

The Crystal Structure of Fenbufen, 3-(4-Biphenylcarbonyl)propionic acid (C₁₆H₁₄O₃), A Non-steroidal Antiinflammatory Agent

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Abstract □ The crystal structure of fenbufen was determined by X-ray diffraction techniques. The compound was recrystallized in orthorhombic crystal system, space group *Pca2₁*, $a = 31.918(10)$, $b = 5.550(2)$, $c = 15.078(9)$ Å, $D_m = 1.26$, $D_x = 1.264$ g/cm³, and $Z = 8$. The structure was solved by direct methods and refined by least-squares procedure to the final R value of 0.051 for 1780 independent reflections. Two molecules in the asymmetric unit are related by a pseudo center of symmetry and dimerized *via* O-H···O hydrogen bonds. The carbonyl group attached to the phenyl ring is nearly coplanar to the ring. In the crystal the molecules are arranged in parallel stacks in the a direction.

Keywords □ non-steroidal antiinflammatory agent, fenbufen, X-ray diffraction

It has been known that the enzyme cyclooxygenase is the target site where the non-steroidal antiinflammatory agents interact¹⁻⁶, and several models about their modes of interaction with the receptor binding site were proposed independently⁷⁻⁹. But they have not been confirmed at the molecular level yet.

3-(4-Biphenylcarbonyl)propionic acid, fenbufen (Fig. 1) can be classified as the arylacetate analogs, one of the subgroups of non-steroidal antiinflammatory agents^{1,2,6}. But it has two more carbon atoms interconnecting the aryl moiety and carboxyl group, so that the distance from the ring to the carboxyl group of the compound is longer than those of other arylacetates.

We were motivated to investigate the crystal structure of the title compound to provide three-dimensional structural data necessary for receptor modeling or new drug design¹⁰⁻¹². We have determined the three dimensional structures of the non-steroidal antiinflammatory agents¹³⁻¹⁵. This paper is an account of the molecular structure of fenbufen, and structural comparisons of the related compounds.

EXPERIMENTAL

Colorless prismatic crystals were grown by the slow evaporation method from dimethylsulfoxide solution at room temperature. The density was

measured by the flotation method in a mixture of cyclohexane and carbon tetrachloride. 0.08 × 0.20 × 0.40 mm dimensioned crystal was mounted on an automatic four circle diffractometer (Rigaku Denki Co. Ltd.) with CuK α radiations. The lattice constants were determined from least-squares refinement of the angular values of 20 diffractometer-measured reflections. The crystallographic data are given in Table I.

Intensities for 2072 independent reflections were recorded by ω - 2θ scan technique (40 kV, 250 mA) with range of $0 \leq h \leq 35$, $0 \leq k \leq 6$, and $0 \leq l \leq 12$. Three standard reflections are monitored after every 100 reflections and showed no noticeable changes. Lorentz and polarization corrections were applied to the data; absorption corrections were not made. Of all 2072 independent reflections, 292 reflections which has $F < 3\sigma(F)$ were treated as unobserved.

The structure was solved by multiresolution tangent refinement method with *SHELX 76*¹⁶ and *MULTAN 84*¹⁷ programs. All the 38 non-hydrogen atoms in one asymmetric unit could be positioned. The structure was refined by block-diagonal least-squares procedure based on F , first isotropically to R value of 0.134, then anisotropically to R value of 0.083 (where $R = (\sum ||F_o| - |F_c||) / \sum |F_o|$). Two independent molecules were refined in alternating cycles. Difference Fourier syntheses revealed 25 hydrogens out of 28. The three H(C10a), H(C10b),

Table I. Crystallographic data

3-(4-Biphenylcarbonyl)propionic acid	
Molecular formula; C₁₆H₁₄O₃	Mol. wt. 254.29
Colorless transparent prism,	Orthorhombic
$a = 31.918(10)$ Å	$b = 5.550(2)$ Å
$c = 15.078(9)$ Å	
Volume of the unit cell;	2176.09 Å ³
$D_x = 1.264$ g/cm ³	$D_m = 1.26$ g/cm ³
$Z = 8$	Space group; $Pca2_1$
$CuK\alpha$, $\lambda = 1.54178$ Å	$\mu(CuK\alpha) = 7.2$ cm ⁻¹
$F(000) = 1072$	

H(02b) hydrogens could not be located in difference Fourier syntheses, their positions were calculated geometrically with idealized bond length (1.08 Å) and angles. Input of these calculated hydrogen atomic positions reduced the R value from 0.069 to 0.066 in the structure factor calculation.

Further refinements including hydrogen atoms converged the R value to 0.051 and wR to 0.067 for 1780 observed reflections (where $wR = [\sum w(|F_o| - |F_c|)^2 / \sum wF_o^2]^{1/2}$). The function minimized in the refinement was $w(|F_o| - |F_c|)^2$, where $w = k / (\sigma^2(F) + gF^2)$, k and g were refined to 26.81 and 0.0046 respectively, and the average and maximum shift/e.s.d. ratio for the parameters are 0.080 and 0.375 for non-hydrogen atoms, and 0.155 and 0.845 for hydrogen atoms in the last cycle of refinement.

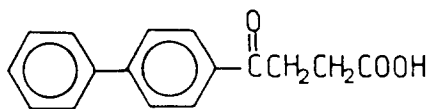
All the calculations were carried out on VAX-11/780 computer system at Seoul National university. The atomic scattering factors were taken from "International Tables for X-ray Crystallography".¹⁸⁾

RESULTS AND DISCUSSION

The final atomic coordinates and temperature factors are listed in Table II and Table III. The observed and calculated structure factors are available upon request.

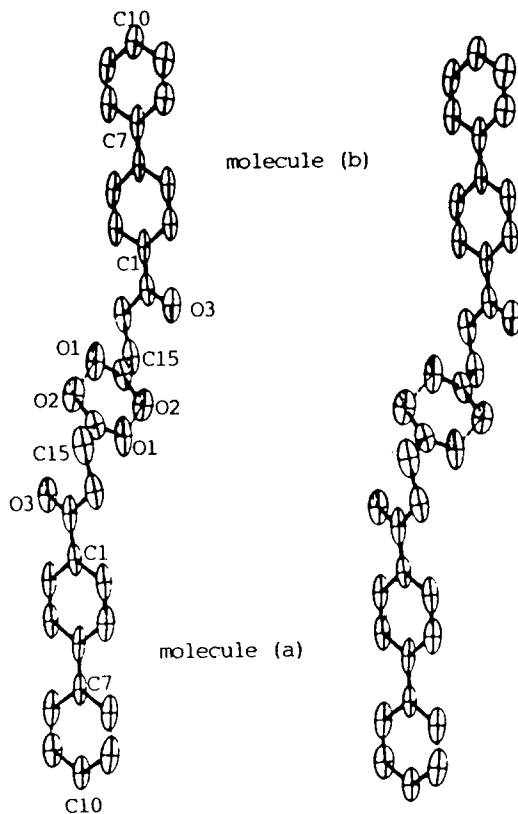
There are two molecules in the asymmetric unit, which are tentatively designated as molecules (a) and (b). They are approximately related by a pseudo center of symmetry at (0.017, 0.759, 0.214) with mean deviation of 0.08 Å. A stereoscopic ORTEP¹⁹⁾ view of the asymmetric unit is presented in Fig. 2. The two molecules are dimerized via O-H...O hydrogen bonds.

The atomic numbering scheme, the bond lengths and angles are shown in Fig. 3. Although the two independent molecules have slightly different values, all the bond lengths and angles of fenbufen

**Fig. 1. Fenbufen.**

are in reasonable range compared to those of other related compounds^{13-15,20-31)}. The dimeric hydrogen bond lengths are 2.653 Å for O(1a)...O(2b) and 2.657 Å for O(2a)...O(1b). The endocyclic angles of the phenyl rings show systematic deviations from 120° according to their substituents as reported by Domenicano *et al.*^{32,33)}.

Fig. 4 shows Newman projections of the atoms around two single bonds. The equations of the least-squares planes of the planar regions of the molecules, the deviations of individual atoms from these planes, and their dihedral angles are collected in Table V. The carboxyl group is nearly perpendicular to the flat area of the molecule. This conformation seems to be a common feature of arylacetate analogs^{13-15,20-31)}.

**Fig. 2. The stereoscopic view of the molecule.**

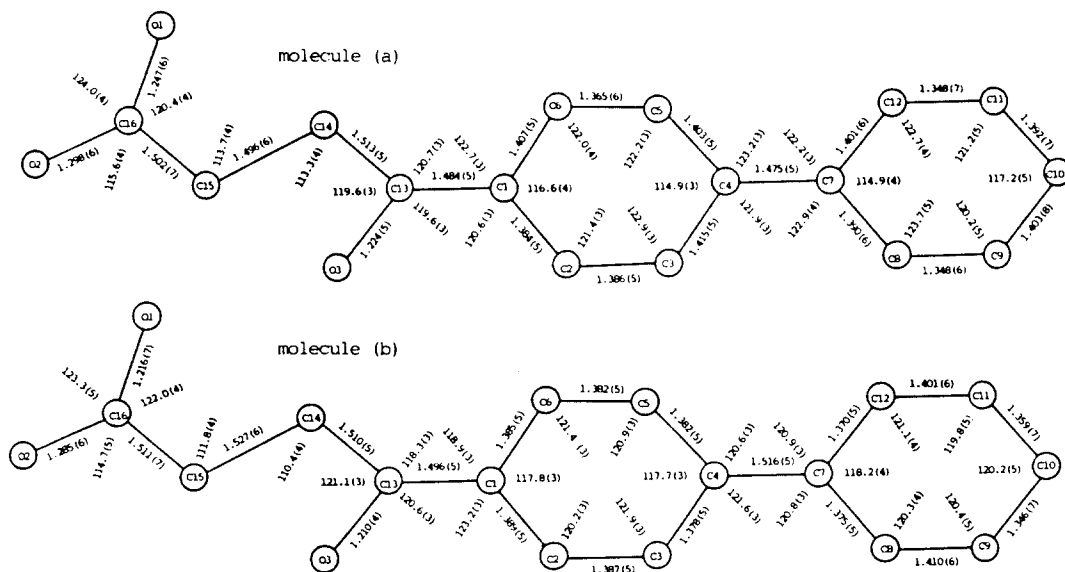


Fig. 3. Bond lengths(Å) and angles(°) of fenbufen with their estimated standard deviations in parentheses.

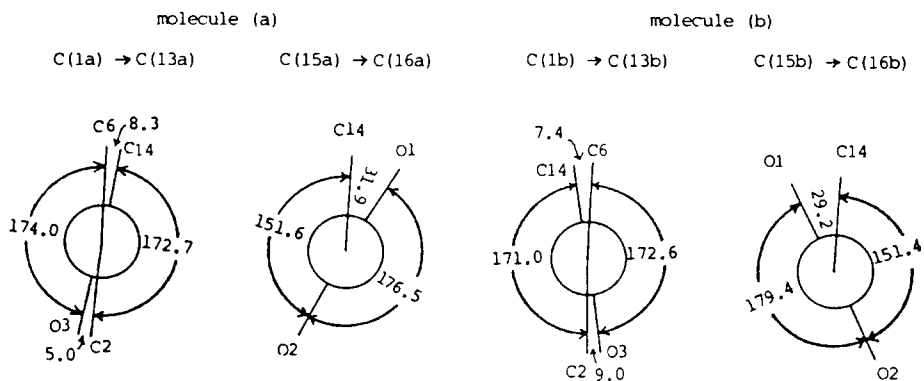


Fig. 4. Newman projections of atoms around four bonds.

Fig. 5 shows the molecular packing of fenbufen. The long dimers are arranged in parallel stacks in the crystallographic *a* direction, and the hydrophobic region of aryl moiety and hydrophilic region of the carboxyl group form alternating sheet-like pattern in the crystal.

It is commonly believed that the ring-acetate moiety is important for the antiinflammatory activity in the receptor models proposed independently by Scherrer⁷, Shen⁸, and Appleton⁹. As pointed out above, the distance from the ring to the carboxyl group of fenbufen is longer than those of other arylacetates. In our results, the carbonyl group attached to the phenyl ring is nearly coplanar to the

ring, and the flat area extends to the C(14) carbon atom as shown in Fig. 4 and Table IV. This is probably due to the extending of the conjugate π electron system of the biphenyl group to the carbonyl group, and the C(13), C(14) and O(3) atoms of the title compound may gain access to the ring-binding area of the proposed model of the receptor⁸. The remaining non-planar portion is the acetate chain as in the case of other arylacetates. Though there may remain other problems such as how electronegative oxygen can be fitted into the ring occupying region, it seems that the title compound may have a similar mode of interaction with the receptor as other arylacetates of indomethacin²⁴, *d*-6-chloro-5-cyclo-

Table II. Final positional ($\times 10^4$) and thermal ($\times 10^3$) parameters with their standard deviations in parentheses. The anisotropic temperature factors are expressed in the form of

$$\exp\{-2\pi^2(U_{11}a^2h^2 + U_{22}b^2k^2 + U_{33}c^2l^2 + 2U_{12}a^*b^*hk + 2U_{13}a^*c^*hl + 2U_{23}b^*c^*kl)\}$$

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
molecule (a)									
C(1a)	1789(1)	5152(6)	3489(2)	66(2)	38(2)	36(2)	3(1)	0(2)	-1(2)
C(2a)	2024(1)	7003(6)	3847(3)	55(2)	36(2)	54(2)	-7(2)	-3(2)	4(2)
C(3a)	2452(1)	6983(6)	3813(3)	61(2)	45(2)	52(2)	-11(2)	-2(2)	-2(2)
C(4a)	2683(1)	5104(6)	3409(2)	55(2)	47(2)	32(2)	3(1)	-3(2)	6(2)
C(5a)	2440(1)	3263(6)	3035(3)	67(2)	41(2)	55(2)	-7(2)	13(2)	5(2)
C(6a)	2011(1)	3286(6)	3069(3)	65(2)	40(2)	52(2)	-10(2)	0(2)	-1(2)
C(7a)	3139(1)	5104(6)	3391(2)	65(2)	47(2)	45(2)	8(2)	4(2)	2(2)
C(8a)	3379(1)	6899(9)	3787(4)	52(2)	64(3)	99(4)	-17(3)	7(2)	-3(2)
C(9a)	3802(1)	6908(10)	3794(4)	60(2)	84(3)	110(4)	-14(3)	10(3)	-3(2)
C(10a)	4025(2)	5069(9)	3361(3)	56(3)	100(4)	77(3)	9(3)	9(2)	11(3)
C(11a)	3792(1)	3277(10)	2946(3)	69(3)	88(3)	72(3)	-12(3)	15(2)	19(3)
C(12a)	3370(1)	3315(8)	2954(3)	67(2)	62(3)	66(3)	-10(2)	3(2)	9(2)
C(13a)	1324(1)	5192(6)	3541(3)	53(2)	43(2)	53(2)	5(2)	-9(2)	1(2)
C(14a)	1069(1)	3036(7)	3248(3)	64(2)	49(2)	74(3)	4(2)	-10(2)	-4(2)
C(15a)	608(1)	3359(9)	3380(4)	62(2)	67(3)	68(3)	10(3)	-7(2)	-12(2)
C(16a)	423(1)	5359(8)	2835(3)	47(2)	78(3)	79(3)	8(3)	-15(2)	-11(2)
O(1a)	572(1)	5852(7)	2090(2)	70(2)	118(3)	72(2)	28(2)	7(2)	17(2)
O(2a)	96(1)	6400(8)	3169(3)	51(2)	122(3)	96(3)	20(2)	9(2)	18(2)
O(3a)	1147(1)	6958(5)	3849(2)	60(1)	56(2)	84(2)	-10(2)	1(1)	6(1)
molecule (b)									
C(1b)	-1449(1)	10066(5)	833(2)	47(2)	38(2)	42(2)	3(1)	-8(1)	2(1)
C(2b)	-1671(1)	8124(6)	499(2)	58(2)	40(2)	49(2)	-4(2)	2(2)	8(2)
C(3b)	-2104(1)	8058(6)	531(3)	58(2)	37(2)	53(2)	-5(2)	-6(2)	-3(2)
C(4b)	-2330(1)	9900(5)	923(2)	59(2)	37(2)	37(2)	7(2)	7(2)	5(1)
C(5b)	-2107(1)	11805(7)	1275(3)	60(2)	40(2)	62(2)	-13(2)	3(2)	9(2)
C(6b)	-1674(1)	11922(6)	1227(3)	61(2)	38(2)	54(2)	-5(2)	-6(2)	-4(2)
C(7b)	-2804(1)	9839(5)	939(2)	48(2)	45(2)	38(2)	1(2)	-1(1)	4(1)
C(8b)	-3021(1)	8032(8)	521(3)	62(2)	66(3)	70(3)	-20(2)	7(2)	0(2)
C(9b)	-3460(1)	7991(9)	525(4)	55(2)	81(3)	93(3)	-23(3)	-2(2)	-10(2)
C(10b)	-3676(1)	9759(8)	949(3)	54(2)	78(3)	62(3)	0(2)	1(2)	3(2)
C(11b)	-3470(1)	11553(10)	1362(4)	66(3)	73(3)	84(3)	-10(3)	11(2)	17(2)
C(12b)	-3029(1)	11618(7)	1360(3)	59(2)	62(2)	68(2)	-14(2)	4(2)	9(2)
C(13b)	-983(1)	10098(6)	733(2)	60(2)	47(2)	44(2)	10(2)	-2(2)	8(2)
C(14b)	-751(1)	12376(8)	973(3)	55(2)	50(2)	74(3)	0(2)	-14(2)	2(2)
C(15b)	-283(1)	12095(9)	779(4)	66(3)	64(3)	94(4)	14(3)	-14(3)	-8(2)
C(16b)	-84(1)	10216(8)	1372(4)	39(2)	85(3)	85(3)	9(3)	-11(2)	-5(2)
O(1b)	-215(1)	9786(7)	2112(2)	75(2)	124(3)	64(2)	12(2)	-7(2)	21(2)
O(2b)	235(1)	9140(9)	1031(3)	57(2)	123(3)	103(3)	29(2)	10(2)	15(2)
O(3b)	-798(1)	8341(5)	463(2)	56(1)	59(2)	87(2)	-11(2)	-1(1)	8(1)

Table III. Fractional coordinates and thermal factors of hydrogen atoms ($\times 10^3$). The isotropic temperature factors are expressed in the form of $\exp(-8\pi^2 U \sin^2 \theta / \lambda^2)$

Atoms	x/a	y/b	z/c	U
molecule (a)				
H(C2a)	191(1)	824(8)	401(3)	73(14)
H(C3a)	264(1)	829(8)	399(3)	65(12)
H(C5a)	259(1)	186(8)	278(3)	75(13)
H(C6a)	191(1)	207(8)	282(3)	70(13)
H(C8a)	326(2)	812(10)	391(4)	92(19)
H(C9a)	398(3)	848(16)	396(6)	168(29)
H(C10a)	432(1)	485(5)	331(2)	28(7)
H(C11a)	395(2)	188(11)	270(4)	113(19)
H(C12a)	323(2)	200(9)	275(4)	86(16)
H(C14-1a)	121(2)	144(9)	354(4)	84(14)
H(C14-2a)	116(1)	268(8)	252(3)	76(13)
H(C15-1a)	49(2)	175(10)	313(4)	93(16)
H(C15-2a)	57(1)	375(6)	392(3)	32(9)
H(O2a)	-2(2)	727(10)	285(4)	93(20)
molecule (b)				
H(C2b)	-151(1)	685(7)	20(3)	53(10)
H(C3b)	-222(1)	682(7)	27(2)	37(9)
H(C5b)	-223(1)	1300(8)	152(3)	50(10)
H(C6b)	-150(1)	1319(6)	147(2)	37(8)
H(C8b)	-289(1)	688(8)	19(3)	58(11)
H(C9b)	-360(2)	675(11)	12(4)	100(17)
H(C10b)	-399(2)	970(9)	96(4)	100(17)
H(C11b)	-359(2)	1256(9)	166(4)	82(16)
H(C12b)	-288(1)	1308(7)	170(3)	59(11)
H(C14-1b)	-84(1)	1372(7)	64(3)	60(11)
H(C14-2b)	-78(1)	1271(7)	167(3)	67(12)
H(C15-1b)	-14(1)	1363(9)	95(3)	79(13)
H(C15-2b)	-15(2)	1153(2)	10(4)	108(18)
H(O2b)	40(4)	860(29)	137(11)	320(45)

Table IV. List of the equations of least-squares planes of the planar regions of fenbufen, the deviations of individual atoms from these planes (\AA), and their dihedral angles ($^\circ$) between these planes. (*; Atoms used for the calculation of the plane)

Equations: Plane (I) (biphenyl group of molecule a)					
0.0193 X - 0.5138 Y + 0.8577 Z = 3.1286					
Plane (II) (biphenyl group of molecule b)					
0.0326 X - 0.5069 Y + 0.8614 Z = -1.8662					
Plane (III) (dimerized carboxyl groups)					
0.6014 X + 0.6866 Y + 0.4086 Z = 4.5809					
Deviations from;					
	Plane(I)		Plane (II)		Plane (III)
C(1a)*	-0.024	C(1b)*	-0.036	C(15a)*	0.048
C(2a)*	0.027	C(2b)*	-0.069	C(16a)*	-0.022
C(3a)*	0.037	C(3b)*	-0.018	O(1a)*	-0.036
C(4a)*	0.011	C(4b)*	0.036	O(2a)*	0.005
C(5a)*	-0.019	C(5b)*	0.070	C(15b)*	0.033
C(6a)*	-0.027	C(6b)*	0.053	C(16b)*	0.002
C(7a)*	0.006	C(7b)*	0.025	O(1b)*	-0.037
C(8a)*	-0.012	C(8b)*	0.048	O(2b)*	0.008
C(9a)*	-0.041	C(9b)*	0.022		
C(10a)*	-0.019	C(10b)*	-0.030		
C(11a)*	0.021	C(11b)*	-0.059		
C(12a)*	0.045	C(12b)*	-0.029		
C(13a)	-0.051	C(13b)	-0.127		
C(14a)	-0.272	C(14b)	-0.431		
O(3a)	-0.002	O(3b)	0.039		
Dihedral Angles					
Between Plane	(I) and (II)				179.1
	(I) and (III)				89.5
	(II) and (III)				91.4

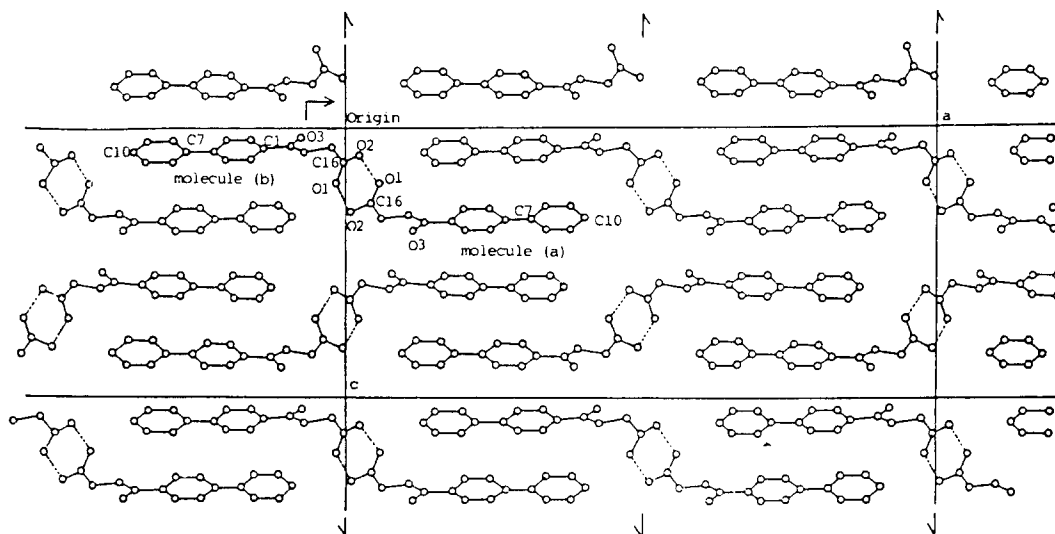


Fig. 5. Molecular packing of fenbufen projected along *b*-axis. The broken lines indicate OH...O type hydrogen bonds.

hexylindan-1-carboxylic acid²⁰⁾ and so on²¹⁻³¹⁾

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