# Hydrogen bonding in two tetracyclic indole alkaloids

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3-Acetyl-1,6,7,12b-tetrahydroindolo[2,3-a]quinolizin-2(12H)-one, $C_{17}H_{16}N_2O_2$, consists of two symmetry-independent molecules and each forms a layered structure stabilized by N—H···O and C—H···O hydrogen bonds. In 3-acetyl-6,7-dihydroindolo[2,3-a]quinolizin-4(12H)-one monohydrate, $C_{17}H_{14}N_2O_2 \cdot H_2O$, the structure is stabilized by O—H···O, N—H···O and C—H···O hydrogen bonds, with the ordered water molecule playing a crucial role in the self-assembly. Contribution from the weak interactions to the strong hydrogen-bonded network is a common feature in both structures.

## Comment

Indole alkaloids and their derivatives continue to attract the attention of organic and medicinal chemists because of their physiological importance, as well as their structural diversity. 3-Acetyl-1,6,7,12b-tetrahydroindolo[2,3-a]quinolizin-2(12H)-one, (1), was synthesized with a view to obtaining different indole alkaloids from a common intermediate. 3-Acetyl-6,7-dihydroindolo[2,3-a]quinolizin-4(12H)-one monohydrate, (2), was synthesized to obtain the alkaloid flavopereirine, which inhibits cancer-producing cells (Giri et al., 1984, 1995). There were ca 90 hits in the Cambridge Structural Database (Version 5.19, April 2000, 215 403 entries; Allen, 1998) that contain the

tetracyclic skeleton of (1) and (2). However, none of these structures is closely related to the title compounds. Given the novelty of (1) and (2) and the fact that their conformation and packing motifs in the solid state will provide useful inputs for structural and medicinal studies currently ongoing in our laboratories, their crystallographic analysis was performed.
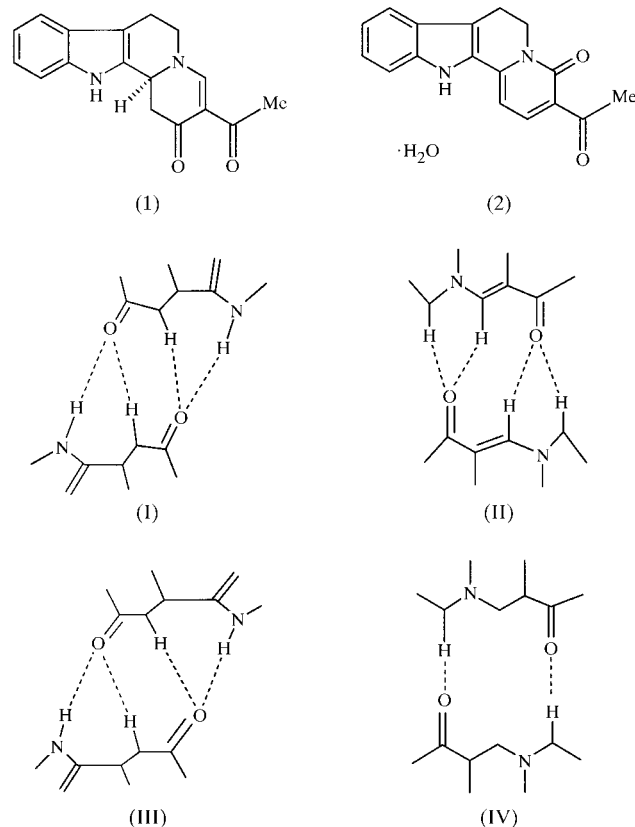
There are two symmetry-independent molecules (A and B) with similar conformations in the crystal structure of (1). Compound (2) crystallizes as a hydrate. The indole moiety is planar while the quinolizine portion adopts chair, half-chair, boat conformations in both compounds. The bond distances and angles in both molecules are in the expected ranges (Orpen et al., 1989). The molecular geometry and numbering of (1) and (2) are displayed in Figs. 1 and 2 (ORTEPII; Johnson, 1976).

The crystal packing in (1) consists of separate hydrogen-bonded layers of A and B molecules, which in turn are close-
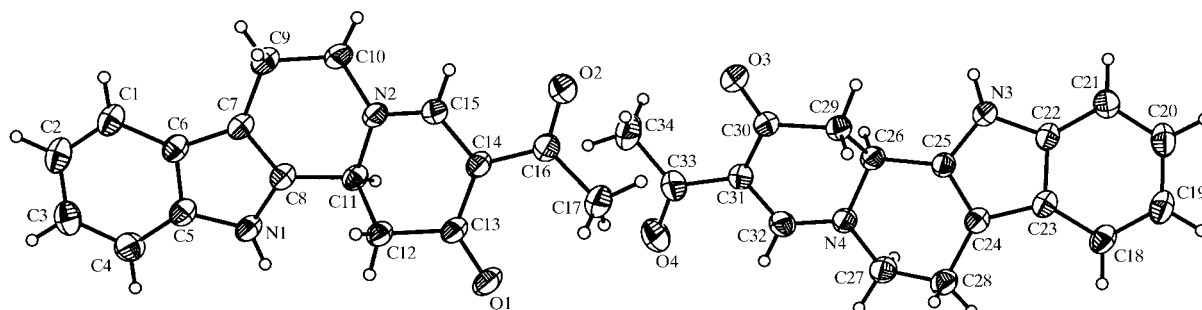


**Figure 1**
ORTEPII (Johnson, 1976) view of (1) with the atomic numbering; displacement ellipsoids are drawn at the 35% probability level for non-H atoms.

**Figure 2**
*ORTEP*II (Johnson, 1976) view of (2) with the atomic numbering; displacement ellipsoids are drawn at the 35% probability level for non-H atoms.

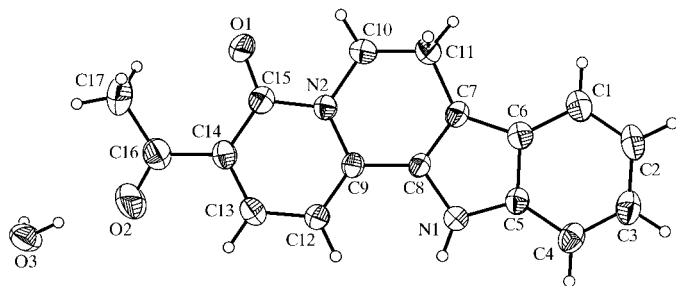packed through van der Waals interactions. The *A* and *B* molecules are in different conformations with maximum deviation in the C11–C15 ring portion and orientation of the acetyl group. The mean r.m.s. deviation in the overlay of skeletal atoms in the two molecules is 0.2616 Å. The *A* layer in (1) is shown in Fig. 3. Inversion-related molecules are connected by N—H···O and C—H···O hydrogen bonds through the multi-point recognition synthon I. C—H···O hydrogen bonds on the other side of the molecule extend through synthon II to form a molecular tape. The molecule being donor rich, both the carbonyl O atoms are bifurcated acceptors of N—H and C—H donors (N1—H1A···O1 2.04, C12—H12B···O1 2.72, C10—H10B···O2 2.36 and C15—H15···O2 2.48 Å). It may be noted that the C—H···O bond that is donating together with the N—H group to O1 (synthon I) is significantly longer than the two C—H···O bonds of synthon II that is solely formed with the weak interactions. Layer *B* (not shown) is constituted of synthons III and IV mediated through one strong and two weak hydrogen bonds (N3—H3B···O3 2.03, C29—H29B···O3 2.57 and C27—H27B···O4 2.34 Å). The presence of multiple molecules in the asymmetric unit of a crystal is often difficult to rationalize
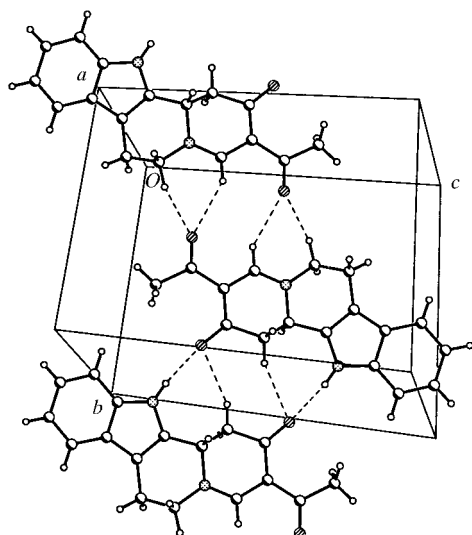
(Steiner, 2000). In the present case, it may be ascribed to different conformations and to distinct intermolecular synthons for each symmetry-independent molecule.

In hydrate (2), translation-related molecules are connected by four different types of hydrogen bonds to the water molecule (Fig. 4) [O3—H3C···O1 1.92 (6), O3—H3B···O2 1.86 (5), N1—H1A···O3 1.98 and C10—H10B···O3 2.76 Å]. In this structure, the ordered water molecule donates hydrogen bonds to different carbonyl groups of the heterocycle and accepts from N—H and C—H donors (Desiraju & Steiner, 1999). The water O atom is tetracoordinated, though the geometry is far from ideal (107.3, 100.3, 78.4, 120.5, 123.2 and 123.3°). Both these crystal structures illustrate the fortification of N—H···O and O—H···O networks by the weak C—H···O hydrogen bonds.
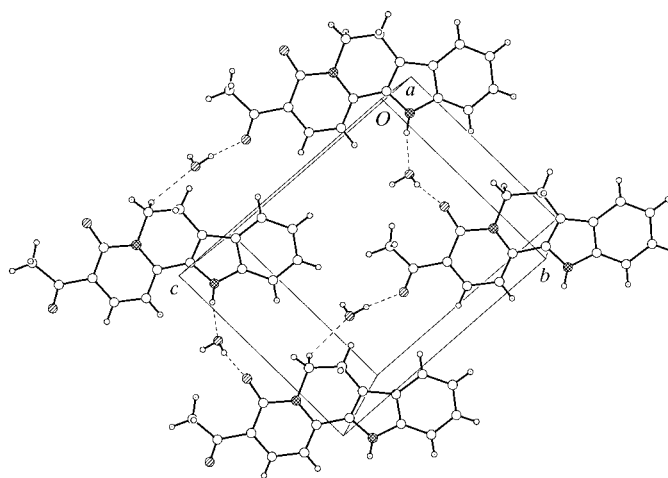


**Figure 4**
The structure of hydrate (2) viewed down [011]. O and N atoms are shaded differently. Hydrogen bonds are shown as dotted lines. Notice the crucial role of water in aggregating translation-related molecules of (2).

## Experimental

The syntheses of (1) and (2) have been reported previously (Giri *et al.*, 1984, 1995). Orange needle-shaped crystals of compounds (1) and (2) were obtained from 1:1 mixtures of methanol and chloroform.

### Compound (1)

*Crystal data*

| | |
|---|---|
| $C_{17}H_{16}N_2O_2$ | $Z = 4$ |
| $M_r = 280.32$ | $D_x = 1.340$ Mg m$^{-3}$ |
| Triclinic, $P\bar{1}$ | Mo $K\alpha$ radiation |
| $a = 8.169$ (16) Å | Cell parameters from 25 |
| $b = 12.841$ (3) Å | reflections |
| $c = 14.772$ (3) Å | $\theta = 9.12$–18.24° |
| $\alpha = 72.60$ (3)° | $\mu = 0.089$ mm$^{-1}$ |
| $\beta = 75.54$ (3)° | $T = 293$ (2) K |
| $\gamma = 72.64$ (3)° | Needle, orange |
| $V = 1389$ (3) Å$^3$ | $0.52 \times 0.48 \times 0.32$ mm |

*Data collection*

| | |
|---|---|
| CAD-4 diffractometer | $h = 0 \rightarrow 9$ |
| $\omega$ scans | $k = -14 \rightarrow 15$ |
| 4883 measured reflections | $l = -16 \rightarrow 17$ |
| 4883 independent reflections | 3 standard reflections |
| 3225 reflections with $I > 2\sigma(I)$ | every 100 reflections |
| $\theta_{max} = 25.00°$ | intensity decay: none |



**Figure 3**
Layered structure of *A* molecules in (1) viewed down [011]. O and N atoms are shaded differently. Hydrogen bonds are shown as dotted lines. Notice the centrosymmetric synthons I and II.

## Refinement

Refinement on $F^2$

$R[F^2 > 2\sigma(F^2)] = 0.047$

$wR(F^2) = 0.131$

$S = 1.072$

4883 reflections

379 parameters

H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0564P)^2 + 0.2875P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = 0.004$

$\Delta\rho_{max} = 0.20$ e Å$^{-3}$

$\Delta\rho_{min} = -0.22$ e Å$^{-3}$

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

| $D-H\cdots A$ | $D-H$ | $H\cdots A$ | $D\cdots A$ | $D-H\cdots A$ |
|---|---|---|---|---|
| N1—H1$A\cdots$O1$^i$ | 0.86 | 2.04 | 2.888 (2) | 167 |
| N3—H3$B\cdots$O3$^{ii}$ | 0.86 | 2.03 | 2.863 (3) | 162 |
| C10—H10$B\cdots$O2$^{iii}$ | 0.97 | 2.36 | 3.245 (3) | 151 |
| C12—H12$B\cdots$O1$^i$ | 0.97 | 2.72 | 3.594 (3) | 150 |
| C15—H15$A\cdots$O2$^{iii}$ | 0.93 | 2.48 | 3.265 (3) | 142 |
| C27—H27$B\cdots$O4$^{iv}$ | 0.97 | 2.34 | 3.191 (3) | 146 |
| C29—H29$B\cdots$O3$^{ii}$ | 0.97 | 2.57 | 3.410 (3) | 145 |

Symmetry codes: (i) $1-x, -y, 1-z$; (ii) $-x, 1-y, 2-z$; (iii) $-x, 1-y, 1-z$; (iv) $1-x, -y, 2-z$.

## Compound (2)

### Crystal data

$C_{17}H_{14}N_2O_2 \cdot H_2O$

$M_r = 296.32$

Triclinic, $P\bar{1}$

$a = 7.307$ (15) Å

$b = 9.405$ (2) Å

$c = 10.989$ (2) Å

$\alpha = 94.82$ (3)°

$\beta = 108.84$ (3)°

$\gamma = 90.96$ (3)°

$V = 712$ (2) Å$^3$

$Z = 2$

$D_x = 1.383$ Mg m$^{-3}$

Mo $K\alpha$ radiation

Cell parameters from 25 reflections

$\theta = 9.12–18.24°$

$\mu = 0.096$ mm$^{-1}$

$T = 293$ (2) K

Needle, orange

$0.48 \times 0.36 \times 0.28$ mm

### Data collection

CAD-4 diffractometer

$\omega$ scans

2490 measured reflections

2490 independent reflections

1072 reflections with $I > 2\sigma(I)$

$\theta_{max} = 24.97°$

$h = 0 \rightarrow 8$

$k = -11 \rightarrow 11$

$l = -13 \rightarrow 12$

3 standard reflections every 100 reflections intensity decay: none

### Refinement

Refinement on $F^2$

$R[F^2 > 2\sigma(F^2)] = 0.062$

$wR(F^2) = 0.117$

$S = 1.156$

2490 reflections

208 parameters

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0604P)^2]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} < 0.001$

$\Delta\rho_{max} = 0.25$ e Å$^{-3}$

$\Delta\rho_{min} = -0.20$ e Å$^{-3}$

Extinction correction: $SHELXL$97 (Sheldrick, 1997)

Extinction coefficient: 0.038 (4)

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

| $D-H\cdots A$ | $D-H$ | $H\cdots A$ | $D\cdots A$ | $D-H\cdots A$ |
|---|---|---|---|---|
| N1—H1$B\cdots$O3$^i$ | 0.86 | 1.98 | 2.819 (4) | 164 |
| O3—H3$C\cdots$O1$^{ii}$ | 0.83 (6) | 1.92 (6) | 2.735 (4) | 168 (6) |
| O3—H3$B\cdots$O2 | 0.93 (5) | 1.86 (5) | 2.783 (4) | 173 (4) |
| C10—H10$B\cdots$O3$^{iii}$ | 0.97 | 2.76 | 3.522 (6) | 136 |

Symmetry codes: (i) $1-x, 2-y, 1-z$; (ii) $1-x, 1-y, 1-z$; (iii) $x, y, z-1$.

In both structures, C—H distances were constrained to distances in the range 0.93–0.98 Å, depending on C-atom type, with $U_{iso} = 1.2U_{eq}$ of the C atom (1.5 for methyl). N—H distances were constrained to be 0.86 Å, with $U_{iso} = 1.2U_{eq}$. Water H atoms in (2) were refined isotropically.

For both compounds, data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *Xtal*3.5 (Hall *et al.*, 1995); program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLUTON-(C)* (Spek, 1979–1997); software used to prepare material for publication: *SHELXL*97.

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