

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters ( $\text{\AA}^2$ )

	$B_{eq} = (4/3)\sum_i \sum_j \beta_{ij} a_i \cdot a_j$			
	x	y	z	$B_{eq}$
O2	0.7270 (3)	0.0274 (3)	0.6011 (8)	4.2 (3)
O1	0.6228 (3)	0.0094 (3)	0.8948 (8)	3.9 (3)
C1	0.5954 (3)	0.0490 (4)	0.726 (1)	2.2 (3)
C2	0.6560 (3)	0.0577 (4)	0.560 (1)	3.0 (3)
C3	0.6380 (4)	0.0959 (5)	0.364 (1)	3.4 (4)
C4	0.5679 (4)	0.1329 (4)	0.296 (1)	4.0 (4)
C5	0.4903 (4)	0.1456 (4)	0.405 (1)	3.5 (4)
C6	0.4648 (4)	0.1187 (4)	0.597 (1)	2.4 (3)
C7	0.5136 (3)	0.0750 (4)	0.743 (1)	2.9 (3)
C8	0.3787 (3)	0.1378 (4)	0.679 (1)	3.1 (3)
C9	0.3148 (4)	0.1656 (5)	0.517 (1)	4.3 (4)
C10	0.3837 (4)	0.1971 (6)	0.852 (1)	5.3 (5)

Table 2. Geometric parameters ( $\text{\AA}$ ,  $^\circ$ )

O2—C2	1.279 (8)	C4—C5	1.44 (1)
O1—C1	1.359 (8)	C5—C6	1.38 (1)
C1—C2	1.447 (9)	C6—C7	1.437 (9)
C1—C7	1.390 (9)	C6—C8	1.514 (9)
C2—C3	1.46 (1)	C8—C9	1.54 (1)
C3—C4	1.36 (1)	C8—C10	1.51 (1)
O1—C1—C2	115.1 (4)	C4—C5—C6	129.5 (4)
O1—C1—C7	113.8 (4)	C5—C6—C7	127.0 (4)
C2—C1—C7	131.1 (4)	C5—C6—C8	120.5 (4)
O2—C2—C1	113.7 (4)	C7—C6—C8	112.4 (4)
O2—C2—C3	122.8 (4)	C1—C7—C6	129.0 (4)
C1—C2—C3	123.5 (4)	C6—C8—C9	115.7 (4)
C2—C3—C4	131.0 (4)	C6—C8—C10	111.3 (4)
C3—C4—C5	128.6 (5)	C9—C8—C10	109.2 (5)
O1—C1—C2—O2	-0.8 (5)	C3—C4—C5—C6	-5.6 (8)
O1—C1—C2—C3	178.0 (7)	C4—C5—C6—C7	4.8 (7)
C7—C1—C2—O2	178.1 (8)	C4—C5—C6—C8	-178.4 (8)
C7—C1—C2—C3	-3.0 (6)	C5—C6—C7—C1	-1.2 (7)
O1—C1—C7—C6	179.6 (8)	C8—C6—C7—C1	-178.2 (8)
C2—C1—C7—C6	0.6 (7)	C5—C6—C8—C9	17.6 (6)
O2—C2—C3—C4	-178.0 (1)	C5—C6—C8—C10	-107.8 (7)
C1—C2—C3—C4	3.3 (8)	C7—C6—C8—C9	-165.2 (7)
C2—C3—C4—C5	0.9 (7)	C7—C6—C8—C10	69.4 (6)

Intensities were measured with a scan rate of  $6^\circ \text{ min}^{-1}$  in  $\theta$  and a scan width of  $\Delta\theta = (1.1 + 0.15\tan\theta)^\circ$ . Background intensities were measured for 3 s at the end of each scan. The structure was solved by direct methods using *MULTAN87* (Debaeremaeker, Germain, Main, Tate & Woolfson, 1987). The initial *E* map gave partial structure around the tropolone skeleton. Positions of the remaining non-H atoms were located stepwise from the subsequent Fourier syntheses. The structure was refined by a block-diagonal least-squares procedure. *The Universal Crystallographic Computation Program System - Osaka* (1979) was used for all calculations.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and bond distances involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71578 (9 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: OH1029]

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## Non-Steroidal Anti-Inflammatory Drugs. III. Structure of Indoprofen: 2-[4-(1-Oxo-2-isoindol-2-yl)phenyl]propionic Acid

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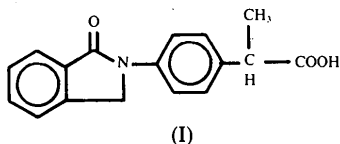
## Abstract

Indoprofen, 4-(1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)- $\alpha$ -methylbenzeneacetic acid,  $C_{17}H_{15}NO_3$ , a non-steroidal anti-inflammatory agent, falls into the class of phenylpropionic acids that includes ibuprofen, ketoprofen and flubiprofen. It adopts a planar conformation apart from the carboxylic acid group. There is a small twist of  $8.8(2)^\circ$  between the mean planes of the isoindol-2-yl and phenyl rings. The rotation of the carboxyl group out of the plane of the adjacent phenyl ring seems to be connected with anti-inflammatory activity and is similar to that found in other 2-phenylpropionic acids. A pair of

intermolecular hydrogen bonds connects two carboxylic acid groups across a centre of symmetry with an O...O distance of 2.61 (1) Å.

### Comment

Non-steroidal anti-inflammatory drugs (Nsaids) are a family of compounds which, chemically, are not very homogeneous. The phenylpropionic acid class has become one of the most widely investigated and developed over the past two decades. Many agents of this class, *e.g.* ibuprofen, naproxen and ketoprofen, are at present used in therapeutic practice. Indoprofen (I) is one of a series of related compounds



prepared by Nannini *et al.* (1973) that have anti-inflammatory activity. Buttinoni *et al.* (1973) established its pharmacological profile as a non-steroidal anti-inflammatory agent. In order to provide a better understanding of the structural features of this class of compound a diffraction analysis of indoprofen has been carried out.

Selected torsion angles defining the orientation of the carboxyl group relative to the adjacent phenyl group in phenyl propionic acid and phenylacetic acid derivatives are presented in Table 3 since these angles may explain the anti-inflammatory activity of these compounds. The propionic acid is twisted significantly out of the plane of the phenyl ring. Its conformation relative to the phenyl ring may be described by  $\tau_1 = \text{C}(11)\text{—C}(12)\text{—C}(15)\text{—C}(17)$  and  $\tau_2 = \text{C}(12)\text{—C}(15)\text{—C}(17)\text{—O}(2)$  (Table 3; Fig. 1). The value of  $\tau_1$  varies considerably from structure to structure, ranging from  $-111.7$  to  $162.6^\circ$ . However, there is more agreement in the position of the  $\text{—CO}_2\text{H}$  group relative to the phenyl ring, defined by the torsion angle  $\tau_2$ . Excluding fenoprofen, because of its coordination to calcium, the average  $\tau_2$  torsion angle is  $93^\circ$  if sign variations are ignored. The theoretical values for the minimum-energy configuration of 2-phenylpropionic acid, calculated using *CNDO/2* and *STD 3G*, are  $\tau_1 = \pm 60, 120^\circ$  and  $\tau_2 = \pm 90^\circ$  (Dupont, Dideberg, Dive, Godfroid & Steiner, 1982). In contrast, the values of the corresponding angles in the phenylacetic acid side chains of anti-inflammatory drugs range from  $24.4$  to  $112.6^\circ$  for  $\tau_1$  and  $-128.6$  to  $25.7^\circ$  for  $\tau_2$  (Table 3). Thus, the crystal structures suggest that the acetic acid side chains may rotate more freely than the propionic acid side chains.

It is interesting to note that while the twist of the carboxylic acid maximizes its intramolecular distance

from the C(16) methyl group, it also facilitates the formation of a centrosymmetric dimer through intermolecular hydrogen bonding [ $\text{O}(3)\cdots\text{O}(2)(-x+2, -y+1, -z+1)$  2.61,  $\text{HO}(3)\cdots\text{O}(2)$ , 1.86 Å,  $\text{O}(3)\text{—H}\cdots\text{O}(2)$   $146.8^\circ$ ] (Fig. 2).

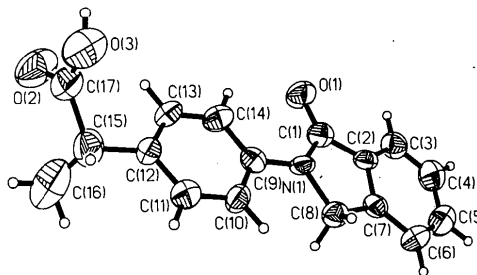


Fig. 1. A perspective view of the title molecule with the atom labelling. Thermal ellipsoids are shown at 50% probability except for H atoms which are represented by spheres of arbitrary size.

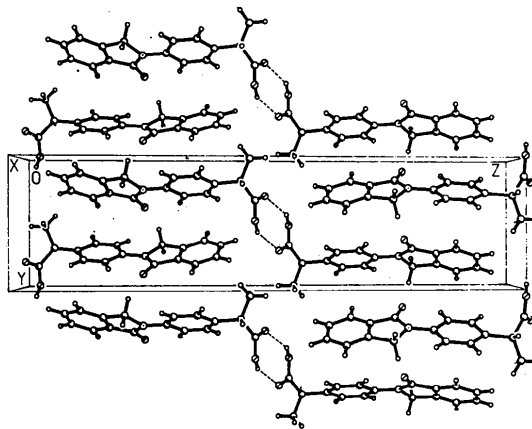


Fig. 2. The molecular packing of indoprofen.

### Experimental

The compound was obtained from the Sigma Chemical Company, USA, and crystals were grown, with great difficulty, from a chloroform-methanol mixture.

#### Crystal data

C<sub>17</sub>H<sub>15</sub>NO<sub>3</sub>

$M_r = 281.3$

Monoclinic

$P2_1/n$

$a = 6.029$  (1) Å

$b = 7.708$  (1) Å

$c = 30.468$  (5) Å

$\beta = 94.84$  (2) $^\circ$

$V = 1410.8$  (4) Å<sup>3</sup>

$Z = 4$

$D_x = 1.324$  Mg m<sup>-3</sup>

$D_m = 1.319$  (3) Mg m<sup>-3</sup>

$D_m$  measured by flotation in aq. KI solution

Mo  $K\alpha$  radiation

$\lambda = 0.71069$  Å

Cell parameters from 25

reflections

$\theta = 15\text{--}22^\circ$

$\mu = 0.085$  mm<sup>-1</sup>

$T = 293$  K

Plates

$0.25 \times 0.21 \times 0.10$  mm

Colourless

## Data collection

Siemens R3m/V diffractometer	$R_{\text{int}} = 0.036$
$\omega/2\theta$ scans	$\theta_{\text{max}} = 22.5^\circ$
Absorption correction: none	$h = 0 \rightarrow 8$
2264 measured reflections	$k = 0 \rightarrow 9$
1869 independent reflections	$l = -32 \rightarrow 32$
1040 observed reflections	2 standard reflections monitored every 98 reflections
$[I \geq 3\sigma(I)]$	intensity variation: $\leq 1\%$

## Refinement

Refinement on $F$	$w = 1/[\sigma^2(F) + 0.0023F^2]$
$R = 0.062$	$(\Delta/\sigma)_{\text{max}} = 0.001$
$wR = 0.069$	$\Delta\rho_{\text{max}} = 0.14 \text{ e } \text{Å}^{-3}$
$S = 1.08$	$\Delta\rho_{\text{min}} = -0.11 \text{ e } \text{Å}^{-3}$
1040 reflections	Atomic scattering factors from <i>SHELXTL-Plus</i> (Sheldrick, 1990)
190 parameters	
H-atom parameters not refined	

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters ( $\text{Å}^2$ )

	$U_{\text{eq}} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j$			
	$x$	$y$	$z$	$U_{\text{eq}}$
O(1)	0.6641 (7)	0.3804 (6)	0.2497 (1)	0.065 (2)
O(2)	0.9836 (5)	0.2972 (6)	0.4865 (1)	0.104 (4)
O(3)	1.2316 (7)	0.4831 (6)	0.4676 (1)	0.093 (3)
N(1)	1.0178 (7)	0.2530 (7)	0.2537 (1)	0.040 (2)
C(1)	0.8196 (9)	0.3119 (9)	0.2321 (1)	0.048 (3)
C(2)	0.8287 (9)	0.2752 (9)	0.1848 (1)	0.040 (3)
C(3)	0.6715 (9)	0.3079 (9)	0.1499 (1)	0.055 (3)
C(4)	0.7162 (9)	0.2541 (9)	0.1083 (1)	0.070 (4)
C(5)	0.9129 (9)	0.1681 (9)	0.1023 (1)	0.066 (4)
C(6)	1.0762 (9)	0.1361 (9)	0.1369 (1)	0.056 (4)
C(7)	1.0255 (9)	0.1909 (9)	0.1785 (1)	0.045 (3)
C(8)	1.1611 (9)	0.1691 (9)	0.2225 (1)	0.047 (3)
C(9)	1.0719 (9)	0.2407 (9)	0.2996 (1)	0.041 (3)
C(10)	1.2809 (10)	0.1738 (9)	0.3159 (1)	0.049 (3)
C(11)	1.3371 (9)	0.1606 (9)	0.3607 (1)	0.057 (4)
C(12)	1.1974 (9)	0.2138 (9)	0.3919 (1)	0.052 (3)
C(13)	0.9898 (9)	0.2814 (9)	0.3747 (1)	0.055 (4)
C(14)	0.9298 (9)	0.2962 (9)	0.3304 (1)	0.053 (3)
C(15)	1.2704 (9)	0.1950 (9)	0.4412 (1)	0.088 (5)
C(16)	1.2382 (10)	0.0293 (10)	0.4579 (2)	0.203 (12)
C(17)	1.1476 (9)	0.3330 (9)	0.4675 (1)	0.071 (4)

Table 2. Selected geometric parameters ( $\text{Å}$ ,  $^\circ$ )

O(1)—C(1)	1.236 (7)	O(2)—C(17)	1.219 (7)
O(3)—C(17)	1.262 (8)	N(1)—C(1)	1.391 (7)
N(1)—C(8)	1.486 (7)	N(1)—C(9)	1.410 (6)
C(1)—C(2)	1.475 (5)	C(2)—C(3)	1.385 (6)
C(2)—C(7)	1.380 (8)	C(3)—C(4)	1.384 (6)
C(4)—C(5)	1.384 (8)	C(5)—C(6)	1.403 (6)
C(6)—C(7)	1.394 (6)	C(7)—C(8)	1.520 (6)
C(9)—C(10)	1.412 (8)	C(9)—C(14)	1.393 (7)
C(10)—C(11)	1.383 (5)	C(11)—C(12)	1.383 (7)
C(12)—C(13)	1.414 (8)	C(12)—C(15)	1.538 (6)
C(13)—C(14)	1.372 (5)	C(15)—C(16)	1.394 (10)
C(15)—C(17)	1.556 (8)		
C(8)—N(1)—C(9)	120.4 (4)	C(1)—N(1)—C(9)	127.5 (4)
C(1)—N(1)—C(8)	111.2 (4)	O(1)—C(1)—N(1)	126.0 (4)
N(1)—C(1)—C(2)	107.4 (5)	O(1)—C(1)—C(2)	126.6 (5)
C(1)—C(2)—C(7)	109.2 (4)	C(1)—C(2)—C(3)	129.4 (5)
C(3)—C(2)—C(7)	121.3 (4)	C(2)—C(3)—C(4)	118.3 (5)
C(3)—C(4)—C(5)	120.0 (4)	C(4)—C(5)—C(6)	122.7 (4)

C(5)—C(6)—C(7)	115.9 (5)	C(2)—C(7)—C(6)	121.7 (4)
C(6)—C(7)—C(8)	128.8 (5)	C(2)—C(7)—C(8)	109.5 (4)
N(1)—C(8)—C(7)	102.6 (4)	N(1)—C(9)—C(14)	123.0 (4)
N(1)—C(9)—C(10)	119.9 (4)	C(10)—C(9)—C(14)	117.1 (4)
C(9)—C(10)—C(11)	120.7 (5)	C(10)—C(11)—C(12)	122.9 (4)
C(11)—C(12)—C(15)	120.2 (5)	C(11)—C(12)—C(13)	115.3 (4)
C(13)—C(12)—C(15)	124.5 (5)	C(12)—C(13)—C(14)	123.1 (5)
C(9)—C(14)—C(13)	120.8 (5)	C(12)—C(15)—C(17)	109.2 (4)
C(12)—C(15)—C(16)	113.9 (5)	C(16)—C(15)—C(17)	110.6 (4)
O(3)—C(17)—C(15)	114.8 (5)	O(2)—C(17)—C(15)	122.0 (7)
O(2)—C(17)—O(3)	123.2 (5)		
C(8)—N(1)—C(9)—C(10)	10.5 (8)		
C(8)—N(1)—C(9)—C(14)	-171.2 (5)		
C(11)—C(12)—C(15)—C(16)	-81.7 (7)		
C(11)—C(12)—C(13)—C(14)	-0.9 (8)		
C(13)—C(12)—C(15)—C(17)	-26.9 (5)		
C(12)—C(15)—C(17)—O(2)	99.7 (6)		
C(16)—C(15)—C(17)—O(3)	153.3 (5)		
C(1)—N(1)—C(9)—C(10)	178.6 (5)		
C(1)—N(1)—C(9)—C(14)	-3.1 (9)		
C(11)—C(12)—C(15)—C(16)	154.0 (5)		
C(13)—C(12)—C(15)—C(16)	97.3 (7)		
C(12)—C(15)—C(17)—O(3)	-80.6 (6)		
C(16)—C(15)—C(17)—O(2)	-26.4 (9)		

Table 3. Comparison of the carboxylic acid group orientation ( $^\circ$ ) in phenylpropionic and phenylacetic acids $\tau_1$ : C(11)—C(12)—C(15)—C(17);  $\tau_2$ : C(12)—C(15)—C(17)—O(2).

	$\tau_1$	$\tau_2$	Reference
Propionic acids			
Indoprofen	154.1	99.7	Present work
Naproxen	-111.7	-90.2	(a)
Ketoprofen	67.6	107.2	(b)
Ibuprofen	96.4	89.3	(c)
Flubiprofen	107.7	77.3	(d)
Benoxaprofen	82.5	88.9	(e)
Fenoprofen	67, 31	41, 52	(f)
CNPA	148.8	67.3	(g)
Nsaids IV	114.7, 162.6	94.9, 96.2	(h)
Nsaids I	144.2	110.0	(i)
IMLA	79.7, 63.2	102.2, 109.7	(j)
Acetic acids			
Nsaids II	101.5	25.7	(k)
Nsaids III	24.4	-128.6	(l)
4BPA	85.8, 38.2	-98.4, -90.7	(m)
4PPA	112.6	7.7	(n)

References: (a) Ravikumar, Rajan, Pattabhi & Gabe (1985); (b) Briard & Rossi (1990); (c) McConnell (1974); (d) Flippen & Gilardi (1975); (e) Drew & Leslie (1986); (f) Rajan (1992); (g) Dupont, Dideberg, Dive, Godfroid & Steiner (1982); (h) Hata, Sato & Tamura (1986d); (i) Hata, Sato & Tamura (1986a); (j) Foulton, Baert, Fourt, Brienne & Jacques (1979); (k) Hata, Sato & Tamura (1986b); (l) Hata, Sato & Tamura (1986c); (m) Bats & Canenbley (1984a); (n) Bats & Canenbley (1984b).

Data collection and cell refinement used Siemens R3m/V software (release 4.11). Intensity data were not corrected for absorption or extinction. *SHELXTL-Plus* (Sheldrick, 1990) was used to solve and refine the structure, and also for the molecular graphics. H atoms were placed at calculated positions and allowed to ride on the parent C atoms. Geometrical calculations and crystal packing were computed using *PARST* (Naradelli, 1983). All computations were performed on a VAX 3100 workstation.

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71491 (10 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: MU1049]

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## Phenyl 3-Fluorobenzoate

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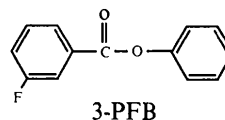
## Abstract

Although the title compound, C<sub>13</sub>H<sub>9</sub>FO<sub>2</sub>, differs from phenyl benzoate only in the presence of an F atom in the molecular structure, their molecular conformations and assemblies are quite different. It could be concluded that the change is due to the presence of the F atom.

## Comment

During the past several years, molecular assembly has attracted special attention from various standpoints. The generation of an assembly with the

desired architectural features requires the design and/or modification of the starting component. This is because the assembling mode would depend on the interaction between components (Lehn, Mascal, Decian & Fischer, 1990). For the purpose of controlling the mode, hitherto components have generally been modified or designed by adding functional groups capable of hydrogen bonding, such as OH, NH<sub>2</sub>, etc. One novel modification we have attempted is to add one F atom onto the starting material. The F atom has the highest electronegativity and, in addition, may form intermolecular hydrogen bonds in the solid state (Shibakami & Sekiya, 1992). Thus, the introduction of an F atom might be an effective modification method. Despite extensive studies of fluorine chemistry, however, there are few systematic studies of the F-atom effect on the assembling mode. Here we report the crystal structure of phenyl 3-fluorobenzoate (3-PFB) as the first example of our study, and compare it with the structure of phenyl benzoate (PB) (Adams & Morsi, 1976).



3-PFB was synthesized according to the conventional Schotten–Baumann method (Schotten, 1884) from 3-fluorobenzoic acid and phenol. The prismatic crystals of 3-PFB were grown from ethanol solution of the compound at room temperature. The crystal structure of 3-PFB is depicted in Fig. 1. As Table 2 shows, bond distances and angles are normal within experimental error. Inequality of the F(1)—C(5)—C(4) and F(1)—C(5)—C(6) angles is found. The angle between the planes of the two benzene rings in 3-PFB is 66.0°, while the corresponding angle in PB is 55.7°. In addition, the —COO group in 3-PFB is twisted by 8.7 and 74.5° with respect to the C(1)—C(6) and C(8)—C(13) rings, respectively; the angles in PB are 9.8 and 65.1°, respectively. These conformational differences are undoubtedly due to the effect of the F atom.

As shown in Fig. 1, it appears that the molecules are assembled through van der Waals interactions. The most striking structural feature is that the arrangement of the molecules differs notably from that of PB, which belongs to space group *P*2<sub>1</sub>/*c* with *a* = 5.74 (1), *b* = 14.75 (2), *c* = 12.45 (2) Å, β = 101.0 (2)°. The arrangement of components along the axes as seen in the present structure was not observed in the PB structure. The shortest intermolecular distance is 2.39 Å from O(1) to H(9)(*x*, *y*, *z* - 1). This distance corresponds to a van der Waals contact. Further, it is noteworthy that the shortest