solvent gave a pure sample, m.p. 247—249⁰, [α]₁₉ + 13⁰ (c = 1.0), which was shown to be identical with epipachyphasamine-D by mixed m.p. and IR (KBr) comparison. Anal. Calcd. for C₁₇H₃₄O₄N₂: C, 79.95; H, 10.29; N, 6.22. Found: C, 79.68; H, 10.51; N, 5.93.

Acid Hydrolysis of Epipachyphasamine-E (VIIc) —— The alkaloid (VIIc) (80 mg.) was hydrolyzed with conc. HCl—acetic acid (1:1, 3 ml.) in the same manner as described for epipachyphaphamine—B (VIIa). The product (60 mg.) showed the IR spectrum (CHCl₃) identical with that of chonemophine (K).

Preparation of Chonemophine β,β-Dimethylacrylate (VIIIc) —— The Schotten—Baumann condensation between chonemophine (64 mg.) and β,β-dimethylacryloyl chloride (0.1 ml.) was performed in the same manner as given for VIIb. The weakly basic product isolated was dissolved in benzene and chromatographed over alumina (0.8 × 3 cm.). Elution with benzene and crystallization from acetone afforded the N-acyl compound (VIIc) (40 mg.) in colorless leaves, m.p. 190—200⁰. After several recrystallizations, it showed m.p. 200—205⁰, [α]₁₉ + 19⁰ (c = 1.0). IR (KBr) and NMR spectra of this substance were identical with those of epipachyphaphamine-E and mixed m.p. did not depress. Anal. Calcd. for C₁₇H₃₄O₄N₂: C, 76.92; H, 11.30; N, 6.41. Found: C, 76.91; H, 11.40; N, 6.32.

Acid Hydrolysis of N-Acyetipachyphaphamine-F (VI) —— A solution of the base (V) (50 mg.) in conc. HCl (1 ml.) and acetic acid (1 ml.) was heated in a sealed tube at 170—190⁰ for 6 hr. After dilution with water and washing with CH₂Cl₂, the mixture was made basic with NH₂OH and extracted with CH₂Cl₂. The extract was dried over K₂CO₃ and evaporated to leave the crude desacyl compound (epipachyphaphamine—F) (50 mg.) which was hardly purified by recrystallization.

N-Methylation of Epipachyphaphamine-F (V) —— The above desacyl compound (V) (50 mg.) was heated with 37% formalin (1 ml.) and formic acid (1 ml.) in a water bath for 3 hr. The product, isolated in the usual way, was chromatographed over alumina (0.7 × 3 cm.) from benzene. Elution with benzene and ether—benzene afforded the crystalline N-methyl compound (Vib) (45 mg.) which was recrystallized from acetone to give a pure material, m.p. 106—108⁰, identified with N,N-dimethylchonemophine (IIb) by mixed m.p. and IR (KBr) comparison. [α]₁₉ + 28⁰ (c = 1.0). Anal. Calcd. for C₁₇H₃₄N₂: C, 80.15; H, 12.58. Found: C, 80.11; H, 12.64.

Lithium Aluminum Hydride Reduction of N-Acyetipachyphaphamine-F (VI) and Subsequent N-Methylation —— A suspension of the alkaloid (V) (70 mg.) and LiAlH₄ (140 mg.) in tetrahydrofuran (20 ml.) was refluxed for 4 hr. After the excess reagent was decomposed with aqueous acetone, the insoluble material was removed by filtration and washed thoroughly with CH₂Cl₂. The filtrate and the washings were combined and evaporated under reduced pressure. The residue was taken in 3% HCl, washed with CH₂Cl₂, basified with NH₂OH, and extracted with CH₂Cl₂. The extract was dried over K₂CO₃ and evaporated to give a crystalline product (VIIa) (50 mg.), which, without further purification, was N-methylated by heating with 37%
formalin (1 ml.)-formic acid (1 ml.) for 4 hr. The product, isolated in the usual way, was chromatographed over alumina (1 × 3 cm.) from benzene and then recrystallized from acetone to yield colorless prisms (Wb) (30 mg.), m.p. 105–107°, $[\alpha]_D^0 +38^\circ$ (c=1.0). This substance was identified with the reduction product of epiphasyamine-A (I), described below, by mixed m.p. and IR (KBr) comparison.

**Lithium Aluminum Hydride Reduction of Epipachysamine-A (I)—** A suspension of epipachysamine-A (I) (45 mg.) and LiAlH₄ (100 mg.) in ether (20 ml.) was refluxed for 3 hr. The product, isolated by the usual treatment, was crystallized from acetone to give the reduction product (Wb) (33 mg.), m.p. 104–105°. Further recrystallization from the same solvent gave a pure sample, m.p. 109.5–110°, $[\alpha]_D^0 +37^\circ$ (c=1.0). Anal. Calcd. for $C_{26}H_{46}N_2$: C, 80.34; H, 12.45. Found: C, 80.44; H, 12.45.

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**39. Tohru Kikuchi, Shoichiro Uyoe, and Toshinari Nishinaga: Pachysandra Alkaloids. VI.** Structure of Terminaline. **(Faculty of Pharmaceutical Sciences, Kyoto University)**

Structure of terminaline, one of minor alkaloids isolated from the strongly basic alkaloid fraction of *Pachysandra terminalis* Sins. at Zucc. (Buxaceae), was investigated and the complete structure (Ia) including absolute configuration was proposed for the alkaloid.

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Terminaline is a minor alkaloid isolated from the strongly basic alkaloid fraction of *Pachysandra terminalis* Sieb. et Zucc. (Japanese name: Fukki-so) along with a number of diaminopregnane type alkaloids. Among the Pachysandra alkaloids isolated so far, terminaline is the only alkaloid carrying one nitrogen function. Among the Pachysandra alkaloids isolated so far, terminaline is the only alkaloid carrying one nitrogen function.

Terminaline (I), m.p. 243–244°, $[\alpha]_D^0 +29°$ (50% MeOH–CHCl₃), was analysed for $C_{26}H_{46}O_2N$, which is consistent with the molecular ion peak at $m/e$ 363 in the mass spectrum. It showed an infrared OH band at 3300 cm⁻¹ (in nujol) and NMR signals.

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*Part V. T. Kikuchi, S. Uyoe, Jr., T. Nishinaga: This Bulletin, 15, 307 (1967).*

*The preliminary report of this work appeared in Tetrahedron Letters, No. 24, 1993 (1965).*

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*In this connection it is of interest that terminaline (Ia) is strongly basic in spite of only one amino function. This is in contrast to the observation that all Pachysandra alkaloids having a basic amino group and a neutral amide group have been isolated from the weakly basic alkaloid fraction.*

*Mass spectra were measured on a Hitachi Mass Spectrometer Model RMU-6D using an all-glass inlet system.*

*Infrared spectra were taken in chloroform solutions unless otherwise described. For identification of compounds, spectra were taken on a Koken DS-301 Spectrometer in KBr disc.*

*All the nuclear magnetic resonance (NMR) spectra were determined on a Varian Associates A-60 High-Resolution NMR Spectrometer at 60 Mc. in deuterochloroform solutions and chemical shifts are reported in $\tau$ values using tetramethylsilane as the internal reference.*