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STRUCTURE OF SPIROPACHYSINE, A NOVEL ALKALOID FROM PACHYSANDRA TERMINALIS SIEB. ET ZUCC.

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A number of alkaloids have recently been isolated from Pachysandra terminalis SIEB. et ZUCC. (Buxaceae) and the structures of them, except a few alkaloids, have been established by us[1] and by Geissman et al.[2]. This communication deals with the structure elucidation of spiropachysine, which was reported as Base VI tentatively in the previous paper[3].

Spiropachysine (Ia), $C_{31}H_{46}ON_2$* (molecular ion peak (M^+) at m/e 462 in the mass spectrum*), m.p. 290-292°*, $[\alpha]_D$ +35°*, is a major alkaloid of leaves of the plant and was obtained from the weakly basic alkaloid fraction. It shows an IR band* at 1673 cm^{-1} (lactam) and its NMR spectrum* reveals the existence of an N,N-dimethyl (7.83 τ), an amide N-methyl (6.62 τ), a sec. methyl (d., 9.12 τ), two tert. methyls (8.99, 9.31 τ) and a phenyl group (4H, 2.10-2.77 τ) in the molecule.

Reduction of spiropachysine (Ia) with $LiAlH_4$ gave a deoxo compound (II), $C_{31}H_{48}N_2$ (M^+ 448), m.p. 175-177°, $[\alpha]_D$ +35°, showing no carbonyl band in the IR spectrum. The NMR spectrum of this compound is characterized by the remarkable high-field shift of the N-methyl signal at 6.62 τ to 7.60 τ and the appearance of a typical AB quartet centered at 6.02 τ which shifts towards lower field on addition of CF_3COOH (4.73, 5.82 τ; AB q., J= 15 c.p.s.). The chemical shift of this AB quartet is indicative of the Ph-CH_2-N grouping, hence benzoylamino grouping in spiropachysine.

Upon oxidation with MnO_2 in $CHCl_3$[4], the compound (II) yielded a product (Ib), $C_{29}H_{42}ON_2 \cdot 1/2H_2O$ (M^+ 434), m.p. 273-276°, $[\alpha]_D$ +36°, IR 1673 cm^{-1};

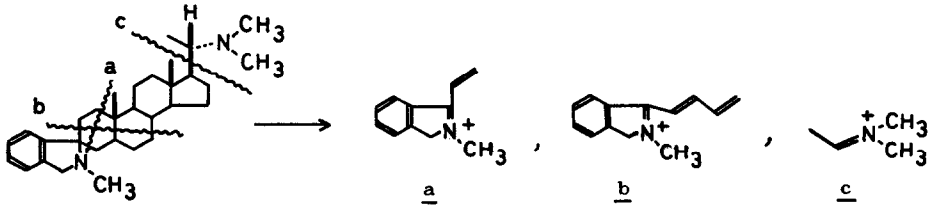
NMR 2.13-2.80 (4H, phenyl), 6.63 (amide N-CH_3), 8.89 (d., sec. CH_3), 9.00, 9.30 τ (two tert. CH_3), which, on N-methylation with HCHO-$NaBH_4$, regenerated spiropachysine (Ia), m.p. 288-290°, $[\alpha]_D$ +41°. Ib was also obtained by treatment of spiropachysine with MnO_2.

The mass spectrum of spiropachysine and of Ib demonstrates a very strong base peak at m/e 72 (c) and m/e 44 (CH_3-$CH=N^+H_2$), respectively, suggesting that the alkaloid is a member of 20-dimethylaminopregnane type alkaloid like other Pachysandra alkaloids[5].

It should be mentioned here that the presence of double bond in the pregnane skeleton is excluded based on NMR studies and chemical experiments such as bromination, CrO_3 and OsO_4 oxidations, catalytic hydrogenation, and so on. Spiropachysine must therefore be hexacyclic on consideration of its molecular formula.

The second nitrogen atom, forming the amide grouping, would locate most likely at 3-position by biogenetic analogy. However, the NMR spectrum of Ia exhibits no signal attributable to the C_3-hydrogen in 4.0-6.5 τ region[6]. Moreover, the signal of the benzene hydrogens has the intensity corresponding to only four hydrogen atoms.

These observations led us to suppose that the alkaloid would have a five-membered spiro-lactam as depicted in the formula Ia. In accord with this view, the mass spectrum of the deoxo compound (II) shows intense peaks at m/e 158 (base peak) and m/e 184, which may be assigned to fragment ions a and b, respectively, along with a peak at m/e 72 (c)[5].

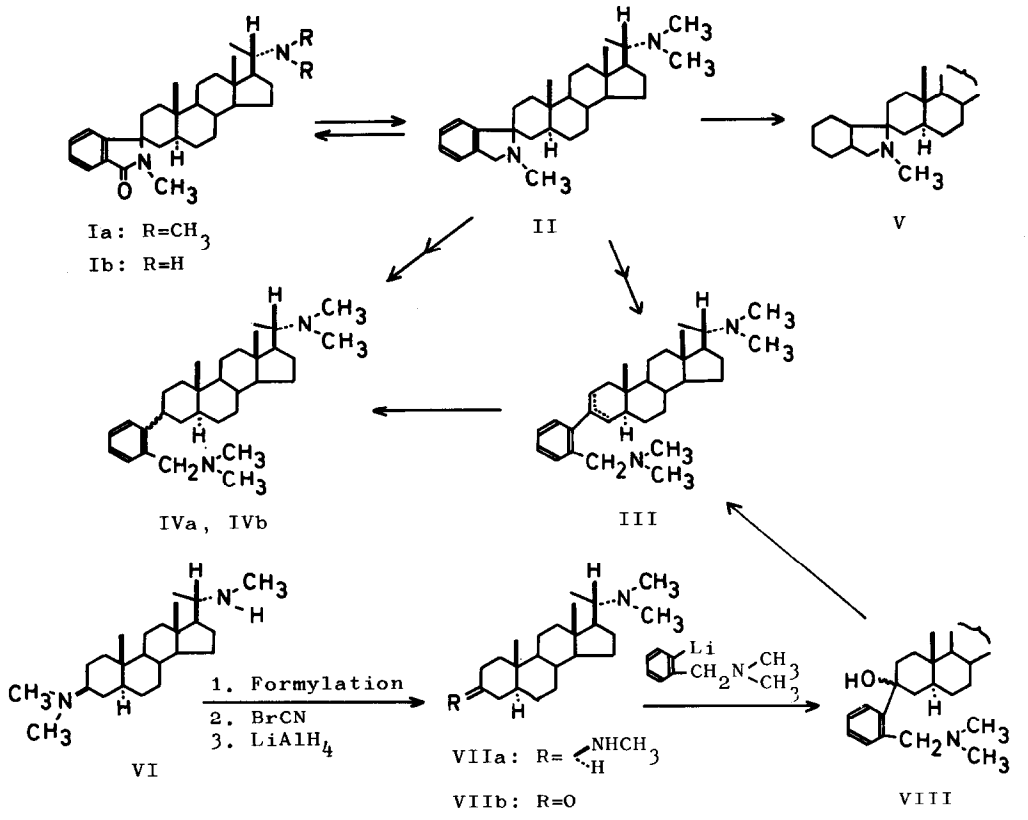


a b c

II

A chemical evidence for the structure of spiropachysine was advanced as follows: The deoxo compound (II) was converted to a dimethiodide and then

Chart 1.



subjected to the Hofmann degradation with t-BuOK in t-BuOH to give two methine bases, one of which crystallized in needles from acetone, m.p. 99–102°. This compound (III) behaved as homogeneous on thin layer chromatography, but was found to be a mixture of Δ^2- and Δ^3-isomers (approximately 4:1) as judged by the NMR spectrum. The separation of each isomer, however, could not be achieved. Subsequent hydrogenation of III over PtO_2 in AcOH gave rise to a single product (IVa), $C_{32}H_{52}N_2$ (M^+ 464), m.p. 120–122°, $[\alpha]_D$ +35°; NMR 7.82, 7.78 (two $N(CH_3)_2$), 6.58 (2H, s., Ph-C$\underline{H}_2$-N), 7.04 τ (1H, br., $W^{1/2}$ about 18 c.p.s., Ph-C$\underline{H}$-).

On the other hand, the Emde degradation of II-dimethochloride with Raney Ni in 17% NaOH led to IVb, $C_{32}H_{52}N_2$ (M^+ 464), m.p. 181–183°, $[\alpha]_D$ +96°, NMR 7.83, 7.80 (two $N(CH_3)_2$), 6.60 τ (3H, Ph-C$\underline{H}_2$-N and Ph-C$\underline{H}$-); NMR (in CF_3COOH–

$CDCl_3$) 7.19 (br., two $N(CH_3)_2$), 6.71 (1H, br., Ph-C<u>H</u>-), 5.72 τ (2H, br., Ph-C<u>H</u>$_2$-N). The latter (IVb) must be the 3-stereoisomer of the dihydro-methine (IVa), since the mass spectra of both compounds are almost superimposable. The configuration at 3-position of the compound IVa and of IVb is considered to be β and α, respectively, based on the NMR examination.

We then undertook the synthesis of IVa starting from epipachysamine-A[7] as shown in chart 1.

Desacylepipachysamine-A (VI)[7], obtained from epipachysamine-A, was transformed by a sequence of reactions into dictyophlebine (VIIa)[8] which was subsequently derived to funtumafrine-C (VIIb) according to Goutarel's description[8]. Reaction of the latter with <u>o</u>-lithiobenzyldimethylamine[9] in dry ether proceeded smoothly and afforded an amino-alcohol (VIII), $C_{32}H_{52}ON_2$, m.p. 158-160°, $[\alpha]_D$ +38°, NMR 2.50-3.00 (4H, phenyl), 6.30 (2H, Ph-C<u>H</u>$_2$-N), 7.79, 7.82 τ (two $N(CH_3)_2$), which upon refluxing with HCl in ethylene glycol gave rise to a mixture of anhydro-compounds (III), m.p. 99-102°. The IR and NMR spectra of this product are almost identical with those of the Hofmann methine base (III).

Catalytic hydrogenation of III, thus obtained, over PtO_2 gave a dihydro compound (IVa), m.p. 119-121°, $[\alpha]_D$ +37°, which was shown to be identical in every respect with IVa derived from spiropachysine.

The structure of spiropachysine is therefore assigned to the structure Ia.

As to the stereochemistry at 3-position, there is no confirmatory evidence at present, but it is suggested by NMR examination that the phenyl group has probably the β-configuration: i.e., in the spectrum of II the 19-methyl group (9.07 τ) is considerably deshielded by the benzene ring, while that of the hexahydro compound (V), m.p. 213-215°, obtained by hydrogenation of II over PtO_2 in AcOH, resonates at 9.24 τ. Further investigation on this problem is now under progress.

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* All compounds given by formulas in this communication gave satisfactory elementary analyses. Mass spectra were taken on a Hitachi Mass Spectrometer Model RMU-6D equipped with a direct inlet system (Model MG-150). All melting points were determined on a Kofler type microscopic hot stage and are uncorrected. Optical rotations were taken at 20-30°C in $CHCl_3$. Unless otherwise stated, IR spectra were measured in $CHCl_3$ and NMR spectra in $CDCl_3$ with $SiMe_4$ as the internal standard.

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