formalin (1 ml.)-formic acid (1 ml.) for 4 hr. The product, isolated in the usual way, was chromatographed over alumina (1 x 3 cm.) from benzene and then recrystallized from acetone to yield colorless prisms (Wb) (30 mg.), m.p. 105-107°, $\left[a\right]_{D}^{28}+38^{\circ}(c=1.0)$. This substance was identified with the reduction product of epiphasamines-A (I), described below, by mixed m.p. and IR (KBr) comparison.

**Lithium Aluminum Hydride Reduction of Epiphasamines-A (I)**—A suspension of epiphasamines-A (I) (45 mg.) and LiAlH$_4$ (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°, $\left[a\right]_{D}^{28}+37^{\circ}(c=1.0)$. Anal. Calcd. for C$_{32}$H$_{46}$N$_2$: C, 80.34; H, 12.45. Found: C, 80.44; H, 12.45.

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**Structure of Terminaline.**

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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.$^9$ Among the Pachysandra alkaloids isolated so far, terminaline is the only alkaloid carrying one nitrogen function.$^9$

Terminaline (I), m.p. 243-244°, $\left[a\right]_{D}^{29}+29^{\circ}$ (50% MeOH-CHCl$_3$), was analysed for C$_{32}$H$_{41}$O$_{2}$N, which is consistent with the molecular ion peak at m/e 363 in the mass spectrum.$^8$ It showed an infrared OH band at 3300 cm$^{-1}$ (in nujol)$^{13}$ and NMR signals.$^7$

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$^3$ Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto (滋東市 西区 京都).

$^4$ 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.

$^5$ Mass spectra were measured on a Hitachi Mass Spectrometer Model RMU-6D using an all-glass inlet system.

$^6$ 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.

$^7$ All the nuclear magnetic resonance (NMR) spectra were determined on a Varian Associates A-60 High-Resolution NMR Spectrometer at 60 Mc. in deuterochlorof orm solutions and chemical shifts are reported in $\tau$ values using tetramethylsilane as the internal reference.

for two protons geminal to hydroxyl groups (6.64 and 6.73\( \tau \)), one N-dimethyl (7.83\( \tau \)), two tertiary C-methyls (9.18 and 9.35\( \tau \)), and one secondary C-methyl (9.13\( \tau \), doublet, J 6 c.p.s.) (Fig. 1).

On acetylation terminaline gave the O,O-diactetyl compound (Ib), \( \text{C}_{27}\text{H}_{46}\text{O}_{2}\text{N} \), m.p. 202–204\( ^{0} \), [\( \alpha \)]\( _{D} \) +40\( ^{0} \) (CHCl\( _{3} \)), demonstrating strong infrared bands for O-acetyl groups (1730 and 1250 cm\(^{-1} \)). The formation of two O-acetyl groups was clearly indicated by their NMR signals at 7.97 and 7.99\( \tau \), as shown in Fig. 2. Mild alkaline hydrolysis of the diacetate (Ib) in methanolic sodium bicarbonate solution reformed terminaline (Ia).

Mass spectra of terminaline (Ia) and its O,O-diacetate (Ib) showed a very intense peak at m/e 72 (\( \bullet \)) which is the characteristic of the pregnane type alkaloids holding
an N-dimethylamino group at the 20-position. These observations are strongly suggestive of the partial structure (I') for the alkaloid.

It was suggested by the positive color test that the two hydroxyl groups in terminaline (Ia) are forming an α-glycol system. This was proved to be the case by the following experiments: Oxidation of the alkaloid (Ia) with periodic acid in 50% acetic acid gave rise to an oily aldehyde (II), which showed an intense carbonyl absorption band at 1720 cm⁻¹ in the infrared spectrum. Sodium borohydride reduction of this aldehyde (II) followed by acetylation led to a diol-diacetate (IIIb), C₂₉H₄₁O₆N, m.p. 147~150°, [α]₀ +16° (CHCl₃).

Biogenetic consideration strongly favored the location of one of the two hydroxyl groups at 3-position. The other hydroxyl group should therefore exist at either 2- or 4-position. But, in view of the analogy with other Pachysandra alkaloids having an oxygen function at 4-position, terminaline was believed to be 3,4-dihydroxy-20α-dimethylaminopregnane derivative. In confirmation of this supposition, conversion of the diosphenol (IV), whose structure had already been confirmed by synthesis, to the diol-diacetate (IIIb) was advanced.

The diosphenol (IV) was reduced with sodium borohydride to give 3β,4β-dihydroxy-20α-dimethylaminopregnane (V), C₃₀H₄₃O₆N·1/2H₂O, m.p. 226~228° which is not identical with terminaline. The assignment of the configuration at 4- and 5-positions of the compound (V) followed from the inspection of its NMR spectrum (Fig. 3) in which the 19-methyl signal occurred in lower field (i.e. 8.98°) than the standard region (i.e. 9.1~9.2°), indicating the 1,3-diaxial correlation between the 19-methyl and the 4-hydroxyl group, while the 3β-hydroxy orientation was given on the basis of the formation of an acetone (V), m.p. 165~167°. Treatment of the 3β,4β-diol (V) with periodic acid, followed by sodium borohydride reduction and acetylation, as run for terminaline afforded the diol-diacetate (IIIb), m.p. 148~150°, [α]₀ +19° (CHCl₃). This compound was

identified with the diol-diacetate (IIb) derived from terminaline by mixed melting point
determination and IR (KBr) comparison. This confirmed the skeletal structure and
5α-configuration of terminaline (Ia).

Turning now to the stereochcmistry of terminaline, the 3β,4α-dihydroxy orientation
was suggested by the observations that in NMR spectrum the 19-methyl signal occurred
in the ordinary region (i.e., 9.18 δ) and that terminaline failed to give acetoneide.8

Finally, we carried out the transformation of the diosphenol (IV) to terminaline by
reduction with sodium in boiling n-amyl alcohol, which is a well-known procedure
leading cyclic ketones to the corresponding equatorial alcohols. The product (Ia),
C18H19O3N, obtained in this procedure, showed m.p. 242-244° and [α]D +26° (50% MeOH-
CHCl3), and was found to be identical with terminaline by mixed melting point
determination and infrared (KBr) comparison.

From the foregoing results, the structure of terminaline can be represented by the
formula Ia.

Experimental9

Terminaline 0.0-Diacetate (Ib) — The alkaloid (Ia) (50 mg.) was dissolved in a warmed mixture of
pyridine (1 ml.) and acetic anhydride (1 ml.) and the solution was allowed to stand overnight at room tempera-
ture. After dilution with water and basification with Na2CO3, the product was taken up in CHCl3,
dried (K2CO3), and evaporated. The crystalline residue (55 mg.) was recrystallized from acetone to give the
O1,0-Diacetate (Ib) (30 mg.), m.p. 202-204°, as colorless plates. [α]D + 40° (c = 1.0). Anal. Calcd. for
C18H19O3N: C, 72.44; H, 10.13; N, 3.13. Found: C, 72.67; H, 10.24; N, 3.15. IR νmax cm⁻¹: 1730 and
1250 (O-Ac). NMR: δ: 5.10 (2H, broad, two CH-OAc), 7.83 (6H, N-(CH3)3), 7.97, 7.99 (6H, two OAc),
9.08, 9.35 (6H, tert. CH3), and 9.13 (3H, doublet, J 6 c.p.s.; sec. CH3). M.S. m/e: 447 (M⁺), 432 (M⁺-15),
72 (base peak), 43 (CH2CO⁺).

Hydrolysis of Terminaline 0.0-Diacetate (Ib) — The O,O-diacetate (Ib) (100 mg.) was dissolved in a
solution of NaHCO3 (1 g.) in MeOH (20 ml.) and water (20 ml.), and refluxed for 4 hr. The reaction mixture
was then poured into water and the resulting precipitate was collected by filtration. In was dissolved in
CHCl3-MeOH (9:1), dried over K2CO3, and evaporated in vacuo. The crystalline residue was recrystallized
from acetone-MeOH to afford needles (Ia) (80 mg.), m.p. 243-246°, identified with terminaline by mixed
m.p. determination and IR (KBr) comparison.

Periodic Acid Oxidation of Terminaline (Ia) — To a stirred solution of the alkaloid (Ia) (200 mg.) in
50% aqueous acetic acid (5 ml.) was added HIO4·2H2O (300 mg.) in small portions and the mixture was kept
at room temperature overnight. The reaction mixture was made basic by addition of dill. Na2CO3 and extracted
with CH2Cl2. The extract was washed successively with 3% HCl and dill. Na2CO3, dried (K2CO3), and
evaporated to leave a colorless oil (II) (150 mg.) which showed a strong infrared band at 1720 cm⁻¹ (CHCl3)
for aldehyde groups. Attempts for crystallization were unsuccessful.

Sodium Borohydride Reduction of the Dialdehyde (II) and Subsequent Acetylation — The above
dialdehyde (II) (150 mg.) was dissolved in MeOH and treated with NaBH4 (200 mg.) at room temperature for
4 hr. Usual working up gave a crystalline mass (diol, IIIa) (140 mg.) which was hardly purified by recrystall-
ization. This crude diol (IIIa) was then treated with acetic anhydride-pyridine (1:1, 2 ml.) and the mixture
kept at room temperature overnight. The product, isolated in the usual manner, was recrystallized from
acetone to afford the diol-diacetate (IIb) (30 mg.) as colorless plates, m.p. 147-150°. [α]D +16° (CHCl3,
c = 1.0). Anal. Calcd. for C27H33O9N: C, 72.12; H, 10.54; N, 3.12. Found: C, 71.90; H, 10.33; N, 2.92. IR
νmax cm⁻¹: 1730 and 1250 (O-Ac).

Synthesis of 3β,4α-Dihydroxy-20α-dimethylamino-5α-pregnane (V). i) Sodium Borohydride Reduction
of the Diosphenol (IV) — The diosphenol (IV) (90 mg.) was dissolved with NaBH4 (180 mg.) in MeOH (15 ml.)-
CHCl3 (2 ml.) for 3 hr. at room temperature. After evaporation of solvents in vacuo and dilution with water,
the product was taken in CHCl3, dried over K2CO3, and evaporated. Crystallization of the residue (80 mg.)
from acetone gave a crystalline product (50 mg.) melting at about 200-210°. This substance, however, showed
3 spots on thin-layer chromatography (Aluminum-oxide acc. to Stahl-CHCl3). Purification was achieved
through the acetonide formation.

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8 Only a few trans 1,2-diols have been reported to form the acetoneide. See B. Tursch, E. Tursch, I. T.

9 All the melting points were determined on a Yanagimoto Micro Melting Point Apparatus and are uncor-
rected. The optical rotations were taken in chloroform solutions unless otherwise specified.
ii) Acetonide (VI)—To a solution of the above, crystalline, crude diol (60 mg.) in acetone (20 ml.) was added p-toluenesulfonic acid (100 mg.) and the resulting suspension was refluxed for 5 hr. After most of the solvent was evaporated under reduced pressure, the residue was diluted with dil. Na₂CO₃ and the precipitate was collected by suction. This was dissolved in CH₂Cl₂ and the solution was washed successively with 3% HCl and dil. Na₂CO₃, dried (K₂CO₃), and evaporated to give the crystalline acetonide (VI) (20 mg.). Recrystallizations from acetone afforded the pure material (10 mg.), m.p. 165~167°. NMR τ : 5.80~6.15 (2H, broad, two CH–O–), 7.82 (6H, N–(CH₃)₃), 8.50, 8.70 (6H, (CH₃)₃CO–O–), 9.12 (3H, doublet, J 7 c.p.s., sec. CH₃), 8.95, and 9.33 (6H, two tert. CH₃).

The usual working up of the HCl-acidic wash solution gave a recovery of the starting material (V), which was repeatedly subjected to the acetonide-p-toluenesulfonic acid procedure to give additional crops of the acetonide (V).

iii) Acid Hydrolysis of the Acetonide (VI)—A solution of the acetonide (VI) (120 mg.) in MeOH (10 ml.) containing conc. HCl (1 ml.) was refluxed for 4 hr. The product (100 mg.), isolated in the usual working up, was recrystallized from acetone to give the 3β,4β-dihydroxy compound (V) (75 mg.), as colorless leaves, m.p. 226~228°. Anal. Calcd. for C₂₃H₉₀O₃N·H₂O : C, 74.14; H, 11.36; N, 3.76. Found : C, 74.35, 74.75; H, 11.63, 11.34; N, 3.62. IR νₐ₅OH cm⁻¹ : 3350 (bonded OH). NMR τ : 4.29, 4.49 (2H, broad, two CH–OH), 7.83 (6H, N–(CH₃)₃), 8.98 (3H, tert. CH₃), 9.12 (3H, doublet, J 6 c.p.s.; sec. CH₃), 9.36 (3H, tert. CH₃).

Periodic Acid Oxidation of 3β,4β-Dihydroxy-20α-dimethylamino-5α-pregnane (V) and the Subsequent Sodium Borohydride Reduction and Acetylation—Oxidation of the 3β,4β-dihydroxy compound (V) (50 mg.) with HIO₄ in 50% aqueous acetic acid was performed in the same way as given for terminaline (Ia). The resulting dialdehyde (I), IR νₐ₅CH=O cm⁻¹ : 1720, was reduced with NaBH₄ and then acetylated in the usual manner. Recrystallization of the crude product (40 mg.) from acetone afforded the pure diol-diacetate (Eb) (10 mg.) as leaves, m.p. 148~150°, [α]₂⁰° +19° (c=1.0). IR νₐ₅CO₂ cm⁻¹ : 1730,1250 (O–Ac). This compound was found to be identical with the diol-diacetate (Eb) obtained from terminaline (Ia) by mixed m.p. and IR (KBr) comparison.

Preparation of 3β,4α-Dihydroxy-20α-dimethylamino-5α-pregnane (Ia)—To a boiling solution of the diosphenol (N) (38 mg.) in n-amyl alcohol (7 ml.) was added, with mechanical agitation, in small portions metallic sodium (0.7 g.) over the period of 30 minutes and the mixture was refluxed for additional 30 minutes. After cooling, water was added to the reaction mixture and the organic phase was separated. Evaporation of the solvent under reduced pressure left a viscous residue which was dissolved in 3% HCl solution, washed with CH₂Cl₂, made alkaline with NH₄OH, and extracted with CH₂Cl₂. The extract was dried over K₂CO₃ and evaporated to leave a crystalline residue (90 mg.). Recrystallization from acetone-MeOH afforded the 3β,4α-diol (Ia) (35 mg.), m.p. 242~244°, [α]₂⁰° +26° (50% CHCl₃–MeOH, c=0.83). This compound (Ia) showed no melting point depression upon admixture with terminaline and both IR (KBr) and NMR spectra are superimposable. Anal. Calcd. for C₃₉H₆₄O₄N : C, 75.98; H, 11.37; N, 3.85. Found : C, 75.87; H, 11.35; N, 4.01.

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