[Chem. Pharm. Bull. 15(3) 307~316 (1967)] UDC 547.94.02 : 582.761

38. Tohru Kikuchi, Shoichiro Uyeo, and Toshinari Nishinaga : Pachysandra Alkaloids. V.*1 Structure of Epipachysamine-A, -B, -C, -D, -E, and -F.*2

(*Faculty of Pharmaceutical Sciences, Kyoto University**3)

Structure determination of epipachysamine-A (I), -B (Ⅷa), -C (Ⅲ), -D (Ⅷb), -E (Ⅷc), and -F (V), new alkaloids isolated from *Pachysandra terminalis* Sieb. et Zucc. (Buxaceae), was described herewith. Among these alkaloids, epipachysamine-B (Ⅷa) 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,*1 the constitutions of another class of Pachysandra alkaloids, for which we proposed the name 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)[1] and they represent the stereoisomer of pachysamine type with respect to the 3-amino grouping.

Epipachysamine-A (I),*2a) m.p. 201~203°, $[\alpha]_D$ −17° ($CHCl_3$), was analyzed for $C_{26}H_{46}ON_2$ and exhibited a tertiary amide band at 1625 cm^{-1} in the infrared spectrum.*4 The nuclear magnetic resonance (NMR) spectrum*5 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°, $[\alpha]_D$ +20° ($CHCl_3$). This compound gave analytical results in agreement with the empirical formula $C_{24}H_{44}N_2 \cdot 1/4H_2O$ and the substitution pattern in its molcule could be demonstrated by its NMR spectrum which showed signals for one N-methyl (7.65τ), one N-dimethyl (7.74τ), one secondary C-methyl (8.93τ, doublet, J 6 c.p.s.), and two tertiary C-methyls (9.24 and 9.33τ). On acetylation, it regenerated the parent alkaloid (I), m.p. 203~205°, $[\alpha]_D$ −14° ($CHCl_3$). This confirmed the presence of an N-acetyl 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°, $[\alpha]_D$ +12° ($CHCl_3$), showing NMR signals for two N-dimethyl groups (7.73 and 7.85τ). This compound was shown to be identical with an authentic sample of N,N-dimethylchonemorphine (Ⅱb)[2] in every respect, establishing the fundamental skeleton and stereochemistry of epipachysamine-A (I).

---

*1 Part Ⅳ. T. Kikuchi, S. Uyeo, Jr. : This Bulletin, **15**, 302 (1967).

*2 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).

*3 Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto (菊池 徹, 上尾庄一郎, 西永俊也).

*4 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.

*5 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 τ values using tetramethylsilane as the internal reference.

1) Part I. M. Tomita, T. Kikuchi, S. Uyeo, Jr., T. Nishinaga, M. Yasunishi (née Ando), A. Yamamoto : Yakugaku Zasshi, **87**, 215 (1967).

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-methylamino-5α-pregnane (IIa) which had been synthesized by Corey, *et al.*,[3] although no direct comparison could be achieved.*[6]

A strong proof for the proposed structure (IIa) for desacylepipachysamine-A was provided by the mass spectrum*[7] 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).*[8]

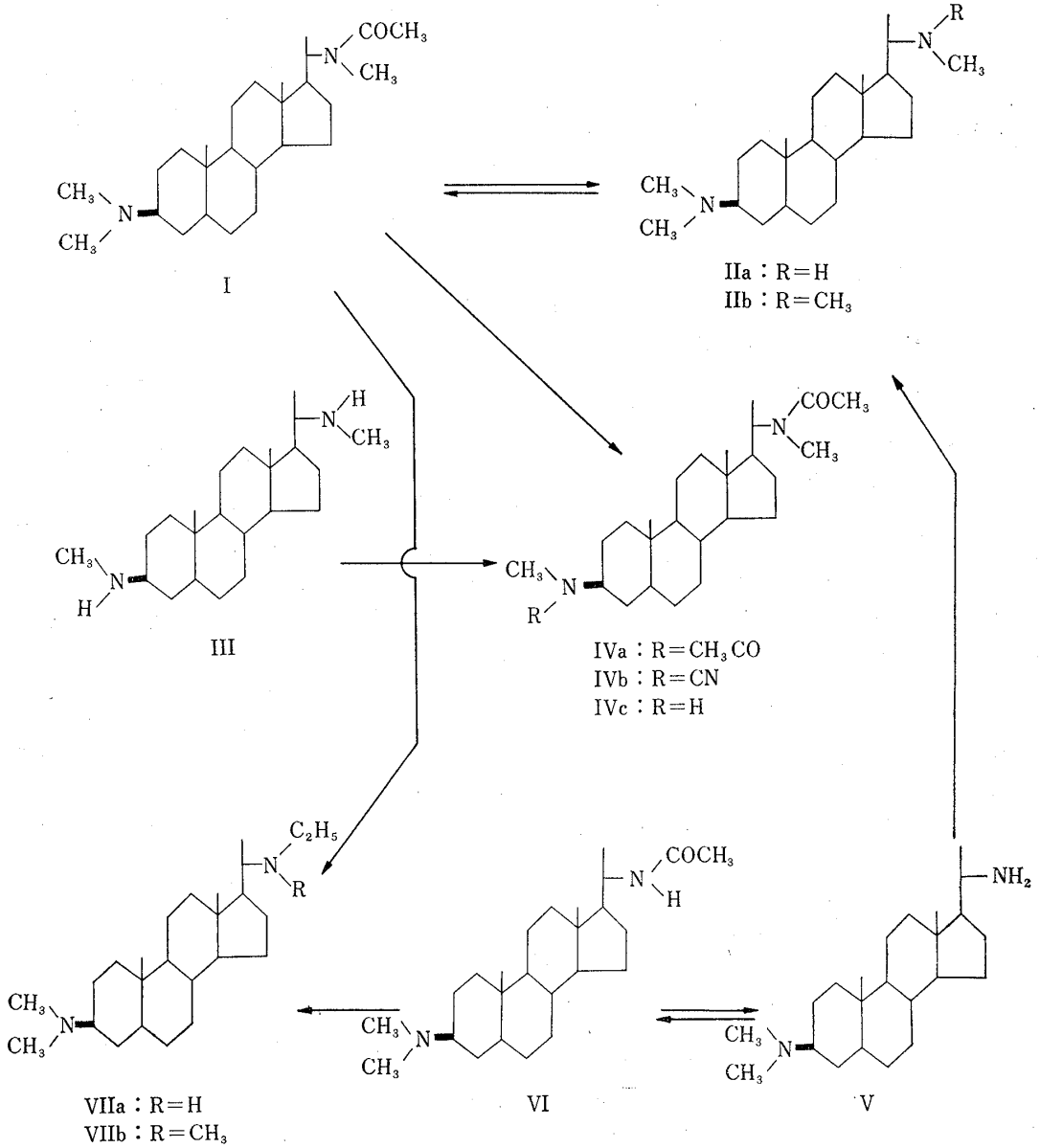


Chart 1.

*6 In this connection it is pertinent to note that the isolation and structure determination of 3β-methylamino-20α-dimethylamino-5α-pregnane (=dictyophlebine) was recently reported by Goutarel and collaborators. The reported melting point (148°) 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.

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

*8 The genesis of the other characteristic peaks at m/e 303 (M^+-57) and 288 (M^+-72) will be discussed in Part VII of this series (Yakugaku Zasshi, in press.

3) E. J. Corey, W. R. Hertler: J. Am. Chem. Soc., **81**, 5209 (1959).

This behavior is in good agreement with the proposed fragmentation mechanism[4] for this type of alkaloids, which can be visualized as shown in Chart 2 and evidently localized the methylamino group at the 20-position. Therefore the structure of epipachysamine-A should be represented by the formula I.*9

Epipachysamine-C (Ⅲ)*2b) 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.[1]

The diacetate (Ⅳa), m.p. 242~243°, $[\alpha]_D$ −16° ($CHCl_3$), was analyzed for $C_{27}H_{46}O_2N_2$ 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 (Ⅳa) 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 3β,20α-bismethylacetylamino-5α-pregnane (Ⅳa) or its 3α-isomer. The former base (Ⅳa) was synthesized from epipachysamine-A (I) *via* the intermediates, Ⅳb and Ⅳc.

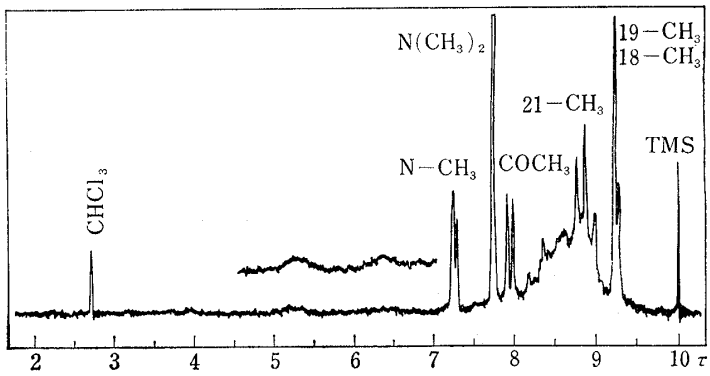


Fig. 1. NMR Spectrum of Epipachysamine-A (I)

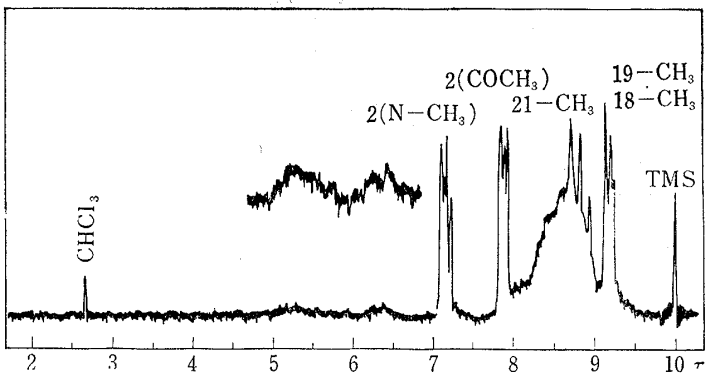


Fig. 2. NMR Spectrum of N,N-Diacetylepipachysamine-C (Ⅳa)

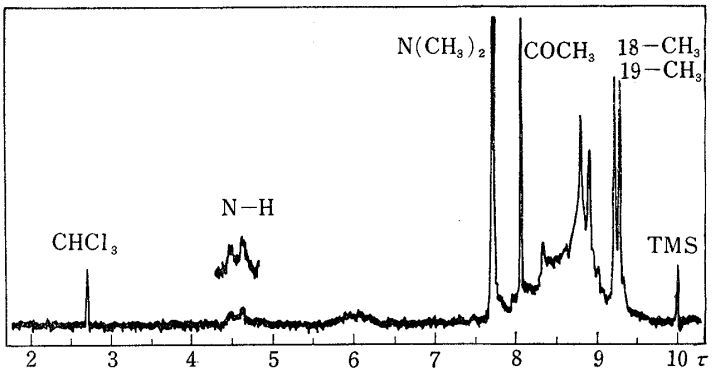


Fig. 3. NMR Spectrum of N-Acetylepipachysamine-F (Ⅵ)

Treatment of epipachysamine-A (I) with cyanogen bromide in boiling benzene gave rise to an N-CN compound (Ⅳb), $C_{26}H_{43}ON_3$, m.p. 234~235°, 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 (Ⅳc), m.p. 206~207°, $[\alpha]_D$ +5° ($CHCl_3$), which, on acetylation, yielded a neutral N,N-diacetate (Ⅳa), $C_{27}H_{46}O_2N_2$,

*9 Recently Chatterjee and collaborators reported the isolation and structural elucidation of saracodine, m.p. 190~192°, from *Sarcococca pruniformis* Lindl., 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)).

4) H. Budzikiewicz, C. Djerassi, D. H. Williams: "Interpretation of Mass Spectra of Organic Compounds," 75 (1964), Holden-Day, Inc., San Francisco; L. Dolejs, V. Hanus, V. Cerny, F. Sorm: Collection Czechoslov. Chem. Communs., **28**, 1584 (1963); W. Vetter, P. Longevialle, F. Khuong-Huu-Laine, Q. Khuong-Huu, R. Goutarel: Bull. soc. chim. France, 1324 (1963).

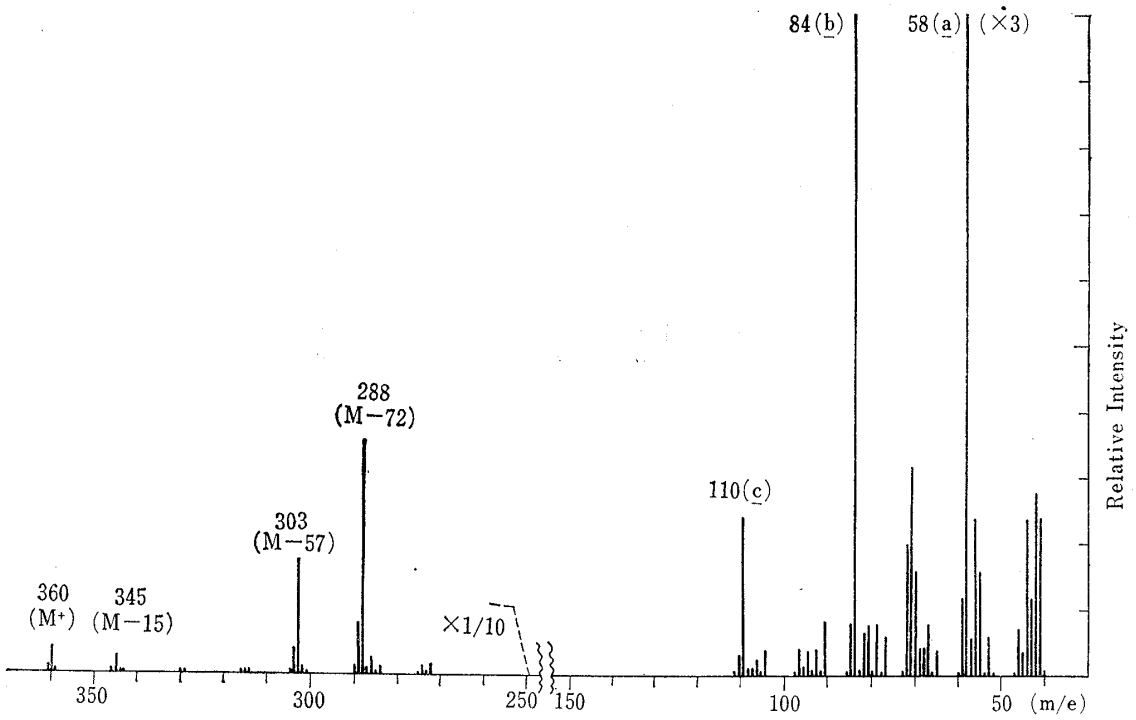


Fig. 4. Mass Spectrum of Desacylepipachysamine-A (IIa)

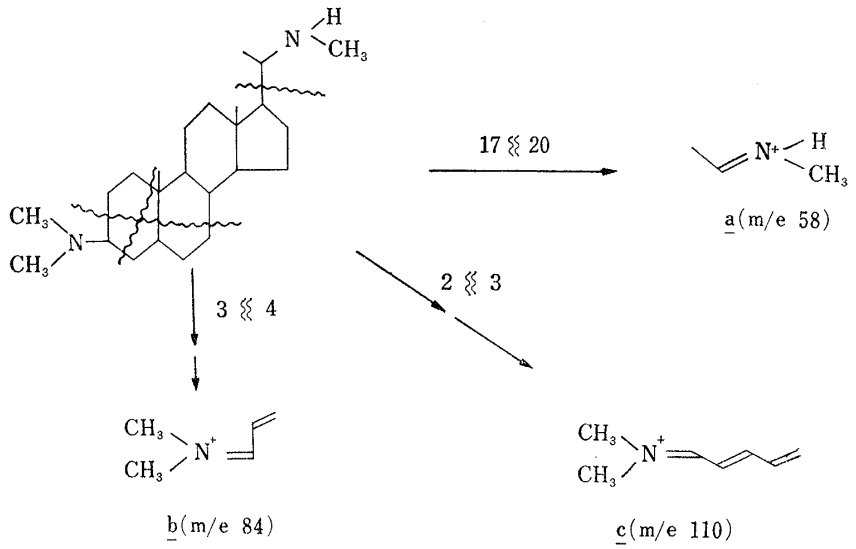


Chart 2.

m.p. 243~244°, $[\alpha]_D$ −22° ($CHCl_3$). The infrared spectrum (KBr) of the above compound (IVa) was shown to be identical with that of N,N-diacetylepipachysamine-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

*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 *Dyctyophleba lucida* (K. Schum) Pierre and they gave the structure III for the alkaloid. Also, they cited in a table two alkaloids obtained form *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. Monseur, M. Truong-Ho, R. Kocjan, R. Goutarel: Bull. soc. chim. France, 3035 (1965)).

Epipachysamine-F (V)*[2c] is also a minor alkaloid obtained as its N-acetate from the acetylated product of strongly basic alkaloid fraction.[1]

The acetate (VI), m.p. 250~253°, $[\alpha]_D$ +6° ($CHCl_3$), showed the infrared bands (3420, 1660, and 1510 cm^{-1}) for a secondary amide group and the NMR signals for one acetyl (8.07τ), one N-dimethyl (7.72τ), one secondary C-methyl (8.87τ, doublet, J 6 c.p.s.), and two tertiary C-methyls (9.23 and 9.30τ) (Fig. 3). Elemental analyses of the acetate gave results which supported the empirical formula $C_{25}H_{44}ON_2 \cdot 1/2\ H_2O$.

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 ($M^+ - CH_3$) suggested strongly the structure VI for the base[4] (except for the configuration of 3-dimethylamino group) (Fig. 5).

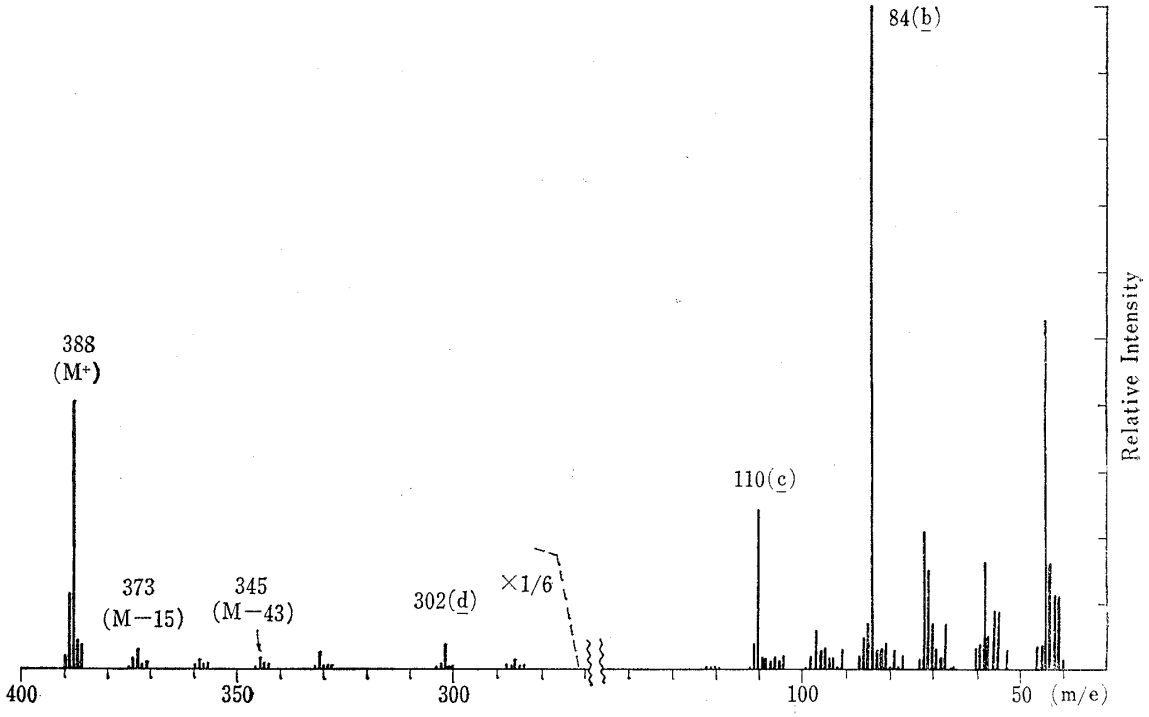


Fig. 5. Mass Spectrum of N-Acetylepipachysamine-F (VI)

Acid hydrolysis of the acetate (VI) and the subsequent N-methylation afforded a diamine (IIb), $C_{25}H_{46}N_2$, m.p. 106~108°, $[\alpha]_D$+28° ($CHCl_3$), identified with an authentic N,N-dimethylchonemorphine (IIb).

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

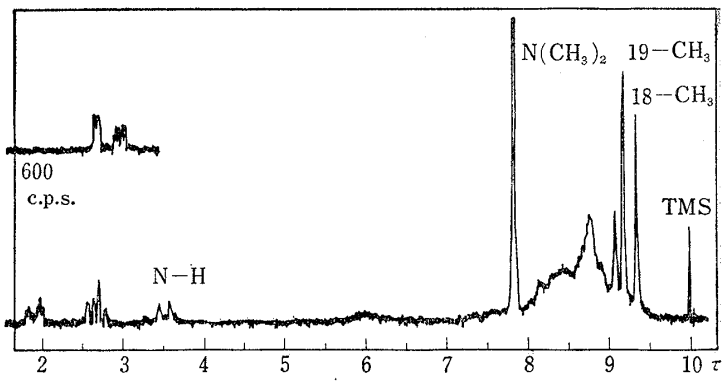


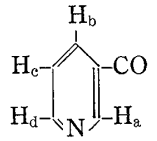
Fig. 6. NMR Spectrum of Epipachysamine-B (VIIa)

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° ($CHCl_3$). This compound was identified by direct comparison

Table I.

	Epipachysamine-B (VIIIa)		Epipachysamine-D (VIIIb)		Epipachysamine-E (VIIIc)	
	Natural	Synthetic	Natural	Synthetic	Natural	Synthetic
Formula	$C_{29}H_{45}ON_3$	$C_{29}H_{45}ON_3$	$C_{30}H_{46}ON_2$	$C_{30}H_{46}ON_2$	$C_{28}H_{48}ON_2$	$C_{28}H_{48}ON_2 \cdot \frac{1}{2}H_2O$
m.p. (°C)	260~262	260~263	245~248	247~249	210~212	200~205
$[\alpha]_D$ ($CHCl_3$) (°C)	+16	+38	+13	+13	+20	+19
IR ($CHCl_3$) (cm^{-1})						
$\nu_{C=O}$	1660		1655		1630	
ν_{N-H}	3400	Identical	3400	Identical	3420	Identical
δ_{N-H}	1515		1515		1500	
Other characteristic bands	1590 (pyridine)		1600, 1580, 1485 (phenyl)		1665 (C=C)	
NMR signals for the acid portion (τ)	2.68, 1.91[a] 1.33, 1.04	Identical	2.1~2.7 (5H) (phenyl)		4.46 (Broad, CH=C) 8.18 (Broad, CH_3-C=C) 7.83 (CH_3-C=C)[b]	Identical

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



H_a: 1.04 τ, doublet, J_{ab} 2 c.p.s.
H_b: 1.91 τ, sextet, J_{bc} 8 c.p.s., $J_{ab,bd}$ 1.5~2 c.p.s.
H_c: 2.68 τ, quartet, J_{bc} 8 c.p.s., J_{cd} 5 c.p.s.
H_d: 1.33 τ, quartet, J_{cd} 5 c.p.s., J_{bd} 1.5 c.p.s.

b) Overlapping on the N,N-dimethyl signal.

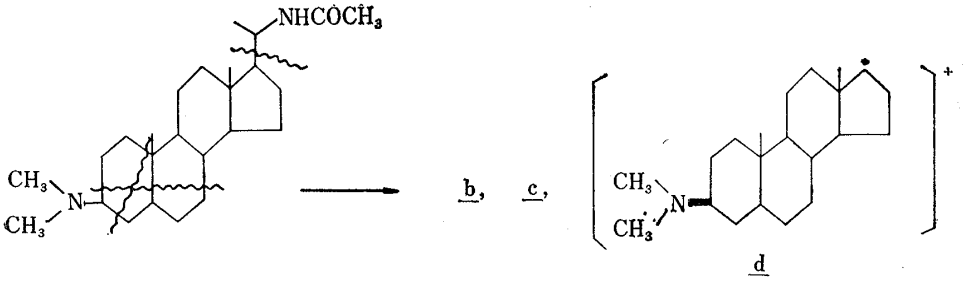


Chart 3.

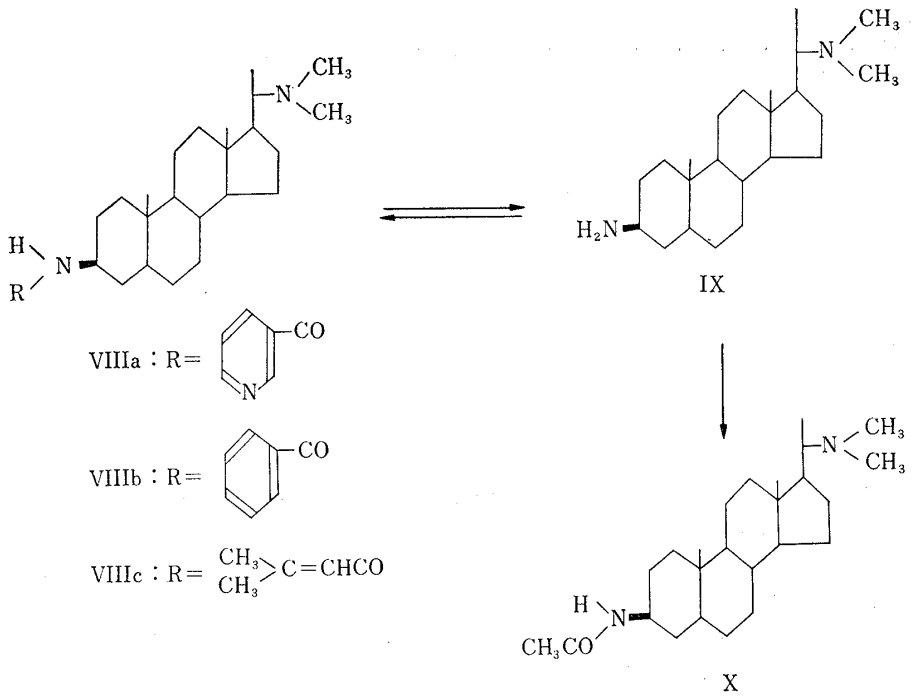


Chart 4.

(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.*10

Epipachysamine-B (Ⅷa),*2b) -D (Ⅷb),*2c) and -E (Ⅷc)*2c) 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 (Ⅸ), m.p. 149~150°, $[\alpha]_D$ +21° ($CHCl_3$), which was identified as chonemorphine (Ⅸ)[2] by direct comparison with a synthetic sample.[5]

Further characterization of this desacyl base was achieved by its transformation to the N,N-dimethyl compound (Ⅱb), $C_{25}H_{46}N_2$, m.p. 105~108°, $[\alpha]_D$ +7° ($CHCl_3$), and to the N-acetyl compound (X), $C_{25}H_{44}ON_2$, m.p. 266~267°, $[\alpha]_D$ +23° ($CHCl_3$). Their identities were confirmed by direct comparison with authentic N,N-dimethylchonemorphine (Ⅱb) and N-acetylchonemorphine (X).[2]

The acid portions consisting of each amide group in epipachysamine-B (Ⅷa), -D (Ⅷb), and -E (Ⅷc) were considered to be nicotinic acid, benzoic acid, and β,β-dimethylacrylic acid, 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 chonemorphine (Ⅸ) with nicotinic acid by mixed anhydride method,[6] and with benzoyl chloride and β,β-dimethylacrylyl chloride by Schotten-Baumann method, whereby obtained the corresponding amides whose properties are summarized in Table I. The synthesized compounds, Ⅷa, Ⅷb, and Ⅷc, 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 (Ⅷa) 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 CH_2Cl_2, made basic with NH_4OH, extracted with CH_2Cl_2, dried over K_2CO_3, 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°, as colorless plates. $[\alpha]_D^{21}$ +20° (c=1.28). *Anal.* Calcd. for $C_{24}H_{44}N_2 \cdot \frac{1}{4}H_2O$: 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.

5) P. Chien, W. E. McEwen, A. W. Burgstahler, N. T. Iyer: J. Org. Chem., **29**, 315 (1964).
6) J. R. Vaughan, Jr.: J. Am. Chem. Soc., **73**, 3547 (1951).
7) M. Cais, D. Ginsburg, A. Mandelbaum: "The 3rd IUPAC Symposium on the Chemistry of Natural Products, Kyoto, Japan," Symposium Abstracts, 95 (1964).

τ : 7.65 (3H, N-CH_3), 7.74 (6H,N-$(CH_3)_2$), 8.93 (3H, doublet, J 6 c.p.s.; *sec.* CH_3), 9.24, 9.33 (6H, two *tert.* CH_3). MS m/e : 360 (M^+), 110 (5%), 84 (25%), 58 (base peak).

From the CH_2Cl_2 washing solution was recovered the unchanged starting material (125 mg.), which showed m.p. 185~198°(50 mg.) after recrystallization from acetone.

Acetylation of Desacylepipachysamine-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°, which was identified with epipachysamine-A (I) by mixed m.p. and IR (KBr) comparison. $[\alpha]_D^{20}$ −14°(c=1.14). *Anal.* Calcd. for $C_{26}H_{46}ON_2$: C, 77.55; H, 11.52. Found : C, 77.84; H, 11.53. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1625 ($NCOCH_3$).

N-Methylation of Desacylepipachysamine-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°, identical with an authentic sample of N,N-dimethylchonemorphine (IIb) by mixed m.p. and IR (KBr) comparison. $[\alpha]_D^{20}$ +12°(c=1.14). *Anal.* Calcd. for $C_{25}H_{46}N_2$: C, 80.15; H, 12.38. Found : C, 80.18; H, 12.54. NMR τ : 7.73, 7.85 (12H, two N-$(CH_3)_2$), 9.13 (3H, doublet, J 6 c.p.s.; *sec.* CH_3), 9.23, and 9.35 (6H, two *tert.* CH_3).

Acid Hydrolysis of Epipachysamine-B (VIIIa)——A solution of the alkaloid (VIIIa) (100 mg.) in conc. HCl (2 ml.) and acetic acid (2 ml.) in a sealed tube was heated at 150°(bath temp.) for 3 hr. The reaction mixture was diluted with water, washed with CH_2Cl_2, made alkaline with NH_4OH, and extracted with CH_2Cl_2. The extract was dried over K_2CO_3 and evaporated to give a pale yellow crystalline residue (IX) (79 mg.). After recrystallization from ethyl acetate it showed m.p. 149~150°, $[\alpha]_D^{28}$ +21°(c=1.18). The IR spectrum ($CHCl_3$) of this compound was identical with that of chonemorphine (IX).

Acetylation of Desacylepipachysamine-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 CH_2Cl_2 and dil. Na_2CO_3, was chromatographed over alumina (1×10 cm.). Elution with CH_2Cl_2 followed by recrystallization from acetone-CH_2Cl_2 gave the N-acetate (X) (40 mg.) in colorless plates, m.p. 264~266°. Pure sample showed m.p. 266~267°, $[\alpha]_D^{25}$ +23°(c=1.0). This was identified with an authentic sample of N-acetylchonemorphine (X) by mixed m.p. and IR (KBr) comparison. *Anal.* Calcd. for $C_{25}H_{44}ON_2$: C, 77.26; H, 11.41. Found : C, 77.40; H, 11.58. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3400, 3300 (NH), 1665, 1515(-$NHCOCH_3$).

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 (IX) (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_2CO_3, extracted with CH_2Cl_2, dried, and evaporated. Recrystallizations of the residue from acetone afforded the nicotinate (VIIIa) (36 mg.), m.p. 256~263°. Further purification by alumina chromatography followed by recrystallization gave a pure material (25 mg.) as colorless leaves, m.p. 260~263°, $[\alpha]_D^{20}$ +38°(c=1.10). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3400, 3300 (NH), 1660, 1515 (NHCOR), 1590, 1485 (pyridine). This material was identified with epipachysamine-B by IR (KBr) and NMR comparisons and mixed m.p. *Anal.* Calcd. for $C_{29}H_{45}ON_3$: C, 77.11; H, 10.04; N, 9.00. Found : C, 76.97; H, 10.19; N, 9.28.

Transformation of Epipachysamine-A (I) to N,N-Diacetylepipachysamine-C (IVa). i) von Braun Reaction of Epipachysamine-A (I)——To a solution of the alkaloid (I) (450 mg.) in benzene (30 ml.) 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, and the residue was dissolved in CH_2Cl_2 and passed through an alumina column (1×10 cm.). Elution with the same solvent and recrystallization from acetone-CH_2Cl_2 gave the N-CN compound (IVb) (330 mg.) as needles, m.p. 234~235°, $[\alpha]_D^{20}$ +22° (c=1.0). *Anal.* Calcd. for $C_{26}H_{43}ON_3$: C, 75.49; H, 10.48; N, 10.16. Found : C, 75.76; H, 10.24; N, 10.24. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2220 (N-CN), 1625 (N-$COCH_3$). NMR τ : 7.13 (3H, NC-N-CH_3), 7.20, 7.25 (3H, two peaks, RCON-CH_3), 7.88, 7.95 (3H, two peaks, N-$COCH_3$), 9.17 (3H, 19-CH_3), 9.23, 9.26 (3H, two peaks, 18-CH_3), and 8.75~8.97 (3H ?, three peaks, 21-CH_3).

ii) 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°. After cooling, the mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed successively with 3% HCl and dil. Na_2CO_3, dried over K_2CO_3, and evaporated to give a crystalline residue (230 mg.). Recrystallizations from acetone gave colorless needles (IVc) (192 mg.), m.p. 206~207°, $[\alpha]_D^{20}$ +5°(c=1.0). *Anal.* Calcd. for $C_{25}H_{44}ON_2 \cdot \frac{1}{4}H_2O$: C, 76.59; H, 11.31; N, 7.15. Found : C, 76.66; H, 11.42; N, 7.12. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1625 ($NCOCH_3$). NMR τ : 7.21, 7.27 (3H, two peaks, N(COR)-CH_3), 7.59 (3H, N-CH_3), 7.88, 7.96 (3H, two peaks, N-$COCH_3$), 9.22 (6H, broad, two *tert.* CH_3), and about 7.85 (3H ?, three peaks, *sec.* CH_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 obtained by usual working up was recrystallized from ether-CH_2Cl_2 to afford the diacetate (Ⅳa) (52 mg.), colorless leaves, m.p. 243~244°, $[\alpha]_D^{20}$ −22° (c=1.0). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1625 ($NCOCH_3$). This compound was identified with N,N-diacetylepipachysamine-C by mixed m.p. and IR (KBr) comparison. *Anal.* Calcd. for $C_{27}H_{46}O_2N_2$: C, 75.30; H, 10.77; N, 6.51. Found: C, 75.57; H, 10.94; N, 6.26.

Acid hydrolysis of Epipachysamine-D (VIIIb)——A solution of the alkaloid (Ⅷb) (200 mg.) in conc. HCl (2 ml.) and acetic acid (2 ml.) was heated in a sealed tube at 150~160°(bath temp.) for 5 hr. Usual working up, as described for epipachysamine-B, afforded the strongly basic hydrolysis product (Ⅸ) (150 mg.), whose IR spectrum ($CHCl_3$) was identical with that of authentic chonemorphine (Ⅸ).

N-Methylation of Desacylepipachysamine-D (IX)——The crude desacyl base (Ⅸ) (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 (Ⅱb) (40 mg.) showed m.p. 105~108°, $[\alpha]_D^{18}$ +7° (c=1.0). This was identified as N,N-dimethylchonemorphine. *Anal.* Calcd. for $C_{25}H_{46}N_2$: C, 81.15; H, 12.38; N, 7.48. Found: C, 79.87; H, 12.40; N, 7.51.

Acetylation of Desacylepipachysamine-D (IX)——The crude hydrolysis product (Ⅸ) (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. Na_2CO_3 and CH_2Cl_2, was recrystallized from acetone to give the N-acetate (Ⅹ) in colorless leaves, m.p. 267~268°, $[\alpha]_D^{19}$ +12°(c=1.06), which was identified with an authentic sample of N-acetylchonemorphine (Ⅹ) by mixed m.p. determination and IR (KBr) comparison. *Anal.* Calcd. for $C_{25}H_{44}ON_2$: C, 77.26; H, 11.41; N, 7.21. Found: C, 77.54; H, 11.41; N, 7.08.

Preparation of Chonemorphine Benzoate (VIIIb)——Benzoyl chloride (0.1 ml.) was added dropwise with mechanical stirring to a solution of chonemorphine (80 mg.) in ether (10 ml.)-CH_2Cl_2 (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 CH_2Cl_2, washed successively with 3% HCl and dil. Na_2CO_3, dried over K_2CO_3, and evaporated. Recrystallization of the residue from acetone gave the benzoate (Ⅷb) (65 mg.), colorless prisms, m.p. 243~247°. Further recrystallizations from the same solvent gave a pure sample, m.p. 247~249°, $[\alpha]_D^{13}$ +13°(c=1.0), which was shown to be identical with epipachysamine-D by mixed m.p. and IR (KBr) comparison. *Anal.* Calcd. for $C_{30}H_{46}ON_2$: C, 79.95; H, 10.29; N, 6.22. Found: C, 79.68; H, 10.51; N, 5.93.

Acid Hydrolysis of Epipachysamine-E (VIIIc)——The alkaloid (Ⅷc) (80 mg.) was hydrolyzed with conc. HCl-acetic acid (1:1, 3 ml.) in the same manner as described for epipachysamine-B (Ⅷa). The product (60 mg.) showed the IR spectrum ($CHCl_3$) identical with that of chonemorphine (Ⅸ).

Preparation of Chonemorphine β,β-Dimethylacrylate (VIIIc)——The Schotten-Baumann condensation between chonemorphine (64 mg.) and β,β-dimethylacrylyl chloride (0.1 ml.) was performed in the same manner as given for Ⅷb. 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 (Ⅷc) (40 mg.) in colorless leaves, m.p. 190~200°. After several recrystallizations, it showed m.p. 200~205°, $[\alpha]_D^{25}$ +19°(c=1.0). IR (KBr) and NMR spectra of this substance were identical with those of epipachysamine-E and mixed m.p. did not depress. *Anal.* Calcd. for $C_{28}H_{48}ON_2 \cdot \frac{1}{2}H_2O$: C, 76.92; H, 11.30; N, 6.41. Found: C, 76.91; H, 11.40; N, 6.32.

Acid Hydrolysis of N-Acetylepipachysamine-F (VI)——A solution of the base (Ⅵ) (50 mg.) in conc. HCl (1 ml.) and acetic acid (1 ml.) was heated in a sealed tube at 170~190° for 6 hr. After dilution with water and washing with CH_2Cl_2, the mixture was made basic with NH_4OH and extracted with CH_2Cl_2. The extract was dried over K_2CO_3 and evaporated to leave the crude desacyl compound (epipachysamine-F) (50 mg.) which was hardly purified by recrystallization.

N-Methylation of Epipachysamine-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 (Ⅱb) (45 mg.) which was recrystallized from acetone to give a pure material, m.p. 106~108°, identified with N,N-dimethylchonemorphine (Ⅱb) by mixed m.p. and IR (KBr) comparison. $[\alpha]_D^{28}$ +28°(c=1.0). *Anal.* Calcd. for $C_{25}H_{46}N_2$: C, 80.15; H, 12.38. Found: C, 80.11; H, 12.64.

Lithium Aluminum Hydride Reduction of N-Acetylepipachysamine-F (VI) and Subsequent N-Methylation——A suspension of the alkaloid (Ⅵ) (70 mg.) and $LiAlH_4$ (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 CH_2Cl_2. The filtrate and the washings were combined and evaporated under reduced pressure. The residue was taken in 3% HCl, washed with CH_2Cl_2, basified with NH_4OH, and extracted with CH_2Cl_2. The extract was dried over K_2CO_3 and evaporated to give a crystalline product (Ⅶa) (50 mg.), which, without further purification, was N-methylated by heatng 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 (Ⅶb) (30 mg.), m.p. 105~107°, $[\alpha]_D^{28}$ +38°(c=1.0). This substance was identified with the reduction product of epipachysamine-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 $LiAlH_4$ (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 (Ⅶb) (33 mg.), m.p. 104~105°. Further recrystallization from the same solvent gave a pure sample, m.p. 109.5~110°, $[\alpha]_D^{20}$ +37°(c=1.0). *Anal.* Calcd. for $C_{26}H_{48}N_2$: C, 80.34; H, 12.45. Found: C, 80.44; H, 12.45.

The authors express their deep gratitude to Professor M. Tomita of this Faculty for his guidance and hearty encouragement, Dr. A. W. Burgstahler of the University of Kansas, U. S. A., for a gift of the synthetic chonemorphine, and Dr. A. Chatterjee of the University of Culcutta, India, for the samples of N,N-dimethylchonemorphine and N-acetylchonemorphine. The authors are also indebted to Dr. T. Shingu and Mr. M. Yamamoto for NMR measurements, Dr. T. Ibuka and Mr. A. Kato for determining the mass spectra, Dr. K. Miyajima and Mr. M. Yamamoto for IR determinations in KBr disc, and Dr. K. Konobu and Miss Y. Mano and collaborators for elemental analyses.

[Chem. Pharm. Bull. 15(3) 316~320 (1967)]

UDC 547.94.02 : 582.761

39. Tohru Kikuchi, Shoichiro Uyeo, and Toshinari Nishinaga: Pachysandra Alkaloids. Ⅵ.*1 Structure of Terminaline.*2

(*Faculty of Pharmaceutical Sciences, Kyoto University**3)

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

(Received May 27, 1966)

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.[1] Among the Pachysandra alkaloids isolated so far, terminaline is the only alkaloid carrying one nitrogen function.*4

Terminaline (I), m.p. 243~244°, $[\alpha]_D$ +29° (50v% MeOH-$CHCl_3$), was analysed for $C_{23}H_{41}O_2N$, which is consistent with the molecular ion peak at m/e 363 in the mass spectrum.*5 It showed an infrared OH band at 3300 cm^{-1} (in nujol)*6 and NMR signals*7

---

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

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

*3 Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto (菊池 徹, 上尾庄一郎, 西永俊也).

*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 deuterochloroform solutions and chemical shifts are reported in τ values using tetramethylsilane as the internal reference.

1) M. Tomita, T. Kikuchi, S. Uyeo, Jr., T. Nishinaga, M. Yasunishi (née Ando), A. Yamamoto: Yakugaku Zasshi, **87**, 215 (1967).