organic compounds

Catharanthinol and dihydrocatharanthinol: two Iboga-class alkaloids

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The title compounds are indole alkaloids of the Iboga class. In both compounds, *viz.* catharanthinol methanol solvate, $C_{20}H_{24}N_2O \cdot CH_4O$, (I), and dihydrocatharanthinol monohydrate, $C_{20}H_{26}N_2O \cdot H_2O$, (II), a nitrogen-containing seven-membered ring is fused to the indole system and shares two sides with a tricyclic isoquinuclidine group. The main difference between (I) and (II) is the presence of a C=C bond in the isoquinuclidine ring in (I). The presence of amine and hydroxy groups in these molecules and of methanol [in (I)] or water [in (II)] solvent molecules results in intra- and/or intermolecular hydrogen bonding.

Comment

Compounds (I) and (II) belong to the Iboga class of alkaloids, characterized by their indoloazepine–isoquinuclidine skeleton. Several members of this family have been characterized crystallographically, such as ibogaine, extracted from West African *Tabernanthe iboga* (Arai *et al.*, 1960; Soriano-García, 1992), coronaridine (Kutney *et al.*, 1973), bonafousine (Damak *et al.*, 1976), epiheyneanine (Vencato *et al.*, 1987), ibogamine (Soriano-García *et al.*, 1988) and hydroxyibogamine (Massiot *et al.*, 1983). Alkaloids of the closely related Voacanga class have also been described (Soriano-García *et al.*, 1989, 1991).
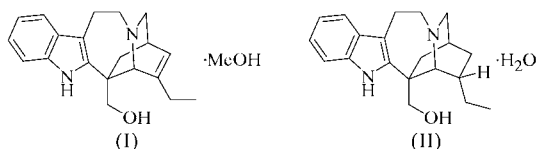
Compounds (I) and (II) have been synthesized from catharanthine, which is a naturally occurring alkaloid isolated from the leaves of the Madagascan periwinkle *Catharanthus roseus*, and whose crystal structure has not yet been elucidated. Compound (I) differs from catharanthine by replacement of the met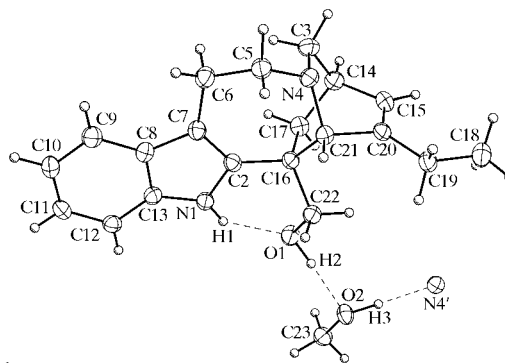hyl ester substituent of the latter with a hydroxymethyl group. Hydrogenation of catharanthine, under heterogeneous conditions, is known to afford dihydrocatharanthine as a single diastereomer. The selectivity of this process can be rationalized by assuming that addition of hydrogen takes place from the less hindered side of the Iboga skeleton. During our studies of the selective reduction of the C15=C20 bond, we envisioned that the stereochemical course of hydrogenation could be influenced by the presence of a neighbouring hydroxymethyl group. Indeed, association of the hydroxymethyl heteroatom with the catalyst surface can lead to delivery of hydrogen from the hindered 'bottom' side. For the purpose of this study, we synthesized the starting substrate, (I), and also compound (II), which results from classical hydrogenation.

Both (I) and (II) crystallize as solvates. The asymmetric unit contains one alkaloid molecule and one methanol or one water molecule in (I) and (II), respectively (Figs. 1 and 2). The two compounds possess a hydroxymethyl substituent on atom C16, common to the seven-membered ring and the isoquinuclidine system, and an ethyl substituent on the latter. The isoquinuclidine ring includes a C15=C20 bond in (I) [bond length 1.329 (4) Å], whereas this bond is hydrogenated in (II) [bond length 1.537 (3) Å], with the ethyl substituent *trans* with respect to isoquinuclidine atom N4. This same substituent is in
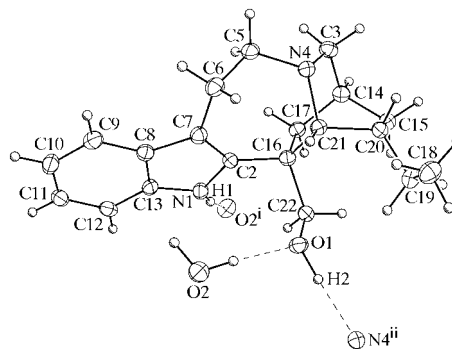

Figure 1
A view of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Hydrogen bonds are shown as dashed lines. The primed atom is in the molecule at symmetry position $(x + \frac{1}{2}, \frac{3}{2} - y, -z)$.

Figure 2
A view of (II), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Hydrogen bonds are shown as dashed lines. The symmetry codes are as given in Table 2.

a *cis* position in ibogaine. To the best of our knowledge, this is the first crystallographic characterization in this family of compounds of a molecule including a double bond in the quinuclidine system. A search of the Cambridge Structural Database (CSD, Version 5.25; Allen, 2002) gives 13 instances of substituted quinuclidine rings including such a bond, with a mean bond length of 1.329 (4) Å, which perfectly matches that in (I). The remaining bond lengths in both compounds are in agreement with those reported for other high-quality structure determinations of indole (Nigović *et al.*, 2000) and alkaloid (Soriano-García *et al.*, 1988, 1989) systems.

The indole ring system is planar, with r.m.s. deviations of 0.007 and 0.009 Å in (I) and (II), respectively. The seven-membered ring is in a chair conformation in (I) and in a distorted boat conformation in (II). Both conformations have previously been encountered in compounds of the same family, with no obvious rationale. This conformation change is mainly due to the different positions of atoms N4 and C5 in (I) and (II); the distances to the indole plane of atoms N4, C5, C6, C16 and C21 of the seven-membered ring are −0.031 (4), 0.429 (5), −0.127 (4), −0.086 (4) and 0.577 (4) Å, respectively, in (I), and 0.997 (3), 1.428 (3), 0.293 (3), 0.037 (3) and −0.185 (3) Å, respectively, in (II). The mean plane defined by the seven-membered ring has r.m.s. deviations of 0.216 and 0.373 Å in (I) and (II), respectively, and has dihedral angles with the indole plane of 7.07 (12)° in (I) and 23.69 (8)° in (II). The dihedral angle between the C21—N4—C3—C14 plane of the isoquinuclidine moiety [r.m.s. deviation = 0.053 Å in (I) and 0.067 Å in (II)] and the indole system is 78.57 (10)° in (I) and 73.53 (7)° in (II); values in the range 69.1 (1)–114.0 (2)° have been reported for other members of this family of compounds (Soriano-García, 1992). The dihedral angle between the same plane and the mean seven-membered ring plane is 85.62 (11)° for (I) and 60.85 (8)° for (II). The two triangular isoquinuclidine planes, *viz.* N4—C16—C20 and C3—C15—C17, define a dihedral angle of 5.6 (2)° in (I) and 1.88 (3)° in (II), and are thus tilted slightly with respect to their parallel position in the ideal conformation.

Apart from van der Waals interactions, the alkaloid molecules are held in the crystal packing by hydrogen bonds involving the solvent molecules in both (I) and (II). In (I), an intramolecular hydrogen bond links the N1—H group and hydroxy atom O1 in the same molecule. The O1—H group itself acts as a donor towards methanol atom O2, the latter being finally hydrogen bonded to isoquinuclidine atom N4 of a neighbouring molecule related to the first by the binary screw axis parallel to the *a* axis (Table 1). This hydrogen-bonding network gives rise to zigzag chains directed along the *a* axis.

No intramolecular hydrogen bond is present in (II). Atom O1 acts as a donor towards atom N4 of a neighbouring molecule related by the binary screw axis parallel to the *b* axis, and as an acceptor from the water molecule. Finally, atom N1 is bound to another water molecule related to the first by the screw axis parallel to the *a* axis (Table 2). The resulting arrangement is three-dimensional.

Some significant C—H···π interactions are present in both compounds. In (I), an interaction involves the H atom of the

isoquinuclidine bridgehead atom, C14, and the six-membered aromatic ring of a second molecule related to the first by the screw axis parallel to the *c* axis [H14···centroid distance = 2.74 Å and C14—H14···centroid angle = 164°], and thus links adjacent hydrogen-bonded chains. In (II), such an interaction is found between the water H atom which is not involved in hydrogen bonding and the indole five-membered ring in the same unit [H4···centroid distance = 2.52 Å and O2—H4···centroid angle = 129°] and two others are found between H atoms bound to atoms C14 and C15 and the indole six- and five-membered rings, respectively, of the molecule related by the screw axis parallel to the *c* axis [H14···centroid distance = 2.81 Å and C14—H14···centroid angle = 138°, and H15A···centroid distance = 2.59 Å and C15—H15A···centroid angle = 159°].

Experimental

Reduction of the ester group of (+)-catharanthine with lithium aluminium hydride gave compound (I), which was recrystallized from methanol. Compound (II) was obtained in two steps from catharanthine, the catalytic hydrogenation of the C15=C20 bond being followed by reduction of the ester group by LiAlH$_4$, as reported in the literature method of Gorman *et al.* (1965). Crystals of (II) were obtained by recrystallization from diethyl ether.

Compound (I)

Crystal data

$C_{20}H_{24}N_2O\cdot CH_4O$	Mo $K\alpha$ radiation
$M_r = 340.45$	Cell parameters from 13 656
Orthorhombic, $P2_12_12_1$	reflections
$a = 10.7136 (5)$ Å	$\theta = 2.9$–$25.7°$
$b = 12.6846 (8)$ Å	$\mu = 0.08$ mm^{-1}
$c = 13.1078 (9)$ Å	$T = 100 (2)$ K
$V = 1781.32 (19)$ Å^3	Platelet, colourless
$Z = 4$	$0.24 \times 0.20 \times 0.08$ mm
$D_x = 1.269$ Mg m^{-3}	

Data collection

Nonius KappaCCD area-detector	$R_{int} = 0.063$
diffractometer	$\theta_{max} = 25.7°$
φ scans	$h = 0 \to 13$
13 656 measured reflections	$k = 0 \to 15$
1927 independent reflections	$l = 0 \to 15$
1707 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0305P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.041$	$+ 0.7559P]$
$wR(F^2) = 0.090$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.05$	$(\Delta/\sigma)_{max} < 0.001$
1927 reflections	$\Delta\rho_{max} = 0.19$ e Å^{-3}
229 parameters	$\Delta\rho_{min} = -0.19$ e Å^{-3}
H-atom parameters constrained	Extinction correction: *SHELXL*97
	Extinction coefficient: 0.022 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O1	0.91	1.91	2.660 (3)	138
O1—H2···O2	0.96	1.72	2.679 (3)	176
O2—H3···N4^i	0.98	1.73	2.703 (3)	177

Symmetry code: (i) $\frac{1}{2} + x, \frac{3}{2} - y, -z$.

organic compounds

Compound (II)

Crystal data

$C_{20}H_{26}N_2O \cdot H_2O$
$M_r = 328.44$
Orthorhombic, $P2_12_12_1$
$a = 10.6728 (4)$ Å
$b = 12.0168 (6)$ Å
$c = 12.8132 (7)$ Å
$V = 1643.33 (14)$ Å^3
$Z = 4$
$D_x = 1.328$ Mg m^{-3}

Mo $K\alpha$ radiation
Cell parameters from 12 617 reflections
$\theta = 3.0–25.7°$
$\mu = 0.09$ mm^{-1}
$T = 100 (2)$ K
Parallelepiped, colourless
$0.25 \times 0.25 \times 0.20$ mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ scans
12 617 measured reflections
1788 independent reflections
1621 reflections with $I > 2\sigma(I)$

$R_{int} = 0.066$
$\theta_{max} = 25.7°$
$h = 0 \rightarrow 12$
$k = 0 \rightarrow 14$
$l = 0 \rightarrow 15$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.035$
$wR(F^2) = 0.088$
$S = 1.07$
1788 reflections
218 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0441P)^2 + 0.4399P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.16$ e Å^{-3}
$\Delta\rho_{min} = -0.20$ e Å^{-3}

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

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$N1-H1\cdots O2^i$	0.92	1.96	2.870 (3)	168
$O1-H2\cdots N4^{ii}$	0.99	1.79	2.778 (3)	176
$O2-H3\cdots O1$	0.97	1.83	2.797 (2)	174

Symmetry codes: (i) $x - \frac{1}{2}, \frac{3}{2} - y, 2 - z$; (ii) $2 - x, y - \frac{1}{2}, \frac{3}{2} - z$.

The amino, hydroxy and water H atoms were found in a difference Fourier map and were introduced as riding atoms, with $U_{iso}(H) = 1.2U_{eq}(O,N)$. All other H atoms were introduced in calculated positions as riding atoms, with C—H bond lengths of 0.93 (aromatic CH), 0.98 (aliphatic CH), 0.97 (CH$_2$) and 0.96 Å (CH$_3$), and with $U_{iso}(H) = 1.2U_{eq}(C)$ for CH and CH$_2$, and $1.5U_{eq}(C)$ for CH$_3$. In the absence of suitable anomalous scatterers, Friedel equivalents could not be used to determine the absolute configuration. Refinement of the Flack (1983) parameter led to inconclusive values (Flack & Bernardinelli, 2000) of −1.4 (16) for (I) and −0.1 (14) for (II). Therefore, the 1439 and 1322 Friedel equivalents for (I) and (II), respectively, were merged before the final refinements. The configuration adopted is that of the precursor of both compounds, *viz.* natural (+)-catharanthine.

For both compounds, data collection: *KappaCCD Server Software* (Nonius, 1997); cell refinement: *DENZO–SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1999); software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2003).

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