Experimental

Crystals [m.p. 419.9–420.11 K, $[\alpha]_D^{21}$ +11.7 (*c*, 0.6, $CHCl_3$)] were grown at room temperature from ethyl ether/ethanol solution.

Crystal data

$C_{14}H_{19}N_3O_7$
M_r = 341.3
Monoclinic
*C*2
a = 21.574 (1) Å
b = 4.5576 (9) Å
c = 17.039 (2) Å
β = 104.238 (5)°
V = 1623.9 (4) Å^3
Z = 4
D_x = 1.396 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 23 reflections
θ = 5.5–21.5°
μ = 0.965 mm^{-1}
T = 293 K
Fine needle elongated along **b**
0.27 × 0.07 × 0.025 mm
Yellow

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: analytical by integration
$T_{\min}$ = 0.887, $T_{\max}$ = 0.972
2491 measured reflections
2403 independent reflections
1371 reflections with $F > 4\sigma(F)$

$R_{\rm int}$ = 0.032
$\theta_{\max}$ = 54°
h = −22 → 22
k = 0 → 4
l = 0 → 17
2 standard reflections frequency: 30 min intensity decay: none

Refinement

Refinement on F^2
R(*F*) = 0.076
$wR(F^2)$ = 0.074
S = 2.342
1804 reflections
217 parameters
H atoms in calculated positions with $U_{\rm iso}$ = 0.05
$w = 1/\sigma^2(F^2)$
$(\Delta/\sigma)_{\max}$ = 0.09

$\Delta\rho_{\max}$ = 0.326 e Å^{-3}
$\Delta\rho_{\min}$ = −0.333 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)
Absolute configuration: Flack *XABS* refined
Flack parameter = 0.5 (1.0)

Table 1. *Selected geometric parameters (Å, °)*

O1—C3	1.427 (14)	N1—C1	1.408 (14)
O1—C4	1.394 (14)	N1—C4	1.471 (14)
O2—C1	1.197 (15)	N2—C9	1.366 (14)
O3—C2	1.391 (16)	C1—C2	1.541 (18)
O5—C4	1.376 (16)	C2—C3	1.502 (16)
N1—N2	1.384 (13)	C3—C6	1.518 (19)
C3—O1—C4	111.4 (8)	N1—C1—C2	113.0 (10)
N2—N1—C1	117.1 (10)	C1—C2—C3	111.7 (9)
N2—N1—C4	112.6 (7)	O1—C3—C2	108.3 (10)
C1—N1—C4	124.8 (9)	O1—C4—N1	110.4 (8)
N1—N2—C9	120.7 (10)		
C4—O1—C3—C2	70.9 (11)	C4—N1—C1—C2	−16.3 (17)
C3—O1—C4—N1	−55.1 (12)	C1—N1—C4—O1	28.7 (17)
C5—O3—C2—C1	100.2 (12)	N1—N2—C9—C10	5.0 (17)
C7—O4—C6—C3	−104.3 (18)	N1—C1—C2—C3	28.6 (16)
C8—O5—C4—N1	127.7 (10)	C1—C2—C3—O1	−55.0 (14)
C1—N1—N2—C9	−89.7 (14)	C2—C3—C6—O4	−162.2 (13)

The coordinates of the H atoms have been calculated.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989). Cell refinement: *Xtal LATCON* (Hall, Flack & Stewart, 1992). Data reduction: *Xtal REFCAL, LSABS* (Blanc, Schwarzenbach & Flack, 1991), *SORTRF*. Program(s) used to solve structure: *MULTAN*87 (Main *et al.*, 1987). Program(s) used to refine structure: *Xtal CRYLSQ*. Molecular graphics: *Xtal ORTEP*. Software used to prepare material for publication: *Xtal BONDLA, CIFIO*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: HA1186). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1997). C**53**, 951–954

Refinement of Ibuprofen at 100 K by Single-Crystal Pulsed Neutron Diffraction

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(*Received 1 November 1996; accepted 24 February 1997*)

Abstract

The structure of racemic ibuprofen [α-methyl-4-(2-methylpropyl)benzeneacetic acid], $C_{13}H_{18}O_2$, has been refined using single-crystal pulsed neutron diffraction data collected at 100 K. Accurate positional and

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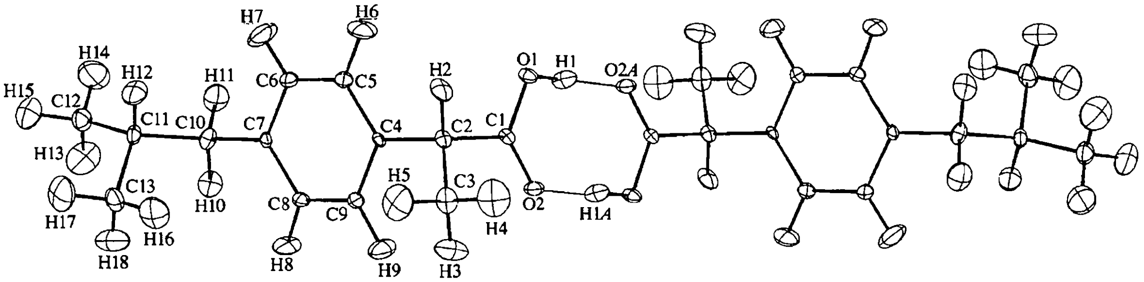
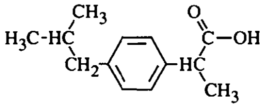


Fig. 1. *ORTEP* (Johnson, 1994) plot of the ibuprofen dimer. Atoms H1*A* and O2*A* are in the molecule related by $(1-x,\ 1-y,\ 1-z)$. Anisotropic displacement ellipsoids are shown at the 25% probability level.

anisotropic displacement (vibration) parameters have been determined for all 33 atoms and the hydrogen-bond geometry of the dimeric crystal-packing motif is well defined.

Comment

Ibuprofen, (I), is a non-steroidal anti-inflammatory drug widely prescribed as an analgesic and in the treatment of rheumatoid arthritis. In order to improve the accuracy of the H-atom positions in the ibuprofen structure, a refinement was carried out using single-crystal neutron diffraction data with the X-ray structure (McConnell, 1974) as the starting model. Further to a preliminary report on this work (Shankland *et al.*, 1996), we present here a detailed account of the molecular and crystal structure at 100 K. The refinement produced good agreement with the X-ray study, with mean aliphatic and aromatic C—C bond lengths of 1.511 (14) and 1.383 (9) Å, respectively. The H-atom positions are much improved on the X-ray structure, with a mean C—H distance of 1.08 (2) Å compared with 0.98 (3) Å from the X-ray determination.



(I)

Molecules form hydrogen-bonded dimers across centres of inversion within the space group $P2_1/c$. The geometry of the intermolecular hydrogen bonds is fully defined, with an O—H distance of 0.963 (13) Å, a H···O distance of 1.664 (10) Å and an O···O separation of 2.627 (7) Å. These values compare favourably (Table 3) with those in other neutron structure determinations of carboxylic acid dimers in the Cambridge Structural Database (Allen & Kennard, 1993). The comparison includes that of benzoic acid at 100 K (Wilson, Shankland & Florence, 1996). The hydrogen bond is the dominant contact, stabilizing the dimer, thereby creating the motif which packs to form the crystal lattice. The C1—O1 and C1—O2 distances are consistent with single- and double-bond character, and the H1 atom shows no evidence of the H-atom disorder that exists in other molecular crystals of carboxylic acids such as benzoic acid (Wilson, Shankland & Florence, 1996).

Experimental

Large single crystals of ibuprofen (supplied by Boots Pharmaceuticals) were obtained from seed crystals by cooling a saturated acetonitrile solution from 311 to 304 K at a rate of *ca* 0.1 K d^{-1}.

Crystal data

$C_{13}H_{18}O_2$
$M_r = 206.3$
Monoclinic
$P2_1/c$
$a = 14.397\ (8)$ Å
$b = 7.818\ (4)$ Å
$c = 10.506\ (6)$ Å
$\beta = 99.70\ (3)^\circ$
$V = 1165.6\ (11)$ Å^3
$Z = 4$
$D_x = 1.175$ Mg m^{-3}
D_m not measured

Pulsed neutron radiation
$\lambda = 0.48$ to 4.8 Å
Cell parameters from 125 reflections
$1.07 \leq d \leq 4.47$ Å
$T = 100$ K
Rectangular plate
5.0 × 2.0 × 1.0 mm
Colourless

Data collection

SXD diffractometer
64 × 64 3 mm pixel scintillator detector
Absorption correction: semi-empirical (Wilson, 1997)
$T_{\min} = 0.538$, $T_{\max} = 1.000$
8085 measured reflections

1528 independent reflections
1449 reflections with $I > 3\sigma(I)$
$R_{\rm int} = 0.06$
$(\sin\theta/\lambda)_{\max} = 0.6$ Å^{-1}
$h = 0 \rightarrow 28$
$k = 0 \rightarrow 15$
$l = -24 \rightarrow 16$

Refinement

Refinement on F
$R = 0.077$
$wR = 0.053$
$S = 1.76$
1449 reflections
298 parameters
All H atoms refined
$w = [2F_o/\sigma(F_o^2)]^2$
$(\Delta/\sigma)_{\max} = 0.03$

Extinction correction: Becker & Coppens (1974*a*,*b*) type 1 Gaussian
Extinction coefficient: 0.05 (1) × 10^{-4}
Scattering factors from *GSAS* (Larsen & Von Dreele, 1994)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$)*

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

	x	y	z	U_{eq}
O1	0.3792 (3)	0.4968 (7)	0.4148 (5)	0.0230
O2	0.4969 (3)	0.3117 (6)	0.4375 (5)	0.0286
C1	0.4162 (2)	0.3483 (5)	0.3962 (4)	0.0152
C2	0.3501 (3)	0.2207 (5)	0.3217 (4)	0.0195
C3	0.3996 (4)	0.1089 (8)	0.2383 (5)	0.0323
C4	0.3038 (2)	0.1238 (5)	0.4203 (4)	0.0141
C5	0.2173 (2)	0.1726 (6)	0.4466 (4)	0.0230
C6	0.1760 (3)	0.0902 (6)	0.5385 (4)	0.0241
C7	0.2203 (2)	−0.0484 (5)	0.6065 (4)	0.0161
C8	0.3079 (2)	−0.0965 (6)	0.5821 (4)	0.0231
C9	0.3486 (3)	−0.0127 (5)	0.4879 (4)	0.0233
C10	0.1741 (3)	−0.1385 (7)	0.7045 (4)	0.0255
C11	0.0970 (3)	−0.2639 (6)	0.6467 (4)	0.0237
C12	0.0414 (4)	−0.3210 (8)	0.7486 (6)	0.0363
C13	0.1373 (4)	−0.4152 (7)	0.5836 (6)	0.0362

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

C1—O1	1.306 (6)	C3—H3	1.081 (15)
C1—O2	1.204 (5)	C3—H4	1.053 (17)
C1—C2	1.503 (5)	C3—H5	1.073 (15)
C2—C3	1.500 (6)	C5—H6	1.103 (11)
C2—C4	1.525 (5)	C6—H7	1.041 (10)
C4—C5	1.374 (5)	C8—H8	1.065 (11)
C5—C6	1.376 (6)	C9—H9	1.077 (9)
C6—C7	1.392 (5)	C10—H10	1.101 (12)
C7—C8	1.380 (5)	C10—H11	1.102 (13)
C8—C9	1.396 (6)	C11—H12	1.085 (13)
C9—C4	1.380 (5)	C12—H13	1.061 (19)
C7—C10	1.493 (6)	C12—H14	1.062 (17)
C10—C11	1.529 (6)	C12—H15	1.097 (15)
C11—C12	1.508 (6)	C13—H16	1.067 (16)
C11—C13	1.519 (7)	C13—H17	1.099 (13)
O1—H1	0.963 (13)	C13—H18	1.044 (18)
C2—H2	1.091 (10)		
O1—C1—O2	123.4 (4)	C7—C8—C9	120.7 (4)
O1—C1—C2	115.4 (4)	C8—C9—C4	120.7 (4)
O2—C1—C2	121.1 (4)	C9—C4—C5	118.2 (3)
C1—C2—C3	111.7 (3)	C9—C4—C2	120.9 (3)
C1—C2—C4	106.7 (3)	C6—C7—C10	120.2 (3)
C3—C2—C4	114.4 (4)	C8—C7—C10	121.8 (4)
C2—C4—C5	120.9 (4)	C7—C10—C11	113.9 (4)
C4—C5—C6	121.6 (4)	C10—C11—C12	110.1 (4)
C5—C6—C7	120.7 (4)	C10—C11—C13	111.5 (4)
C6—C7—C8	118.0 (4)	C12—C11—C13	111.5 (4)

Table 3. *Hydrogen-bond geometry (Å, °)*

REFCODE	O—H	H···O	O···O	O—H···O
ACETPA01	0.992 (8)	1.699 (6)	2.688 (4)	175.2 (5)
ACETPA01	0.986 (7)	1.697 (6)	2.681 (4)	175.4 (5)
BITCEM11	0.950 (3)	1.717 (3)	2.666 (3)	179.0 (2)
FEROCA12	0.996 (4)	1.636 (4)	2.632 (2)	178.4 (3)
FEROCA12	1.008 (4)	1.593 (4)	2.600 (2)	176.0 (3)
FEROCA12	1.005 (3)	1.601 (3)	2.606 (2)	179.1 (2)
FEROCA12	0.997 (3)	1.663 (3)	2.660 (2)	178.4 (2)
NBZOAC05	0.964 (18)	1.677 (19)	2.640 (12)	175.5 (15)
SALIAC12	0.987 (16)	1.650 (15)	2.637 (10)	178.9 (14)
SUBRAC03	1.009 (2)	1.634 (2)	2.642 (2)	176.5 (2)
SUCACB03	1.006 (2)	1.670 (2)	2.673 (1)	174.3 (1)
TEPHTH06	1.014 (10)	1.610 (10)	2.623 (10)	178.0 (7)
VALREF	1.03 (6)	1.60 (6)	2.630 (6)	178 (11)
WAKCIU	1.026 (8)	1.643 (7)	2.668 (6)	176.3 (6)
IBUPROFEN	0.963 (13)	1.664 (10)	2.627 (7)	179.5 (7)
BENZOIC	0.993 (13)	1.616 (13)	2.606 (4)	174.6 (8)

Intensity data were collected on the single-crystal Laue diffractometer SXD at the ISIS pulsed neutron source (Wilson, 1990) using the DISPLEX cryostat attachment for the instrument. The crystal was cooled to 100 K at a rate of 1 K min^{-1}. The combination of the position sensitive detector and the wide range of wavelengths allows a large number of reflections to be collected simultaneously from the stationary crystal. The region of reciprocal space measured in this way is termed a frame. Data are thus collected from the sample in a series of frames by stepped rotation of the sample. There is a large overdetermination of equivalent reflections between adjacent frames and subsequent normalization and merging procedures showed no evidence of significant crystal decay. The unit cell was determined and refined from one frame and found to be in good agreement with the earlier X-ray study. Note that due to the method of data collection on SXD not all the scattered intensities collected in a single frame reach the same $\sin\theta/\lambda$. Reflection intensities were extracted and reduced to structure factors according to standard SXD data processing procedures (Wilson, 1997). Racemic ibuprofen crystals have a tendency to be highly strained and the low ratio of reflections to parameters is a consequence of the limited quality of the available samples.

Initial structural refinement and corrections were carried out in the least-squares program *SFLSQ*, a member of the Cambridge Crystallographic Subroutine Library (Brown & Matthewman, 1993). The variable wavelength absorption correction was determined using a 'semi-empirical' approach based upon path-length calculations and measured scattering from the crystal at various angles in the detector. Extinction was corrected with a variable wavelength method using one angular mosaic parameter in a Becker–Coppens Gaussian model (Becker & Coppens, 1974*a*,*b*). Wavelength-dependent corrections for the incident flux and crystal absorption were applied at the data normalization stage. The extinction was determined by refining scale and isotropic temperature factors, with mosaic spread as the only variable parameter.

Cell refinement: *SXD*95 (Wilson, 1990, 1997). Data reduction: *SFLSQ* (Brown & Matthewman, 1993) and *SXD*95. Program(s) used to refine structure: *GSAS* (Larsen & Von Dreele, 1994). Molecular graphics: *ORTEP* (Johnson, 1994).

Access to ISIS was made possible by the EPSRC and BBSRC.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1126). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1997). C**53**, 954–956

Novel Oxidative Rearrangement Product of the First *trans,cis,cis,cis*-[5.5.5.5]Fenestrane Derivative

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(*Received 6 November 1996; accepted 4 February 1997*)

Abstract

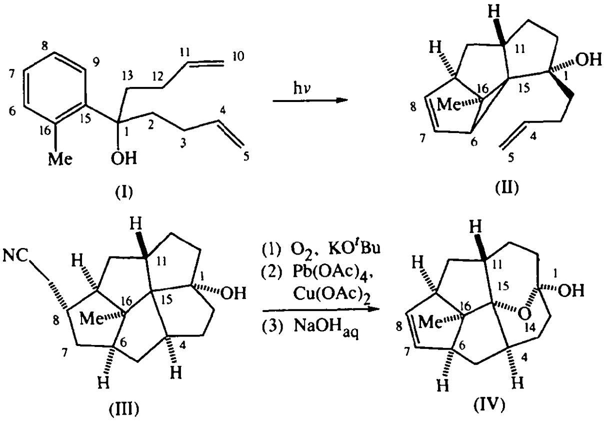
The structure of *rel*-(4*S*,6*R*,9*S*,11*S*)-1-hydroxy-16-methyl-14-oxapentacyclo[7.4.3.$0^{4,15}$.$0^{11,15}$.$0^{6,16}$]hexadeca-7-ene, $C_{16}H_{22}O_2$, (IV), has been determined. This study thus establishes compound (III), the precursor of (IV), as the first *trans,cis,cis,cis*-[5.5.5.5]fenestrane. The geometry around the central quaternary C atom of (IV) shows relatively little distortion. The C=C bond in the cyclopentene subunit is slightly shorter [1.305 (4) Å] than normal. Similarly, small departures from normal are seen in several C—C single bonds.

Comment

Fenestranes (Luef & Keese, 1993) are tetracycles sharing a central C atom. This connectivity feature gives rise to unique topologies along with the potential for severe strain. Several syntheses of the *cis,cis,cis,cis*-[5.5.5.5]fenestranes have been reported (Thommen, Gerber & Keese, 1991; Keese, Guidetti-Grept & Herzog, 1992). Prior to the current work, however, no synthesis of a *trans,cis,cis,cis*-[5.5.5.5]fenestrane system had been reported, despite impressive efforts toward this goal (Luyten & Keese, 1986). The strain of such fenestranes accounts in part for the difficulty associated with their synthesis as well as that encountered in the preparation of even the simpler *trans*-bicyclo[3.3.0]octanes. This strain and its manifestation in unusual geometries for carbon have also resulted in considerable theoretical interest in the fenestranes (Monkhorst, 1968; Hoffmann, Alder & Wilcott, 1970; Wiberg, Ellison & Wendoloski, 1976; Collins *et al.*, 1976; Kubiak, Fu, Gupta & Cook, 1990). Calculations on the fenestranes consistently predict a higher strain (*ca* 10 kcal mol^{-1}) for the *trans* isomer compared to the all-*cis* isomer (*e.g.* Kubiak, Fu, Gupta & Cook, 1990).

Recent studies on a novel variant of the arene–alkene photocycloaddition reaction have led to a successful synthesis of the first *trans,cis,cis,cis*-[5.5.5.5]fenestrane (Wender, Dove & deLong, 1996; deLong, 1992). In this synthesis, the arene–bisalkene (I), upon irradiation, gave the tetracycle (II). Earlier studies (Wender & Howbert, 1982, 1983; Wender & Singh, 1985, 1990; Wender & deLong, 1990) have shown that the vinyl cyclopropane subunit of these cycloadducts can be cleaved by free-radical addition to the vinyl group. In the current study, this cleavage involving the C6—C15 cyclopropane bond produces a radical at C15 which is trapped internally by the C4—C5 alkene. The resultant C5 radical then adds to the C6=C7 double bond to produce, after H-atom abstraction from the solvent, the fenestrane (III).

Compound (III) is not crystalline and its NMR spectrum lacks sufficient signal dispersion for complete assignment. Consequently, efforts were taken to convert (III) to a crystalline derivative in order to secure its structure by X-ray analysis. Oxidation of the acetonitrile group in (III) gave an acid which upon treatment with [$Pb(OAc)_4$] and [$Cu(OAc)_2$] and subsequent hydrolysis afforded crystalline fenestrane (IV). Compound (IV) results from a novel oxidative cleavage of a σ bond, assisted presumably by the strain of the fenestrane system. A full description of the synthesis is given elsewhere (deLong, 1992). The structure of (IV) is described herein. This determination establishes the structure of (III) as a *trans,cis,cis,cis*-[5.5.5.5]fenestrane. The power of this synthetic strategy rests in its capacity to produce novel fenestranes in only three steps from commercially available starting materials.



The H atoms at C4 and C11 in (IV) are in a *trans* relationship to each other, thus establishing the stereochemistry of this fenestrane derivative. There is some distortion in the molecule towards planar bonding as can be seen from the bond angles around the central C atom: C4—C15—C11 = 116.5 (2) and O14—C15—C16 = 111.9 (1)°. However, this strain is less than that ex-

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Acta Crystallographica Section C
ISSN 0108-2701 © 1997