Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: JZ1085). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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1-(4-Iodobenzoyl)-5-methoxy-2-methyl-3-indoleacetic Acid, an Iodinated Indomethacin Analog

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Abstract

The crystal structure of 1-(4-iodobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid, $C_{19}H_{16}INO_4$, an analog of indomethacin, is reported. Bond distances and angles in the title compound closely resemble those reported for indomethacin and reflect the presence of steric strain at the site of the linkage between the 4-iodobenzoyl group

and the indole moiety. The orientation of the 4-iodobenzoyl group with respect to the indole ring is not the same in the title compound as it is in indomethacin; the two structures are related by a rotation of 186° about the C2—N1—C10—C11 torsion angle.

Comment

Indomethacin is a well studied member of the class of compounds known as the nonsteroidal anti-inflammatory drugs (NSAIDs). In the course of our studies of the interactions of NSAIDs with their target, prostaglandin H_2 synthase, we synthesized the title compound, (I), an indomethacin analog. The IC_{50} value of (I) for inhibition of the cyclooxygenase activity of prostaglandin H_2 synthase is roughly threefold lower than that of indomethacin. We have recently determined a low-resolution structure of (I) complexed with its target, allowing us to elucidate its mode of binding (Loll, Picot, Ekabo & Garavito, 1995).
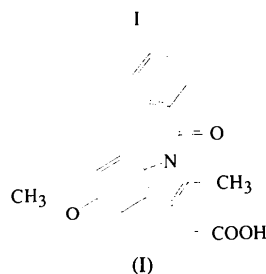

(I)

Fig. 1 shows a perspective view of the title compound. Evidence for steric strain is seen at the point where the 4-iodobenzoyl group joins the indole ring. The carbonyl group, comprising atoms O1 and C10, is prevented from lying in the plane of the indole ring by the close approach of O1 and the H atom bound to C8. The torsion angle C2—N1—C10—C11 is −35.0 (8)°;
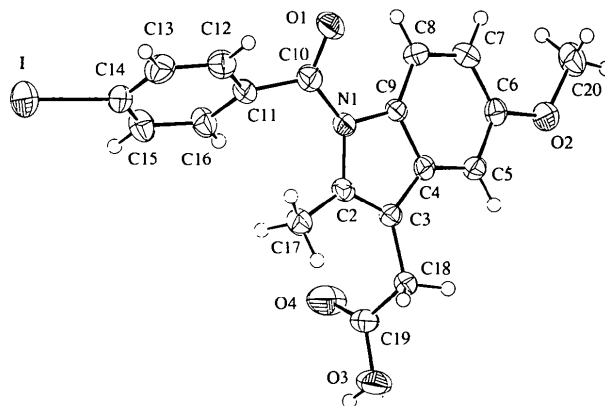

Fig. 1. View of the title compound showing the atomic labeling scheme (*ORTEP*II; Johnson, 1976). Displacement ellipsoids for non-H atoms are plotted at the 50% probability level and H atoms are drawn as spheres of arbitrary radii.

the loss of double-bond character in the amide linkage is further shown by the N1—C10 distance of 1.383 (6) Å, longer than the lengths of 1.33–1.34 Å commonly associated with amides (Allen *et al.*, 1987). The phenyl ring is not coplanar with the carbonyl group either, as this would bring atom C16 unacceptably close to the methyl substituent at C2; the C12—C11—C10—O1 torsion angle is −38.3 (8)°. Small distortions from ideal 120° bond angles are seen around atom C11, with the C10—C11—C12 angle being 118.7 (4)°, while the C10—C11—C16 angle is 122.0 (5)°.

Bond lengths appear normal. The methoxy group at atom C6 lies essentially in the plane of the indole ring system, with C20 departing from the mean indole plane by only 0.097 (9) Å. The plane formed by the acetic acid moiety makes an angle of 80.5 (2)° with the indole plane.

Bond lengths and angles for the title compound agree closely with those reported for indomethacin (Kistenmacher & Marsh, 1972), with both compounds showing similar indications of strain in the vicinity of the indole–benzoyl linkage. However, the structure of (I) and that of indomethacin differ significantly in three details. Firstly, the C2—N1—C10—C11 torsion angle is flipped by 186° in (I) relative to the angle in indomethacin. Secondly, the methoxy groups at C6 adopt conformations 180° apart in the two structures, with atom C20 making a close approach to C5 in indomethacin and to C7 in the title compound. Thirdly, the acetic acid torsion angles differ slightly between the two structures; in indomethacin, the C2—C3—C18—C19 and C3—C18—C19—O3 torsion angles are 100 and 147°, respectively, while the corresponding values in (I) are 76.2 (7) and 188.0 (5)°. There is no evidence to suggest that substituting an I for a Cl atom on the benzoyl group should shift the favored conformations of the three indole substituents. Rather, it is likely that packing considerations dictate which conformations are more favored in a given lattice. Indeed, it has been observed that indomethacin exhibits crystalline polymorphism (Yamamoto, 1968*a*) and it is possible that the crystal form observed for the title compound is a homolog of one of the indomethacin forms for which a structure determination has not been carried out.

Details of the packing are shown in Fig. 2. An intermolecular hydrogen bond (Table 2) is formed between atom H3 of the carboxylic acid and the amide O1 atom of the molecule located at $x - 1$, y, z. The indole rings of adjacent molecules pack in a parallel overlapping manner, with the five-membered ring of one molecule being directly over the six-membered indole ring of a neighbor. The interplanar distance for these neighboring rings is approximately 3.43 Å. A close contact is seen between the I atom and the carboxylic acid O4 atom of the molecule at $-x - 1$, $y + \frac{1}{2}$, $-z$. The distance between these two atoms is 3.162 (5) Å, substantially less than the minimum distance of 3.30 Å
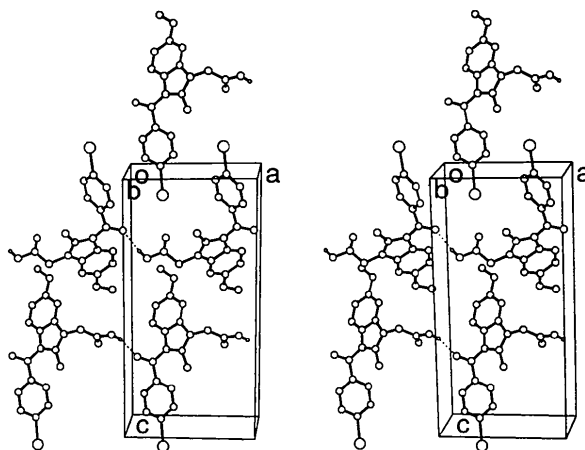

Fig. 2. Stereoview of the crystal packing of the title compound. Intermolecular hydrogen bonds are drawn as dashed lines.

predicted from the sum of the van der Waals radii (Nyburg & Faerman, 1985). This appears to represent an interaction between an unshared electron pair on the O atom and an empty orbital on the I atom.

Experimental

The title compound was prepared according to the method of Yamamoto (1967, 1968*a,b*), with details to be published elsewhere (Loll, Picot, Ekabo & Garavito, 1995). Crystals for X-ray diffraction studies were grown from 2-ethoxyethanol/water mixtures.

Crystal data

C$_{19}$H$_{16}$INO$_4$	Mo $K\alpha$ radiation
$M_r = 449.23$	$\lambda = 0.71073$ Å
Monoclinic	Cell parameters from 250
$P2_1$	reflections
$a = 9.5060 (10)$ Å	$\theta = 4.5–20.8°$
$b = 4.7250 (10)$ Å	$\mu = 1.885$ mm^{-1}
$c = 19.166 (8)$ Å	$T = 296 (2)$ K
$\beta = 91.790 (10)°$	Blade
$V = 860.4 (4)$ Å^3	$0.35 \times 0.06 \times 0.02$ mm
$Z = 2$	Yellow
$D_x = 1.734$ Mg m^{-3}	

Data collection

Enraf–Nonius Fast area-detector diffractometer	1721 observed reflections
	$[I > 2\sigma(I)]$
Rotation method, on-line box integration scans	$R_{int} = 0.063$
	$\theta_{max} = 27.48°$
Absorption correction: none	$h = 0 \rightarrow 12$
	$k = 0 \rightarrow 6$
8940 measured reflections	$l = -24 \rightarrow 24$
2185 independent reflections	No standard reflections

Refinement

Refinement on F^2	$\Delta\rho_{max} = 0.573$ e Å^{-3}
$R(F) = 0.0335$	$\Delta\rho_{min} = -0.632$ e Å^{-3}

$wR(F^2) = 0.0813$
$S = 1.003$
2185 reflections
229 parameters
H-atom parameters not
refined
$w = 1/[\sigma^2(F_o^2) + (0.0390P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$

Atomic scattering factors
from *International Tables
for Crystallography* (1992,
Vol. C, Tables 4.2.6.8 and
6.1.1.4)
Absolute configuration:
Flack (1983) parameter
= 0.08 (3)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
I	−0.25945 (4)	−0.25290 (11)	−0.10592 (2)	0.0586 (2)
C10	−0.1618 (5)	−0.5299 (12)	0.2149 (3)	0.0342 (12)
O1	−0.0385 (4)	−0.5694 (12)	0.2312 (2)	0.0520 (11)
C11	−0.1991 (5)	−0.4413 (12)	0.1424 (3)	0.0327 (11)
C12	−0.1115 (5)	−0.2522 (20)	0.1094 (2)	0.0411 (10)
C13	−0.1324 (6)	−0.1904 (14)	0.0399 (3)	0.044 (2)
C14	−0.2387 (6)	−0.3227 (12)	0.0018 (3)	0.039 (2)
C15	−0.3266 (6)	−0.5137 (13)	0.0333 (3)	0.0417 (13)
C16	−0.3074 (6)	−0.5709 (13)	0.1034 (3)	0.0369 (12)
N1	−0.2672 (4)	−0.5791 (9)	0.2616 (2)	0.0265 (8)
C2	−0.3981 (5)	−0.4389 (10)	0.2677 (3)	0.0285 (10)
C3	−0.4585 (5)	−0.5269 (10)	0.3263 (3)	0.0284 (10)
C4	−0.3680 (4)	−0.7329 (16)	0.3606 (2)	0.0265 (8)
C5	−0.3805 (5)	−0.8958 (12)	0.4202 (3)	0.0296 (10)
C6	−0.2727 (5)	−1.0823 (11)	0.4386 (3)	0.0298 (10)
C7	−0.1548 (5)	−1.1062 (12)	0.3976 (3)	0.0335 (11)
C8	−0.1411 (5)	−0.9454 (11)	0.3384 (3)	0.0327 (11)
C9	−0.2469 (4)	−0.7605 (16)	0.3208 (2)	0.0257 (8)
C17	−0.4516 (5)	−0.2151 (16)	0.2193 (3)	0.0367 (12)
O2	−0.2928 (3)	−1.2360 (15)	0.4984 (2)	0.0431 (8)
O3	−0.8417 (4)	−0.4330 (11)	0.3310 (3)	0.0566 (12)
O4	−0.7170 (4)	−0.7347 (17)	0.2708 (3)	0.073 (2)
C18	−0.5982 (5)	−0.4272 (12)	0.3520 (3)	0.0333 (11)
C19	−0.7213 (5)	−0.5514 (13)	0.3133 (3)	0.0381 (13)
C20	−0.1798 (7)	−1.4071 (15)	0.5231 (3)	0.049 (2)

Table 2. *Selected geometric parameters (Å, °)*

I—C14	2.094 (5)	C3—C4	1.444 (7)
C10—O1	1.218 (6)	C3—C18	1.507 (6)
C10—N1	1.383 (6)	C4—C5	1.384 (8)
C10—C11	1.483 (7)	C4—C9	1.407 (5)
C11—C12	1.388 (8)	C5—C6	1.389 (7)
C11—C16	1.396 (8)	C6—O2	1.375 (7)
C12—C13	1.372 (7)	C6—C7	1.393 (7)
C13—C14	1.378 (8)	C7—C8	1.376 (7)
C14—C15	1.381 (8)	C8—C9	1.367 (8)
C15—C16	1.377 (8)	O2—C20	1.414 (7)
N1—C2	1.418 (6)	O3—C19	1.328 (6)
N1—C9	1.431 (7)	O4—C19	1.191 (8)
C2—C3	1.343 (7)	C18—C19	1.487 (7)
C2—C17	1.487 (8)		
O1—C10—N1	121.2 (5)	C2—C3—C18	125.5 (5)
O1—C10—C11	118.9 (5)	C4—C3—C18	125.5 (4)
N1—C10—C11	119.8 (4)	C5—C4—C9	119.2 (5)
C12—C11—C16	118.7 (5)	C5—C4—C3	133.3 (4)
C12—C11—C10	118.7 (4)	C9—C4—C3	107.5 (4)
C16—C11—C10	122.0 (5)	C4—C5—C6	118.8 (4)
C13—C12—C11	120.6 (5)	O2—C6—C5	115.2 (4)
C12—C13—C14	120.0 (6)	O2—C6—C7	124.2 (5)
C13—C14—C15	120.6 (5)	C5—C6—C7	120.6 (5)
C13—C14—I	119.8 (4)	C8—C7—C6	121.3 (5)
C15—C14—I	119.6 (4)	C9—C8—C7	117.9 (4)
C16—C15—C14	119.4 (5)	C8—C9—C4	122.3 (5)
C15—C16—C11	120.7 (5)	C8—C9—N1	131.1 (4)
C10—N1—C2	129.1 (4)	C4—C9—N1	106.5 (4)

C10—N1—C9	122.1 (4)	C6—O2—C20	117.2 (4)
C2—N1—C9	108.1 (4)	C19—C18—C3	113.6 (4)
C3—C2—N1	108.9 (4)	O4—C19—O3	122.0 (5)
C3—C2—C17	126.6 (5)	O4—C19—C18	125.9 (5)
N1—C2—C17	124.3 (4)	O3—C19—C18	112.2 (5)
C2—C3—C4	109.0 (4)		

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O3—H3$\cdots$O1[i]	0.82	1.92	2.711 (6)	161

Symmetry code: (i) $x - 1, y, z$.

The coordinates of the iodine position were located from a sharpened Patterson synthesis. A difference Fourier map was calculated using phases calculated from the iodine position and atoms were placed for one of the two mirror-related benzoyl groups seen in this map. The remaining non-H atoms were found using successive cycles of refinement and difference Fourier maps. After anisotropic refinement, a difference Fourier map revealed the positions of all the H atoms. H atoms were positioned using a riding model, with displacement parameters equal to $1.5U_{eq}$ of their respective carrier atoms, and O—H = 0.82 and C—H = 0.93–0.96 Å.

Data collection: *MADNES* (Messerschmidt & Pflugrath, 1987). Cell refinement: *MADNES*. Data reduction: *MADNES*. Program(s) used to solve structure: *CCP4 Suite* (Collaborative Computational Project, Number 4, 1994). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *FRODO* (Jones, 1982), *ORTEP*II (Johnson, 1976) and *PLUTO* (Motherwell & Clegg, 1978).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: FG1089). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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