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

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*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).

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

On acetylation terminaline gave the O,O-diacetyl compound (Ib), $C_{27}H_{45}O_4N$, m.p. 202~204°, $[\alpha]_D$ +40° ($CHCl_3$), 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 7.99τ, 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 (a) which is the characteristic of the pregnane type alkaloids holding

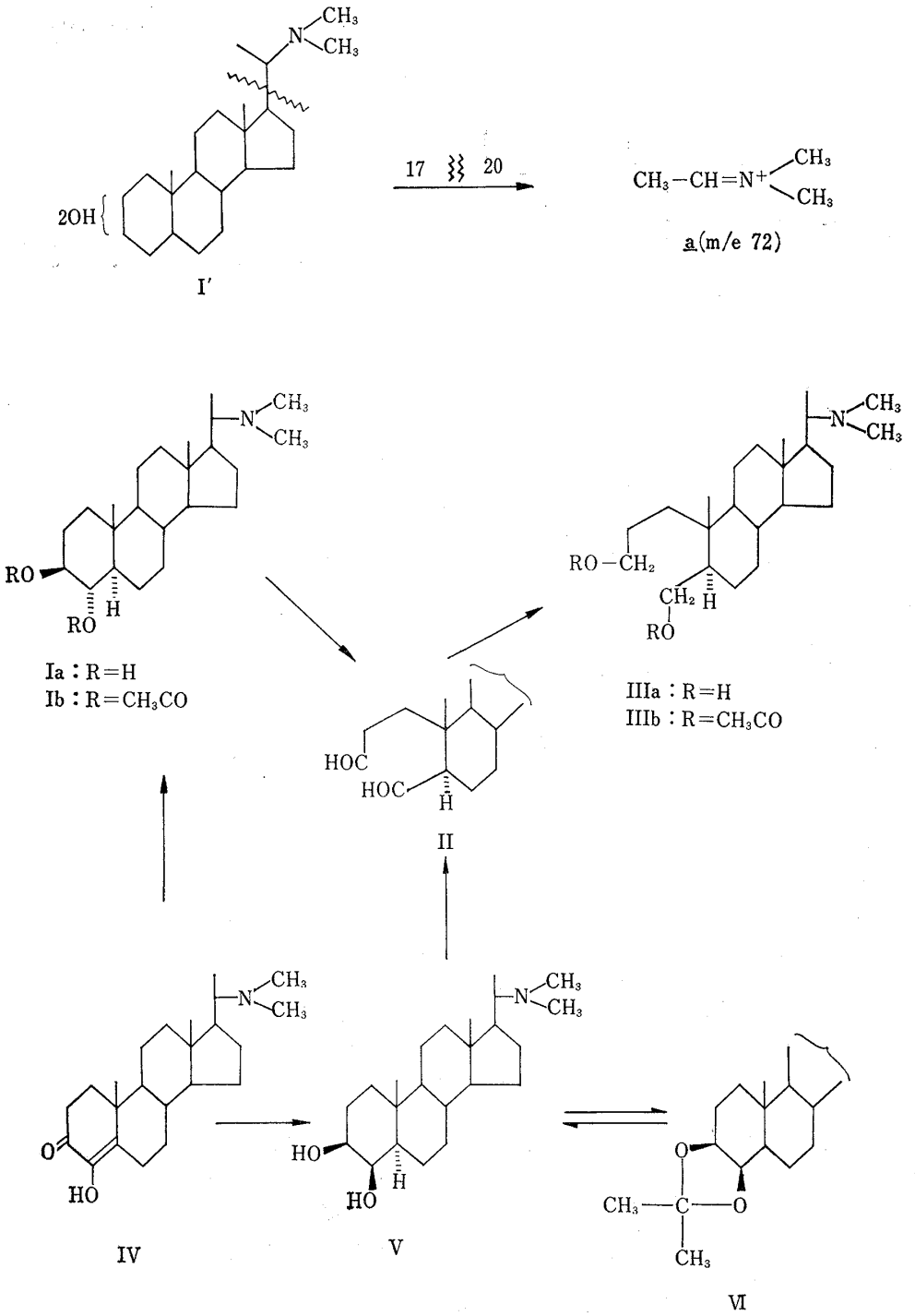

Chart 1.

an N-dimethylamino group at the 20-position.[2] These observations are strongly suggestive of the partial structure (I′) for the alkaloid.

It was suggested by the positive color test[3] 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), $C_{27}H_{47}O_4N$, m.p. 147~150°, $[\alpha]_D$ +16° ($CHCl_3$).

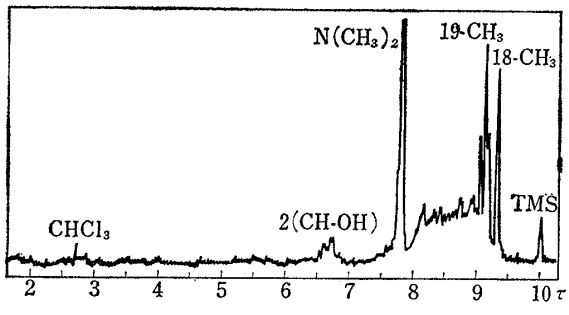

Fig. 1. NMR Spectrum of Terminaline (Ia)

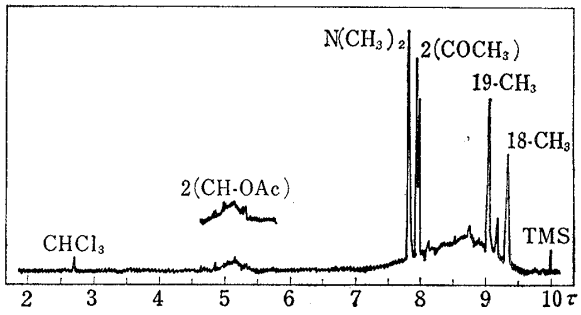

Fig. 2. NMR Spectrum of Terminaline O,O-Diacetate (Ib)

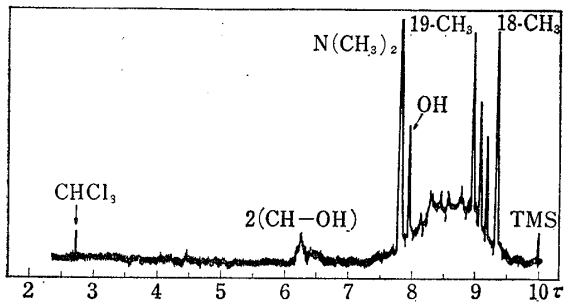

Fig. 3. NMR Spectrum of Synthetic 3β,4β-Dihydroxy-20α-dimethylamino-5α-pregnane (V)

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,[4] to the diol-diacetate (IIIb) was advanced.

The diosphenol (IV) was reduced with sodium borohydride to give 3β,4β-dihydroxy-20α-dimethylamino-5α-pregnane (V), $C_{23}H_{41}O_2N \cdot 1/2H_2O$, 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.* 8.98τ) than the standard region (*i.e.* 9.1~9.2τ), indicating the 1,3-diaxial correlation between the 19-methyl and the 4-hydroxyl group,[5] while the 3β-hydroxy orientation was given on the basis of the formation of an acetonide (VI), 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°, $[\alpha]_D$ +19° ($CHCl_3$). This compound was

2) 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).

3) F. Feigl: "Spot Test in Organic Analysis" (Maruzen Asian Edition), 189 (1960), Maruzen Co., Ltd. (Elsevier Publishing Co.).

4) M. Tomita, S. Uyeo, Jr., T. Kikuchi: This Bulletin, **15**, 193 (1967).

5) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, K. Tsuda: This Bulletin, **10**, 338 (1962).

identified with the diol-diacetate (IIIb) 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 stereochemistry 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.* 9.18τ) and that terminaline failed to give acetonide.*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), $C_{23}H_{41}O_2N$, obtained in this procedure, showed m.p. 242~244° and $[\alpha]_D$ +26° (50% MeOH-$CHCl_3$), 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.

Experimental*9

Terminaline O,O-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 temperature. After dilution with water and basification with Na_2CO_3, the product was taken up in CH_2Cl_2, dried (K_2CO_3), and evaporated. The crystalline residue (55 mg.) was recrystallized from acetone to give the O,O-diacetate (Ib) (30 mg.), m.p. 202~204°, as colorless plates. $[\alpha]_D^{22}$ +40° (c=1.0). *Anal.* Calcd. for $C_{27}H_{45}O_4N$: C, 72.44; H, 10.13; N, 3.13. Found: C, 72.67; H, 10.24; N, 3.15. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 and 1250 (O-Ac). NMR τ: 5.10 (2H, broad, two C$\underline{H}$-OAc), 7.83 (6H, N-$(CH_3)_2$), 7.97, 7.99 (6H, two OAc), 9.08, 9.35 (6H, *tert.* CH_3), and 9.13 (3H, doublet, J 6 c.p.s.; *sec.* CH_3). M.S. m/e: 447 (M^+), 432 (M^+-15), 72 (a, base peak), 43 (CH_3CO^+).

Hydrolysis of Terminaline O,O-Diacetate (Ib)——The O,O-diacetate (Ib) (100 mg.) was dissolved in a solution of $NaHCO_3$ (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 CH_2Cl_2-MeOH (9:1), dried over K_2CO_3, 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 $HIO_4 \cdot 2H_2O$ (300 mg.) in small portions and the mixture was kept at room temperature overnight. The reaction mixture was made basic by addition of dil. Na_2CO_3 and extracted with CH_2Cl_2. The extract was washed successively with 3% HCl and dil. Na_2CO_3, dried (K_2CO_3), and evaporated to leave a colorless oil (II) (150 mg.) which showed a strong infrared band at 1720 cm^{-1} ($CHCl_3$) 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 $NaBH_4$ (200 mg.) at room temperature for 4 hr. Usual working up gave a crystalline mass (diol, IIIa) (140 mg.) which was hardly purified by recrystallization. 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 (IIIb) (50 mg.) as colorless plates, m.p. 147~150°. $[\alpha]_D$ +16° ($CHCl_3$, c=1.0). *Anal.* Calcd. for $C_{27}H_{47}O_4N$: C, 72.12; H, 10.54; N, 3.12. Found: C, 71.90; H, 10.33; N, 2.92. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 and 1250 (O-Ac).

Synthesis of 3β,4β-Dihydroxy-20α-dimethylamino-5α-pregnane (V). i) Sodium Borohydride Reduction of the Diosphenol (IV)——The diosphenol (IV) (90 mg.) was treated with $NaBH_4$ (180 mg.) in MeOH (15 ml.)-CH_2Cl_2 (2 ml.) for 3 hr. at room temperature. After evaporation of solvents *in vacuo* and dilution with water, the product was taken in CH_2Cl_2, dried over K_2CO_3, and evaporated. Crystallization of the residue (80 mg.) from acetone gave a crystalline product (60 mg.) melting at about 200~210°. This substance, however, showed 3 spots on thin-layer chromatography (Aluminum-oxide acc. to Stahl-$CHCl_3$). Purification was achieved through the acetonide formation.

*8 Only a few *trans* 1,2-diols have been reported to form the acetonide. See B. Tursch, E. Tursch, I. T. Harrison, G. B. C. T. d. C. B. da Silva, H. J. Monteiro, B. Gilbert, W. B. Mors, C. Djerassi: J. Org. Chem., **28**, 2390 (1963).

*9 All the melting points were determined on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. The optical rotations were taken in chloroform solutions unless otherwise specified.

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. Na_2CO_3 and the precipitate was collected by suction. This was dissolved in CH_2Cl_2 and the solution was washed successively with 3% HCl and dil. Na_2CO_3, dried (K_2CO_3), 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 C$\underline{H}$-O-), 7.82 (6H, N-$(CH_3)_2$), 8.50, 8.70 $\left(6H, (CH_3)_2C\langle^{O-}_{O-}\right)$, 9.12 (3H, doublet, J 7 c.p.s., *sec.* CH_3), 8.95, and 9.33 (6H, two *tert.* CH_3).

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

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 $C_{23}H_{41}O_2N \cdot \frac{1}{2}H_2O$: C, 74.14; H, 11.36; N, 3.76. Found : C, 74.35, 74.75; H, 11.63, 11.34; N, 3.62. IR ν_{max}^{Nujol} cm^{-1} : 3350 (bonded OH). NMR τ : 4.29, 4.49 (2H, broad, two C$\underline{H}$-OH), 7.83 (6H, N-$(CH_3)_2$), 8.98 (3H, *tert.* CH_3), 9.12 (3H, doublet, J 6 c.p.s.; *sec.* CH_3), 9.36 (3H, *tert.* CH_3).

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 HIO_4 in 50% aqueous acetic acid was performed in the same way as given for terminaline (Ia). The resulting dialdehyde (II), IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1720, was reduced with $NaBH_4$ and then acetylated in the usual manner. Recrystallization of the crude product (40 mg.) from acetone afforded the pure dioldiacetate (IIIb) (10 mg.) as leaves, m.p. 148~150°, $[\alpha]_D^{22}$ +19° (c=1.0). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1730,1250 (O-Ac). This compound was found to be identical with the diol-diacetate (IIIb) 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 (IV) (98 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 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 leave a crystalline residue (90 mg.). Recrystallization from acetone-MeOH afforded the 3β,4α-diol (Ia) (35 mg.), m.p. 242~244°, $[\alpha]_D$ +26° (50v% $CHCl_3$-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 $C_{23}H_{41}O_2N$: C, 75.98; H, 11.37; N, 3.85. Found : C, 75.87; H, 11.35; N, 4.01.

The authors express their deep gratitude to Professor M. Tomita of this Faculty for his guidance and hearty encouragement. Also the authors wish to thank Dr. T. Shingu for the NMR measurements, Dr. T. Ibuka and Mr. A. Kato for taking Mass spectra, Dr. K. Miyajima and Mr. M. Yamamoto for the IR determinations in KBr, and Dr. K. Konobu and Miss Y. Mano and collaborators for elemental analyses.