

1'-Methylcyclooctane-1-spiro-3'-pyrrolidine-2'-spiro-3''-indoline-2,2''-dione and 1,1'-dimethylpiperidine-3-spiro-3'-pyrrolidine-2'-spiro-3''-indoline-2'',4-dione

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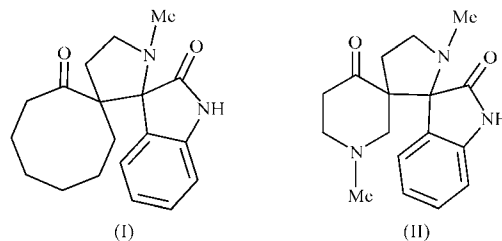
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In both title compounds, $C_{19}H_{24}N_2O_2$, (I), and $C_{17}H_{21}N_3O_2$, (II), respectively, there are two molecules in the asymmetric unit and the pyrrolidine rings adopt envelope conformations. The conformations of the cyclooctane [in (I)] and 1-methylpiperidone [in (II)] rings are boat–chair and chair, respectively. The indolin-2-one group is almost perpendicular to the pyrrolidine ring. Intermolecular $C-H\cdots O$, $N-H\cdots O$ and $N-H\cdots N$ interactions provide stability to the structures.

Comment

Pharmacologically active compounds and many alkaloids have a substituted pyrrolidine substructure. 1,3-Dipolar cycloaddition of azomethine ylides with diverse dipolarophiles represents one of the most versatile approaches for the construction of highly functionalized five-membered ring heterocycles (Padwa, 1984). The spiro ring systems are of great interest as they exhibit a wide range of biological activities (Kobayashi *et al.*, 1991; James *et al.*, 1991). Spiro-pyrrolidines have attracted much attention as potential anti-leukaemic and anticonvulsant agents (Abou Gharbia *et al.*, 1979), with antiviral (Lundahl *et al.*, 1972) and local anaesthetic (Kornett & Thio, 1976) activities. Isatin and its derivatives have interesting biological activities and hence are widely used as precursors of many natural products (Saxton, 1983; Cui *et al.*, 1996; Xue *et al.*, 2000). Spiro-pyrrolidine–indolin-2-one ring systems are also found in a number of alkaloids of biological importance (Hilton *et al.*, 2000). Our interest in preparing pharmacologically active pyrrolidines led us to the title compounds, (I) and (II), and we have undertaken X-ray crystal structure determinations of these compounds in order to establish their conformations.

The asymmetric units of (I) and (II) contain two independent molecules; each pair has almost identical geometry (Figs. 1 and 2). In both (I) and (II), the bond lengths and angles show



normal values and agree with each other (Allen *et al.*, 1987), except for the bonds at the spiro junctions. The sums of the angles at atoms N11 and N21 of the pyrrolidine rings [340.4 (2) and 341.5 (2)°, respectively, in (I), and 336.8 (2) and 336.1 (3)°, respectively, in (II)] are in accordance with sp^3 -hybridization (Beddoes *et al.*, 1986; Kumar *et al.*, 2006; Jeyabharathi *et al.*, 2001), and the sums of the angles at atoms N12 and N22 of the

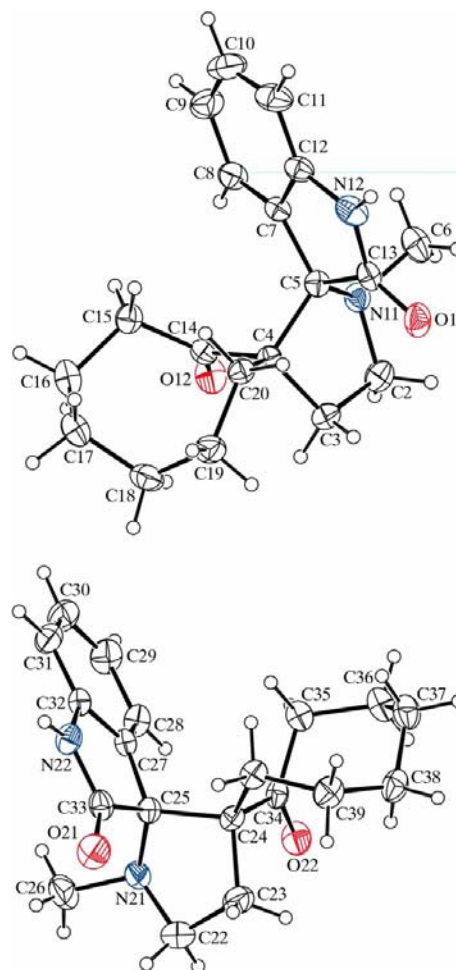


Figure 1

The two independent molecules of the asymmetric unit of (I), showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

indolin-2-one moiety [359.6 (2) and 359.9 (2)°, respectively, in (I), and 360 (2) and 360 (3)°, respectively, in (II)] are in accordance with sp^2 -hybridization (Govind *et al.*, 2004; Kumar *et al.*, 2006; Jeyabharathi *et al.*, 2001). In (I) and (II), the bond lengths within the indolin-2-one moiety match those in similar structures (Kumar *et al.*, 2006; Jeyabharathi *et al.*, 2001), but the C—C and C—N bonds within the pyrrolidine ring are shorter (Table 6). The mean value of the Csp^3 — Csp^3 bond lengths in cyclooctane (I) [1.528 (3) Å] is comparable with those in compounds with similar configurations [1.533 (2) (Latvala *et al.*, 1993), 1.523 (5) (Hesse *et al.*, 1993) and 1.525 (5) Å (Jacobsen *et al.*, 2002)].

In compounds (I) and (II), the five-membered pyrrolidine rings have envelope conformations with flap atoms C5 and C25 in (I), and N11 and N21 in (II). Puckering parameters (q_2 and φ_2 ; Cremer & Pople, 1975) and the smallest displacement asymmetry parameters (Δ ; Nardelli, 1983) are shown in Table 5. The dihedral angles formed by the mean planes C4/

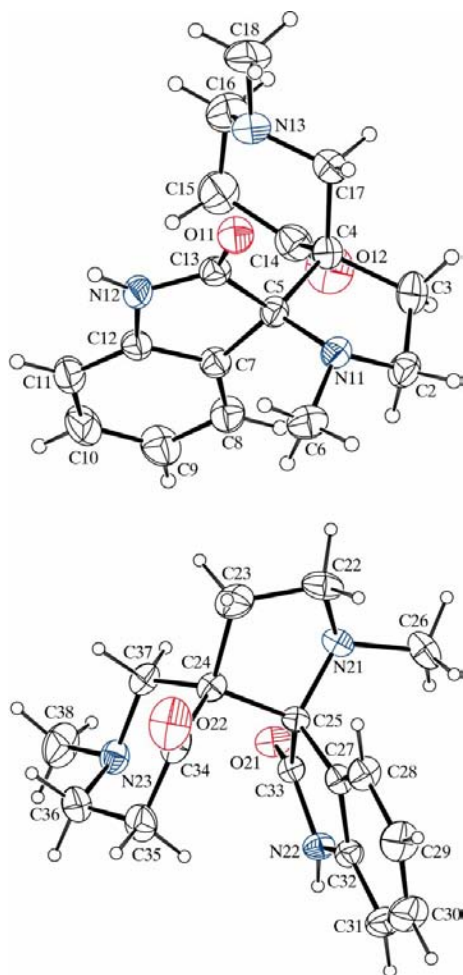


Figure 2

The two independent molecules of the asymmetric unit of (II), showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 30% probability level for the upper molecule and at the 20% probability level for the lower molecule, for clarity. H atoms are shown as small spheres of arbitrary radii.

C14/C18/C19 with C20/C19/C4 and C14/C15/C17/C18 with C15/C16/C17 in the cyclooctane substituted at C4 are 55.29 (2) and 57.59 (4)°, respectively; similar values are observed for the cyclooctane substituted at C24. These values are different from those in similar structures [60.09 (2) and 49.22 (4)°; Kumar *et al.*, 2006]. The chair conformation of the 1-methylpiperidone ring in (II) is evident from the torsion angles (Table 3).

In the indolin-2-one systems, the benzene and pyrrole rings are individually planar and make dihedral angles of 6.2 (2) and 6.7 (1)° in (I) and 4.2 (1) and 1.2 (1)° in (II), respectively, while atoms O11 and O21 deviate from the pyrrole ring of the indolin-2-one system by -0.145 (4) and -0.192 (4) Å, respectively, in (I), and by -0.220 (4) and -0.232 (4) Å, respectively, in (II), because of the different interactions in which these O atoms are involved (Tables 2 and 4). The indolin-2-one systems are in a nearly perpendicular configuration with the respective to the pyrrolidine rings, as can be seen from the dihedral angles [81.7 (1) and 80.7 (1)° in (I), and 87.3 (1) and 89.1 (1)° in (II)]. In both compounds, in the benzene ring of the indole system, the endocyclic angles at C7, C11, C27 and C31 are contracted, while those at C10, C12, C30 and C32 are expanded (Tables 1 and 3). This may be due to the effect of the fusion of the smaller pyrrole ring to the six-membered benzene ring, with the strain taken up by angular distortion rather than by bond-length distortions (Sethu Sankar *et al.*, 2002). Compounds (I) and (II) are in centrosymmetric space groups, so there must be equal numbers of opposite enantiomers; they contain chiral atoms C4, C5, C24 and C25. Of the four possible stereoisomers, those present in compound (I) are *S,S* and its enantiomer *R,R*, and in compound (II) *S,R* and its enantiomer *R,S*.

The structure of (I) is stabilized by C—H...O and N—H...O interactions. The C11—H11...O11 and N12—H12...O21 interactions (Table 2) generate primary graph-set

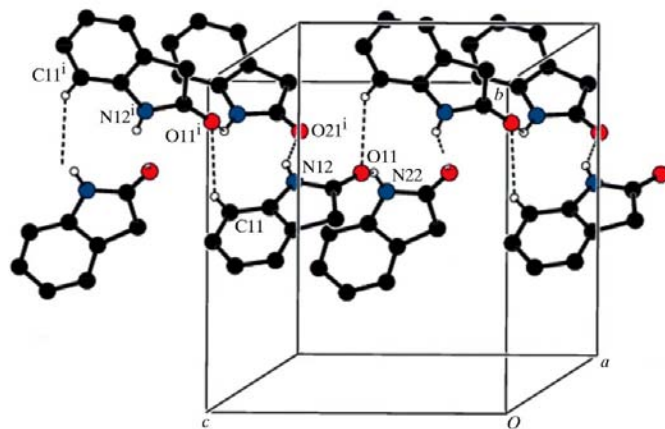
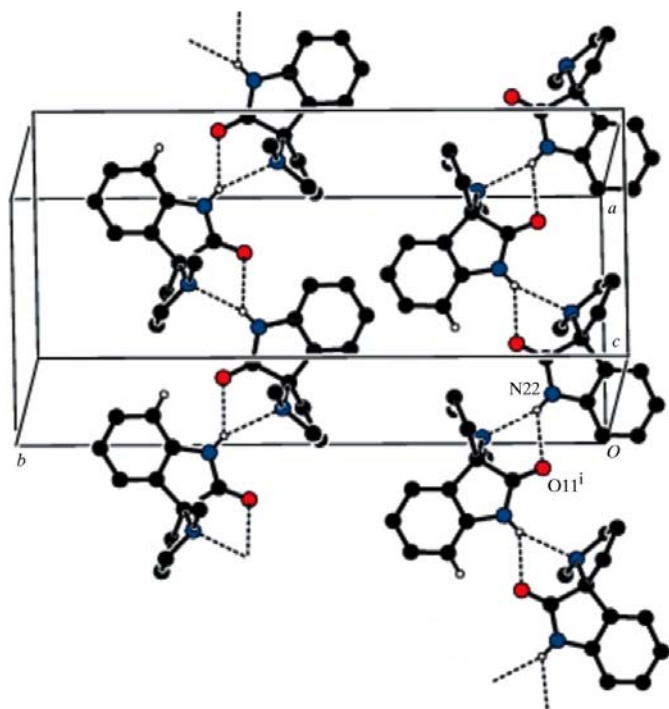


Figure 3

A partial packing view showing the intermolecular N—H...O and C—H...O interactions (dashed lines) in compound (I). H atoms and some ring atoms not involved in hydrogen-bonding interactions have been omitted for clarity. [Symmetry code: (i) $x, -y + \frac{3}{2}, z + \frac{1}{2}$]


Figure 4

A partial packing view showing the intermolecular N—H...O and N—H...N interactions (dashed lines) generating an $R_1^2(5)$ graph-set motif in compound (II). H atoms and some ring atoms not involved in hydrogen-bonding interactions have been omitted for clarity. [Symmetry code: (i) $x - 1, y, z$.]

motifs (Etter *et al.*, 1990) of $C_1^1(6)$ and $C_2^2(8)$ and form a zigzag linear double chain parallel to the c axis (Fig. 3). These two interactions, along with an intermolecular N22—H22...O11 interaction, generate a secondary $R_3^2(10)$ graph-set motif. In addition to this, a weaker intermolecular C29—H29...O22 (Table 2) interaction generates a $C_1^1(8)$ graph-set motif.

In compound (II), the intermolecular N22—H22...O11 and N22—H22...N11 (Table 4 and Fig. 4) bifurcated interactions together generate an $R_1^2(5)$ graph-set motif. This, along with some weak interactions, pack the molecules to form a linear chain running along the a axis. Adjacent chains are only interconnected by means of van der Waals interactions.

Experimental

For the preparation of compound (I), a mixture of isatin (1 mmol), sarcosine (2 mmol) and cyclooctanone (1 mmol) in methanol (20 ml) was refluxed in a water bath for 6 h. After completion of the reaction (monitored by thin-layer chromatography), the excess solvent was removed under vacuum and the residue was subjected to flash column chromatography using petroleum ether–ethyl acetate (8:2 *v/v*) as eluant (yield 46%; m.p. 448–449 K). For the preparation of (II), a mixture of isatin (1 mmol), sarcosine (2 mmol) and 1-methyltetrahydropyridin-4(1*H*)-one (1 mmol) in methanol (20 ml) was refluxed in a water bath for 6 h. After completion of the reaction (monitored by thin-layer chromatography), the excess solvent was removed under vacuum and the residue was subjected to flash column chromatography using petroleum ether–ethyl acetate (8:2 *v/v*) as eluant (yield 57%; m.p. 403–404 K).

Compound (I)

Crystal data

$C_{19}H_{24}N_2O_2$
 $M_r = 312.40$
 Monoclinic, $P2_1/c$
 $a = 29.0670$ (11) Å
 $b = 11.2560$ (9) Å
 $c = 10.1480$ (7) Å
 $\beta = 96.580$ (5)°

$V = 3298.3$ (4) Å³
 $Z = 8$
 Mo $K\alpha$ radiation
 $\mu = 0.08$ mm⁻¹
 $T = 293$ (2) K
 $0.19 \times 0.15 \times 0.11$ mm

Data collection

Nonius MACH3 four-circle diffractometer
 Absorption correction: ψ scan (North *et al.*, 1968)
 $T_{\min} = 0.982$, $T_{\max} = 0.985$
 6828 measured reflections

5781 independent reflections
 3081 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.042$
 3 standard reflections
 frequency: 60 min
 intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.043$
 $wR(F^2) = 0.120$
 $S = 1.00$
 5781 reflections
 450 parameters

H atoms treated by a mixture of independent and constrained refinement
 $\Delta\rho_{\max} = 0.19$ e Å⁻³
 $\Delta\rho_{\min} = -0.18$ e Å⁻³

Table 1

Selected geometric parameters (Å, °) for (I).

C2—N11	1.462 (3)	C22—N21	1.454 (3)
C5—N11	1.455 (3)	C25—N21	1.453 (3)
C6—N11	1.461 (3)	C26—N21	1.451 (3)
C12—C7—C8	119.7 (2)	C31—C32—C27	122.4 (2)
C9—C10—C11	122.1 (3)	C5—N11—C6	116.7 (2)
C12—C11—C10	117.2 (3)	C5—N11—C2	108.78 (19)
C11—C12—C7	122.0 (3)	C6—N11—C2	114.9 (2)
C28—C27—C32	119.1 (2)	C26—N21—C25	117.2 (2)
C31—C30—C29	121.4 (3)	C26—N21—C22	115.0 (2)
C32—C31—C30	117.6 (3)	C25—N21—C22	109.3 (2)

Table 2

Hydrogen-bond geometry (Å, °) for (I).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C11—H11...O11 ⁱ	0.93	2.60	3.320 (3)	135
N12—H12...O21 ⁱ	0.86	2.29	3.041 (3)	145
C29—H29...O22 ⁱⁱ	0.93	2.58	3.499 (3)	170
N22—H22...O11	0.86	2.28	2.829 (3)	122

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

Compound (II)

Crystal data

$C_{17}H_{21}N_3O_2$
 $M_r = 299.37$
 Monoclinic, $P2_1/n$
 $a = 9.5194$ (7) Å
 $b = 21.8847$ (14) Å
 $c = 15.5413$ (11) Å
 $\beta = 93.86$ (4)°

$V = 3230.3$ (4) Å³
 $Z = 8$
 Mo $K\alpha$ radiation
 $\mu = 0.08$ mm⁻¹
 $T = 293$ (2) K
 $0.19 \times 0.16 \times 0.11$ mm

Data collection

Nonius MACH3 four-circle diffractometer
 Absorption correction: ψ scan (North *et al.*, 1968)
 $T_{\min} = 0.985$, $T_{\max} = 0.991$
 6392 measured reflections

5685 independent reflections
 2327 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.025$
 3 standard reflections
 frequency: 60 min
 intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.048$

$wR(F^2) = 0.134$

$S = 0.97$

5685 reflections

402 parameters

H-atom parameters constrained

$\Delta\rho_{\max} = 0.14 \text{ e } \text{\AA}^{-3}$

$\Delta\rho_{\min} = -0.15 \text{ e } \text{\AA}^{-3}$

Table 3Selected geometric parameters (\AA , $^\circ$) for (II).

C2–N11	1.457 (3)	C22–N21	1.465 (4)
C5–N11	1.464 (3)	C25–N21	1.469 (3)
C6–N11	1.464 (3)	C26–N21	1.460 (4)
C12–C7–C8	119.1 (3)	C31–C32–C27	123.2 (3)
C9–C10–C11	121.4 (3)	C2–N11–C5	106.7 (2)
C12–C11–C10	117.5 (3)	C2–N11–C6	115.0 (2)
C11–C12–C7	122.3 (3)	C5–N11–C6	115.2 (2)
C28–C27–C32	118.9 (3)	C26–N21–C22	114.1 (3)
C29–C30–C31	122.0 (4)	C26–N21–C25	115.5 (2)
C32–C31–C30	116.3 (4)	C22–N21–C25	106.4 (2)
C17–C4–C14–C15	–48.7 (4)	C34–C35–C36–N23	57.9 (4)
C4–C14–C15–C16	48.8 (4)	C34–C24–C37–N23	–53.5 (3)
C14–C15–C16–N13	–52.7 (4)	C4–C17–N13–C16	–66.7 (4)
C14–C4–C17–N13	56.0 (3)	C15–C16–N13–C17	62.9 (4)
C37–C24–C34–C35	51.2 (4)	C24–C37–N23–C36	62.9 (3)
C24–C34–C35–C36	–55.5 (4)	C35–C36–N23–C37	–62.6 (4)

Table 4Hydrogen-bond geometry (\AA , $^\circ$) for (II).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N22–H22 \cdots O11 ⁱ	0.86	2.49	3.144 (3)	133
N22–H22 \cdots N11 ⁱ	0.86	2.27	3.066 (3)	153
N12–H12 \cdots O21	0.86	2.30	3.008 (3)	140
N12–H12 \cdots N21	0.86	2.47	3.198 (3)	143
C11–H11 \cdots O21	0.93	2.44	3.173 (4)	136

Symmetry code: (i) $x - 1, y, z$.**Table 5**Pyrrolidine puckering parameters in compounds (I) and (II) (q_2 in \AA , φ_2 in $^\circ$ and Δ in \AA); see *Comment* for discussion.

Parameter	Molecule 1 of (I)	Molecule 2 of (I)	Molecule 1 of (II)	Molecule 2 of (II)
q_2	0.401 (3)	0.381 (3)	0.399 (3)	0.398 (3)
φ_2	136.8 (4)	–40.2 (5)	–177.8 (4)	–6.4 (5)
$\Delta_2(C2)$	0.048 (1)			
$\Delta_s(C5)$	0.036 (1)			
$\Delta_2(C22)$		0.056 (1)		
$\Delta_s(C25)$		0.019 (2)		
$\Delta_2(C3)$			0.084 (1)	
$\Delta_s(N11)$			0.015 (2)	
$\Delta_2(C23)$				0.050 (1)
$\Delta_s(N21)$				0.033 (2)

H atoms bound to atoms C15, C20, C35 and C40 of compound (I) were found in a difference Fourier map and their positional and isotropic displacement parameters were refined. The remaining H atoms were placed in calculated positions and allowed to ride on their parent atoms, with $C-H = 0.93\text{--}0.97 \text{ \AA}$ and $N-H = 0.86 \text{ \AA}$, and with $U_{\text{iso}} = 1.2U_{\text{eq}}(C,N)$ for CH_2 , NH and CH groups, and $1.5U_{\text{eq}}(C)$ for CH_3 groups.

Table 6Selected bond lengths (\AA) in compounds (I), (III) (Kumar *et al.*, 2006) and the two molecules of (IV) (Jeyabharathi *et al.*, 2001).

Bond	(I)	(III)	Molecule A in (IV)	Molecule B in (IV)
C5–N11	1.455 (3)	1.470 (2)	1.460 (3)	1.472 (4)
C5–C4	1.579 (3)	1.608 (2)	1.596 (3)	1.588 (4)
C4–C3	1.545 (3)	1.573 (2)	1.579 (3)	1.572 (3)
C5–C13	1.555 (3)	1.573 (2)	1.571 (4)	1.572 (3)
C13–O11	1.227 (3)	1.218 (2)	1.213 (4)	1.225 (3)
C13–N12	1.352 (4)	1.354 (2)	1.360 (3)	1.343 (4)
C12–N12	1.407 (3)	1.399 (2)	1.397 (3)	1.397 (3)
C12–C11	1.376 (4)	1.379 (3)	1.377 (3)	1.374 (3)
C10–C11	1.380 (4)	1.381 (3)	1.381 (2)	1.377 (3)
C10–C9	1.377 (5)	1.379 (4)	1.378 (3)	1.375 (3)
C9–C8	1.384 (4)	1.394 (3)	1.386 (3)	1.395 (3)
C8–C7	1.385 (3)	1.375 (3)	1.385 (3)	1.374 (3)
C5–C7	1.507 (3)	1.518 (2)	1.523 (3)	1.518 (4)
C12–C7	1.381 (4)	1.394 (3)	1.398 (4)	1.400 (3)

For both compounds, data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *XCAD4* (Harms & Wocadlo, 1996); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); 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: GA3060). Services for accessing these data are described at the back of the journal.

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