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,3R,4aS,5’aS,10’aS)-1,2,5,5’a,7,8,10’,10’-a-octahydro-1’-methyl-2-oxospiro[3H-indole-3,6’(4’aH’)-1H]pyrano[3,4-f]-indolizine]-4’-carboxylic acid methyl ester, C_{21}H_{24}N_{2}O_{4}-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,3S,4aS,5’aS,10’aS)-1,2,5,5’a,7,8,10’,10’-a-octahydro-1’-methyl-2-oxospiro[3H-indole-3,6’(4’aH’)-1H]pyrano[3,4-f]-indolizine]-4’-carboxylic acid methyl ester, C_{21}H_{24}N_{2}O_{4}, has an absolute configuration with the spiro C atom as acceptors, as detailed in Tables 1 and 2. In the case of the 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_{2}O_{4}), were isolated from Peruvian *Uña de Gato* (*Uncaria tomentosa*), and were characterized as the Z’(R) and Z’(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.

The structures reported herein are in agreement with the tentative isomer assignment using NMR methods that (I) (Fig. 1) is the Z’(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’ > 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, β = 97.012 (5)° and V = 2900.2 (3) Å³, determined using the same crystal and Cu *Ka* 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.

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](Image 316x610 to 557x693)

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 C2 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.

The three independent molecules of (II). 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 C2 twist at C6.

The three independent molecules of (II). 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 C2 twist at C6.

Compound (I)

**Crystal data**

C₂₁H₂₄N₂O₄·CHCl₃

Mᵣ = 487.79

Monoclinic, P2₁

a = 9.3190 (5) Å

b = 7.7083 (7) Å

c = 16.8160 (14) Å

β = 102.422 (4)

V = 1179.63 (16) Å³

Z = 2

Dₐ = 1.373 Mg m⁻³

Mo Kα radiation

Cell parameters from 5602 reflections

θ = 2.5–32.0°

μ = 0.419 mm⁻¹

T = 293 K

Needle fragment, colorless

0.32 × 0.12 × 0.08 mm

**Data collection**

KappaCCD diffractometer (with Oxford Cryosystems Cryostream cooler)

Absorption correction: multi-scan

(HKL SCALEPACK; Otwinowski & Minor, 1997)

Tmin = 0.88, Tmax = 0.97

wR(F²) = 0.059

S = 0.98

5101 reflections

296 parameters

H-atom parameters constrained

Refinement

Refinement on F²

R(F²) = 0.059

wR(F²) = 0.160

S = 0.98

8241 measured reflections

5101 independent reflections

3176 reflections with I > 2σ(I)

R[Fo > Fc] = 0.021

wR[Fo] = 0.059

where P = (Fo² + 2Fc²)/3

Δρmax = 0.65 e Å⁻³

Δρmin = −0.65 e Å⁻³

Absolute structure: 740 Friedel pairs (Flack, 1983)

Flack parameter = −0.09 (9)

**Table 1**

Selected torsion angles (°) for (I).

| C₁⁻→N₂⁻→C₃⁻→C₁₄ | 62.7 (3) | C₂₀⁻→C₁₅⁻→C₁₆⁻→C₁₇ | 21.6 (4) |
| C₅⁻→N₂⁻→C₅⁻→C₆ | −45.8 (3) | C₁₅⁻→C₁₆⁻→C₁₇⁻→O₂ | 2.6 (6) |
| C₃⁻→N₂⁻→C₅⁻→C₆ | 44.1 (3) | C₁₉⁻→O₂⁻→C₁₂⁻→C₁₇ | 6.6 (5) |
| C₂⁻→N₂⁻→C₆⁻→C₇ | −24.6 (3) | O₂⁻→C₁₀⁻→C₂₀⁻→C₁₅ | 63.7 (3) |
| C₅⁻→C₆⁻→C₇⁻→C₃ | 2.6 (6) | C₁₄⁻→C₁₅⁻→C₂₀⁻→C₂₁ | −51.8 (3) |
| C₅⁻→C₆⁻→C₇⁻→C₃ | −2.4 (3) | C₁₆⁻→C₁₅⁻→C₂₀⁻→C₁₉ | −52.8 (3) |
| C₅⁻→C₆⁻→C₇⁻→C₃ | −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).

<table>
<thead>
<tr>
<th>D⁻→H···A</th>
<th>D⁻→H</th>
<th>H⁻→···A</th>
<th>D⁻→A</th>
<th>D⁻→H⁻→A</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₁⁻→H₁⁻→O¹</td>
<td>0.88</td>
<td>2.01</td>
<td>2.759 (4)</td>
<td>142</td>
</tr>
<tr>
<td>C₉⁻→H⁻→O²</td>
<td>0.95</td>
<td>2.50</td>
<td>3.330 (4)</td>
<td>146</td>
</tr>
<tr>
<td>C₂₄⁻→H₂⁻→O₃</td>
<td>1.00</td>
<td>2.24</td>
<td>3.167 (6)</td>
<td>153</td>
</tr>
</tbody>
</table>

Symmetry codes: (i) 1−x, ½+y, 1−z; (ii) x−1, y, z.

Compound (II)

**Crystal data**

C₂₁H₂₄N₂O₄

Mᵣ = 368.42

Monoclinic, P2₁

a = 10.9943 (8) Å

b = 21.062 (3) Å

c = 12.3039 (15) Å

β = 96.860 (6)

V = 2828.7 (5) Å³

Z = 6

Dₐ = 1.298 Mg m⁻³

Mo Kα radiation

Cell parameters from 6595 reflections

θ = 2.5–25.0°

μ = 0.090 mm⁻¹

T = 293 K

Needle, colorless

0.58 × 0.07 × 0.05 mm

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 CHCl₃/n-hexane as plates [m.p. 492–493 K; δD ᶝ−106° (c = 0.2, CHCl₃)], while (II) was recrystallized as plates from acetone/n-hexane [m.p. 471–472 K; δD ᶝ−80.5° (c = 0.554, CHCl₃)]. 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).
The solvent molecule of uncarine C chloroforol solvate exhibits a small disorder, with C24 and C13 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 C13. 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: $U_{	ext{iso}} = 1.2U_{	ext{eq}}$ of the attached atom or 1.5$U_{	ext{eq}}$ 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: SIR92 (Altomare et al., 1994); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: ORTEPIII (Burnett & Johnson, 1996); software used to prepare material for publication: SHELXL97.

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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.

### References


