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STUDIES ON THE ALKALOIDS OF PACHYSANDRA TERMINALIS SIEB. ET ZUCC. (4). : STRUCTURE OF EPIPACHYSAMINE-B, -C AND TERMINALINE.

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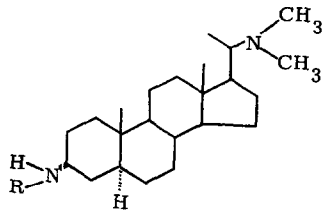
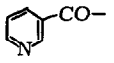
In the preceeding communication[1] we reported the isolation and characterization of epipachysamine-B and base XIX from the strongly basic alkaloid fraction of Pachysandra terminalis SIEB. et ZUCC. For the latter base we proposed the name terminaline. These alkaloids were now shown to have the structure Ia and IIa, respectively. Also the structure of epipachysamine-C, newly isolated from the same source, was established to be VIII.

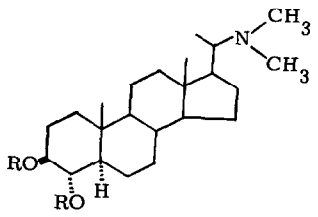
Epipachysamine-B (Ia), $C_{29}H_{45}ON_3$[2], m.p. 260-262°[3], $[\alpha]_D$ +16°[4], showed IR $\nu_{max}^{CHCl_3}$ 1665 cm^{-1} (secondary amide). Its NMR spectrum[5] revealed the presence of an N-dimethyl group (7.84 τ), two tertiary methyl groups (9.20, 9.37 τ) and one secondary methyl group (9.15 τ, doublet, J=6 c.p.s.). Acid hydrolysis of Ia gave an amine (Ib), m.p. 149-150°, $[\alpha]_D$ +21°, whose IR spectrum in $CHCl_3$ was identical with that of chonemorphine[6] (Ib). On acetylation Ib gave an N-acetate (Ic), $C_{25}H_{44}ON_2$, m.p. 266-267°, $[\alpha]_D$ +23°, identified with authentic N-acetyl chone-



Ia R= 

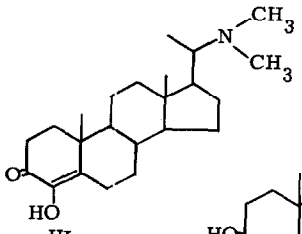
Ib R=H

Ic R=Ac



IIa R=H

IIb R=Ac



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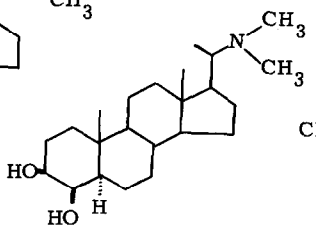

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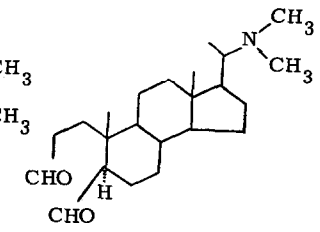

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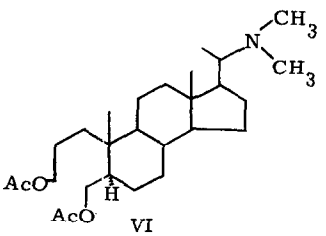

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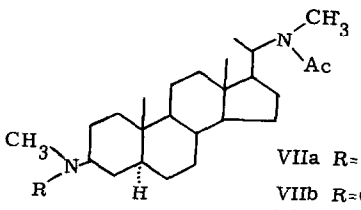
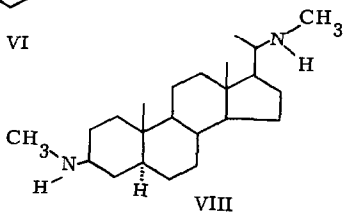


VIIa R=CH_3

VIIb R=CN

VIIc R=H

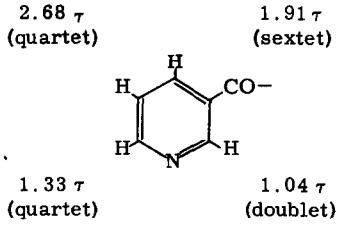
VIId R=Ac



VIII

morphine (Ic)[7] (mixed m.p. and IR (KBr)).

The N-acyl grouping of epipachysamine-B was believed to be N-nicotinate from the consideration of the empirical formula (C_6H_4ON) and its NMR spectrum, which resembles that of nicotinamide.



The confirmative proof was provided by the synthesis of Ia from chonemorphine (Ib) and nicotinic acid by the mixed anhydride method.[8] The synthesized product (Ia), $C_{29}H_{45}ON_3$, m.p. 260-263°, $[\alpha]_D$ +38°, was shown to be identical with epipachysamine-B by mixed m.p. determination and IR comparison.

Terminaline (IIa), $C_{23}H_{41}O_2N$ (molecular ion peak at m/e 363 in mass spectrum[9]), m.p. 243-244°, $[\alpha]_D$ +29° (50 v % MeOH-$CHCl_3$), showed NMR signals at 6.64, 6.78 (2H, two C<u>H</u>-OH), 7.83 (6H, singlet, N-$(CH_3)_2$), 9.18, 9.35 (6H, two tert. CH_3) and 9.13 τ (3H, doublet, J: 6 c.p.s., sec. CH_3). Acetylation of IIa gave O,O-diacetate (IIb), $C_{27}H_{45}O_4N$, m.p. 202-204°, $[\alpha]_D$ +40°, IR $\nu_{max}^{CHCl_3}$ 1730 cm^{-1} Mild alkaline hydrolysis of IIb afforded IIa.

Oxidation of terminaline with periodic acid in 50 % AcOH gave an

aldehyde (V), IR $\nu_{max}^{CHCl_3}$ 1720 cm^{-1}, which upon $NaBH_4$ reduction followed by acetylation gave a diol-diacetate (VI), $C_{27}H_{47}O_4N$, m.p. 146-150°, $[\alpha]_D$ +16°. Therefore, terminaline should have an α-glycol group.

Considering the empirical formula, NMR spectrum together with the correlation to other Pachysandra alkaloids having oxygen function at 4-position, terminaline was believed to be 20-dimethylamino-pregnan-3, 4-diol derivative. Also the appearance of base peak at m/e 72 ($(CH_3)_2N^+=CH\text{-}CH_3$) in its mass spectrum[10] supported the 20-dimethylamino-pregnane structure. This was verified by the conversion of the diosphenol[11] (III), derived from ergosterol, to the diol-diacetate (VI).

The diosphenol (III) was reduced with $NaBH_4$ to give 3β, 4β-dihydroxy-20α-dimethylamino-5α-pregnane (IV), $C_{23}H_{41}O_2N\cdot 1/2H_2O$, m.p. 226-228°. The assignment of the configuration at 3, 4 and 5-positions followed from the formation of the acetonide, m.p. 165-167°, and the inspection of NMR spectrum in which the 19-methyl signal occurred in lower field (i.e. 8.98 τ) than the standard region (i.e. 9.1-9.2 τ)[12]. Treatment of IV with periodic acid, followed by $NaBH_4$ reduction and acetylation, afforded the diol-diacetate (VI), $C_{27}H_{47}O_4N$, m.p. 146-148°, $[\alpha]_D$ +19°, which was identified with the diol-diacetate already derived from IIa (mixed m.p., IR (KBr)). This confirmed the skeletal structure and 5α-configuration of terminaline (IIa).

The 3β, 4α-dihydroxy orientation of IIa was suggested by the facts that in NMR spectrum the 19-methyl signal occurred in the ordinary region (i.e. 9.18 τ) and that IIa failed to give acetonide. Finally IIa was synthesized from the diosphenol (III) by reduction with sodium in boiling n-amyl-

alcohol. The product (IIa), $C_{23}H_{41}O_2N$, m.p. 242-244°, $[\alpha]_D$ +26° (50 v % MeOH-$CHCl_3$), was found to be identical with terminaline by mixed m.p. determination and IR comparison (KBr).

Epipachysamine-C was isolated as its neutral diacetate from the acetylated products of strongly basic alkaloid fraction[1]. The diacetate (VIId), $C_{27}H_{46}O_2N_2$, m.p. 242-243°, $[\alpha]_D$ -16°, showed strong tertiary amide band in the IR spectrum ($CHCl_3$, 1620 cm^{-1}). The structure of this diacetate was considered to be 3, 20-bis-methylacetylamino-pregnane derivative (VIId) on the basis of its empirical formula, neutrality, IR spectrum and NMR spectrum[12]. An attempt was then made to synthesize VIId from the already determined alkaloid, epipachysamine-A (VIIa)[1].

Treatment of VIIa with BrCN in boiling benzene afforded an N-CN compound (VIIb), $C_{26}H_{43}ON_3$, m.p. 234-235°, $[\alpha]_D$ +22°, IR $\nu_{max}^{CHCl_3}$ 2200 (-CN), 1620 cm^{-1} (N-Ac), which was then hydrolyzed with KOH in diethyleneglycol to give an N-H compound (VIIc), m.p. 206-207°, $[\alpha]_D$ +5°, IR $\nu_{max}^{CHCl_3}$ 1620 cm^{-1} (N-Ac). Acetylation of VIIc gave a neutral compound (VIId), $C_{27}H_{46}O_2N_2$, m.p. 243-244°, $[\alpha]_D$ -22°. The IR spectrum (KBr) of this compound was identical with that of epipachysamine-C diacetate and also the mixed m.p. did not depress.

Since no amide band was observed in IR spectum of the original, crude alkaloid fraction, epipachysamine-C should be 3β, 20α-bismethylamino-5α-pregnane (VIII).

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2. All the compounds with cited empirical formulas gave satisfactory elemental analyses.
3. All the melting points are uncorrected.
4. All the optical rotations reported in this communication were taken in $CHCl_3$ solutions at 10-20° C, unless otherwise specified.
5. All NMR spectra were determined on a Varian Associates recording spectrometer (A-60) at 60Mc. in $CDCl_3$. Chemical shifts are reported in τ values, using tetramethylsilane as the internal reference.
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9. Mass spectrum was taken with a Hitachi Mass Spectrometer Model

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13. NMR spectrum of this compound gave a complicated pattern.