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Two stereoisomeric pentacyclic oxindole alkaloids from *Uncaria tomentosa*: uncarine C and uncarine E

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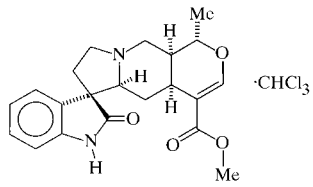
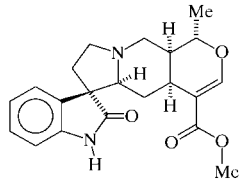
The chloroform solvate of uncarine C (pteropodine), (1′*S*,3*R*,4′a*S*,5′a*S*,10′a*S*)-1,2,5′,5′a,7′,8′,10′,10′a-octahydro-1′-methyl-2-oxospiro[3*H*-indole-3,6′(4′a*H*)-[1*H*]pyrano[3,4-*f*]-indolizine]-4′-carboxylic acid methyl ester, $C_{21}H_{24}N_2O_4\cdot CHCl_3$, has an absolute configuration with the spiro C atom in the *R* configuration. Its epimer at the spiro C atom, uncarine E (isopteropodine), (1′*S*,3*S*,4′a*S*,5′a*S*,10′a*S*)-1,2,5′,5′a,7′,8′,10′,-10′a-octahydro-1′-methyl-2-oxospiro[3*H*-indole-3,6′(4′a*H*)-[1*H*]pyrano[3,4-*f*]indolizine]-4′-carboxylic acid methyl ester, $C_{21}H_{24}N_2O_4$, has $Z' = 3$, with no solvent. Both form intermolecular hydrogen bonds involving only the oxindole, with N···O distances in the range 2.759 (4)–2.894 (5) Å.

Comment

The *allo*-heteroyohimbine-type title molecules uncarine C, (I), and uncarine E, (II) (both $C_{21}H_{24}N_2O_4$), were isolated from Peruvian Uña de Gato (*Uncaria tomentosa*) and were characterized as the C7(*R*) and C7(*S*) epimers, respectively, by a detailed high-field two-dimensional NMR study. They are the two major biochemical markers of Uña de Gato (Cat's Claw), which is considered an important immunomodulatory botanical that displayed interesting activity against AIDS (Jones, 1995; Keplinger & Keplinger, 1994; Keplinger *et al.*, 1986), as well as Alzheimer's disease and other amyloidoses (Castillo & Snow, 2000). Out of 12 reported heteroyohimbine-type isomers (Shamma *et al.*, 1967; Seki *et al.*, 1993), only the relative stereochemistry of uncarine C was previously determined by X-ray crystallography (Laus *et al.*, 1996) in a study of the monohydrate hemimethanol solvate. In order to conclusively establish the configurations of all five asymmetric centers of (I) and (II), and to ascertain the relationships between the spiro *B* and *C* rings, crystal structure determinations were undertaken. Fortuitously, uncarine C crystallized as the $CHCl_3$ solvate, which also allowed direct determination of its absolute configuration, and by extension, also that of uncarine E.



(I)



(II)

The structures reported herein are in agreement with the tentative isomer assignment using NMR methods that (I) (Fig. 1) is the C7(*R*) *allo*-isomer of (II) (Fig. 2), with the *C* and *D* rings *trans*, and the *D* and *E* rings *cis*. Our determination of the chloroform solvate also confirms the relative configurations of the asymmetric centers from the previous determination of the water/methanol solvate of uncarine C (Laus *et al.*, 1996).

Uncarine C chloroform solvate has $Z' = 1$, while uncarine E has $Z' = 3$, as shown in Fig. 3. However, no pseudosymmetry is apparent, and the fact that Z' is greater than 1 is not a result of the low temperature of the determination, since uncarine E also has $Z' = 3$ at room temperature. Cell dimensions at 296 K are: $a = 11.0790$ (8), $b = 21.2420$ (17), $c = 12.4165$ (6) Å, $\beta = 97.012$ (5)° and $V = 2900.2$ (3) Å^3, determined using the same crystal and Cu $K\alpha$ radiation. In both compounds, all N—H groups form intermolecular hydrogen bonds with oxindole O1 atoms as acceptors, as detailed in Tables 1 and 2. In the case of the $Z' = 3$ uncarine E, the hydrogen bonds link molecules into chains in the *a* direction (order ...*ACBACB*...). Intermolecular C—H···O hydrogen bonding is also present in both structures. These interactions are detailed in Tables 2 and 4.

The conformation of the 5–6–6 ring system is fairly constant across the three molecules of uncarine E and uncarine C. The central six-membered ring is a chair. The O-containing six-membered ring, in both cases, has a conformation in which C15, C16, C17, O2, and C19 lie within 0.083 (3) Å or less of a common plane. Atom C20 lies out of this plane by 0.709 (3) Å in uncarine C and by 0.683 (4), 0.658 (4), and 0.679 (4) Å for

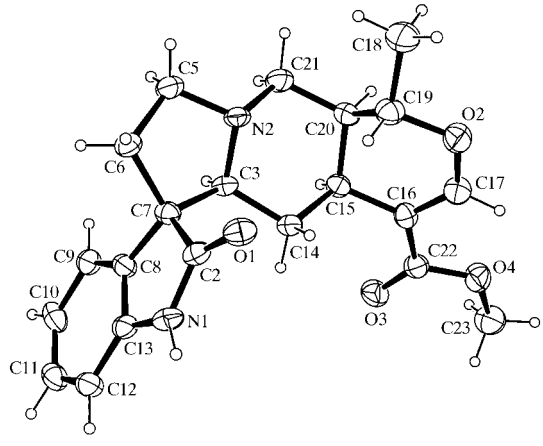


Figure 1
A view of the structure of (I) showing the atom-numbering scheme and ellipsoids at the 50% probability level. The solvent is not shown.

the *A*, *B*, and *C* molecules, respectively, of uncarine E. There is somewhat more variability in the conformation of the five-membered ring containing N2. In uncarine C, it is nearest to an N2 envelope, in the *B* molecule of uncarine E, is nearest a C3 envelope, while in the *A* and *C* molecules of uncarine E, it is nearest a C_2 twist at C6.

The structure of (±)-21-oxoisopteropodine (Lynch *et al.*, 1991), which differs from uncarine E only by having a keto oxygen at C21, has been reported.

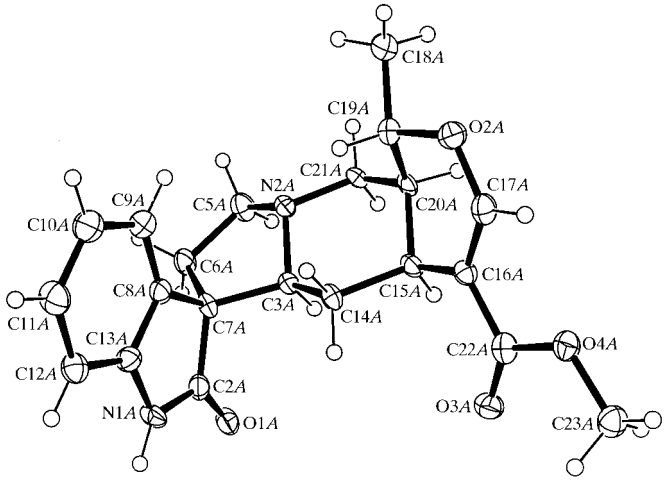


Figure 2
A view of one of the three independent molecules of (II) showing the atom-numbering scheme and ellipsoids at the 50% probability level.

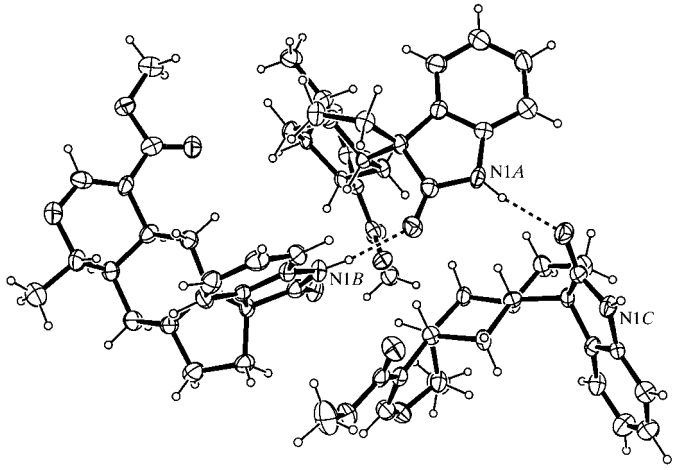


Figure 3
The three independent molecules of (II).

Experimental

Compounds (I) and (II) were isolated in a large scale from the inner stem bark of *Uncaria tomentosa* (Wild.) DC. (*Rubiaceae*) using a standardized procedure (Wagner *et al.*, 1985). Compound (I) was recrystallized from $CHCl_3$/*n*-hexane as plates [m.p. 492–493 K; $[\alpha]_D$ −106° (c = 0.2, $CHCl_3$)], while (II) was recrystallized as plates from acetone/*n*-hexane [m.p. 471–472 K; $[\alpha]_D$ −80.5° (c = 0.554, $CHCl_3$)]. The initial physical and NMR data recorded at 500 MHz, using a Bruker Avance DRX-500 instrument, were in agreement with those reported in the literature (Phillipson & Hemingway, 1975; Seki *et al.*, 1993).

Compound (I)

Crystal data

$C_{21}H_{24}N_2O_4{\cdot}CHCl_3$	D_x = 1.373 Mg m^{-3}
M_r = 487.79	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 5602 reflections
a = 9.3190 (5) Å	θ = 2.5–32.0°
b = 7.7083 (7) Å	μ = 0.419 mm^{-1}
c = 16.8160 (14) Å	T = 120 K
β = 102.422 (4)°	Needle fragment, colorless
V = 1179.63 (16) Å^3	0.32 × 0.12 × 0.08 mm
Z = 2	

Data collection

KappaCCD diffractometer (with Oxford Cryosystems Cryostream cooler)	8241 measured reflections
	5101 independent reflections
	3176 reflections with $I > 2\sigma(I)$
ω scans with κ offsets	R_{int} = 0.037
Absorption correction: multi-scan (*HKL SCALEPACK*; Otwinowski & Minor, 1997)	θ_{max} = 32.0°
	$h = -13 \rightarrow 13$
	$k = -11 \rightarrow 11$
T_{min} = 0.88, T_{max} = 0.97	$l = -24 \rightarrow 25$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0998P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.059	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.160	$\Delta\rho_{max}$ = 1.16 e Å^{-3}
S = 0.98	$\Delta\rho_{min}$ = −0.65 e Å^{-3}
5101 reflections	Absolute structure: 740 Friedel pairs (Flack, 1983)
296 parameters	Flack parameter = −0.09 (9)
H-atom parameters constrained	

Table 1
Selected torsion angles (°) for (I).

C21—N2—C3—C14	62.7 (3)	C20—C15—C16—C17	21.6 (4)
C5—N2—C3—C7	−45.8 (3)	C15—C16—C17—O2	2.6 (6)
C3—N2—C5—C6	44.1 (3)	C19—O2—C17—C16	6.6 (5)
N2—C5—C6—C7	−24.6 (3)	O2—C19—C20—C15	63.7 (3)
N2—C3—C7—C6	28.3 (3)	C14—C15—C20—C21	−51.8 (3)
C5—C6—C7—C3	−2.4 (3)	C16—C15—C20—C19	−52.8 (3)
N2—C3—C14—C15	−54.0 (3)	C3—N2—C21—C20	−63.7 (3)
C3—C14—C15—C20	49.8 (3)	C15—C20—C21—N2	57.5 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O1^{i}	0.88	2.01	2.759 (4)	142
C9—H9···O2^{ii}	0.95	2.50	3.330 (4)	146
C24—H24···O3	1.00	2.24	3.167 (6)	153

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

Compound (II)

Crystal data

$C_{21}H_{24}N_2O_4$	D_x = 1.298 Mg m^{-3}
M_r = 368.42	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 6595 reflections
a = 10.9943 (8) Å	θ = 2.5–25.0°
b = 21.062 (3) Å	μ = 0.090 mm^{-1}
c = 12.3039 (15) Å	T = 120 K
β = 96.860 (6)°	Needle, colorless
V = 2828.7 (5) Å^3	0.58 × 0.07 × 0.05 mm
Z = 6	

Data collection

KappaCCD diffractometer (with Oxford Cryosystems Cryostream cooler)	4478 reflections with $I > 2\sigma(I)$
ω scans with κ offsets	$R_{int} = 0.058$
13 122 measured reflections	$\theta_{max} = 25.1^\circ$
8293 independent reflections	$h = -13 \rightarrow 13$
	$k = -23 \rightarrow 25$
	$l = -14 \rightarrow 14$

Refinement

Refinement on F^2	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.052$	$w = 1/[\sigma^2(F_o^2) + (0.0282P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.108$	$(\Delta/\sigma)_{max} = 0.001$
$S = 0.894$	$\Delta\rho_{max} = 0.21$ e Å^{-3}
8293 reflections	$\Delta\rho_{min} = -0.25$ e Å^{-3}
736 parameters	

Table 3
Selected torsion angles (°) for (II).

C21*A*—N2*A*—C3*A*—C14*A*	62.1 (5)	C20*A*—C15*A*—C16*A*—C17*A*	18.2 (6)
C5*A*—N2*A*—C3*A*—C7*A*	−50.6 (4)	C15*A*—C16*A*—C17*A*—O2*A*	5.8 (7)
C3*A*—N2*A*—C5*A*—C6*A*	40.0 (4)	C19*A*—O2*A*—C17*A*—C16*A*	4.7 (6)
N2*A*—C5*A*—C6*A*—C7*A*	−13.8 (5)	C17*A*—O2*A*—C19*A*—C20*A*	−38.2 (5)
C5*A*—C6*A*—C7*A*—C3*A*	−15.6 (5)	O2*A*—C19*A*—C20*A*—C15*A*	61.7 (5)
N2*A*—C3*A*—C7*A*—C6*A*	39.9 (5)	C16*A*—C15*A*—C20*A*—C19*A*	−50.7 (5)
N2*A*—C3*A*—C14*A*—C15*A*	−59.5 (5)	C14*A*—C15*A*—C20*A*—C21*A*	−53.6 (5)
C3*A*—C14*A*—C15*A*—C20*A*	55.2 (5)	C3*A*—N2*A*—C21*A*—C20*A*	−58.8 (5)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1*A*—H1N*A*···O1*C*	0.88	1.99	2.864 (5)	171
N1*B*—H1N*B*···O1*A*	0.88	2.05	2.894 (5)	161
N1*C*—H1N*C*···O1*B*^{i}	0.88	2.03	2.873 (5)	159
C10*B*—H10*B*···O2*A*^{ii}	0.95	2.60	3.263 (5)	127
C15*C*—H15*C*···O1*A*	1.00	2.60	3.528 (6)	155
C20*A*—H20*A*···O1*C*^{iii}	1.00	2.59	3.459 (6)	145

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

The solvent molecule of uncarine C chloroform solvate exhibits a small disorder, with C24 and Cl3 each occupying two sites. The populations of the major and minor sites of both were constrained to sum to unity, and refined to 0.808 (5) and 0.192 (5), with the minor carbon position isotropic. The maximum residual peak was in the disordered solvent region, 1.2 Å from Cl3. H atoms were placed in calculated positions with C—H bond distances of 0.95–1.00 Å and an N—H distance of 0.88 Å, and thereafter treated as riding; U_{iso} = $1.2U_{eq}$ of the attached atom or $1.5U_{eq}$ for methyl C atoms. A torsional parameter was refined for methyl groups.

For compound (I), data collection: *COLLECT* (Nonius, 1999); for both compounds, cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BJ1025). Services for accessing these data are described at the back of the journal.

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