VINOXINE, A NOVEL TYPE OF INDOLE ALKALOID*

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The constitution and configuration of vinoxine isolated from *Vinca minor* L. was deduced on the basis of spectral evidence.

The isolation and characterization of vinoxine (*I*), an amorphous alkaloid from *Vinca minor* L., was reported in our preceding paper[1]. An assumption based upon infrared spectrum, that this alkaloid does not contain a hydroxyl group[1], turned out to be improper. In this paper the structure of vinoxine is elucidated by physical methods.

The ultraviolet spectrum of *I* showed absorption maxima characteristic of an indole chromophore[2]. The mass spectral fragmentation of vinoxine suggested a novel skeletal type for this alkaloid. The high resolution measurement of the molecular radical ion proved the correctness of the molecular formula $C_{20}H_{24}N_2O_3$ (M calculated: 340·1787; found: 340·1795) determined by elemental analysis. The infrared spectrum revealed vibrational bands of 4 neighbouring hydrogens of an aromatic ring at 738 cm^{-1}, of a primary hydroxyl group at 1070 and 3430 cm^{-1} (diffuse), of the indole skeleton (1450, 1562, 1628 cm^{-1}) and of an ester group at 1210 and 1775 cm^{-1}; the latter underwent in CCl_4 solution a splitting into a doublet at 1735 and 1760 cm^{-1}. A like feature displayed[3] the alkaloid 16-epipleiocarpamine (*II*). The correctness of the postulated structure of vinoxine was verified by ^{13}C-NMR spectroscopy. Chemical shifts of the particular carbon atoms are listed in Table I.

Considering the above-mentioned data one is entitled to say that an indole skeleton substituted in positions 1 and 2, with a hydrogen atom at $C_{(7)}$ (ref.[4]) and an RR'N—CH_2—CH_2—OH grouping are embodied in the molecule of vinoxine. The ^{1}H-NMR spectrum (on the δ scale in ppm) offered the complemental data: the doublet at 1·60 (3 H, J = 7 Hz) was ascribed to protons of the $C_{(18)}$-methyl group bound to an exocyclic double bond, the two-proton singlet at 2·88 to a methylene group

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in the vicinity of which no protons are located; this requirement met the $C_{(21)}$-methylene between the nitrogen atom and the exocyclic double bond. The one-proton singlet at 3·05, disappearing after deuterium labelling, was characteristic of a hydroxyl group. The triplet at 3·57 (2 H, J = 9 Hz) and the singlet at 3·67 were attributed to the methylene in the neighbourhood of a hydroxyl group and to the methyl in a methoxycarbonyl grouping, respectively. The triplet at 4·01 (H, J = 7 Hz) was associated with the hydrogen at $C_{(3)}$. The doublet at 4·84 (H, J = 7 Hz) belonged to the hydrogen at $C_{(16)}$ in the vicinity of an electron attracting group; the splitting evidenced that only one proton is located at the adjoining carbon $C_{(15)}$, characterized by a singlet at 3·50; consequently, it is the locus of annelation of a further ring. The quartet centred at 5·32 (H, J = 7 Hz) belonged to a vinyl proton at $C_{(19)}$ in an interaction with the $C_{(18)}$-methyl, the one-proton singlet at 6·24 to a vinyl proton at $C_{(7)}$ in the indole moiety of the alkaloid. Protons of the benzene ring were seen as multiplets centred at 7·0 to 7·6. The region characteristic of protons bound to nitrogen was signal-free. Also this spectrum resembled that of 16-epipleiocarpamine[3].

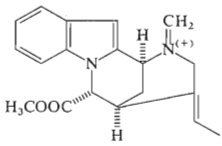
As it follows from arguments so far presented, the molecule of vinoxine possess ten loci of unsaturation: six of them absorbed the indole chromophore, one the ethylidene grouping, one the carbonyl, whereas the remaining two had to fall on additional two rings. Respecting these facts, vinoxine could be assigned the structural formula *I*; the stereochemical arrangement is supported by following arguments: the CD curves of vinoxine and pleiocarpamine (*III*) displayed an analogous course from which could be – with an admissible bit of probability – decuced the identical absolute configuration of both alkaloids at the carbon attached directly to $C_{(2)}$. Rings D and E could be only *cis* fused. The orientation of the $C_{(16)}$-methoxycarbonyl group was adduced from ^{1}H-NMR spectral data. The doublet of the proton at $C_{(16)}$ in pleiocarpamine (*III*) resonated at 5·26, whereas the position of the same proton in 16-epipleiocarpamine (*II*) was reported to be at 4·74 (*cf.*[3]). The considerable

TABLE I

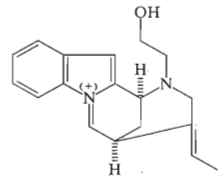
Chemical Shifts (in ppm Relative to Tetramethylsilane) in the ^{13}C-NMR Spectrum of Vinoxine

2	133·3	9	119·3	15	31·1
3	59·9	10	120·0	16	51·5
5	54·7	11	118·9	17	169·4
6	57·7	12	108·5	18	12·4
7	101·5	13	136·0	19	121·9
8	127·6	14	31·1	20	132·7
				21	56·2

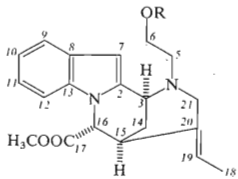
upfield shift is of diagnostic utility for this steric arrangement. The position of the corresponding doublet at 4·84 coincided with that of *II* and hence the $C_{(16)}$-methoxycarbonyl group of vinoxine is assigned the α-configuration.



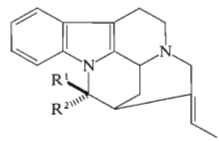
a



b



I, R = H
IV, R = Ac
V, 19-dihydro



II, R^1 = H, R^2 = $COOCH_3$
III, R^1 = $COOCH_3$, R^2 = H

Bearing in mind the above-mentioned findings one can interpret the mass spectral fragmentation of vinoxine: the parent peak at *m/e* 309, due to an ion generated by loss of a hydroxymethyl radical from the molecular radical ion, was ascribed the structure *a*. The fragment at *m/e* 281, with a metastable ion at *m/e* 232·2, can be formulated by structure *b*. Further ions, the composition of which was verified by high resolution measurement, ought to be particles stabilized by conjugation of double bonds originated by a deep collapse of the molecular radical ion; we have not investigated the mechanism of their formation. The O-acetyl derivative *IV* prepared by acetylation of vinoxine displayed mass spectral fragmentation leading *inter alia* to the formation of ion *a*. The IR-vibrational band ν_{C-O} was shifted to 1 060 cm^{-1} and further bands indicative of an ester group at 1 245 and 1 750 cm^{-1} appeared. The ^{1}H-NMR spectrum showed a singlet of protons associated with the methyl of the acetyl group at 2·07; the triplet of the $C_{(6)}$ methylene group in the neighbourhood of the ester group was shifted by 0·68 downfield to 4·25. Catalytic hydrogenation of vinoxine in ethanol furnished 19-dihydrovinoxine (*V*). Saturation of the

exocyclic double bond influenced the mass spectral fragmentation; nonetheless the formation of ion *a* is substitution independent. The formation of ion *a* from dihydro derivative is suppressed in favour of that at *m/e* 167. The ^{1}H-NMR spectrum of dihydrovinoxine displayed a new doublet of the $C_{(20)}$-proton centred at 3·93, protons at $C_{(21)}$ arised as a multiplet centred at 2·97 and the quartet due to the vinylic proton of the original vinoxine at 5·32 disappeared.

EXPERIMENTAL

The optical rotation was measured with a Bendix-Ericson, model 143 D, instrument in chloroform, CD-spectra with a Dichrograph Roussel Juan II, UV-spectra with a UV/ORD-5 Jasco spectrophotometer in 95% ethanol, IR-spectra with a Perkin-Elmer, model 457, spectrophotometer in KBr discs, mass spectra with an AEI MS 902 S apparatus. The ^{1}H-NMR spectra were recorded with a Tesla BS 487 B and ^{13}C-NMR spectrum with a Bruker HX 90 E FT instruments in deuteriochloroform with tetramethylsilane as internal reference substance. Alumina (Reanal) for column chromatography, neutral, was of activity grade II, TLC chromatography was carried out with alumina Woelm, neutral, in solvent systems benzene–methanol 19 : 1 (S_1) and light petroleum–acetone 3 : 2 (S_2).

Vinoxine (*I*)

$C_{20}H_{24}N_2O_3$, amorphous, $[\alpha]_D^{24}$ −18,6° (R_F 0·70 (S_1), R_F 0·13 (S_2) was isolated from *Vinca minor* L. (*cf.*[1]). UV spectrum: λ_{max} 221, 273, 282, 291 nm (log ε 4·56, 3·95, 3·90 and 3·77). Mass spectrum: *m/e* 340 (M^+, 63%), 325 (M—CH_3, 4%), 309 (M − 31, 100%), 281 (M − $COOCH_3$, 25%), 220·1134 (for $C_{15}H_{14}N$ calculated: 220·1126, 34%), 168 (23%), 167·0741 (for $C_{12}H_9N$ calculated: 167·0734, 42%), 134 (16%), 125 (16%), 57 (17%), CD: 310 nm, Δε 0; 295, +0·45; 293, 0; 292, −0·26; 290·5, 0; 287, +1·8; 282, +1·1; 278, +1·95; 276, +2·3; 266·5, +3·4; 262, +2·9; 259, +2·7; 245, +0·45; 241·5, +0·26; 239·5, 0; 223·5, −3·31; 210, 0.

O-Acetylvinoxine (*IV*)

Vinoxine (20 mg) dissolved in acetic anhydride and pyridine (1 ml each) was acetylated 24 h at room temperature. The acetylation mixture was distilled off and the residue was chromatographed over alumina (2 g), eluant benzene. Yield 14 mg, amorphous, $[\alpha]_D^{24}$ −30·8°, R_F 0·60 (S_2). Mass spectrum: *m/e* 382 (M^+, 89%), 367 (7%), 323 (63%), 309 (100%), 220 (79%), 167 (92%), 87 (27%).

19-Dihydrovinoxine (*V*)

A solution of vinoxine (61 mg) in 95% ethanol (10 ml) was hydrogenated over a platinum catalyst (30 mg) 48 h at room temperature. The crude product was chromatographed on alumina (2 g), eluant ether. Yield 52 mg, amorphous, $[\alpha]_D^{21}$ −12·8°, R_F 0·67 (S_1). Mass spectrum: *m/e* 342 (M^+, 19%), 323 (3%), 311 (M − 31, 88%), 168 (52%), 167 (100%), 57 (31%).

The ^{1}H-NMR, *mass and* IR *spectra were recorded in the Department of analytical chemistry, Institute of Chemistry, Slovak Academy of Sciences, Bratislava. The* ^{13}C-NMR *spectrum was measured in the Institut de Chimie des Substances Naturelles, Gif sur Yvette.*

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