organic compounds

Three tetrahydroisoquinolinedione derivatives

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N-(2-Chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione, $C_{16}H_{12}ClNO_2$, crystallizes in $P2_1/n$ with three crystallographically independent molecules in the asymmetric unit, which differ slightly in conformation, N-(2-bromo-4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione, $C_{16}H_{12}BrNO_2$, crystallizes in $P2_1/n$ with one molecule in the asymmetric unit and N-(2,3-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione, $C_{15}H_9Cl_2NO_2$, crystallizes in $P2_1/c$ with one molecule in the asymmetric unit. In all three structures, the heterocyclic rings adopt approximately planar conformations. The pyridine rings are orthogonal to the substituted phenyl rings. In all three structures, the crystal packing is stabilized by intermolecular C—H···O hydrogen bonds.

Comment

Isoquinoline is a well known ligand that has been used in studies of the formation of various adducts of group IVA
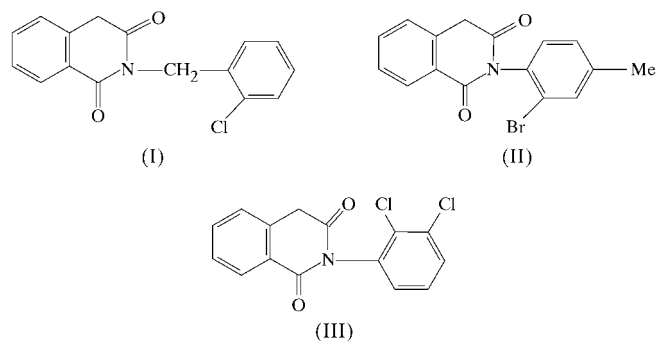
halides (Miller & Onyszchuk, 1967). Tetrahydroisoquinolines represent a class of biologically active phenyl ethylamines (Brzezinska, 1994), and these compounds are of great interest due to their biological and pharmacological properties. They

are also useful as key intermediates in the synthesis of isoquinoline alkaloids, such as cherylline and latifine (Honda et al., 2001). Isoquinoline fused-ring systems, such as pyrroloisoquinoline, show valuable pharmacological activity, e.g. antileukemic (Anderson et al., 1998), muscaricinic, agonostic (Loesel et al., 1987) and antidepressant properties (Elwan et al., 1996). Their marked antidepressant, tranquilizing (Sulkowski & Willie, 1969), analgesic and sedative (Hamamato & Kajiwara, 1966) activity renders 1(2H)-isoquinolinones an important class of compounds. These compounds have also been used as intermediates in the synthesis of a number of naturally occurring alkaloids (Kobayashi, 1950; Walker et al., 1964). A variety of 1,2,3,4-tetrahydroisoquinoline derivatives have been studied extensively in the past in order to elucidate their antidepressant-like activity. The title compounds, N-(2-chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione, (I), N-(2-bromo-4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione, (II), and N-(2,3-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione, (III), are of interest as intermediates in the synthesis of
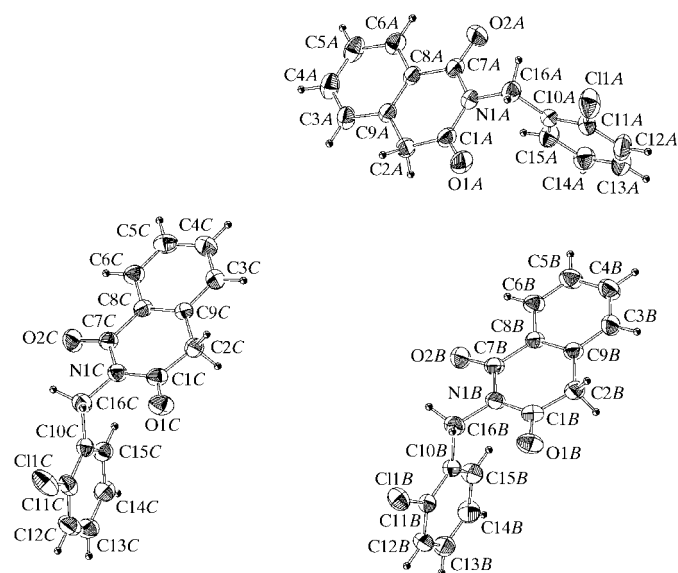

Figure 1
A view of the three independent molecules of (I) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.
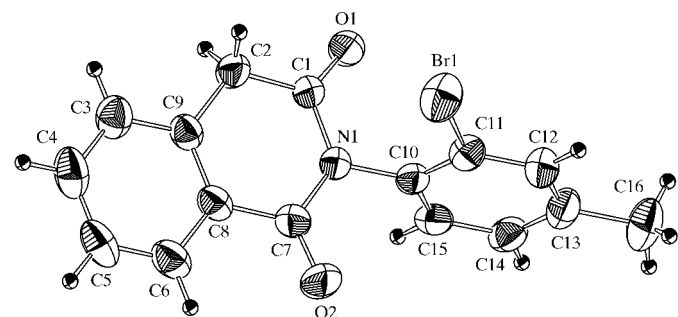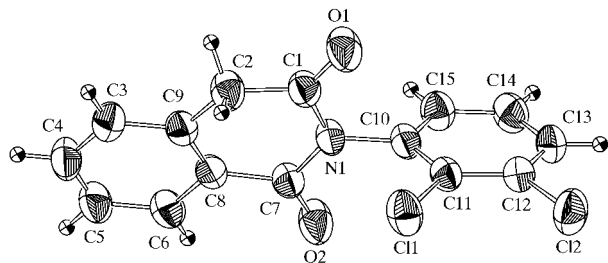

Figure 2
A view of the molecular structure of (II) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

Figure 3
A view of the molecular structure of (III) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

alkaloids such as corgoine (Kametani *et al.*, 1975) and sendaverine (Kametani *et al.*, 1979).

The structures in the present study consist of an isoquinoline moiety and a substituted phenyl ring. Structure (I) contains three molecules in the asymmetric unit, designated (I*A*), (I*B*) and (I*C*) (Fig. 1). Structures (II) (Fig. 2) and (III) (Fig. 3) contain one molecule per asymmetric unit.

The C=O bond lengths in all three structures, and bond length Csp^2—Br in (II) and Csp^2—Cl in (III), are comparable with the values found in a search of the Cambridge Structural Database (2001 Release; Allen *et al.*, 1987). The bond distances and angles of the isoquinoline moiety in these structures are in good agreement with the values reported for other 1,2,3,4-tetrahydroisoquinoline derivatives (Bellard *et al.*, 1982; Płvaczyk *et al.*, 1984). Selected geometric parameters for (I), (II) and (III) are given in Tables 1, 3 and 5, respectively.

In (I), the phenyl rings of the benzyl groups are twisted with respect to the isoquinoline system. The torsion angles around the N1—C16 and C16—C10 single bonds are almost equal for (I*B*) and (I*C*), but are different for (I*A*). This shows that the orientation of the benzyl group in (I*A*) is different from that in (I*B*) and (I*C*).

The isoquinoline moiety is slightly folded about the line passing through atoms C8 and C9, and the dihedral angle between the two halves ranges from 2.2 (1) to 3.7 (1)°. The phenyl ring in all three structures is orthogonal to the isoquinoline moiety, forming a dihedral angle of 87.6 (1)° in (I*A*), 85.7 (1)° in (I*B*), 84.5 (1)° in (I*C*), 76.6 (1)° in (II) and 69.9 (1)° in (III). It can be seen that the value in (III) is lower than that in (II), and this is probably a result of the heavier substituents on the phenyl ring of (II).

The dihedral angle between the least-squares planes of the substituted phenyl and benzo-fused rings is 88.2 (1)° for (I*A*), 85.2 (1)° for (I*B*), 84.4 (1)° for (I*C*), 75.6 (0)° for (II) and 69.3 (1)° for (III). The deviations of atoms O1 and O2 from the mean planes defined by atoms N1, C1, C2, C9, C8 and C7 are −0.098 (2) and 0.040 (1) Å, respectively, in (I*A*), −0.084 (3) and 0.071 (3) Å, respectively, in (I*B*), −0.108 (3) and 0.086 (3) Å, respectively, in (I*C*), −0.072 and 0.016 Å, respectively, in (II), and −0.237 (2) and 0.149 (2) Å, respectively, in (III).

In all three structures, the bond lengths and angles, the dihedral angles between the two halves of the isoquinoline moiety, and the dihedral angles between the isoquinoline

moiety and the phenyl ring are comparable with those observed in similar structures (Ammon & Wheeler, 1974).

In addition to normal van der Waals interactions, the crystal packing in all three structures is stabilized by intermolecular C—H···O hydrogen bonds. In (I), five intermolecular C—H···O hydrogen bonds occur, with H···O distances less than the sum of the van der Waals radii (Bondi, 1964). In this structure, the symmetry-related isoquinoline molecules are arranged in a head-to-head manner and are alternately parallel to each other. This type of stacking is also found in 1,4-dihydroisoquinoline (Minter *et al.*, 1996). In (II), an intermolecular C—H···O hydrogen bond between atoms C5 and O1 stabilizes the crystal packing. The interesting feature of the crystal structure of (III) is that a single C—H···O hydrogen bond links the molecules into cyclic centrosymmetric dimers formed by an $R_2^2(16)$ ring system. This is a layered structure, with layers parallel to the *ac* plane. Details of the hydrogen-bond geometry in (I), (II) and (III) are given in Tables 2, 4 and 6, respectively.

The most remarkable feature of the crystal structure of (II) is the existence of a short intermolecular halogen···O contact, Br1···O2^i 3.012 (3) Å [symmetry code: (i) $\frac{1}{2} - x$, $y + \frac{1}{2}$, $\frac{3}{2} - z$], between the phenyl ring and the isoquinoline moiety.

Experimental

The title compounds were synthesized from homophthalic acid and the corresponding substituted aromatic amines. The yield was 75% (m.p. 435–437 K) for (I), 71% (m.p. 395–397 K) for (II) and 68% (m.p. 471–473 K) for (III). The compounds were dissolved in a mixture of ethyl acetate and hexane (4:1). Slow evaporation of the solvent at room temperature produced crystals from which the experimental samples were obtained.

Compound (I)

Crystal data

$C_{16}H_{12}ClNO_2$	$D_x = 1.410$ Mg m^{-3}
$M_r = 285.72$	Cu $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 25
$a = 7.7922$ (14) Å	reflections
$b = 21.538$ (4) Å	$\theta = 20–30°$
$c = 24.351$ (5) Å	$\mu = 2.52$ mm^{-1}
$\beta = 98.92$ (2)°	$T = 293$ K
$V = 4037.4$ (13) Å^3	Prism, colourless
$Z = 12$	$0.50 \times 0.41 \times 0.20$ mm

Table 1
Selected geometric parameters (Å, °) for (I).

Cl1*A*—C11*A*	1.743 (4)	N1*B*—C16*B*	1.472 (4)
N1*A*—C1*A*	1.385 (4)	O1*B*—C1*B*	1.210 (4)
N1*A*—C7*A*	1.396 (4)	O2*B*—C7*B*	1.218 (4)
N1*A*—C16*A*	1.462 (4)	Cl1*C*—C11*C*	1.751 (4)
O1*A*—C1*A*	1.213 (4)	N1*C*—C1*C*	1.391 (4)
O2*A*—C7*A*	1.212 (4)	N1*C*—C7*C*	1.394 (4)
Cl1*B*—C11*B*	1.742 (3)	N1*C*—C16*C*	1.459 (4)
N1*B*—C7*B*	1.388 (4)	O1*C*—C1*C*	1.205 (4)
N1*B*—C1*B*	1.394 (4)	O2*C*—C7*C*	1.209 (4)

C1*A*—N1*A*—C16*A*—C10*A*	80.2 (4)	C15*A*—C10*A*—C16*A*—N1*A*	19.3 (5)
C1*B*—N1*B*—C16*B*—C10*B*	−81.8 (4)	C15*B*—C10*B*—C16*B*—N1*B*	−29.8 (5)
C1*C*—N1*C*—C16*C*—C10*C*	−83.1 (4)	C15*C*—C10*C*—C16*C*—N1*C*	−30.8 (4)

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
C5A—H5A$\cdots$O1C^i	0.95	2.45	3.294 (4)	148
C5C—H5C$\cdots$O1B^{ii}	0.95	2.51	3.238 (5)	133
C2A—H2A2$\cdots$O1C^{iii}	0.99	2.46	3.292 (5)	141
C2B—H2B2$\cdots$O1B^{iv}	0.99	2.56	3.391 (5)	141
C5B—H5B$\cdots$O1A^v	0.95	2.59	3.265 (5)	129

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

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: empirical via ψ scans (North et al., 1968)
$T_{min} = 0.366$, $T_{max} = 0.633$
7916 measured reflections
7348 independent reflections
5013 reflections with $I > 2\sigma(I)$

$R_{int} = 0.039$
$\theta_{max} = 68.2°$
$h = 0 \rightarrow 9$
$k = 0 \rightarrow 25$
$l = -29 \rightarrow 28$
3 standard reflections
every 200 reflections
intensity decay: 0.6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.065$
$wR(F^2) = 0.200$
$S = 1.06$
7348 reflections
542 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.1067P)^2 + 1.2945P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.38$ e Å^{-3}
$\Delta\rho_{min} = -0.34$ e Å^{-3}
Extinction correction: SHELXL97 (Sheldrick, 1997)
Extinction coefficient: 0.0016 (2)

Compound (II)

Crystal data

$C_{16}H_{12}BrNO_2$
$M_r = 330.18$
Monoclinic, $P2_1/n$
$a = 15.847$ (2) Å
$b = 7.9190$ (7) Å
$c = 11.0602$ (11) Å
$\beta = 94.750$ (9)°
$V = 1383.2$ (3) Å^3
$Z = 4$

$D_x = 1.586$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 5.0-10.2°$
$\mu = 2.97$ mm^{-1}
$T = 293$ (2) K
Prism, colourless
$0.35 \times 0.30 \times 0.30$ mm

Table 3
Selected geometric parameters (Å, °) for (II).

Br1—C11	1.881 (4)	N1—C10	1.431 (4)
N1—C1	1.393 (4)	O1—C1	1.200 (4)
N1—C7	1.407 (5)	O2—C7	1.198 (4)
C1—N1—C10—C15	−102.7 (4)		

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
C6—H6$\cdots$O2	0.93	2.53	2.808 (5)	98
C5—H5$\cdots$O1^i	0.93	2.61	3.451 (5)	151

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

Data collection

Enraf–Nonius FR-590 diffractometer
Non-profiled $\omega/2\theta$ scans
2554 measured reflections
2421 independent reflections
1818 reflections with $I > 2\sigma(I)$
$R_{int} = 0.019$
$\theta_{max} = 25°$

$h = -18 \rightarrow 18$
$k = 0 \rightarrow 9$
$l = 0 \rightarrow 13$
3 standard reflections
every 100 reflections
frequency: 120 min
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.042$
$wR(F^2) = 0.126$
$S = 1.02$
2421 reflections
182 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0839P)^2 + 0.3218P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.002$
$\Delta\rho_{max} = 0.59$ e Å^{-3}
$\Delta\rho_{min} = -0.83$ e Å^{-3}

Compound (III)

Crystal data

$C_{15}H_9Cl_2NO_2$
$M_r = 306.13$
Monoclinic, $P2_1/c$
$a = 15.6702$ (8) Å
$b = 6.1560$ (5) Å
$c = 14.5889$ (7) Å
$\beta = 112.236$ (4)°
$V = 1302.67$ (14) Å^3
$Z = 4$

$D_x = 1.561$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 6.2-10.3°$
$\mu = 0.50$ mm^{-1}
$T = 293$ (2) K
Prism, colourless
$0.25 \times 0.25 \times 0.20$ mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Non-profiled $\omega/2\theta$ scans
Absorption correction: empirical via ψ scan (North et al., 1968)
$T_{min} = 0.886$, $T_{max} = 0.907$
2391 measured reflections
2287 independent reflections
1872 reflections with $I > 2\sigma(I)$

$R_{int} = 0.015$
$\theta_{max} = 25°$
$h = -18 \rightarrow 17$
$k = 0 \rightarrow 7$
$l = 0 \rightarrow 17$
3 standard reflections
every 100 reflections
frequency: 120 min
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.036$
$wR(F^2) = 0.156$
$S = 1.01$
2287 reflections
181 parameters

H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.128P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.24$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}

Table 5
Selected geometric parameters (Å, °) for (III).

Cl1—C11	1.722 (2)	N1—C10	1.441 (3)
Cl2—C12	1.727 (3)	O1—C1	1.203 (3)
N1—C1	1.398 (3)	O2—C7	1.207 (3)
N1—C7	1.403 (3)		
C1—N1—C10—C11	74.0 (3)		

Table 6
Hydrogen-bonding geometry (Å, °) for (III).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
C13—H13$\cdots$O1^i	0.93	2.52	3.161 (3)	126

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

For all three compounds, all H atoms were fixed geometrically and allowed to ride on their parent atoms, with C—H = 0.93–0.99 Å, and $U_{iso} = 1.5U_{eq}(C)$ for methyl H atoms and $1.2U_{eq}(C)$ for other H atoms.

For compound (I), data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1985). For compounds (II) and (III), data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *XCAD*4 (Harms & Wocadlo, 1995). For all three compounds, program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ZORTEP* (Zsolnai, 1997); software used to prepare material for publication: *SHELXL*97 and *PARST* (Nardelli, 1995).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1552). Services for accessing these data are described at the back of the journal.

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