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Vindoline and 16-demethoxyvindoline: two catharanthus-derived alkaloids

Joanna Ruszkowska,[a] Robert Chrobak,[a] Jan K. Maurin[b,c]* and Zbigniew Czarnocki[a]

[a]Chemistry Department, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland, [b]National Institute of Public Health, Chełmska 30/34, 00-725 Warsaw, Poland, and [c]Institute of Atomic Energy, 05-400 Otwock-Swierk, Poland
Correspondence e-mail: maurin@urania.il.waw.pl

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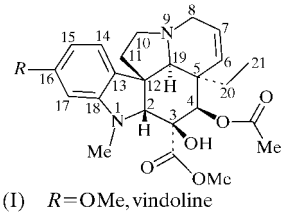
Vindoline, $C_{25}H_{32}N_2O_6$, and 16-demethoxyvindoline, $C_{24}H_{30}N_2O_5$, both of which are naturally occurring biologically active products derived from plants, are important as possible starting materials for the synthesis of valuable anticancer antibiotics, *viz*. vincristine and vinblastine, and other pharmaceuticals. The vindoline framework consists of two five- and three six-membered condensed rings. One of the six-membered rings adopts a boat conformation, one adopts a sofa conformation and the third is planar. Both five-membered rings have envelope structures. The intramolecular hydrogen bonds present in the structures are characteristic of vinca alkaloids.

Comment

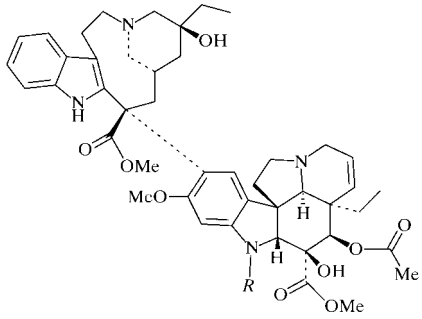
The monomeric and bisindole catharanthus alkaloids are important plant-derived natural products that have had a considerable impact on medicinal chemistry and modern pharmacology (Taylor & Farnsworth, 1975; Brossi, 1990).

Recently, we have successfully applied a solid-phase extraction (SPE) method to the isolation and purification of these alkaloids from home-grown plant material (Ruszkowska *et al.*, 1994). This method enabled us to start a more detailed on-going study of chemical transformations of some monoindole alkaloids.

Vindoline, (I), a predominant monoindole alkaloid, and its congener 16-demethoxyvindoline, (II), were first obtained from *Catharanthus roseus* (L.) G. Don. by Gorman *et al.* (1959, 1962). Oncolytic bisindoles vinblastine (VBL), (III), and vincristine (VCR), (IV), which are widely used for treatment of a variety of malignant diseases, have been isolated (Gorman *et al.*, 1959; Svoboda, 1961). The chemical transformation of (I) is of great importance because of its relative abundance in plant material and the possible utilization in the hemisynthesis of biologically active cytotoxic bisindoles, which are far less readily available.



(I) R=OMe, vindoline
(II) R=H, 16-demethoxyvindoline



(III) R=Me, vinblastine
(IV) R=CHO, vincristine

The goal of our work was to obtain *N*1-formyl derivatives of vindoline and its congeners by oxidation of *N*1-methyl compounds. However, the oxidation of (I) with potassium dichromate surprisingly led to the dimeric product instead of the expected *N*-formyl monoindole derivative (Ruszkowska *et al.*, 2003). Our first successful oxidative coupling reactions yielding bisindole compounds inspired us to study the possibility of preparing other vindoline derivatives.

Having in mind highly diversified courses of vindoline oxidation (Kutney *et al.*, 1976, 1977, 1983; Nabih *et al.*, 1978; Sima Sariaslani *et al.*, 1984, 1985; Raucher *et al.*, 1987; Bolcskei *et al.*, 1989; Honty *et al.*, 1993; Tabakovic & Tabakovic, 1996) and in order to rationalize further attempted transformations, we decided to perform a more detailed investigation of the substrate structure. Surprisingly, no X-ray data were available for either (I) or (II). Since the electron density on both N atoms (N1 and N9) and on atoms C3, C6, C7 and C15 might be of interest for *ab initio* quantum-chemical modelling, we initially decided to obtain (I) and (II) in the form of single crystals and resolve their structures using X-ray crystallographic methods. Accordingly, we isolated and purified vindoline and its demethoxy analog by repeated column chromatography. Single crystals of (I) and (II) suitable for X-ray diffraction experiments were obtained by crystallization from diethyl ether.

It has been known for some time that vindoline derivatives have the same chirality sense on all stereogenic centres, which is chemically and biosynthetically correlated within this group (Kozmin & Rawal, 1998). In addition, many mono- (Riche & Pascard-Billy, 1976; Chiaroni *et al.*, 1977; Lamotte *et al.*, 1980) and bisindole alkaloid structures (Guilhem *et al.*, 1976; Leger *et al.*, 1991; Lynch *et al.*, 1991*a*,*b*; Hardouin *et al.*, 2000), including the absolute stereochemistry assignment for VCR

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methiodide (Moncrief & Lipscomb, 1966), have been published. Therefore, it was not our intention to establish the absolute configuration for structures of the title compounds; rather, we aimed to establish their overall conformations and geometry.

The molecular conformations of (I) and (II) are presented in Figs. 1 and 2, respectively. The molecular framework consists of five condensed rings. In both vindoline and demethoxyvindoline, the C13–C18 ring is planar. In (I), the central six-membered ring, C2–C5/C19/C12, is in a boat conformation, with atoms C3 and C19 lying 0.681 (4) and 0.419 (4) Å, respectively, out of the plane defined by the four remaining atoms (the r.m.s. deviation is 0.069 Å). The corresponding values for (II) are 0.651 (3), 0.443 (3) and 0.070 Å. The last six-membered ring, C5–C8/N9/C19, adopts a sofa conformation, with atoms N9 and C8 on the same side of the plane defined by the four remaining atoms [the r.m.s. deviations for the fitted atoms are 0.043 and 0.047 Å for (I) and (II), respectively]. Atoms N9 and C8 deviate from the plane by 0.800 (5) and 0.285 (5) Å in (I), and by 0.837 (4) and 0.361 (5) Å in (II), respectively. The two five-membered rings present in both molecules adopt envelope conformations. However, the N9/C10–C12/C19 ring is more distorted in both structures. The respective r.m.s. deviations for the four fitted atoms N9, C10, C11 and C12 are 0.111 and 0.063 Å for (I) and (II). The fifth atom deviates from the plane by 0.538 (4) and 0.534 (3) Å, respectively. The N1/C2/C12/C13/C18 rings have almost ideal envelope conformations in both structures, with atom C2 deviating from the plane defined by the four remaining atoms by 0.305 (4) and 0.275 (3) Å in (I) and (II), respectively. The hydroxy group at atom C3 is in an axial position, enabling the formation of a strong intramolecular hydrogen bond; in Figs. 1 and 2, these intramolecular O—H···N hydrogen bonds are indicated by dashed lines. The intramolecular hydrogen bond and the conformations of (I) and (II) described above seem to be characteristic of vinca alkaloids. Apart from the aforementioned hydrogen-bonding interactions, there are only weak intermolecular C—H···O contacts present in the structure. There are no bond distances with unusually long or short values. The dimensions of the intramolecular hydrogen bonds are presented in Tables 1 and 2.

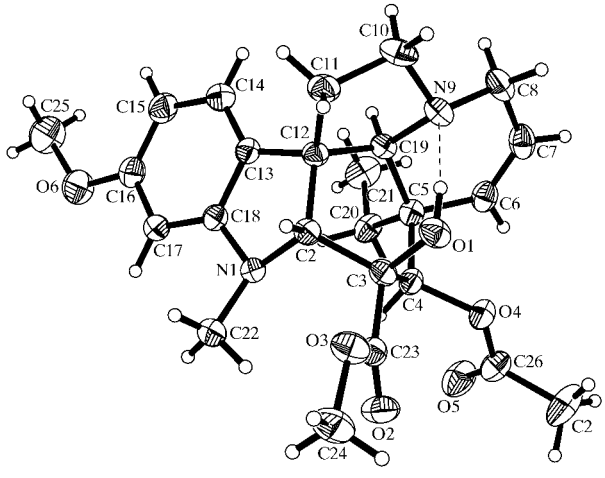

Figure 1
The molecular conformation of (I). Non-H atoms are shown as 30% probability displacement ellipsoids.

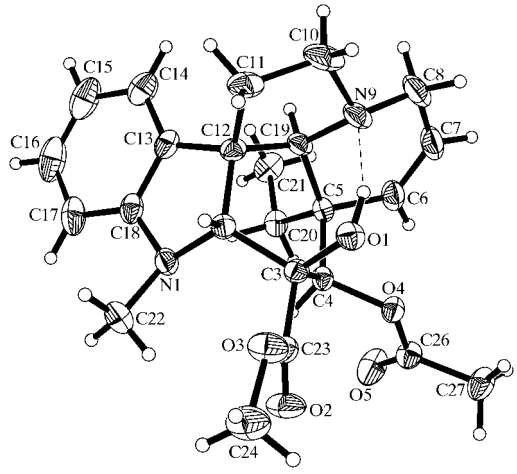

Figure 2
The molecular conformation of (II). Non-H atoms are shown as 30% probability displacement ellipsoids.

Compounds (I) and (II) have very similar overall conformations; moreover, they crystallize in the same space group. However, the orientations of the molecules with respect to the symmetry elements in the crystal lattice and unit-cell dimensions differ substantially. The results of further studies will be presented in due course. The structures described here are, as yet, the only solved structures of natural, not chemically modified, molecules of this class, and therefore seem to be of special interest. The crystal structures of (I) and (II) have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers CCDC 223360 and 223361, respectively).

Experimental

Compounds (I) and (II) were obtained from monomeric alkaloid fractions collected at pH 3 after extraction with dilute sulfuric acid and *via* a standard SPE work-up procedure using a low polar resin (Ruszkowska *et al.*, 1994). A sample of the crude pH 3 fraction (5 g) was subjected to gradient chromatography on silica gel (150 g, 230–400 mesh), using hexane–acetone mixtures with the acetone content ranging from 28 to 50% (*v*/*v*). Fractions 15–17 and 18–28, containing (II) and (I), respectively, were collected, evaporated and rechromatographed on the same kind of silica gel (50 g), yielding 0.103 g (0.02%) of pure (II) and 1.31 g (26.2%) of (I) (percentage yields are with respect to the crude fraction). For (I): m.p. 448–450 K (diethyl ether); MS (LSI–MS): *m*/*e* 457 (M^+ + H), 479 (M^+ + Na). For (II): m.p. 431–432.5 K (diethyl ether); MS (LSI–MS): *m*/*e*: 427 (M^+ + H), 449 (M^+ + Na). Other spectral data of (I) and (II) agreed in all respects with those reported in the literature (Gorman *et al.*, 1962).

Compound (I)

Crystal data

$C_{25}H_{32}N_2O_6$
M_r = 456.53
Orthorhombic, $P2_12_12_1$
a = 9.5440 (19) Å
b = 15.711 (3) Å
c = 15.888 (3) Å
V = 2382.3 (8) Å^3
Z = 4
D_x = 1.273 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 8.2–8.7°
μ = 0.09 mm^{-1}
T = 293 (2) K
Plate, colourless
0.50 × 0.40 × 0.15 mm

Data collection

Kuma KM-4 κ-axis diffractometer
ω–2θ scans
4297 measured reflections
4253 independent reflections
2199 reflections with $I > 2\sigma(I)$
R_{int} = 0.012
θ_{max} = 30.0°
$h = -1 \rightarrow 13$
$k = 0 \rightarrow 22$
$l = 0 \rightarrow 22$
3 standard reflections
every 200 reflections
intensity decay: 1.6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.145
S = 1.03
4253 reflections
302 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0776P)^2 + 0.2206P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···N9	0.88 (4)	1.84 (4)	2.693 (3)	164 (4)

Compound (II)

Crystal data

$C_{24}H_{30}N_2O_5$
M_r = 426.50
Orthorhombic, $P2_12_12_1$
a = 8.0800 (16) Å
b = 11.320 (2) Å
c = 24.212 (5) Å
V = 2214.6 (8) Å^3
Z = 4
D_x = 1.279 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 8.0–8.7°
μ = 0.09 mm^{-1}
T = 293 (2) K
Columnar, colourless
0.62 × 0.50 × 0.37 mm

Data collection

Kuma KM-4 κ-axis diffractometer
ω–2θ scans
4424 measured reflections
4333 independent reflections
2550 reflections with $I > 2\sigma(I)$
R_{int} = 0.091
θ_{max} = 30.0°
$h = -2 \rightarrow 11$
$k = 0 \rightarrow 15$
$l = 0 \rightarrow 30$
3 standard reflections
every 200 reflections
intensity decay: 0.6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.135
S = 1.03
4333 reflections
284 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0802P)^2 + 0.1619P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 2
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···N9	0.94 (4)	1.76 (4)	2.677 (3)	162 (3)

The hydroxy H atoms of (I) and (II) were located in Fourier difference maps and refined isotropically; see Tables 1 and 2 for refined distances. All other H atoms were allowed for as riding, with C—H distances in the range 0.93–0.98 Å and U_{iso} values set at 1.2 times the U_{eq} values of the parent atoms.

For both compounds, data collection: *KM*-4 *Software* (Kuma, 2000); cell refinement: *KM*-4 *Software*; data reduction: *KM*-4 *Software*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* (Bruker, 1998); software used to prepare material for publication: *SHELXL*97.

Dry *Catharanthus roseus* leaves imported from India were kindly provided by the Pharmaceutical Institute, Warsaw. X-ray data were collected at the Institute of Nuclear Chemistry and Technology, Warsaw, and mass spectra were recorded at the Institute of Organic Chemistry, Polish Academy of Sciences.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV1168). Services for accessing these data are described at the back of the journal.

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