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THE STRUCTURES OF PERAKSINE (RP-5) AND RP-7 CONSTITUENTS OF THE LEAVES AND STEMS OF *RAUWOLFIA PERAKENSIS*

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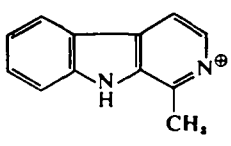
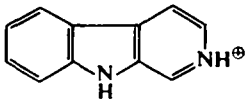
Abstract—Peraksine (Va) an alkaloid from *Rauwolfia perakensis* is shown to be a representative of a new type of hexacyclic indole alkaloid related to perakine. Its structure was established from the analysis of the X-ray diffraction data obtained from the methiodide and by the chemical and mass spectral evidence. RP-7 is shown by partial synthesis from tetraphyllicine to be 1-demethyl-21-deoxy-ajmaline-1,19-diene-17-O-acetate (XVI).

IN PREVIOUS studies[1,2] of *Rauwolfia perakensis*, King et Gamble, it was reported that the roots gave ajmaline, isoreserpiline, reserpine, sarpagine, perakine, RP-1 (aricine), RP-2 and RP-3; the leaves gave aricine, perakine and RP-5; and the stems yielded aricine, neoreserpiline, α-yohimbine, sarpagine, 10-deoxysarpagine (tombozine), RP-5 and RP-7. The alkaloid, RP-5, now renamed peraksine, was shown by mass spectroscopy to have the formula $C_{19}H_{22}N_2O_2$ a fact not readily derived from combustion analysis since the free base crystallized from aqueous alcohol in a hydrated form.[2] It is now observed that this water of solvation can be displaced by chloroform upon crystallization from the latter. This property of solvation was also noted in the transformation products of peraksine.

Peraksine does not contain a methoxyl or N-methyl group. Its UV absorption spectrum is typical of a 2,3-disubstituted indole. It contained no carbonyl group according to the IR spectrum and was inert towards catalytic hydrogenation. It reacted with benzoyl chloride to furnish an O-benzoyl derivative whose IR spectrum now showed only a band in the OH/NH region typical for a hydrogen on an indole nitrogen. It became apparent that the second oxygen was present in peraksine as a cyclic ether when it was found that although peraksine did not react with hydrazine derivatives, it was reducible with sodium borohydride to furnish a diol, dihydro-peraksine, which was further characterized as its O,O-diacetate. This diol readily lost the elements of water upon acid treatment to afford a new ether, deoxyperaksine. Because of these properties peraksine was considered to possess a cyclic hemiacetal moiety.



I



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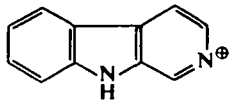
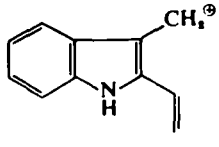


III



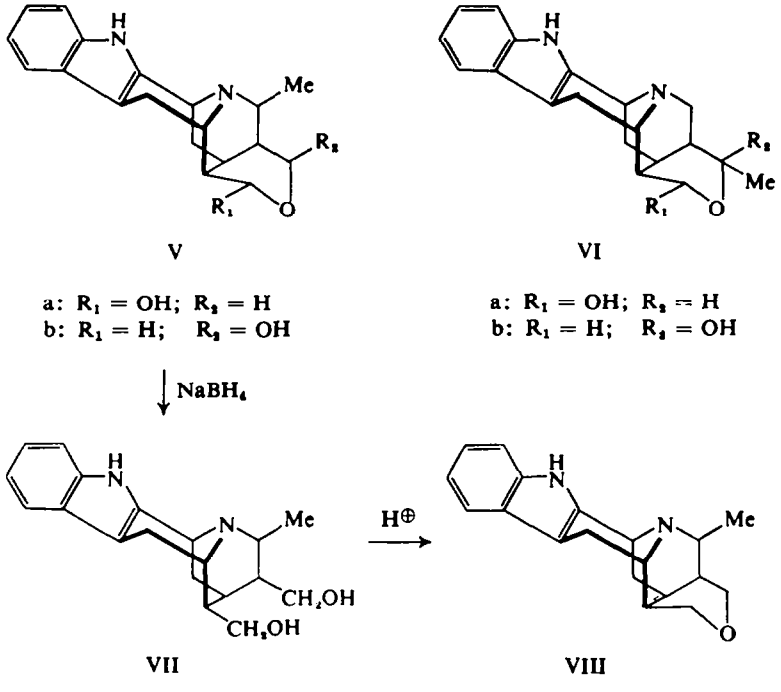
IV

[1] A. K. Kiang, H. Lee, J. Goh and A. S. C. Wan, *Lloydia* 27, 220 (1964).
[2] A. K. Kiang and A. S. C. Wan, *J. Chem. Soc.* 1394 (1960); Proc. UNESCO Symposium on Phytochemistry, Kuala Lumpur, UNESCO S. E. A. Science Co-operation Office, Djakarta, 1957, p. 181.

The mass spectrum of peraksine showed peaks *m/e* 182, 169, 168 and 156 which are characteristic of tetrahydro-β-carboline alkaloids and correspond with ions I, II, III and IV or their equivalents, respectively. The intense peak at *m/e* 309 (M-1) further suggested a sargagine-like structure which received support from the mass spectrum of dihydroperaksine which had the expected strong peak at *m/e* 281 (M—CH_2OH).

The NMR of peraksine confirmed the absence of any olefinic double bonds to which protons were attached. No ethyl group could be detected. Instead there was a terminal methyl (doublet centered at 1·28 ppm) split by an adjacent proton, probably of the type CH_3·CHX (X = O or N). A multiplet at about 3·0 ppm was interpreted as protons on a —CH_2O— moiety. Dihydroperaksine showed additional multiplicity in the latter area which was not much better resolved in its O,O-diacetate. Like typical sarpagine derivatives the diacetate did not show the appreciable downfield shift characteristic of simpler compounds in going from —CH_2OH to —CH_2OAc.[3]

From the above information the structures illustrated by V and VI were considered for peraksine. Of these VIa and VIb[4] were eliminated because neither dihydroperaksine nor its methiodide gave a positive test in the iodoform reaction. A distinction between Va and Vb was made as a result of an independent analysis of the X-ray diffraction data derived from peraksine methiodide.



[3] Cf. L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J. M. Wilson, L.J. Durham and C. Djerassi, *J. Amer. Chem. Soc.* **84**, 2161 (1962).

[4] This is the hemiketal system which is present in voacoline, a sarpagine type alkaloid isolated from *Voacanga chalotiana* Pierre ex Stapf (G. Lhoest, R. De Neys, N. Defay, J. Seibl, J. Pecher and R. H. Martin, *Bull. Soc. Chim. Belges* **74**, 534 (1965).

All the X-ray photographs were obtained on a crystal approximately 0·5 mm in size. Unit cell dimensions obtained from oscillation and zero-layer Weissenberg photographs about the *c* and *b* axes are a = 12·02, b = 11·95, c = 13·44 + 0·05 Å. A study of the photographs enables an assignment of space group $P2_12_12_1$ to be made. Measurement of the crystal density by the flotation method yielded a value of 1·58 g cm^{-3} while the calculated density for 4 molecules per unit cell is 1·56 g cm^{-3}.

The intensity data for the layers $\lambda = 0$ to 8 were recorded on multiple film equi-inclination Weissenberg photographs with nickel-filtered CuKα radiation. The integrated intensities were estimated by eye against a standard scale. The structure amplitudes of 1197 independent reflections were evaluated.

The initial coordinates of the iodide ion were established from a consideration of the iodine–iodine vectors which gave easily recognizable peaks in the three-dimensional Patterson map. The Patterson synthesis and subsequent Fourier syntheses were calculated by a program[5] written for the IBM 1401. Structure factors were then calculated for the iodine atoms alone with another program[5] prepared for the IBM 1401 computer. The value of R, the average discrepancy between the calculated and measured structure amplitudes, was 35·3% at this point. A three-dimensional Fourier series was summed with phases based on the iodine atom. The resulting electron density distribution was displayed as contour sections on sheets of Plexiglass. Study of these sections revealed the position of other atoms. Subsequent rounds of structure factor and Fourier calculations with the inclusion of all non-hydrogen atoms soon reduced R to 21·9%. Several cycles of least squares adjustment of the positional and isotropic temperature parameters of the atoms[6] reduced the value of R to 16·4%. The final electron density distribution for peraksine methiodide is shown in Fig. 1 as superimposed contour sections drawn parallel to (001) and covering the region of one molecule; the corresponding atomic arrangement is explained in Fig. 2. These results unambiguously define the structures of peraksine (Va), dihydroperaksine (VII) and deoxyperaksine (VIII).

The drawings assume the same absolute stereochemistry as other Type I alkaloids[7] isolated from *Rauwolfia*. Peraksine is yet another variant of the sarpagine–ajmaline group of alkaloids[8] closely related to the hypothetical proximal precursors of vomilenine (IX)[9] and its isomerization product, perakine (X).[9,10] The relative stereochemistry of the 19,20 vicinal substituents in perakine has not been determined, but because of the possibilities for equilibration they would be assumed to be in the least hindered orientation, i.e. *trans* rather than *cis*-diaxial on the quinuclidine residue. We favor the *trans* orientation depicted in X since it is isosteric with isoajmaline (XIII) the base

[5] These unpublished programs were written by one of us (G. J. P.) for an IBM 1401 computer with an 8K memory and four tape drives. The programs for the three-dimensional Fourier and Patterson syntheses were written in autocoder language and the structure factor, Lorentz polarization and scattering factor programs were written in FORTRAN language.

[6] Least squares refinement program (LLX R6) written for the IBM 7094 computer by J. H. Van den Hende.

[7] J. Le Men and W. I. Taylor, *Experientia* **21**, 508 (1965).

[8] *The Ajmaline–Sarpagine Alkaloids*, W. I. Taylor in *The Alkaloids*, Vol. VIII (Edited by R. H. F. Manske). Academic Press, New York (1965).

[9] W. I. Taylor, A. J. Frey and A. Hofmann, *Helv. Chim. Acta* **45**, 611 (1962).

[10] P. R. Ulshafer, M. F. Bartlett, L. Dorfman, M. A. Gillen, E. Schlittler and E. Wenkert, *Tetrahedron Letters* No. 11, 363 (1961).

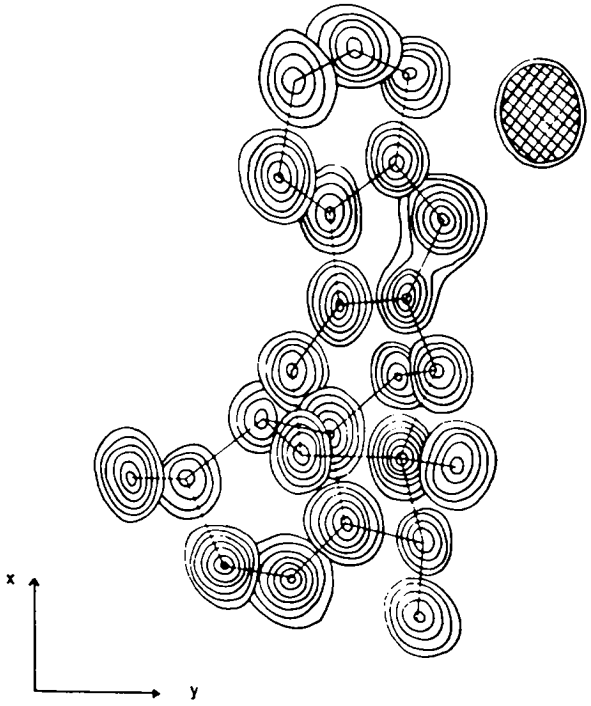


FIG. 1. Final three-dimensional electron density distribution for peraksine methiodide shown by means of superimposed contour sections drawn parallel to (001).

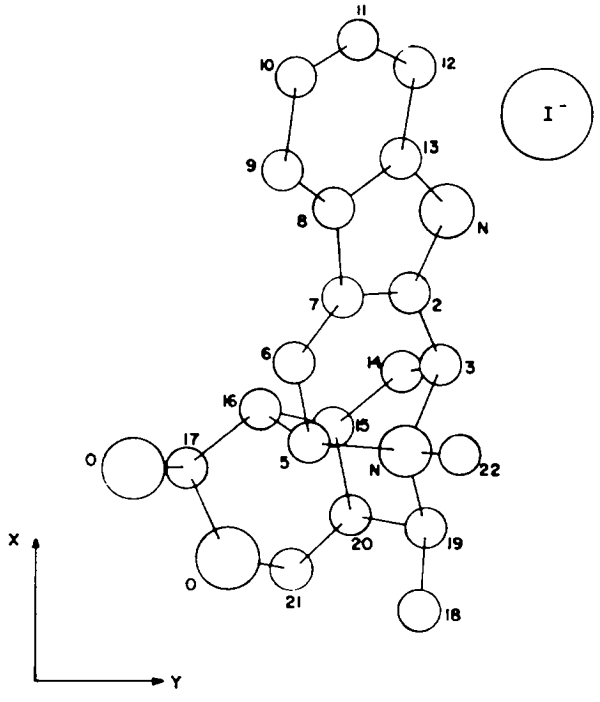
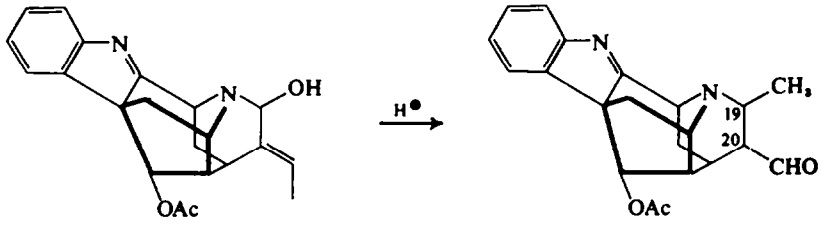


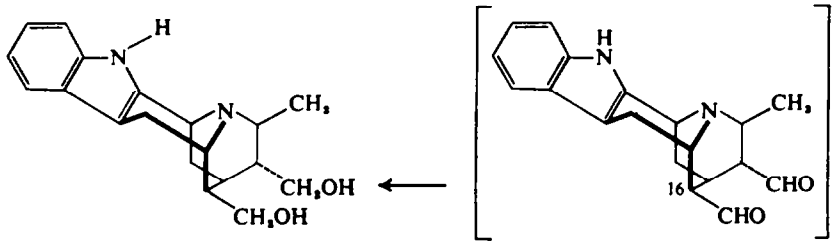
FIG. 2. Atomic arrangement corresponding to Fig. 1.

catalysed isomerization product of ajmaline (XIV). A partial confirmation of this opinion was realized as a result of the following experiments.

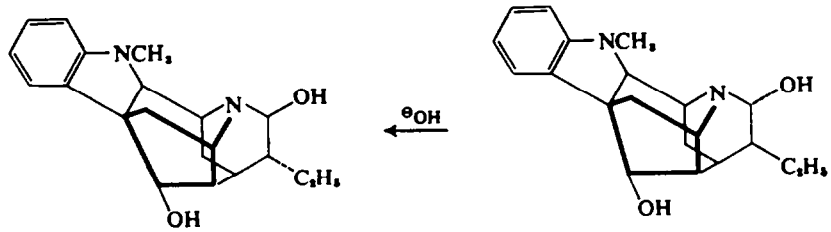
Brief treatment of perakine with base gave the intermediate dialdehyde (XI) (cf. conversion of XVI to XV)[11] which was reduced to the diol (XII) which unlike dihydroperaksine, did not yield an ether under acidic conditions. The same diol (XII) was also formed when perakine was first reduced to dihydroperakine (CHO → CH_2OH, this fixes the configuration at C-19 and C-20) before base treatment. Although these reactions provide chemical evidence for the configuration of the aldehyde function in perakine, the orientation of the C-19 methyl remains circumstantial.



IX X



XII XI

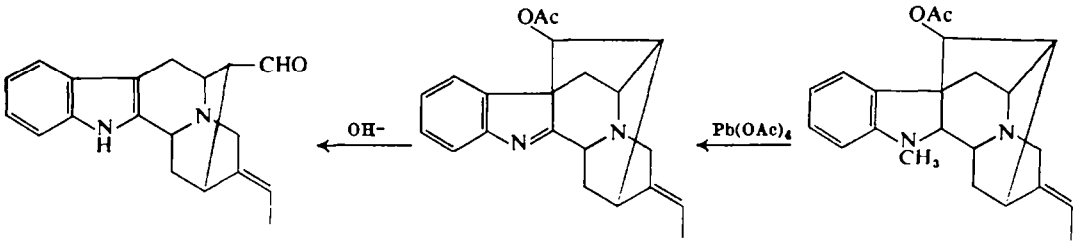


XIII XIV

The structure of the alkaloid RP-7 (XVI) is now established by its alkaline degradation or pyrolysis to vellosimine (XV) and by its partial synthesis by the lead

[11] Compare closely related ring openings of indolenines to desoxyajamal-B, M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Bringi and E. Wenkert, *J. Amer. Chem. Soc.* **84**, 622 (1962).

tetraacetate oxidation of tetraphyllicine O-acetate (XVII).[12] The previously reported formula, $C_{22}H_{24}N_2O_2$ for this alkaloid[2] requires to be corrected to $C_{21}H_{22}N_2O_2$.



XV XVI XVII

EXPERIMENTAL

All m.ps were uncorrected and the UV absorption spectra was recorded as mμ (log ε) in EtOH and IR spectra in $CHCl_3$. The mass spectra were obtained with an ATLAS CH-4 using a direct inlet system. The optical rotations were recorded at ambient temp, about 25°.

Peraksine (Va). Crude peraksine, purified by conversion into nitrate (crystallizable from MeOHaq) and regeneration of the free base followed by further crystallization from MeOH, had m.p. 196–98°, $[\alpha]_D$ +40·3° (*c*, 1 in pyridine), pK_a' 7·5 (in 50% MeOHaq), λ_{max} 226 (4·53), 278 (4·02) and shoulder at 290 (3·19). The mass spectrum showed a molecular ion at 310 (95%) as well as *m/e* 309 (100), 223 (8), 207 (27),[14] 182 (8), 169 (18), 168 (18), 163 (26), 156 (6).

Peraksine was crystallized in two separate lots from $CHCl_3$ and the crystals were air dried. (Found, Sample A: C, 64·0, 63·7; H, 6·4, 6·4; N, 7·9, 8·2; Cl, 14·7, 14·4. Sample B: C, 64·9; 64·0; H, 6·5, 6·5; N, 7·9, 7.6; Cl, 12·5. $C_{19}H_{22}N_2O_2 \cdot 0{\cdot}5CHCl_3$ requires: C, 63·4; H, 6·1; N, 7·6; Cl, 14·4% $C_{19}H_{22}N_2O_2 \cdot 0{\cdot}4CHCl_3$ requires: C, 65·0; H, 6·3; N, 7·8; Cl, 12·5%.) In the NMR spectrum no singlet methyl peaks were observed; there was a doublet centered at 1·28 ppm.

Peraksine methiodide, needles from MeOH, has m.p. 210° (decomp.) (Found: C, 53·0, 53·1; H, 6·0, 5·9. $C_{19}H_{22}N_2O_2 \cdot CH_3I$ requires: C, 53·1; H, 5·6%.)

O-Benzoylperaksine. Peraksine (50 mg) and benzoyl chloride (0·8 ml) were refluxed in benzene (10 ml) for 24 hr. The solvent was removed *in vacuo*, the residue was triturated with 2N NaOH until the odor of benzoyl chloride disappeared and extracted into $CHCl_3$. The organic phase was washed successively with dil. HCl [yielded unreacted peraksine (15 mg)], water, dried and concentrated to dryness. The oily residue upon crystallization from EtOHaq yielded O-benzoylperaksine, m.p. 205–206°, pK_a' < 4 (50% MeOHaq), λ_{max} 226 (4·61), 276 (3·72) with shoulders at 282 (3·70) and 290 (3·53); $\nu_{C=O}$ 1730 cm^{-1}. For analysis it was dried at 60° in high vacuum for 24 hr. (Found: C, 73·8, 74·1; H, 6·4, 6·3. $C_{26}H_{26}N_2O_2 \cdot 0{\cdot}5H_2O$ requires: C, 73·8; H, 6·4%.) Saponification of the O-benzoate regenerated peraksine.

Dihydroperaksine (VII). $NaBH_4$ (250 mg) was added over a period of 30 min to a soln of peraksine (100 mg) in EtOH (20 ml). The cloudy soln was refluxed for 1 hr and the solvent removed *in vacuo*. Trituration of the residue with water on a steam bath gave colorless crystals (107 mg) which were sublimed at 230–240° in high vacuum yielding prisms (90 mg), m.p., 290–291°, (some sublimation at 280°), $[\alpha]_D$ +40·8° (*c*, 1 in pyridine), pK_a' 7·75 in 50% MeOHaq. The mass spectrum showed a molecular ion at 312 (100%) as well as *m/e* 311 (85), 295 (8), 281 (46), 239 (20), 169 (41), 168 (36) and 156 (8). (Found: C, 72·7, 72·5; H, 7·9, 8·0; N, 9·6. $C_{19}H_{24}N_2O_2$ requires: C, 73·0; H, 7·7; N, 9·0%.)

Crystallization of the sublimate from MeOHaq furnished the hydrated product, m.p. 289–290°

[12] Cf. M. F. Bartlett, B. F. Lambert and W. I. Taylor, *J. Amer. Chem. Soc.* **86**, 2620 (1964).

[13] In an early determination a sample of peraksine was sublimed into the mass spectrometer and in contrast with the direct measurement the base peak was *m/e* 169 and the heaviest mass peak was at *m/e* 306 (60%). Also the ions *m/e* 182 and 156 of low density by the indirect method now assumed prominence and were 80 and 60% respectively of the base peak.

[14] This peak was accompanied by *m/e* 208 and 209 and is possibly due to a trace of silicon oil.

(some sublimation at 265°), the UV absorption spectrum was identical with peraksine. (Found: C, 69·7, 69·1; H, 8·2, 8·2; N, 8·5, 8·7. $C_{19}H_{26}N_2O_2 \cdot H_2O$ requires: C, 69·1; H, 7·9; N, 8·5%.)

Dihydroperaksine methiodide, needles from MeOH, decomposed at 300°. (Found, dried at 80° *in vacuo*: C, 53·0; H, 6·3. $C_{19}H_{24}N_2O_2 \cdot CH_3I$, C, 52·9; H, 6·0%.)

Dihydroperaksine 0,0-diacetate, prepared by heating dihydroperaksine and Ac_2O in pyridine on a steam bath had m.p. 103–105° from MeOH. (Found: C, 68·2; H, 7·2. $C_{23}H_{28}N_2O_4 \cdot 0{\cdot}5H_2O$ requires: C, 68·3; H, 7·4%.)

Deoxyperaksine (VIII). Dihydroperaksine (87 mg) was dissolved in 70% H_2SO_4 (0·6 ml) and warmed for 15 min on a steam bath. The cooled soln was poured into ice water (10 ml) and heated on a steam bath while being neutralized with solid $BaCO_3$. The precipitate was filtered off and washed with hot water (2 × 10 ml). The filtrate and washings were extracted with ether (3 × 25 ml) and the organic phase was dried (Na_2SO_4) and reduced to dryness. The residue (44 mg) after two crystallizations from ether gave deoxyperaksine, needles which changed into prisms at 230° and melted at 255–257°, and its UV spectrum was identical with peraksine. Deoxyperaksine sublimed readily at 180–200°/0·05 min and the sublimed base exhibited the same m.p. behavior as shown by the crystallized sample. In the mass spectrum there was the molecular ion at 294 (69%), doubly charged ion 147 (6); as well as *m/e* 293 (100), 207 (24),[18] 169 (14), 168 (16). (Found: C, 77·4; H, 7·7. $C_{19}H_{22}N_2O$ requires: C, 77·5; H, 7·5%.)

Dihydroperakine. Perakine (200 mg) in MeOH (80 ml) was treated at −5° with $NaBH_4$ (200 mg) in ice cold water (3 ml) and stirred for 2 hr. Several drops of AcOH were added followed by basification with $NaHCO_3$ and dilution with water (150 ml.). Extraction with CH_2Cl_2 furnished dihydroperakine (145 mg) crystals from acetone aq, m.p. 250–253° $[\alpha]_D$ +12° (*c*, 0·7 in $CHCl_3$, λ_{max} 220 (4·30) and 258 (3·69), λ_{min} 236 (3·52); $\nu_{C=O}$ 1720 cm^{-1}, ν_{OH} 3500 cm^{-1}. (Found: C, 71·1; H, 6·9. $C_{21}H_{24}N_2O_2$ requires: C, 71·5; H, 6·9%.)

The indole hydroxyaldehyde from dihydroperakine. Dihydroperakine (101 mg) was allowed to stand for 15 min in 50% MeOHaq to which 3 drops of 2N NaOH had been added. The qualitative UV absorption spectrum of the soln became typically indolic with maxima at 223, 278 and 287 mμ. Extraction with $CHCl_3$ yielded the hydroxy aldehyde (96 mg), which after crystallization from AcOEt had m.p. 143–145°, $[\alpha]_D$ +59° (*c*, 0·9 in MeOH, λ_{max} 224 (4·47), 280 (3·80) and 289 (3·72), λ_{min} 248 (3·40), $\nu_{C=O}$ 1709 cm^{-1}. (Found: C, 71·3, 71·4; H, 7·5, 7·9. $C_{19}H_{22}N_2O_2 \cdot 0{\cdot}5EtOAc$ requires: C, 71·3; H, 7·4%.)

The diol (XII). A. The indole hydroxyaldehyde (100 mg) in MeOH (20 ml) was treated with $NaBH_4$ (100 mg) in water (2 ml) and allowed to stand at room temp for 2 hr. The diol crystallized directly out of the reaction mixture, m.p. 190–191°, $[\alpha]_D$ +18° (*c*, 0·3 in AcOH).

B. Perakine (500 mg) was allowed to stand for 10 min in MeOHaq NaOH by which time the conversion to an indole (as judged by quantitative UV spectroscopy) was complete. $NaBH_4$ (100 mg) in water (0·5 ml) was added and after 1·5 hr the diol began to crystallize out. It was recrystallized for analysis from MeOHaq, m.p. 190–192°, $[\alpha]_D$ +68° (*c*, 0·8 in pyridine), $[\alpha]_D$ +26° (*c*, 0·9 in AcOH). The samples of the diol prepared by these two methods could not be distinguished by their TLC behavior or by their IR spectra and they were too insoluble for examination of their NMR spectra. (Found: C, 68·4; H, 8·30. $C_{19}H_{24}N_2O_2 \cdot 1.25\ H_2O$ requires: C, 68·3; H, 8·1%.)

RP-7 *from tetraphyllicine.* A suspension of tetraphyllicine (150 mg) in pyridine (20 ml) and Ac_2O (5 ml) was left at room temp for 36 hr by which time there was complete soln. After concentration to dryness the residue was dissolved in benzene and filtered through a short column of alumina (activity III) to furnish amorphous tetraphyllicine-17-O-acetate (147 mg). The derivative in benzene (15 ml) was stirred for 1 hr in the presence of dry $(AcO)_4Pb$ (1 g). The resulting mixture was passed through a plug of alumina followed by a washing with benzene containing 10% CH_2Cl_2 and final elution with CH_2Cl_2. From the latter, a glassy material (70 mg) with a typical indolenine UV absorption spectrum was obtained. Treatment of this material with a few drops HNO_3 in MeOH gave RP-7 nitrate m.p. and mixed m.p. 235–237 (dec.) whose IR spectrum was superimposible upon that of the natural derivative. (Found: C, 63·4; H, 6·2. $C_{21}H_{22}N_2O_2 \cdot HNO_3$ requires: C, 63·5; H, 5·8.)

Vellosimine (XV) *from* RP-7. When the amorphous base liberated from RP-7 nitrate was heated to 180–190° at 0·05 mm a colorless crystalline sublimate was obtained, which recrystallized well from $CHCl_3$ or acetone. It had m.p. >300° (some sublimation at 260°), $\nu_{C=O}$ 1700 cm^{-1}. The same product could be obtained more simply by treating RP-7 nitrate in EtOH with 2N NaOH for a few min followed by a $CHCl_3$ extraction. Crystals, m.p. >300°, were obtained upon concentration of the

organic phase. Neither sample depressed the m.p. of an authentic sample of vellosimine[15] and the IR spectra were superimposable.

Acknowledgements—The authors are indebted to T. Doyne, Villanova Univ., for his continued advice and assistance in their X-ray work. They are also grateful to G. Sim and A. McPhail, Univ. of Illinois, for their interest and encouragement in the latter phase of the X-ray work, and to H. Hürzeler (CIBA-Basel) for the mass spectral measurements. They are also obliged to Mrs. H. K. Tong for microanalyses and to Mr. J. Goh for some technical assistance

[15] Sample kindly provided by H. Rapoport and R. E. Moore [*J. Org. Chem.* **27**, 2981 (1962)].