Refinement of the Structure of Alclofenac, 4-Allyloxy-3-Chlorophenyl acetic acid ($C_{11}H_{11}O_3Cl$)

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Abstract □ The structure of alclofenac was determined by single crystal X-ray diffraction analysis. The compound was recrystallized from chloroform solution in monoclinic system, space group C2/c, with $Z=8$, $a=23.349$ (9), $b=14.295$ (3), $c=7.192$ (2) Å, $\beta=111.32$ (3)°, and $d_{obs}=1.29$, $d_{calc}=1.30$. The structure was solved by direct method and refined by least-squares procedure to the final R-value being 0.044 for 1055 reflections ($F \geqq 6\sigma(F)$). The molecules are dimerized by OH···O type hydrogen bonds related by two-fold axis.

Keywords □ Anti-inflammatory agent, Alclofenac, X-ray diffraction, Direct method, Hydrogen bond.

The investigation of the molecular structure of related drugs and elucidation of the relationship between the molecular conformations and their physiological functions are of interest.

4-Allyloxy-3-chlorophenyl acetic acid, alclofenac (Fig.1) is a non-steroidal anti-inflammatory agent which inhibits prostaglandin synthesis (1-3). Some non-steroidal anti-inflammatory drugs show their structural similarities in the carboxyl group and it was reported that the structure of this part may relate to the drug action.

We already presented the molecular structure of this compound briefly (12). This paper deals with the precise structure analysis of alclofenac and comparison of the molecular structure with those of related compounds.

EXPERIMENTAL METHODS

The compound was recrystallized by the evaporation method from chloroform solution as colorless, transparent crystals. The space group was determined from Weissenberg photographs, and lattice constants were obtained from precise measurement on a diffractometer with MoKα radiations. The density was measured by the flotation method in a mixture of benzene and carbon tetrachloride. The crystallographic data are listed in Table I.

Intensities for 1690 independent reflections limited within $\sin\theta/\lambda = 0.601$ Å^{-1} were measured on a computer-controlled automatic four circle diffractometer (Rigaku Denki Co. Ltd.) with Zr-filtered MoK α radiations by ω-2θ scan technique, 3°/min. With a 0.2×0.3×0.6 mm dimensioned crystal.

All the reflections were corrected for usual Lorentz and polarization effects, but no absorption correction being made. Of all 1690 independent reflections, 635 reflections which had $F<6\sigma(F)$ were treated as unobserved.

The structure was solved by direct method using the program *SHELX* 76 (5) on VAX-11/780 computer system at Seoul National University. All the non-hydrogen atoms could be found by the successive Fourier syntheses.

It was refined by full matrix least-squares procedure with isotropic temperature factors, and R-value was decreased from 0.318 to 0.167. Further refinement with anisotropic temperature factors reduced R-value to 0.079.

A difference Fourier synthesis calculated at this

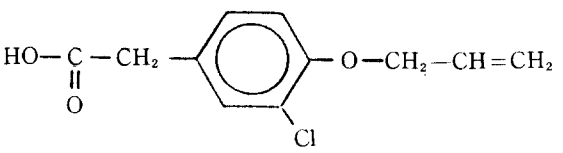


Fig.1. alclofenac.

Table I. Crystallographic data.

4-Allyloxy-3-chlorophenyl acetic acid	
Molecular formula: $C_{11}H_{11}O_3Cl$	M. W. 226.66
Colorless transparent needle	Monoclinic
$a=23.349(9)$Å	$b=14.295(3)$ Å
$c=7.192(2)$ Å	$\beta=111.32(3)°$
Volume of unit cell	2236.2 Å^3
$d_{obs}=1.29$ g/cm^3	$d_{calc}=1.30$ g/cm^3
Space group : C2/c	Z=8

stage revealed all hydrogen atoms, and refinement including hydrogen atoms was continued.

The final R-value was 0.044 for 1055 reflections with $F \geqq 6\sigma(F)$. The average and maximum ratios of parameter shift to e.s.d. after refinement were 0.007 and 0.064 for non-hydrogen atoms, 0.007 and 0.071 for hydrogen atoms, respectively.

The used atomic scattering factors were from *International Tables for X-ray Crystallography* (6).

RESULTS AND DISCUSSION

The final positional and thermal parameters are listed in Table II and Table III, together with their estimated standard deviations. The observed and calculated structure factors are listed in Table IV.

As shown in Fig.2, the bond lengths and angles

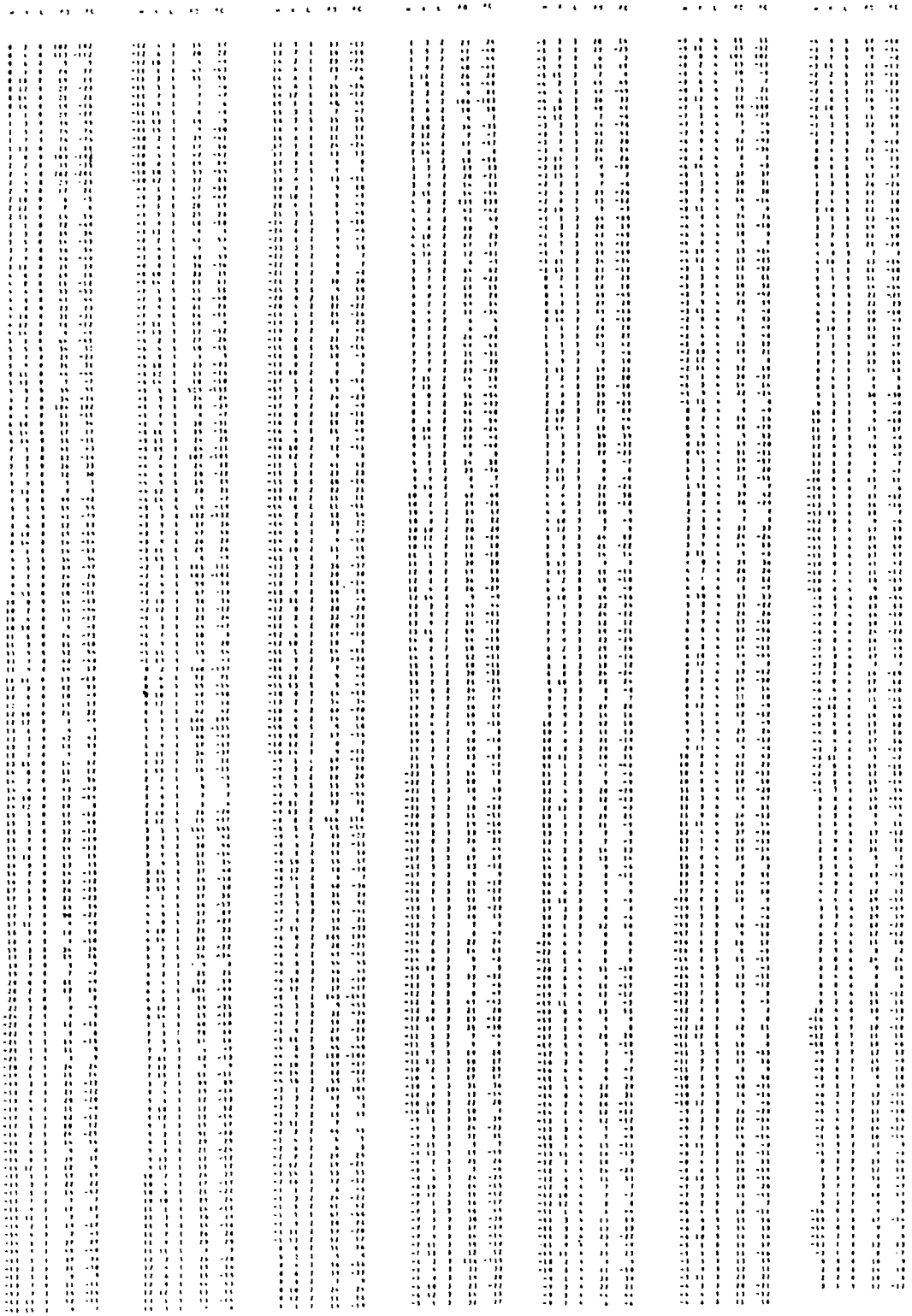
Table III. Fractional coordinates of hydrogen atoms ($\times 10^3$). The isotropic temperature factors are expressed in the form of $\exp(-(8\pi^2U)\sin^2\theta/\lambda^2)$

Atom	bound to	x/a	y/b	z/c	U
H1	C2	323(2)	222(3)	330(6)	79(13)
H2	C4	347(2)	-44(3)	455(5)	66(12)
H3	C5	246(2)	-89(3)	318(6)	81(13)
H4	C7	401(2)	178(3)	567(6)	83(15)
H5	C7	417(2)	79(3)	616(6)	76(14)
H6	C9	142(2)	-108(3)	228(6)	85(14)
H7	C9	164(2)	-109(3)	34(6)	89(14)
H8	C10	60(3)	-52(5)	-125(9)	183(31)
H9	C11	39(3)	-157(4)	178(9)	152(27)
H10	C11	-13(3)	-133(5)	-10(10)	195(33)
H11	O3	532(2)	129(3)	396(7)	143(18)

Table II. Final positional and thermal parameters with their estimated standard deviations in parentheses ($\times 10^4$). The anisotropic temperature factors are expressed in the form of $\exp(-2\pi^2(U_{11}a^{*2}h^2+U_{22}b^{*2}k^2+U_{33}c^{*2}l^2+2U_{12}a^*b^*hk+2U_{13}a^*c^*hl+2U_{23}b^*c^*kl))$

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
CL	1776(1)	2178(1)	1278(2)	962(8)	589(6)	990(9)	42(6)	91(7)	136(6)
C1	2312(2)	1331(3)	2386(5)	741(29)	632(25)	510(22)	5(20)	166(21)	82(22)
C2	2897(2)	1599(3)	3365(6)	864(35)	652(30)	586(26)	-14(22)	193(24)	-51(27)
C3	3339(2)	937(3)	4239(5)	736(29)	859(31)	439(22)	-3(21)	158(20)	-29(26)
C4	3160(2)	10(3)	4099(6)	794(34)	824(33)	520(26)	145(23)	182(24)	177(30)
C5	2574(2)	-270(3)	3113(6)	832(34)	597(27)	548(25)	93(22)	205(24)	48(25)
C6	2135(2)	390(3)	2245(5)	722(28)	593(25)	476(22)	4(20)	197(20)	31(23)
C7	3982(2)	1219(5)	5294(7)	842(33)	1057(43)	553(27)	-34(31)	96(24)	-3(32)
C8	4422(2)	1254(3)	4074(6)	756(30)	745(27)	525(24)	-46(22)	75(23)	-17(22)
C9	1369(2)	-777(3)	1052(8)	880(38)	658(30)	745(33)	15(25)	260(31)	-22(26)
C10	723(3)	-837(4)	-58(10)	905(41)	858(37)	1101(47)	95(34)	114(36)	-184(32)
C11	316(4)	-1318(5)	391(14)	1022(53)	1042(47)	1695(75)	172(47)	322(62)	-100(41)
O1	1545(1)	195(2)	1255(4)	737(19)	594(17)	733(18)	23(14)	126(16)	-8(14)
O2	4267(1)	1309(2)	2327(4)	709(18)	1423(28)	476(16)	-2(18)	52(14)	-155(18)
O3	5006(1)	1256(4)	5022(4)	716(19)	1487(30)	555(15)	54(18)	-14(16)	148(19)

Table IV. Observed and calculated structure factors.



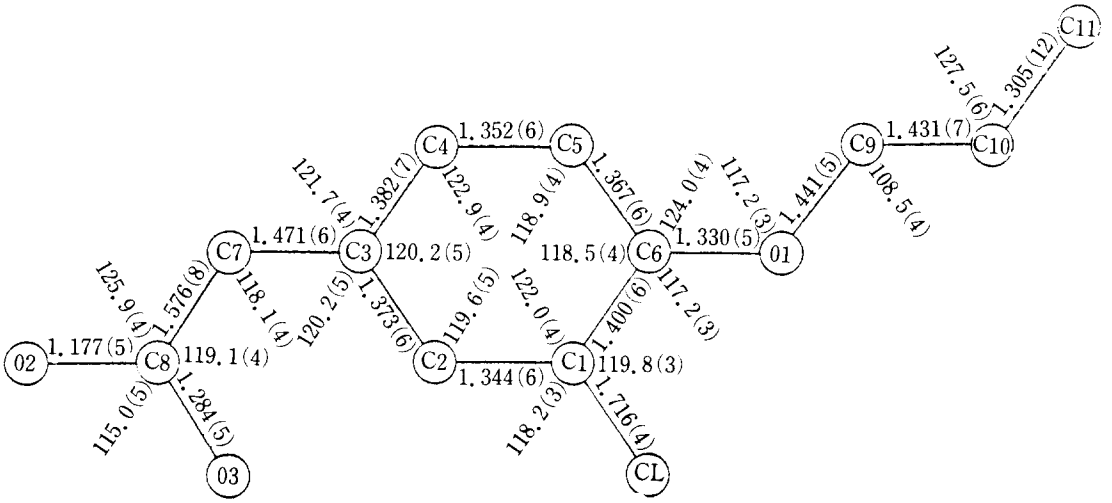


Fig.2. Bond lengths (Å) and angles (°) of alclofenac.
The estimated standard deviations are shown in parentheses.

are reasonable values compared with those of other compounds such as naproxen (7), flurbiprofen (8), indomethacin (9), (2-phenyl-4(*p*-chlorophenyl)-5-thiazolyl) acetic acid (10) and ibuprofen (11) The bond lengths and angles of the acetyl group, the noticed part, in alclofenac and the related compounds are listed in Table V. These values are very similar to those of other compounds.

The benzene ring and carboxyl group are planar. The equations of the two least-square planes and the deviations of the individual atoms from these planes are listed in Table VI. The dihedral angle between these planes is 97.87°. The skeletal conformation of C6, O1, C9, C10 and C11 is trans-trans form. The torsion angles around four bonds are shown in Fig.3.

The molecules are dimerized through the O3-H ---O2 hydrogen bonds (2.798A°) related by two

Table V. Comparison of bond lengths and angles of alclofenac with related compounds.

	Alclofenac	Ibuprofen	Flurbiprofen	Naproxen
Lengths (Å)				
C7-C8	1.567	1.509	1.515	1.539
C8-O2	1.177	1.221	1.206	1.200
C8-O3	1.284	1.305	1.288	1.301
Angles (°)				
C7-C8-O2	125.9	122.9	122.8	123.3
C7-C8-O3	119.1	114.5	114.0	111.5
O2-C8-O3	115.0	122.6	123.2	125.2

Table VI. The equations of the least-square planes of benzene ring and carboxyl group and the deviations of individual atoms from these planes (Å).

Equations: Plane A (benzene ring)
0.52567X − 0.08442Y − 0.84649Z = 0.99428
Plane B (carboxyl group)
−0.01719X + 0.99825Y + 0.05161Z = 1.78381

Deviations: Atom	from Plane A	from Plane
CL	−0.0223	−1.3037
C1*	−0.0017	−0.1165
C2*	0.0024	−0.5138
C3*	−0.0042	0.4147
C4*	0.0050	1.7362
C5*	−0.0042	2.1509
C6*	0.0027	1.2251
C7**	−0.0160	−0.0032
C8**	−1.4114	0.0121
C9	−0.0386	2.9067
C10	−0.0350	3.0098
C11	0.7229	3.6625
O1	0.0058	1.5184
O2**	−2.4454	−0.0043
O3**	−1.4600	−0.0045

* : Atoms used for the calculation of plane A.
* : Atoms used for the plane B.

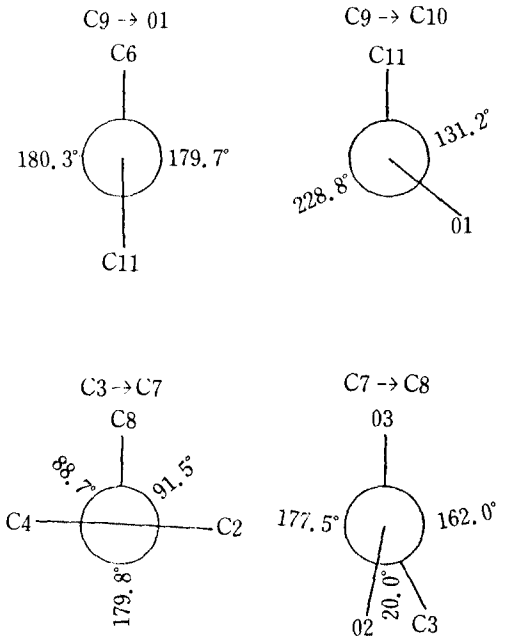


Fig.3. Newman projections of atoms around four bonds.

The arrow indicates the bond direction viewing down from front to back of paper.

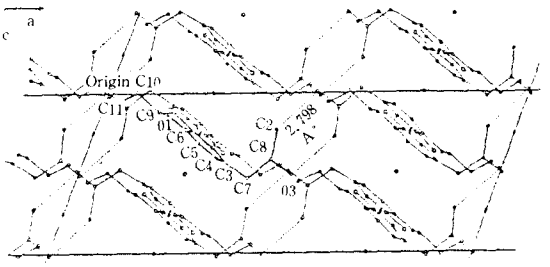


Fig.4. Molecular packing for alclofenac projected along b-axis.

The broken lines indicate hydrogen bonds.

-fold axis, and the intermolecular contacts between adjacent molecules are kept by van der Waals distances. The molecular packing is shown in Fig.4.

LITERATURE CITED

1. Famaey, J.P., Fontaine, J. and Reuse, J.: Effect on high concentrations of non-steroidal and steroidal anti-inflammatory drugs on prostaglandin-induced contraction of the guinea-pig isolated ileum. *Prostaglandins.* **13**, 107(1977).
2. Bray, M.A. and Godon, D.: Prostaglandin production by macrophages and the effect of anti-inflammatory drugs. *Br. J. Pharmac.*, **63**, 635(1978).
3. Lombardino, J.G., Otterness, I.G. and Wiseman, E.H.: Acidic anti-inflammatory agents-correlations of some physical, pharmacological and clinical data. *Arzneim.-Forsch.*, **25**, 1629(1975).
4. Appleton, R.A. and Brown, K.; Conformational requirements at the prostaglandin cyclooxygenase receptor site: A template for designing non-steroidal anti-inflammatory drugs. *Prostaglandins*, **18**, 29(1979).
5. Sheldrick, G.M.: "*The SHELX Crystal Structure Calculation Program*"., Univ. of Cambridge, England(1976).
6. The international union of crystallography: "*International Tables for X-ray Crystallography*", Kynoch press, Birmingham, England (1974).
7. Unpublished results.
8. Flippen, J.L. and Gilardi, R.D.: (±)-2-(2-Fluoro-4-biphenyl) propionic acid (Flurbiprofen). *Acta Cryst.*, **B31**, 926(1975).
9. Kistenmacher, T.J. and Marsh, R.E.: Crystal and molecular structure of an anti-inflammatory agent, Indomethacin, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. *J. Am. Chem. Soc.*, **94**, 1340(1972).
10. Destro, R.: (2-Phenyl-4(*p*-chlorophenyl)-5-thiazolyl) acetic acid. *Acta Cryst.*, **B34**, 959(1978).
11. McConnell, J.F.: 2-(4-Isobutylphenyl) propionic acid. $C_{13}H_{18}O_2$ Ibuprofen or Prufen. *Cryst. Struct. Comm.*, **3**, 73(1974).
12. Kim, Y.B., Kim, S.J. and Kim, B.K.: The molecular structure of Alclofenac determined by X-ray method. *Seoul Univ. J. Pharmac. Sci.*, **9**, 41(1984).