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Pachysandra Alkaloids. XIII.[1] Structure and Stereochemistry of Spiropachysine, a Novel Spiro-lactam Alkaloid[2]

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The structure of spiropachysine, a major alkaloid of the leaves of *Pachysandra terminalis* Sieb. et Zucc. (Buxaceae), was investigated and assigned to the formula I, including absolute configuration, on the basis of chemical and spectroscopic evidences. The stereochemistry at the C_3-position was clarified by the circular dichroism study in comparison with the compounds having analogous aromatic chromophores and the known absolute stereochemistry. This alkaloid is unique in the structural feature possessing a five-membered spiro-lactam system.

Systematic examination of the alkaloidal components of *Pachysandra terminalis* Sieb. et Zucc. (Japanese name: Fukki-so), a Buxaceae plant, has revealed the presence of a number of new pregnane type alkaloids, whose structures except for a few ones have already been established.[4] In this paper we wish to present the full detail of structure determination of base-VI,[4] for which we proposed the name spiropachysine.

Spiropachysine (I), mp 290—292°, $[\alpha]_D$ +35° ($CHCl_3$), is a major alkaloid of leaves of the plant and was obtained from the weakly basic fraction. The combustion analyses data and the molecular ion peak (*m/e* 462) in the mass spectrum[5] of this alkaloid confirmed its molecular formula to be $C_{31}H_{46}ON_2$. The ultraviolet (UV) spectrum (in ethanol) shows absorption bands at 249, 274 (sh.), and 281 (sh.) nm associated with a benzene chromophore, whereas the infrared (IR) spectrum[6] exhibits a strong amide band at 1673 cm^{-1} and weak aromatic bands at 1618, 1600, and 1475 cm^{-1}. As shown in Fig. 1, its nuclear magnetic resonance (NMR) spectrum[7] indicates the presence of a phenyl (τ 2.10—2.77, 4H), an amide N-methyl (τ 6.62, 3H), an N-dimethyl (τ 7.83, 6H), a secondary C-methyl (τ 9.12, 3H, doublet, J=6 Hz), and two tertiary C-methyl groups (τ 8.99 and 9.31, each 3H). The framework of spiropachysine was suggested by the appearance of the extremely strong base peak at *m/e* 72 in the mass spectrum, which is diagnostic for the 20-dimethylaminopregnane skeleton.[8]

The alkaloid (I) resisted alkaline and acidic hydrolyses even under drastic conditions, but on treatment with lithium aluminum hydride in boiling tetrahydrofuran, it afforded a

1) Part XII: T. Kikuchi, T. Nishinaga, S. Uyeo, Jr., O. Yamashiro, and K. Minami, *Chem. Pharm. Bull.* (Tokyo), **19**, 1893 (1971).
2) Preliminary accounts of this work appeared in *Tetrahedron Letters*, **1968**, 2077; *idem, ibid.*, **1969**, 2522.
3) Location: *a) Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto; b) Sagisu-kamidori, Fukushima-ku, Osaka.*
4) M. Tomita, T. Kikuchi, S. Uyeo, Jr., T. Nishinaga, M. Yasunishi (née Ando), and A. Yamamoto, *Yakugaku Zasshi*, **87**, 215 (1967) and references cited therein.
5) Mass spectra were measured on a Hitachi Mass Spectrometer RMU-6D equipped with an all-glass inlet system.
6) IR spectra were determined in chloroform solutions unless otherwise specified.
7) All the NMR spectra were taken on a Varian Associates A-60 Spectrometer in deuterated chloroform solutions and chemical shifts are recorded in τ values using tetramethylsilane as the internal reference.
8) T. Kikuchi, S. Uyeo, Jr., T. Nishinaga, T. Ibuka, and A. Kato, *Yakugaku Zasshi*, **87**, 631 (1967) and references cited therein.

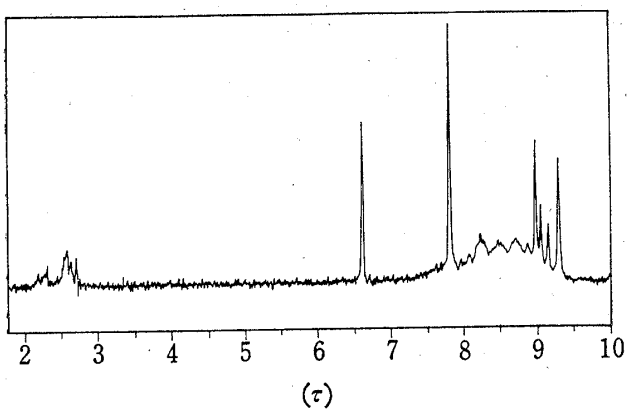


Fig. 1. NMR Spectrum of Spiropachysine (I)

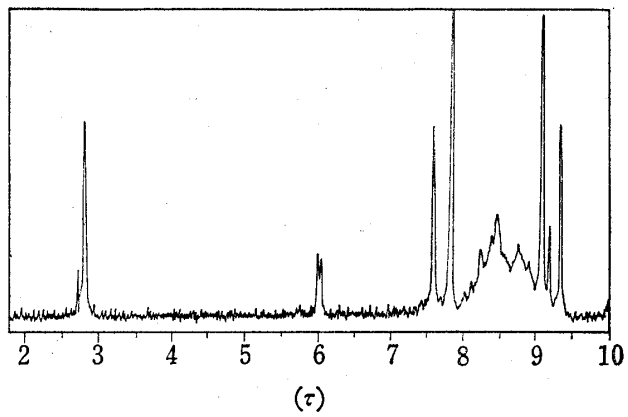


Fig. 2. NMR Spectrum of Deoxospiropachysine (II)

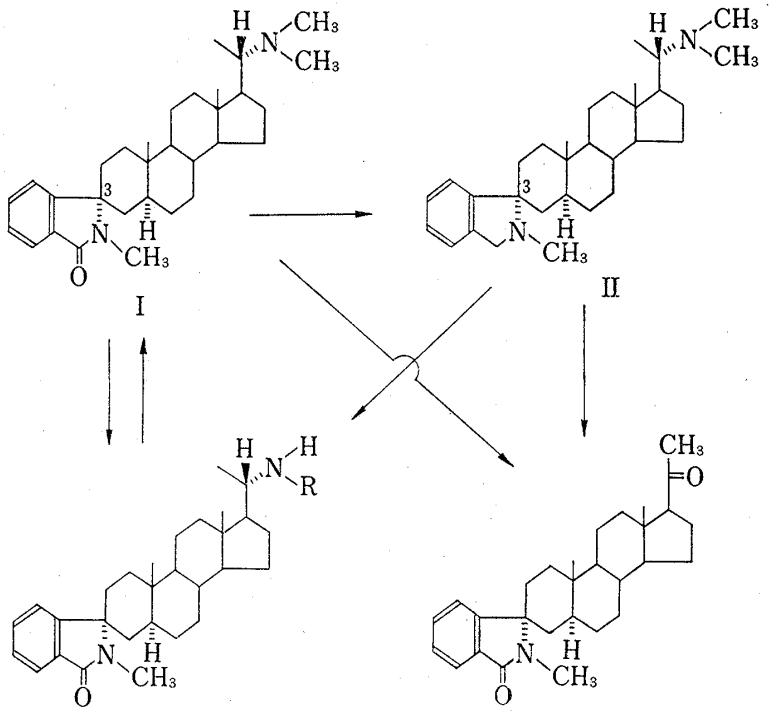


Chart 1

deoxo compound (II), $C_{31}H_{48}N_2$, mp 175—177°, as the strongly basic product, which shows no longer amide band in the IR spectrum. The NMR spectrum of this product (II) is characterized by several remarkable changes compared with the parent alkaloid (I): *i.e.*, 1) the signal of aromatic protons turns to a singlet (τ 2.83); 2) the N-methyl signal at τ 6.62 shows a high-field shift to τ 7.60; 3) a typical AB quartet appears newly at the position centered at τ 6.02 (J= 15 Hz) (see Fig. 2). On addition of trifluoroacetic acid, this AB quartet shifts to lower field (τ 4.73 and 5.82, two doublets, J=15 Hz).

The above result is suggestive of the presence of an N-methyl-N-benzoyl grouping, which can be converted to a methylbenzylamino grouping, in spiropachysine (I).

Treatment of the deoxo compound (II) with manganese dioxide in refluxing chloroform gave rise to an amide (IIIa), $C_{29}H_{42}ON_2$, mp 273—276°, whose IR spectrum demonstrates a carbonyl band at 1673 cm^{-1} and an NH band at 3350 cm^{-1}. Its NMR spectrum reveals the disappearance of N,N-dimethyl and benzyl methylene signals together with considerable

low-field shifts of the secondary C-methyl (τ 8.89) and the N-methyl signal (τ 6.63), whereas the mass spectrum shows the molecular ion peak at *m/e* 434 and the very strong base peak at *m/e* 44 assignable to the ion CH_3–CH=N^+H_2.[8] This amide (IIIa) was also obtained by the same oxidation of spiropachysine (I) and it regenerated the latter (I) upon N-methylation by the formalin-sodium borohydride procedure.[9]

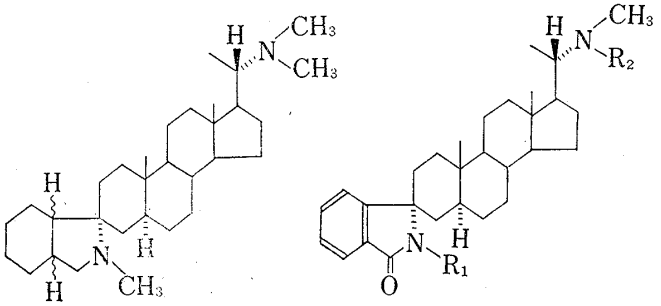
Thus, it was considered feasible that, in this reaction, oxidation took place at the benzylic methylene group and simultaneously oxidative de-methylation at the 20-dimethylamino group.[10] Furthermore, two other amides were isolated as minor products in this oxidation. The one, amorphous powder, $C_{30}H_{42}O_2N_2$ (molecular ion peak at *m/e* 462 in the mass spectrum), was proved to be the N-formyl compound (IIIb) of IIIa by comparison of its IR and NMR spectra with those of an authentic sample (IIIb) derived from IIIa, while the structure of the other product, $C_{29}H_{39}O_2N$ (molecular ion peak at *m/e* 433), mp 252—255°, was deduced to be IV on the basis of its spectral data.

These findings supported strongly the assumption that spiropachysine is a member of 20-dimethylaminopregnane type alkaloid like other Pachysandra alkaloids and besides, it has a benzoyl amide grouping. In consideration of its molecular formula coupled with the fact that no olefinic proton signal is observed in the NMR spectrum, it might be a hexacyclic compound. However, a possibility that the alkaloid is pentacyclic and has a tetrasubstituted double bond could not be excluded at this stage.

Several attempts were then made in order to settle this problem. First, catalytic reduction[11] of I or II under usual conditions resulted in recovery of the starting material, whereas vigorous hydrogenation of II over PtO_2 in acetic acid at 80° afforded a hexahydro compound (V), $C_{31}H_{54}N_2$, mp 213—215°, the structure of which was thought to be V based on its NMR and mass spectral data.

Next, oxidation of I with chromium trioxide in acetic acid yielded no allylic oxidation product, but instead a secondary lactam (VIa),[12] $C_{30}H_{44}ON_2$, mp 283—285°, whose structure was deduced to be VIa from its IR spectrum (3430 and 1687 cm^{-1} (NH–CO)) and NMR spectrum (disappearance of the amide N-methyl signal with no appreciable change in other region). On the other hand, chromium trioxide oxidation of I in pyridine gave rise to a neutral N-formate (VIb), $C_{31}H_{44}O_2N_2$, mp 266—268°, as expected.

Also, treatment of I with osmium tetroxide in pyridine gave the above N-formate (VIb), instead of a dihydroxy compound which is expected if the alkaloid has a double bond in its



V

VIa : R_1=H, R_2=CH_3
VIb : R_1=CH_3, R_2=CHO
VIc : R_1=CH_3, R_2=H

Chart 2

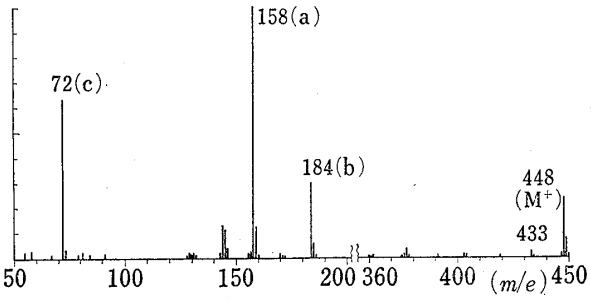


Fig. 3. Mass Spectrum of Deoxospiropachysine (II)

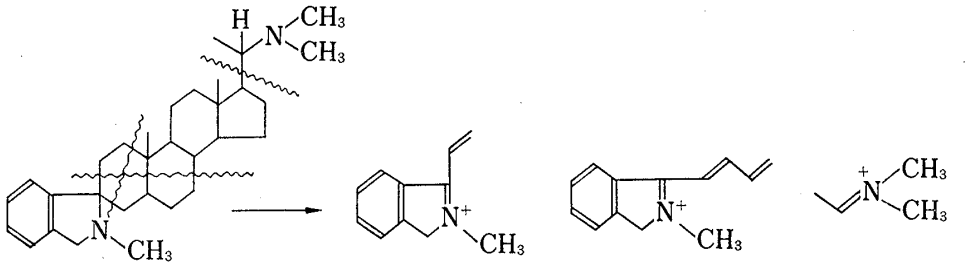
9) K.A. Schellenberg, *J. Org. Chem.*, **28**, 3259 (1963).
10) H.B. Henbest and A. Thomas, *J. Chem. Soc.*, **1957**, 3032.
11) As to examples of catalytic reduction of tetrasubstituted double bonds, see M. Freifelder, "Practical Catalytic Hydrogenation," John Wiley & Sons, Inc., New York, 1971, p. 127.
12) K. Hess, C. Uibrig, and A. Eichel, *Chem. Ber.*, **50**, 344 (1917).

skeleton. Furthermore, reaction with selenium dioxide or with N-bromosuccinimide was tried and resulted in failure.

Meanwhile, attempted bromination of I in acetic acid gave a complex mixture, from which a crystalline substance, $C_{30}H_{44}ON_2$ (molecular ion peak at *m/e* 448 in the mass spectrum), mp 287—289°, was isolated by silica gel chromatography. The structure of this compound was assigned to the formula VIc judged from its spectroscopic data. A similar N-demethylation reaction with bromine has already been reported by Ayling, *et al.*[13]

These results led us to conclude that the alkaloid (I) has no isolated double bond in the molecule.

Of two nitrogen atoms in spiropachysine (I), the amide nitrogen would locate most likely at the C_3-position of the pregnane skeleton from the biogenetic analogy with other Pachysandra alkaloids, but the inspection of its NMR spectrum revealed the absence of a signal attributable to the C_3-hydrogen in the range τ 4—7 (see Fig. 1).[14] Thus, the alkaloid should have a five-membered spiro-lactam structure as depicted in the formula I.



II a b c

Chart 3

A strong support was provided by the mass spectrum of deoxospiropachysine (II), in which three intense peaks are noticed at *m/e* 158 (base peak), 184, and 72 as seen in Fig. 3. These peaks are reasonably ascribed to the fragment ion a, b, and c (Chart 3),[8] respectively, and the correctness of this fragmentation is confirmed by the appearance of corresponding metastable peaks. It must also be mentioned that, contrary to usual 3,20-diaminopregnane alkaloids, the comparatively greater intensity of the fragment a than c is consistent with the structure II, for the initial bond cleavage at the C_3–C_4 linkage may be facilitated in such a structure.

The chemical evidence for the suggested structure (I) of spiropachysine was advanced as follows.

The deoxo compound (II) was converted to a dimethiodide and then submitted to Hofmann degradation with potassium *t*-butoxide in refluxing *t*-butanol to give two methine bases, separation of which could be easily achieved by taking advantage of their basicity difference.

The weakly basic methine (VII) crystallized in needles from acetone, mp 65—68°, and reveals new absorption bands at 1640, 1000, and 910 cm^{-1} (end vinyl group) in the IR spectrum. Its NMR spectrum is characterized by the appearance of signals with complex pattern for newly introduced olefinic hydrogens at τ 4.0—5.2, corresponding to four protons, and the disappearance of signals for the secondary methyl group. Accordingly, this compound was considered to be VII[15] produced by the double β-elimination of quarternary ammonium groups at the C_3- and C_{20}-positions.

13) E.E. Ayling, J.H. Gorvin, and L.E. Hinkel, *J. Chem. Soc.*, **1942**, 755.

14) In this series of alkaloids the hydrogen geminal to the C_3-acylamino group resonates usually in τ 5.2—6.7 region.

15) This substance (VII) is probably a mixture of Δ^2- and Δ^3-isomers judged from the NMR pattern in olefinic proton region.

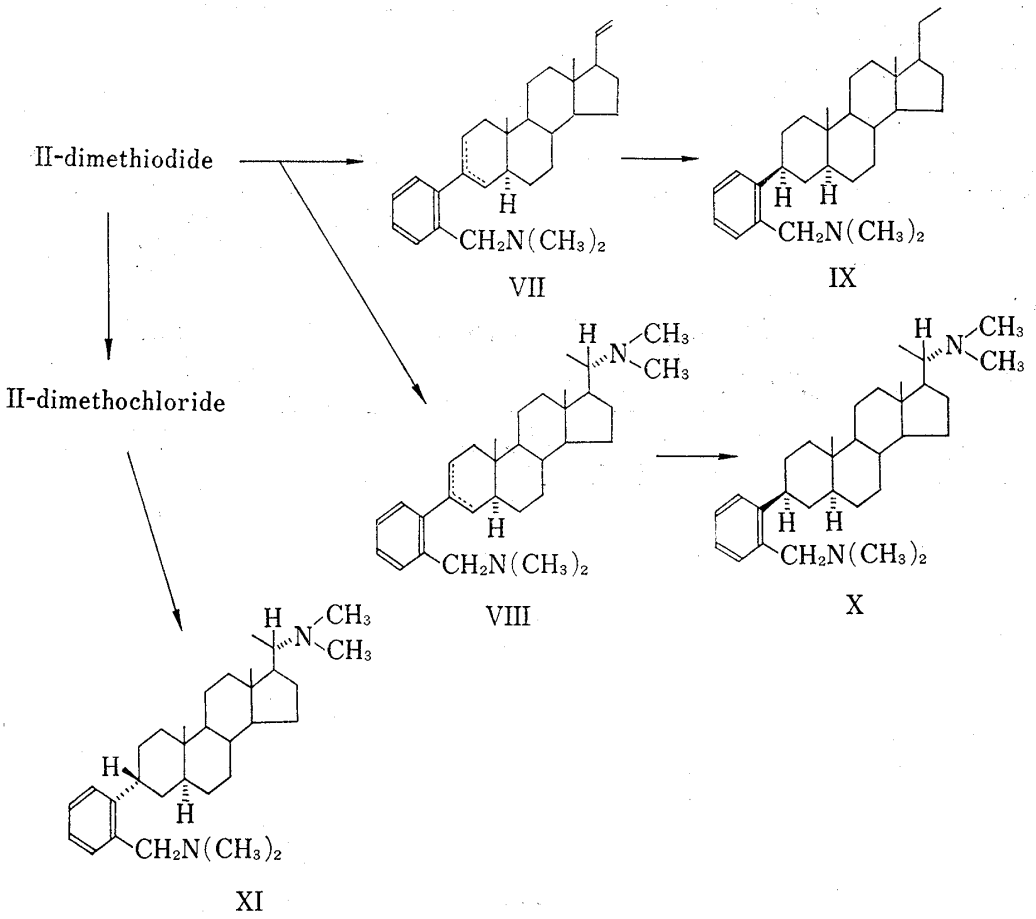


Chart 4

Hydrogenation of the above methine base (VII) over PtO_2 in acetic acid yielded a tetrahydro base (IX), $C_{30}H_{47}N$, mp 114—116°, whose NMR spectrum shows no longer olefinic proton signal, but a new signal attributable to the C_3-hydrogen at τ 7.10 (1H, broad, $W^{1/2}$ about 18 Hz).[16]

The strongly basic methine (VIII) was also obtained in crystalline form, melting at about 98—102°.[17] The mass spectrum of this methine exhibits the molecular ion peak at *m/e* 462 ($C_{32}H_{50}N_2$) and the very strong base peak at *m/e* 72 (CH_3–CH=$N^+(CH_3)_2$) and the NMR spectrum shows signals of two N-dimethyl groups at τ 7.81 and 7.82 along with other signals for the benzyl methylene, secondary methyl, two tertiary methyl, and aromatic protons. Besides, two signals corresponding to one olefinic hydrogen are observed newly at τ 4.53 and 4.81 in an approximate ratio of 4: 1.

From these spectral data, the structure of this methine base should be assigned to the formula VIII, but it is probably a mixture of Δ^2- and Δ^3-compounds as judged from the NMR signal pattern of the olefinic hydrogen, although it behaves just like a single compound on thin-layer chromatography (TLC).

Subsequent catalytic reduction of VIII afforded solely a dihydro compound (X), $C_{32}H_{52}N_2$, mp 120—122°, $[\alpha]_D$ +35° ($CHCl_3$). In its NMR spectrum, the geminal hydrogen to the aromatic substituent appears as a broad signal with the half-band width of about 18 Hz at τ 7.04.

16) The configuration of C_3-phenyl grouping in the tetrahydro compound (IX) may be assigned to β based on the half-band width of C_3-hydrogen signal. The triplet signal due to the C_{21}-methyl group in IX could not be recognized because of overlapping with other signals.

17) In the UV spectrum of VIII, typical absorption of the styrene chromophore is not observed because of steric inhibition to the planar orientation of this system.

On the other hand, Emde degradation of II-dimethochloride with Raney nickel in aqueous sodium hydroxide yielded a single product (XI), $C_{32}H_{52}N_2$, mp 181—183°, $[\alpha]_D$ +96° ($CHCl_3$). Its NMR spectrum resembles closely to that of the above mentioned dihydro methine (X) except a considerable paramagnetic shift of a signal assignable to the C_3-hydrogen which is overlapping upon the benzylic methylene signal (τ 6.60). In the presence of trifluoroacetic acid, they are resolved into two signals at τ 6.71 (1H, broad, $W^{1/2}$ about 11 Hz, C_3–H) and 5.72 (2H, broad singlet, C_6H_4–CH_2–N). Furthermore, the mass spectrum of this compound (XI) is almost superimposable with that of X described above.

Therefore, it is reasonable to consider that the Emde methine (XI) is the C_3-stereoisomer of X and the configuration of their C_3-substituents is α (axial) in the former (XI)[18] and β (equatorial) in the latter (X).

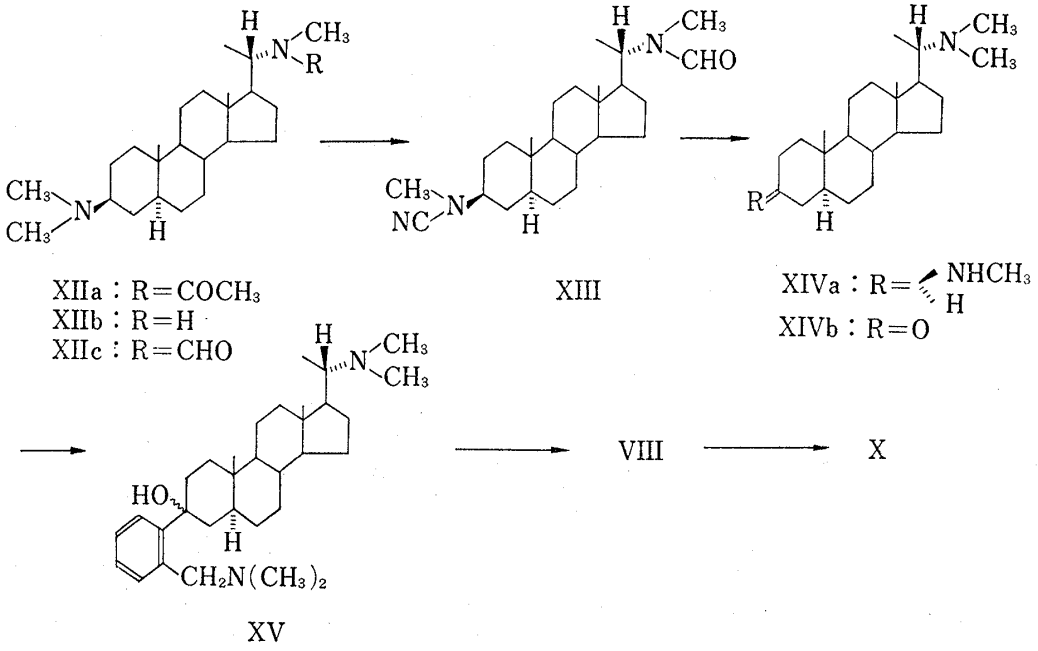


Chart 5

Then, we carried out the partial synthesis of the compound X starting from epipachysamine-A (XIIa)[19] according to the scheme given in Chart 5.

Reductive hydrolysis of XIIa with calcium in liquid ammonia afforded a des-acyl compound (XIIb), which was formylated in the usual manner to give an N-formate (XIIc), $C_{25}H_{44}ON_2$, mp 193—196°. Treatment of XIIc with cyanogen bromide in benzene yielded an N–CN compound (XIII), $C_{25}H_{41}ON_3$, mp 218—220°, whose IR spectrum demonstrates clearly a C≡N band at 2200 cm^{-1} and an amide band at 1660 cm^{-1}. Subsequent reduction of the latter (XIII) with lithium aluminum hydride gave rise to a diamine (XIVa), $C_{24}H_{44}N_2$, mp 148—151°, $[\alpha]_D$ +32° ($CHCl_3$), which was proved to be identical with dictyophlebine (XIVa)[20] by IR comparison (KBr) and mixed fusion with an authentic sample.

Ruschig degradation of XIVa was then performed according to the Goutarel's description,[20] whereupon was obtained a 3-keto compound (XIVb), mp 160—165°, ν: 1705 cm^{-1},

18) Although the stereochemical course of Emde degradation has not been established yet, it is noteworthy that in this case the reaction proceeded with inversion of configuration at the C_3-position. *cf.* H.O. House, "Modern Synthetic Reactions," 2nd Ed., W.A. Benjamin, Inc., Menlo Park, 1972, p. 19; S. Mitsui, *Kagaku-no-Ryoiki*, **14**, 447 (1960).

19) T. Kikuchi, S. Uyeo, Jr., and T. Nishinaga, *Chem. Pharm. Bull.* (Tokyo), **15**, 307 (1967).

20) Q. Khuong-Huu, X. Monseur, M. Truong-Ho, R. Kocjan, and R. Goutarel, *Bull. Soc. Chim. France*, **1965**, 3035.

whose identity with funtumafrine-C (XIVb)[20] was confirmed by IR comparison with an authentic sample.

Condensation of the above ketone (XIVb) with *o*-lithio-dimethylbenzylamine,[21] prepared from dimethylbenzylamine and butyllithium, proceeded smoothly to give an amino-alcohol (XV) as a sole product, $C_{32}H_{52}ON_2$, mp 158—160°, the IR spectrum of which reveals a hydroxyl band at 3050 cm^{-1} and the NMR spectrum shows signals for aromatic protons (τ 2.50—3.00, 4H), a benzylic methylene (τ 6.30, 2H, singlet), and two N-dimethyl groups (τ 7.79 and 7.82, each 6H). Upon treatment with hydrochloric acid in boiling ethyleneglycol, it gave a mixture of dehydrated compounds (VIII) which crystallized in needles from acetone, mp 99—102°. This substance showed the same *Rf* value on TLC as that of the aforementioned Hofmann methine (VIII) and both their IR and NMR spectra were almost identical with each other.

Catalytic hydrogenation of VIII, thus obtained, over PtO_2 afforded singly a dihydro compound (X), $C_{32}H_{52}N_2$, mp 119—121°, $[\alpha]_D$ +37° ($CHCl_3$), which was found to be identical in every respect with the compound X derived from spiropachysine.

On the basis of foregoing observations, the structure of spiropachysine is unambiguously assigned to the formula I except for the stereochemistry at the C_3-position. Apparently this alkaloid is the first member of a new class of pregnane type alkaloid, unique in the structural feature involving a five-membered spiro-lactam ring.

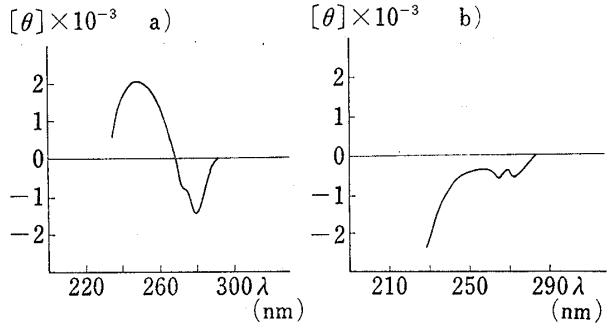


Fig. 4. CD Curves of a) Spiropachysine (I) (in Methanol) and b) Deoxospiropachysine (II) (in Dioxane)

The configuration of C_3-nitrogen function in the alkaloid (I) would be assigned to α(axial)-orientation on consideration of the fact that the Hofmann elimination of deoxospiropachysine dimethiodide proceeded readily at the C_3-position as mentioned before. However, this can not be the confirmatory evidence in our present case, for there might be a possibility of E1 type elimination[22] through a cationic intermediate or *cis* elimination[23] in the alternative β(equatorial)-ammonium structure.

Thus, we undertook a study of circular dichroism (CD)[24] of spiropachysine (I) and the deoxo base (II), which enabled the C_3-configurational allotment to be made firmly.

As shown in Fig. 4 (see also Table I), the CD curves of I and II exhibit multiple Cotton effects between 230 and 280 nm, which are due to the aromatic π—π^* transitions associated with the phthalimidine chromophore in the former (I) and the isoindoline chromophore in the latter (II).

Recent development of optical rotatory dispersion (ORD) and CD equipments permitted the detailed studies on optically active aromatic compounds and several attempts[25] have been made to correlate the sign of Cotton effects to the absolute configuration of asymmetric centres near phenyl chromophores or to the chirality of aromatic molecules. However, it seems a generalized rule which is applicable to our present problem has not so far been estab-

21) F.N. Jones, R.L. Vaulx, and C.R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963).
22) C.K. Ingold, "Structure and Mechanism in Org. Chem.," 2nd ed., Cornell Univ. Press, Ithaca, 1969, p. 700.
23) J.L. Coke and M.P. Cooke, Jr., *J. Am. Chem. Soc.*, **89**, 6701 (1967); *idem*, *Tetrahedron Letters*, **1968**, 2253.
24) CD spectra were recorded on a JASCO ORD UV-5 Spectropolarimeter.
25) P. Crabbe and W. Klyne, *Tetrahedron*, **23**, 3449 (1967); K. Kuriyama, T. Iwata, M. Moriyama, K. Kotera, Y. Hamada, R. Mitsui, and K. Takeda, *J. Chem. Soc.* (B), **1967**, 46; G.G. DeAngelis and W.C. Wildman, *Tetrahedron*, **25**, 5099 (1969) and references cited therein.

Table I. CD Data

Compound	Solvent	Molecular ellipticity λ_{max} (nm) ([θ])		
Spiropachysine (I)	MeOH	279(−1680)	274^{sh}(−700)	250(+1960)
Deoxospiropachysine (II)	dioxane	273(−590)	266(−560)	
l-β-Hydrastine (XVIa)	MeOH	315(−10900)	304(−12100)	273(−12000)
		220(+48000)		
l-α-Narcotine (XVIb)	MeOH	313(−14000)	252^{sh}(−13500)	240(−37800)[a]
l-α-Hydrastine (XVIIa)	MeOH	302(+10000)	278(−4000)	256(+3000)
		235(−61000)	216(−118000)	
l-β-Narcotine (XVIIb)	MeOH	318(+2600)	270(+3400)	240(−29200)

a) last reading
sh: shoulder

lished and therefore we decided to compare the CD curve of spiropachysine (I) or deoxospiropachysine (II) with those of compounds having similar chromophore and known absolute configuration.

An ORD study on hydrastine-narcotine alkaloids (XVIa, XVIb, XVIIa, and XVIIb), whose absolute stereochemistry was determined on the basis of chemical and spectrometric evidence,[26,27] has been done by Ohta, *et al.*,[26] who reported that in these compounds the signs of the longest wave-length Cotton effects at about 310 nm are enantiomeric depending upon the absolute configuration at C_9-position adjacent to the aromatic ring.

In order to make a direct comparison, we measured the CD curves of the above alkaloids and obtained a result in accord with the Ohta's observation. As given in Table I, they demonstrate multiple Cotton effects in 210—320 nm region, among which the longest wave-length Cotton effect is negative for the 9*S* series (XVIa, XVIb) in contrast to the positive sign for the 9*R* series (XVIIa, XVIIb).

The phthalide chromophore in hydrastine-narcotine alkaloids may be regarded as optically analogous with the phthalimidine chromophore in spiropachysine (I), since the lactone oxygen atom in the former and the lactam nitrogen in the latter would have similar contribution to the aromatic π—π^* transition because they locate at the same position in a five-membered ring of almost planar conformation. Also two methoxyl substituents attached to the phthalide system would not alter the optical rotatory property of the aromatic transition because of the remote disposition from the asymmetric centre C_9, although they cause some changes in wave-length and amplitude of the Cotton effect.[28] It follows, therefore, that the same configurational relationship at the benzylic asymmetric carbon atoms in these systems would give the same sign for the longest wave-length Cotton effects.

As the sign of the first Cotton effect of spiropachysine is negative, it can be reasonably correlate to XVIa and XVIb, thus being assigned to the structure I in which the C_4-alkyl residue is bulkier than the C_2-residue.

A support for this allotment was given by comparison with the Cotton effects of oxindole alkaloids represented by general formulas XVIII and XIX.

26) M. Ohta, H. Tani, and S. Morozumi, *Chem. Pharm. Bull.* (Tokyo), **12**, 1072 (1964); M. Ohta, H. Tani, S. Morozumi, and S. Kodaira, *ibid.*, **12**, 1080 (1964).
27) A.R. Battersby and H. Spencer, *Tetrahedron Letters*, **1964**, 11.
28) After the preliminary report of this paper was published, a detailed analysis of CD and ORD data of a series of phthalideisoquinoline alkaloids, including hydrastines and narcotines, and of several simple model compounds was reported by Snatzke, *et al.*, who resolved the CD bands of these compounds into Gaussian-shaped partial bands and determined their stereochemistry by inspection of these partial bands. Correlation between the configuration at C_9-position and the sign of the longest wave-length Cotton effect agrees well with our experimental result; see G. Snatzke, G. Wollenberg, J. Hrbek, Jr., F. Santavy, K. Blaha, W. Klyne, and R.J. Swan, *Tetrahedron*, **25**, 5059 (1969).

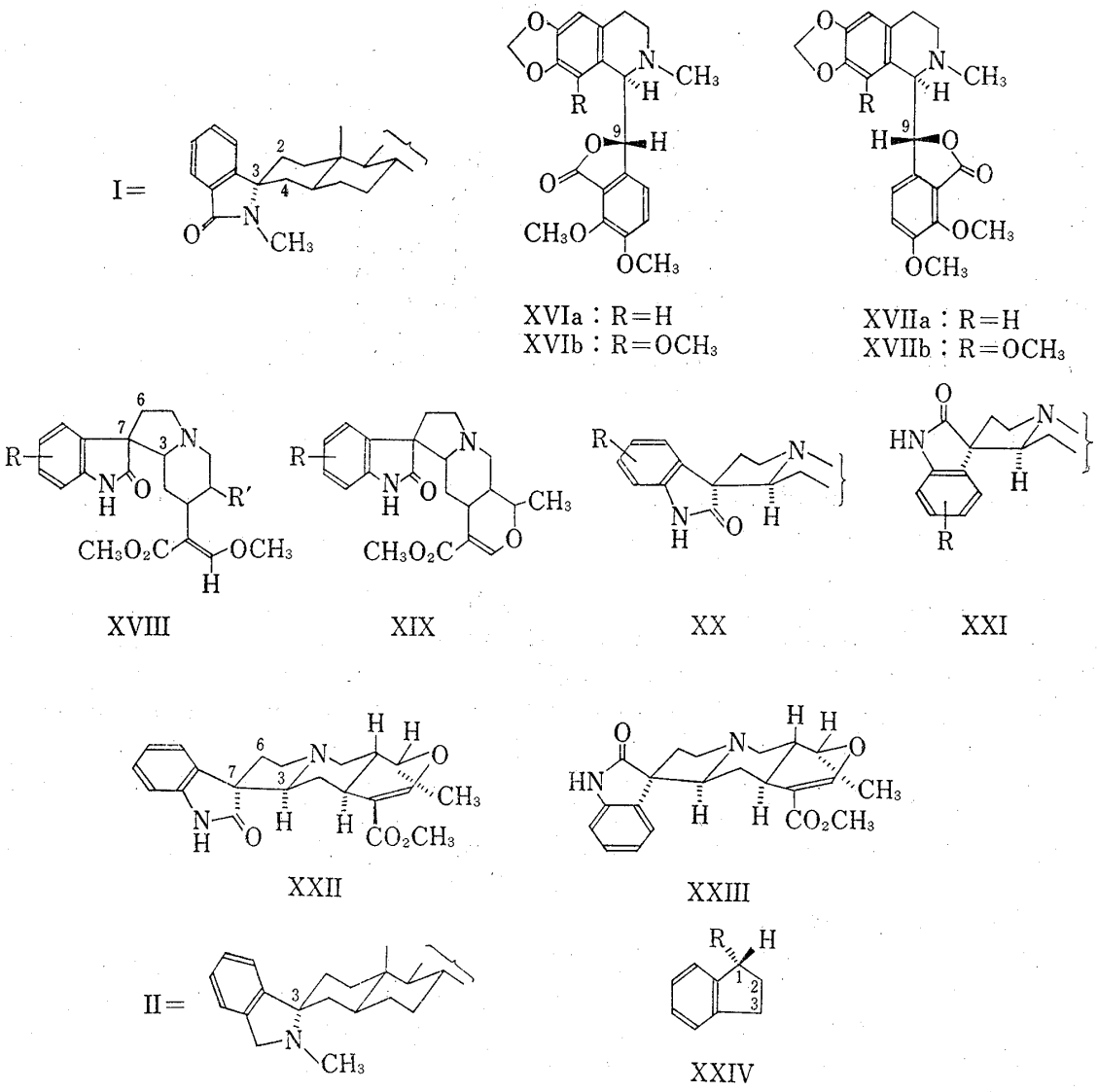


Chart 6

Extensive studies have been done on ORD and CD curves of this type of alkaloids[29] and it was reported that the sign of their longest wave-length Cotton effects centered at about 300 nm is governed by the absolute configuration of the spiro carbon atoms at C_7-position; *viz.*, the compounds with a partial formula XX (R=H or OCH_3) give the negative sign independent of the stereochemistry at other asymmetric centers and the compounds with a partial formula XXI show the positive one. Isomitraphylline (XXII), for instance, gives a negative Cotton effect at 285 nm, while mitraphylline (XXIII) a positive one at 290 nm.

Since the rotatory nature of the longest wave-length transition associated with the aromatic chromophore in these oxindole alkaloids would be roughly the same as that of phthalimidine chromophore in spiropachysine (I) on consideration of their structural similarity, the configuration of C_3 spiro carbon atom in the latter base may be the same as the C_7 configuration of isomitraphylline (XXII) in which the C_7–C_3 bond is bulkier than the C_7–C_6 bond, supporting the β-orientation of the phenyl ring in spiropachysine (I).

29) J.L. Pousset, J. Poisson, and M. Legrand, *Tetrahedron Letters*, **1966**, 6283; J.L. Pousset, J. Poisson, R.J. Shine, and M. Shamma, *Bull. Soc. Chim. France*, **1967**, 2766; A.F. Beecham, N.K. Hart, S.R. Johns, and J.A. Lamberton, *Tetrahedron Letters*, **1967**, 991; *idem*, *Aust. J. Chem.*, **21**, 491 (1968); W.F. Trager, C.M. Lee, J.D. Phillipson, R.E. Haddock, D. Dwuma-Badu, and A.H. Beckett, *Tetrahedron*, **24**, 523 (1968).

Next, we examined the CD curve of deoxospiropachysine (II) in comparison with those of optically active 1-substituted indane derivatives which differ structurally from the isoindoline chromophore of II only in the replacement of a nitrogen atom by a carbon. Brewster, *et al.*[30] and Snatzke, *et al.*[31] demonstrated recently that a series of 1(*R*)-substituted indanes represented by the formula XXIV (R=NH_2, $NHCH_3$, $N(CH_3)_2$, CH_2OH, COOH, OH, *etc.*) show the multiple Cotton effects around 250—300 nm region and their Cotton effects due to the longest wave-length band (α band) are positive.

Because the nitrogen atom in the isoindoline nucleus of II locates on the C_{2v} local symmetry axis of aromatic chromophore, it would not influence practically on the optical nature of the α-band. Therefore, it is expected that the opposite sign of the longest wave-length Cotton effect for the above two chromophores indicates the opposite absolute stereochemistry at the benzylic asymmetric centres. In consequence, deoxospiropachysine (II) with the negative Cotton effect at 273 nm can be safely correlated to 1(*S*)-indane series and hence the C_3-phenyl group in this compound is allotted to the β-configuration.

These observations confirm the absolute stereochemistry of spiropachysine as represented by the formula I.

Experimental[32]

Extraction of Spiropachysine (I) from the Leaves of *Pachysandra terminalis* Sieb. et Zucc.——Dried leaves (about 50 kg) collected in Shiranuka District, Hokkaido, in October, 1966 were extracted four times with boiling MeOH. After evaporation of the combined extracts under reduced pressure, the residue was dissolved in 5% aqueous citric acid (*ca.* 30 liters), the insoluble part being removed by filtration. The acidic aqueous solution was basified with NH_4OH and the precipitate extracted thoroughly with $CHCl_3$, washed with water, dried, and concentrated to about 2 liters. The above $CHCl_3$ solution was then shaken well with an equal volume of 3% HCl in order to separate the strongly basic and the weakly basic alkaloids. Basification of the aqueous layer, followed by extraction with CH_2Cl_2, afforded a mixture of strongly basic alkaloids (*ca.* 140 g). On the other hand, the $CHCl_3$ layer was evaporated *in vacuo* and the residue dissolved in ether. The ethereal solution was extracted with 3% HCl and the acidic solution was again made alkaline by addition of conc. NH_4OH, extracted with CH_2Cl_2. After drying, evaporation of the solvent left a mixture of weakly basic alkaloids (*ca.* 250 g). Upon trituration with acetone, the latter gave a crystalline mass which was recrystallized from the same solvent to afford spiropachysine (I) as colorless needles (9.1 g), mp 290—292°, $[\alpha]_D^{24}$ +35° (*c*=1.0). *Anal.* Calcd. for $C_{31}H_{46}ON_2$: C, 80.47; H, 10.02; N, 6.06. Found: C, 80.37; H, 10.23; N, 6.30. Mass Spectrum *m/e*: 462 (M^+), 72 (base peak, CH_3–CH=$N^+(CH_3)_2$). UV λ_{max}^{EtOH} nm(ε): 249 (5600), 274 (sh) (2870), 281 (sh) (1830). IR ν_{max} cm^{-1}: 1673 (lactam), 1618, 1600, and 1475 (phenyl). NMR τ: 2.10—2.77 (4H, multiplet, aromatic protons), 6.62 (3H, amide N–CH_3), 7.83 (6H, N–$(CH_3)_2$), 8.99 (3H, *tert*-CH_3), 9.12 (3H, doublet, J=6 Hz, *sec*-CH_3), and 9.31 (3H, *tert*-CH_3).

Lithium Aluminum Hydride Reduction of Spiropachysine (I)——A solution of spiropachysine (1.00 g) in tetrahydrofuran (50 ml) was added under stirring to a suspension of $LiAlH_4$ (1.00 g) in tetrahydrofuran (50 ml) and the mixture refluxed for 3 hr. After the excess reagent was decomposed by careful addition of aq. tetrahydrofuran, insoluble material was removed by filtration and washed thoroughly with $CHCl_3$. The filtrate and the washings were combined and evaporated under reduced pressure. The residue was taken up into 3% HCl, washed with $CHCl_3$, basified with NH_4OH, and extracted with CH_2Cl_2. The extract was dried and evaporated to give a crystalline product (II) (940 mg), which was recrystallized from CH_2Cl_2–acetone to afford a pure sample (860 mg) in colorless prisms, mp 175—177°, $[\alpha]_D^{30}$ +35° (*c*=1.0). *Anal.*

30) J.H. Brewster and J.G. Buta, *J. Am. Chem. Soc.*, **88**, 2233 (1966). See also H.E. Smith and T.C. Willis, *Tetrahedron*, **26**, 107 (1970).

31) G. Snatzke, M. Kajtar, and F. Snatzke, "Fundamental Aspects and Recent Developments in ORD and CD," ed. by F. Ciardelli and P. Salvadori, Heyden & Son, Ltd., London, 1973, pp. 148—172.

32) All the melting points were determined on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. All the specific rotations were measured in chloroform solutions unless otherwise specified. For drying the solutions of bases, anhydrous potassium carbonate was employed unless otherwise noted. TLC was carried out on Merck Aluminiumoxid G acc. to Stahl or Kieselgel G acc. to Stahl using chloroform or acetone-chloroform or methanol-chloroform mixture in varying proportions as developing solvent. Coloring reagent: iodine vapour or Dragendorff reagent. Preparative TLC was performed by use of Merck Kieselgel GF_{254} with methanol-chloroform mixture and plates were examined under UV light. For extraction of substances from the Kieselgel, methylene chloride or methanol-methylene chloride was employed as solvent.

Calcd. for $C_{31}H_{48}N_2$: C, 82.97; H, 10.78; N, 6.24. Found: C, 82.74; H, 10.96; N, 6.19. Mass Spectrum *m/e*: 448 (M^+), 433 (M^+-15), 184 (b), 158 (a, base peak), and 72 (c). Metastable peak *m/e*: 75.5 (448→184; Calcd.: 75.6) and 55.9 (448→158; Calcd.: 55.7). NMR τ: 2.83 (4H, singlet, aromatic protons), 6.02 (2H, AB quartet, $J=15$ Hz, C_6H_4–CH_2–N), 7.60 (3H, N–CH_3), 7.82 (6H, N–$(CH_3)_2$), 9.12 (3H, doublet, $J=6$ Hz, *sec*-CH_3), 9.07, and 9.32 (each 3H, two *tert*-CH_3).

Manganese Dioxide Oxidation of Deoxospiropachysine (II)——The deoxo compound (II) (150 mg) was stirred with activated MnO_2 (7.5 g) in refluxing $CHCl_3$ (50 ml) for 14 hr. After removal of MnO_2 by filtration, the $CHCl_3$ solution was evaporated *in vacuo* to leave a syrup which was chromatographed over alumina (0.6×6 cm). Elution with benzene afforded a complex mixture (80 mg) and subsequent elution with MeOH–$CHCl_3$ (1:9) gave a crystalline substance (IIIa) (60 mg). Two recrystallizations of the latter from hexane gave an analytical sample (IIIa) as colorless needles (40 mg), mp 273—276°, $[\alpha]_D^{19}$ +36° ($c=1.0$). *Anal.* Calcd. for $C_{29}H_{42}ON_2\cdot 1/2H_2O$: C, 78.51; H, 9.77. Found: C, 78.71; H, 9.58. Mass Spectrum *m/e*: 434 (M^+) and 44 (base peak, CH_3–$CH=N^+H_2$). IR ν_{max} cm^{-1}: 3350 (NH) and 1673 (lactam). NMR τ: 2.13—2.80 (4H, aromatic protons), 6.63 (3H, lactam N–CH_3), 8.89 (3H, doublet, $J=6$ Hz, *sec*-CH_3), 9.00, and 9.30 (each 3H, two *tert*-CH_3).

The above benzene eluate was subjected to preparative TLC, whereupon was obtained an additional crop of IIIa (20 mg) from the most polar fraction. The next polar fraction (15 mg) was an amorphous compound (IIIb). Mass Spectrum *m/e*: 462 (M^+, $C_{30}H_{42}O_2N_2$). IR ν_{max} cm^{-1}: 3400, 1500 (amide NH), and 1670 (lactam and formamide). NMR τ: 1.90 (1H, CHO), 2.1—2.7 (4H, aromatic protons), 4.43 (1H, broad, NH), 6.62 (3H, lactam N–CH_3), 8.80 (3H, doublet, $J=6$ Hz, *sec*-CH_3), 8.98, and 9.22 (each 3H, two *tert*-CH_3). This compound was identified with the N-formate (IIIb) of IIIa by direct comparison of their IR and NMR spectra. On the other hand, the least polar fraction (23 mg) obtained by the preparative TLC furnished colorless needles (IV) (14 mg) upon recrystallization from MeOH, mp 252—255°, $[\alpha]_D^{32}$ +90° ($c=1.0$). Mass Spectrum *m/e*: 433 (M^+, $C_{29}H_{39}O_2N$), 418 (M^+-15), 390 (M^+-COCH_3), 173 (base peak), and 43 (CO^+CH_3). IR ν_{max} cm^{-1}: 1675 (lactam and ketone). NMR τ: 2.1—2.7 (4H, aromatic protons), 6.63 (3H, lactam N–CH_3), 7.87 (3H, $COCH_3$), 9.00, and 9.35 (each 3H, two *tert*-CH_3).

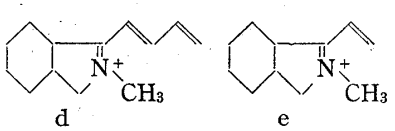
N-Methylation of the Compound IIIa——To a solution of the compound IIIa (20 mg) in MeOH (10 ml) was added 37% formalin (0.2 ml) and the mixture stirred for 2 hr at room temperature. Thereafter $NaBH_4$ (0.4 g) was added to this mixture in small portions and the stirring continued for several hr. After evaporation of the solvent *in vacuo*, the residue was diluted with water and extracted with CH_2Cl_2. The extract was then washed with water, dried, and evaporated. The residue was dissolved in benzene, filtered through an alumina column (0.7×3 cm), and evaporated to leave a crystalline material (I) (18 mg). Recrystallizations from acetone afforded colorless needles (I), mp 288—290°, $[\alpha]_D^{18}$ +41° ($c=1.0$), which were identified with spiropachysine (I) by mixed fusion and IR (KBr) comparison.

N-Formylation of the Compound IIIa——The compound IIIa (20 mg) was dissolved in the formylating reagent (3 ml), which had been prepared by heating a 1:1 mixture of formic acid and acetic anhydride at 70° for 1 hr, and left standing for 20 hr at room temperature. The reaction mixture was poured into ice-water, basified with Na_2CO_3, extracted with ether, and the extract was dried and evaporated. Purification of the residue (25 mg) by means of preparative TLC gave an amorphous compound (IIIb) (15 mg). Mass Spectrum *m/e*: 462 (M^+, $C_{30}H_{42}O_2N_2$). The IR and NMR spectra of this N-formate were fully identical with those of the compound IIIb described above.

Manganese Dioxide Oxidation of Spiropachysine (I)——Spiropachysine (200 mg) was oxidized with activated MnO_2 in the same manner as described for II and the crude product (173 mg) was chromatographed over alumina (0.7×7 cm) with benzene and MeOH–CH_2Cl_2 (1:9). Repeated recrystallization of the MeOH–CH_2Cl_2 (1:9) eluate (85 mg) from hexane gave IIIa as small needles, mp 274—277°, $[\alpha]_D^{23}$ +33° ($c=1.0$). Mass Spectrum *m/e*: 434 (M^+), 419 (M^+-15), and 44 (base peak, CH_3–$CH=N^+H_2$). This compound was proved to be identical with the specimen (IIIa) obtained from deoxospiropachysine (II) by IR and NMR comparison and mixed fusion. On the other hand, preparative TLC of the benzene eluate (88 mg) afforded IIIb (14 mg), amorphous powder, IR ν_{max} cm^{-1}: 3400, 1500 (amide NH), and 1670 (lactam and formamide), and IV (10 mg), mp 243—250°, IR ν_{max} cm^{-1}: 1675 (lactam and ketone). Identities of these products were confirmed by IR and NMR comparison with those of the samples derived from II.

Catalytic Hydrogenation of Deoxospiropachysine (II)——To a solution of II (140 mg) in AcOH (8 ml) was added PtO_2 (140 mg). The mixture was kept at 80° in a water bath and vigorously stirred under hydrogen atmosphere for 6 hr. After removal of the catalyst by filtration, followed by dilution with water, the solution was basified by addition of aq. NH_4OH and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated to leave a crystalline residue (135 mg). Four recrystallizations of this residue from acetone gave colorless prisms (V) (50 mg), mp 213—215°. Mass Spectrum *m/e*: 454 (M^+, $C_{31}H_{54}N_2$), 439 (M^+-15), 190, 164 (base peak),[33] and 72 (CH_3–$CH=N^+(CH_3)_2$). Metastable ion peak *m/e*:

33) The peaks at *m/e* 190 and 164 may be ascribed to the fragment ions d and e, respectively.



d e

59.5 (454→190; Calcd.: 59.2) and 79.5 (454→164; Calcd.: 79.5). NMR τ: 7.45 (3H, N-CH_3), 7.85 (6H, N-$(CH_3)_2$), 9.15 (3H, doublet, J=6 Hz, *sec*-CH_3), 9.25, and 9.37 (each 3H, two *tert*-CH_3).

Chromium Trioxide Oxidation of Spiropachysine (I) in Acetic Acid——A solution of CrO_3 (120 mg) in AcOH (3 ml) containing a few drops of water was added dropwise under vigorous stirring to a solution of I (60 mg) in AcOH (2 ml) at room temperature. After the stirring continued for 7 hr, the reaction mixture was poured into ice-water, made alkaline with dil. NH_4OH, and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated to yield a crystalline residue (50 mg), which was chromatographed over alumina (0.5×9 cm). Combined eluates with ether–benzene (1: 9 and 1: 1) were crystallized from acetone to give a secondary lactam (VIa) as colorless leaves, mp 283—285°, $[\alpha]_D^{18}$ +54° (c=1.0). *Anal.* Calcd. for $C_{30}H_{44}ON_2$: C, 80.30; H, 9.89. Found: C, 80.54; H, 10.12. Mass Spectrum *m/e*: 448 (M^+), 433 (M^+-15) and 72 (base peak). IR ν_{max} cm^{-1}: 3430 and 1687 (NH–CO). NMR τ: 2.07—2.85 (4H, aromatic protons), 7.83 (6H, N-$(CH_3)_2$), 9.12 (3H, doublet, J=6 Hz, *sec*-CH_3), 9.03, and 9.32 (each 3H, two *tert*-CH_3).

Chromium Trioxide Oxidation of Spiropachysine (I) in Pyridine——A solution of the alkaloid (I) (150 mg) in pyridine (2 ml) was added to a mixture of CrO_3 (300 mg) and pyridine (5 ml) and the mixture allowed to stand overnight at room temperature. The reaction mixture was then poured into an aqueous Na_2CO_3 solution and extracted with ether. The ethereal extract was washed successively with 3% HCl and dil. Na_2CO_3, dried over anhyd. $MgSO_4$, and evaporated to afford a neutral substance (88 mg) which was dissolved in benzene and filtered through an alumina column (0.7×4 cm). Evaporation of the filtrate followed by crystallization from hexane gave colorless prisms (VIb) (70 mg), mp 266—268°, $[\alpha]_D^{15}$ +30° (c=1.0). *Anal.* Calcd. for $C_{31}H_{44}O_2N_2$: C, 78.10; H, 9.30; N, 5.88. Found: C, 78.04; H, 9.34; N, 5.93. IR ν_{max} cm^{-1}: 1665 (lactam and formamide). NMR τ: 1.91, 2.01 (1H, two peaks, CHO), 2.11—2.80 (4H, aromatic protons), 6.61 (3H, lactam N-CH_3), 7.18, 7.24 (3H, two peaks, N(CHO)-$C\underline{H}_3$), 8.68, 8.73, 8.78 (3H, three peaks, *sec*-CH_3), 8.99 (3H, C_{19}-CH_3), 9.18, and 9.22 (3H, two peaks, C_{18}-CH_3).

Osmium Tetroxide Oxidation of Spiropachysine (I)——The alkaloid (I) (18 mg) was allowed to react with OsO_4 (25 mg) in pyridine (1 ml) at room temperature for 2 days. Thereafter, a solution of sodium bisulfite (80 mg) in water (1.3 ml) and pyridine (0.9 ml) was added to the reaction mixture and it was stirred for 45 min. The mixture was poured into ice-water, basified with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed successively with 3% HCl and dil. $NaCO_3$, dried ($MgSO_4$), and evaporated. Preparative TLC of the residue gave a crystalline mass (12 mg) which was further recrystallized from ether–hexane to give prisms (VIb) (9 mg), mp 265—267°. This was found to be identical with VIb obtained by the CrO_3-pyridine oxidation of I by IR and NMR comparison.

Reaction of Spiropachysine (I) with Bromine——To a solution of I (50 mg) in AcOH (1 ml) was added a solution of bromine (0.05 ml) in AcOH (1 ml) and the mixture stirred for 1 hr at room temperature. The reaction mixture was then poured into ice-water, the deposited solid being collected by filtration. This was suspended in an aqueous Na_2CO_3 solution and extracted with CH_2Cl_2, washed with water, dried, and evaporated. The residue, showing five spots on TLC, was chromatographed over silica gel (0.5×6 cm), whereupon was obtained a crystalline substance (15 mg) from combined eluates with MeOH–$CHCl_3$ (1: 9 and 1: 4). Recrystallization from acetone gave small prisms (VIc), mp 287—289°. Mass Spectrum *m/e*: 448 (M^+, $C_{30}H_{44}ON_2$), 435 (M^+-15), and 58 (base peak, CH_3-CH=$N^+H(CH_3)$). IR ν_{max} cm^{-1}: 3300 (NH), 1673 (lactam), 1617, and 1600 (phenyl). NMR τ: 2.13—2.83 (4H, aromatic protons), 6.63 (3H, lactam N-CH_3), 7.62 (3H, N-CH_3), 8.90 (3H, doublet, J=6 Hz, *sec*-CH_3), 8.99, and 9.28 (each 3H, two *tert*-CH_3).

Hofmann Degradation of the Dimethiodide of Deoxospiropachysine (II)——The compound II (400 mg) was refluxed with methyl iodide (5 ml) in MeOH (40 ml) for 2 hr. Removal of the solvent *in vacuo* left a viscous residue (dimethiodide, 650 mg) which showed a single spot on TLC. This dimethiodide was then heated under reflux with potassium *t*-butoxide (5 g) in *t*-butanol (50 ml) for 3 hr. The reaction mixture was concentrated *in vacuo*, diluted with water, and the product was taken up in CH_2Cl_2. After evaporation of the solvent, the residue was partitioned between 3% HCl and $CHCl_3$. Basification of the aqueous layer with NH_4OH and extraction with CH_2Cl_2 afforded a strongly basic substance (125 mg). The above organic layer, after being washed with water, was dried and evaporated to give a residue (250 mg) which was dissolved again in ether and shaken with 3% HCl. The ethereal phase was washed with dil. Na_2CO_3, dried, and evaporated to afford a weakly basic product (160 mg), whereas the aqueous acidic phase furnished an additional crop of the strongly basic substance (80 mg) by the usual working up.

The above weakly basic fraction was chromatographed over alumina (0.6×6 cm) and the benzene eluate (132 mg) was recrystallized from aqueous acetone and then from acetone, giving colorless needles (VII), mp 65—68°, which showed a single spot on TLC. IR ν_{max} cm^{-1}: 1640, 1000, and 910 (-CH=CH_2). NMR τ: 2.45—3.00 (4H, aromatic protons), 4.2—5.2 (4H, unresolved multiplet, olefinic protons), 6.59 (2H, singlet, C_6H_4-CH_2-N), 7.81 (6H, N-$(CH_3)_2$), 9.10, and 9.37 (each 3H, two *tert*-CH_3). On the other hand, the combined strongly basic fractions were dissolved in hexane and chromatographed over alumina (0.7×10 cm). Elution with hexane (60 ml) and with benzene (40 ml) gave a crystalline substance (180 mg), which was recrystallized from aqueous acetone to afford needles (VIII) (125 mg), melting at about 98—102°. They behaved as homogeneous on TLC. Mass Spectrum *m/e*: 462 (M^+, $C_{32}H_{50}N_2$), 447 (M^+-15), and 72 (CH_3-CH=$N^+(CH_3)_2$, base peak). NMR τ: 2.45—3.0 (4H, aromatic protons), 4.53, 4.81 (1H, two

broad peaks, integral intensity ratio about 4: 1, olefinic proton), 6.60 (2H, singlet, C_6H_4–CH_2–N), 7.81, 7.82 (each 6H, two N–$(CH_3)_2$), 9.12 (3H, doublet, J=6 Hz, *sec*-CH_3), 9.12, and 9.32 (each 3H, two *tert*-CH_3).

Catalytic Hydrogenation of the Methine Base VII——The above weakly basic methine base (VII) (122 mg) was hydrogenated in AcOH (10 ml) over pre-reduced PtO_2 (70 mg) for 5 hr at room temperature and atmospheric pressure. The product, obtained by the usual working up, was chromatographed over alumina (0.6×11 cm) and after elution of a small amount of impure material with hexane, further elution with the same solvent afforded a tetrahydro compound (IX) (80 mg). Recrystallization from acetone gave colorless needles, mp 114—116°, $[\alpha]_D^{19}$ +23° (c=1.0). *Anal.* Calcd. for $C_{30}H_{47}N$: C, 85.44; H, 11.24; N, 3.32. Found: C, 85.20; H, 11.37; N, 3.08. Mass Spectrum *m/e*: 421 (M^+), 406 (M^+-15), and 376 (base peak). NMR τ: 2.60—2.90 (4H, aromatic protons), 6.58 (2H, singlet, C_6H_4–CH_2–N), 7.10 (1H, broad, $W^{1/2}$ about 18 Hz, C_6H_4–CH), 7.78 (6H, N–$(CH_3)_2$), 9.08, and 9.41 (each 3H, two *tert*-CH_3).

Catalytic Hydrogenation of the Methine Base VIII——The strongly basic Hofmann methine (VIII) (170 mg) was catalytically hydrogenated in the same manner as run with VII. Alumina chromatography (0.7×7 cm) of the crude product (160 mg) with benzene gave a homogeneous dihydro compound (X) (100 mg). Two recrystallizations from acetone gave the pure sample (X), colorless needles, mp 120—122°, $[\alpha]_D^{18}$ +35° (c=1.0). *Anal.* Calcd. for $C_{32}H_{52}N_2$: C, 82.69; H, 11.28; N, 6.03. Found: C, 82.67; H, 11.44; N, 6.20. Mass Spectrum *m/e*: 464 (M^+), 449 (M^+-15), 393 (M^+-71), and 72 (CH_3–CH=$N^+(CH_3)_2$, base peak). NMR τ: 2.60—2.90 (4H, aromatic protons), 6.58 (2H, singlet, C_6H_4–CH_2–N), 7.04 (1H, broad, $W^{1/2}$ about 18 Hz, C_6H_4–CH), 7.78, 7.82 (each 6H, two N–$(CH_3)_2$), 9.12 (3H, doublet, J=6 Hz, *sec*-CH_3), 9.10, and 9.32 (each 3H, two *tert*-CH_3).

Emde Degradation of the Dimethochloride of Deoxospiropachysine (II)——Deoxospiropachysine dimethiodide, prepared from II (105 mg) as above, was converted to the dimethochloride by treatment with AgCl in MeOH in the usual manner. The latter was dissolved in 17% NaOH (5 ml) and cooled in an ice-water bath. To this solution was added freshly prepared Raney Ni W7 (about 1 g)[34] in small portions over a period for 1 hr under vigorous stirring. After being stirred for 2 days at room temperature, the reaction mixture was filtered and the insoluble material extracted thoroughly with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried, and evaporated to furnish a crystalline mass, which was chromatographed over alumina (0.7×5 cm). Elution with ether–benzene (1: 1) followed by crystallization from acetone afforded colorless leaves (XI) (36 mg), melting at 175—176°, which on further recrystallizations from the same solvent showed mp 181—183°, $[\alpha]_D^{25}$ +96° (c=1.0). *Anal.* Calcd. for $C_{32}H_{52}N_2$: C, 82.69; H, 11.28; N, 6.03. Found: C, 82.53; H, 11.52; N, 6.04. Mass Spectrum *m/e*: 464 (M^+), 449 (M^+-15), 393 (M^+-71), and 72 (base peak, CH_3–CH=$N^+(CH_3)_2$). NMR τ: 2.36—2.93 (4H, aromatic protons), 6.60 (3H, broad, C_6H_4–CH_2–N and C_6H_4–CH), 7.80, 7.83 (each 6H, two N–$(CH_3)_2$), 9.13 (3H, doublet, J=6 Hz, *sec*-CH_3), 9.12, and 9.33 (each 3H, two *tert*-CH_3); τ ($CDCl_3$+CF_3COOH): 5.72 (2H, broad singlet, C_6H_4–CH_2–N) and 6.71 (1H, broad, $W^{1}/^{2}$ about 11 Hz, C_6H_4–CH).

Transformation of Epipachysamine-A (XIIa) into Dictyophlebine (XIVa)——1) Reductive Hydrolysis of Epipachysamine-A (XIIa): The alkaloid (XIIa) (3.06 g) was allowed to react with Ca metal (2.5 g) in liquid ammonia (400 ml) at −70° in the usual manner. The crude product (about 2.5 g) was recrystallized repeatedly from acetone to give desacylepipachysamine-A (XIIb) (1.0 g), mp 193—194°.

2) N-Formylation of Desacylepipachysamine-A (XIIb): The compound XIIb (490 mg) was treated at room temperature for 2 days with the formylating mixture (40 ml) prepared by heating a 1: 1 mixture of formic acid and acetic anhydride at 70° for 1 hr. The mixture was concentrated *in vacuo*, diluted with water, and extracted with CH_2Cl_2. After the extract was washed successively with 3% HCl, dil. Na_2CO_3, and water, it was dried and evaporated to afford a crystalline mass (XIIc) (580 mg), which was submitted to alumina chromatography (0.6×5 cm). The eluate (340 mg) with benzene–CH_2Cl_2 (1: 1) was recrystallized from acetone to give the N-formate (XIIc) as small prisms (240 mg), mp 193—196°, $[\alpha]_D^{32}$ +1° (c=1.0). *Anal.* Calcd. for $C_{25}H_{44}ON_2$: C, 77.26; H, 11.41; N, 7.21. Found: C, 77.14; H, 11.49; N, 7.09. IR ν_{max} cm^{-1}: 1660 (N–CHO). NMR τ: 1.93, 2.03 (1H, two peaks, N–CHO), 7.22, 7.28 (3H, two peaks, N(CHO)–$C\underline{H}_3$), 7.74 (6H, N–$(CH_3)_2$), 8.78 (3H, doublet, J=6 Hz, *sec*-CH_3), 9.22, and 9.28 (each 3H, two *tert*-CH_3).

3) von Braun Reaction of the N-Formate (XIIc): A solution of XIIc (100 mg) in benzene (10 ml) was added to a benzene solution (5 ml) of cyanogen bromide (0.5 g) at room temperature and the mixture stirred for 20 min. The excess reagent and the solvent were removed by evaporation under reduced pressure, the residue being dissolved in CH_2Cl_2, and the solution filtered through an alumina column (0.7×4 cm). Evaporation of the filtrate gave an N–CN compound (XIII), which was recrystallized from acetone–CH_2Cl_2 to afford colorless prisms (50 mg), mp 218—220°, $[\alpha]_D^{32}$ +24° (c=1.0). *Anal.* Calcd. for $C_{25}H_{41}ON_3$: C, 75.14; H, 10.34; N, 10.52. Found: C, 74.85; H, 10.53; N, 10.39. IR ν_{max} cm^{-1}: 2200 (N–CN) and 1660 (N–CHO). NMR τ: 1.92, 2.03 (1H, two peaks, N–CHO), 7.15 (3H, N(CN)–CH_3), 7.21, 7.25 (3H, two peaks, N(CHO)–$C\underline{H}_3$), 8.77 (3H, doublet, J=6 Hz, *sec*-CH_3), 9.17 (3H, *tert*-CH_3), 9.23, and 9.28 (3H, two peaks, *tert*-CH_3).

34) An attempt of the reaction using Raney Ni alloy (S. Sugasawa and H. Matsuo, *Chem. Pharm. Bull.* (Tokyo), **6**, 601 (1958)) did not give a satisfactory result.

4) Lithium Aluminum Hydride Reduction of the N–CN Compound (XIII): A suspension of the compound XIII (1.2 g) and $LiAlH_4$ (1.0 g) in a mixture of ether (100 ml) and tetrahydrofuran (20 ml) was refluxed for 4 hr with mechanical swirling and then worked up as usual. The product was chromatographed over alumina (1.2×9 cm) from CH_2Cl_2 and then recrystallized from acetone to furnish colorless needles (XIVa) (610 mg), mp 135—145°. Further recrystallizations from the same solvent gave an analytical sample, mp 148—151°, $[\alpha]_D^{30}$ +32° (c=1.0). *Anal.* Calcd. for $C_{24}H_{44}N_2$: C, 79.93; H, 12.30; N, 7.75. Found: C, 79.74; H, 12.48; N, 7.90. This compound was identified with an authentic sample of dictyophlebine (XIVa) by mixed mp determination and IR (KBr) comparison.

Transformation of the Compound XIVa (Dictyophlebine) to the Compound X——1) Ruschig Degradation of XIVa: To a solution of XIVa (300 mg) in CH_2Cl_2 (20 ml) was added dropwise under vigorous stirring a solution of N-chlorosuccinimide (150 mg) in CH_2Cl_2 (20 ml) over a period of 1 hr at room temperature and the stirring continued for additional 10 min. Thereafter the solution was washed with water, dried over anhydrous $MgSO_4$, and the solvent was evaporated *in vacuo* at room temperature, giving a crystalline N-chloro compound. This was dissolved in 10% methanolic NaOMe solution (25 ml) and refluxed for 1.5 hr under nitrogen stream. The reaction mixture was poured into ice-cooled 5% H_2SO_4 (200 ml) and allowed to stand overnight at room temperature. It was then made alkaline with NH_4OH and extracted with CH_2Cl_2. The extract was washed successively with 3% HCl and dil. Na_2CO_3, dried, and evaporated. The residue (200 mg) was dissolved in a minimum amount of benzene and chromatographed over alumina (1.5×5 cm). Elution with CH_2Cl_2–benzene (1: 9) gave a ketone (XIVb) (157 mg), which on recrystallization from acetone showed mp 160—165°. The IR spectrum of this compound was superimposable upon that of authentic funtumafrine-C (XIVb).

2) Condenzation of the Ketone (XIVb) with *o*-Lithio-benzyldimethylamine: To benzyldimethylamine (1.83 g) placed in a 100 ml flask was added a 4N butyllithium solution in hexane (1.8 ml). The flask was filled completely with anhydrous ether, tightly stoppered, and allowed to stand at room temperature for 22 hr. The resulting *o*-lithio-benzyldimethylamine solution was added to a boiling solution of XIVb (170 mg) in anhydrous ether (50 ml) contained in a 200 ml flask and it was again filled with anhydrous ether, tightly stoppered. The resulting mixture was allowed to stand at room temperature for 17 hr, then hydrolyzed by cautious addition of water. The ethereal layer was separated and extracted with 3% HCl. The acidic extract was washed with CH_2Cl_2 in order to remove the weakly basic material, then made basic with Na_2CO_3, and extracted with CH_2Cl_2, dried, and evaporated. The residue, after nearly thorough removal of benzyldimethylamine by vacuum distillation, was chromatographed over alumina (1.2×10 cm) with hexane and benzene and crystallization of the benzene eluate (150 mg) from acetone yielded an amino-alcohol (XV) as colorless plates (66 mg) melting at 148—150°. Further recrystallizations from acetone raised the mp to 158—160°. $[\alpha]_D^{21}$ +38° (c=1.0). *Anal.* Calcd. for $C_{32}H_{52}ON_2$: C, 79.94; H, 10.90; N, 5.83. Found: C, 79.83; H, 11.18; N, 5.76. IR ν_{max} cm^{-1}: 3050 (OH). NMR τ: 2.50—3.00 (4H, aromatic protons), 6.30 (2H, singlet, C_6H_4–CH_2–N), 7.79, 7.82 (each 6H, two N–$(CH_3)_2$), 9.12 (3H, doublet, J=6 Hz, *sec*-CH_3), 9.11, and 9.32 (each 3H, two *tert*-CH_3).

3) Dehydration of the Amino-alcohol (XV) and Subsequent Catalytic Hydrogenation of the Dehydration Product (VIII): A solution of the amino-alcohol (XV) (135 mg) in ethyleneglycol (16 ml) containing conc. HCl (3 ml) was heated under reflux for 3 hr. The mixture was diluted with water, basified with NH_4-OH, extracted with ether, dried, and evaporated. The residue (115 mg) was crystallized from acetone to give VIII (46 mg) in colorless needles, mp 99—102°, which was shown to be identical with the sample (VIII) derived from deoxospiropachysine (II) in IR, NMR, and TLC behaviours.

The above VIII (45 mg) was hydrogenated over PtO_2 (30 mg) in AcOH (4 ml) in the same manner as described above and the crude product (38 mg), thereby obtained, was chromatographed over alumina (0.7×4 cm). Recrystallizations of the benzene eluate from acetone gave colorless needles (X) (20 mg), mp 119—121°, $[\alpha]_D^{15}$ +37° (c=1.0). *Anal.* Calcd. for $C_{32}H_{52}N_2 \cdot 1/2H_2O$: C, 81.12; H, 11.28. Found: C, 81.24; H, 11.39. This compound was proved to be identical with the specimen (X) obtained from deoxospiropachysine by mixed fusion and by IR (KBr) and NMR comparison.

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