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The Crystal Structure of Pirprofen ($C_{13}H_{14}ClNO_2$), A Non-Steroidal Antiinflammatory Agent

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The molecular structure of pirprofen, 3-chloro-4-(2,5-dihydro-1*H*-pyrrol-1-yl)-α-methylbenzeneacetic acid, was determined by single crystal X-ray diffraction analysis. The compound was recrystallized from a mixture of chloroform and toluene in triclinic, space group $P\bar{1}$, with a=4.577(1), b=11.213(2), c=12.485(2) Å, α=107.39(1), β= 97.79(1), γ=92.03(2), and Z=2. The calculated density is 1.384 g/cm^3. The structure was solved by the direct method and refined by full matrix least-squares procedure to the final R value of 0.034 for 1681 independent reflections. The non-aromatic dihydropyrrol group is found to be coplanar to the central aromatic ring. The molecules are dimerized through the intermolecular hydrogen bonds at the carboxyl group in the crystal.

Key Words : Pirprofen, Antiinflammatory agent, Crystal structure, X-ray diffraction, Hydrogen bond

INTRODUCTION

Pirprofen (Fig. 1) is a non-steroidal antiinflammatory drug (NSAID), related structurally to drugs such as ibuprofen, ketoprofen, and naproxen (Korolkovas, 1988). The compound is widely used in rheumatoid arthritis, osteoarthritis, etc. However gastrointestinal complaints are the side effects reported most frequently as in cases of other NSAIDs (Todd and Beresford, 1986).

It is known that the NSAIDs inhibit prostaglandin biosynthesis, or more specifically the enzyme cyclooxygenase (Bray and Gordon, 1978; Tomlinson *et al.*, 1972). As an attempt to understand the mode of interaction of the drug molecules to the target enzyme, we have determined the 3D structures of some NSAIDs during the days (Kim *et al.*, 1986; 1987; 1988; 1989; 1990; 1993a; 1993b). And in this paper, we are reporting the structure of pirprofen to provide precise and useful informations necessary for the understanding and designing of a more useful NSAID.

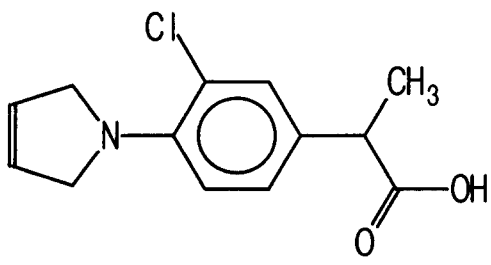

Fig. 1. Pirprofen.

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MATERIALS AND METHODS

The compound was kindly supplied from Searle Ciba-Geigy Korea Ltd. Colorless prismatic crystals were grown by the slow evaporation from a mixture of chloroform and toluene at room temperature. A crystal of suitable size was mounted on an Enraf-Nonius CAD4 diffractometer. After obtaining cell parameters, intensity data within range of $\theta \leq 60^\circ$ were collected precisely. The significant descriptors explaining the experimental procedure in detail are summerized in Table I.

The structure was solved by the direct method with *MULTAN84* (Main *et al*, 1984) and refined by full matrix least squares procedure to the final R value of 0.034 (unit weght) with *SHELX76* (Sheldrick, 1976) and *MolEN* (Fair, 1990). The calculations were performed on a microVAX 3100 and a personal computer. The atomic scattering factors were taken from " *International Tables for X-ray Crystallography*" (The International Union of Crystallography, 1974).

RESULTS AND DISCUSSION

The final atomic coordinates and equivalent iso-

Table I. Descriptors for the experimental procedure

CRYSTAL DATA	
$C_{13}H_{14}ClNO_2$	CuKα radiation
M_r=251.71	λ=1.5418 Å
Triclinic	Cell parameters from 25 reflections
$P\bar{1}$	θ=12.7-31.4°
a=4.577(1) Å	μ=2.592 mm^{-1}
b=11.213(2) Å	T=293°K
c=12.485(2) Å	Prism
α=107.39(1)°	0.22×0.25×0.27 mm
β=97.79(1)°	Colorless
γ=92.03(2)°	
V=603.9(2) $Å^3$	
Z=2	
D_x=1.384 g/cm^3	
D_m=1.38 g/cm^3 by flotation in KI solution	

DATA COLLECTION	
Enraf-Nonius CAD-4 diffractometer	R_{int}=0.021
ω/2θ scans	θ_{max}=60.0°
Absorption correction: none	h=-5→5
1924 measured reflections	k=-12→12
1759 independent reflections	l=0→14
1681 observed reflections [F>3σ (F)]	3 standard reflections frequency: 60 min intensity decay: 1.7 %

REFINEMENT	
Refinement on F	Unit weights applied
R=0.035	$(\Delta/\sigma)_{max}$=0.005
wR=0.034	$\Delta\rho_{max}$=0.256 e/$Å^3$
S=0.394	$\Delta\rho_{min}$=-0.207 e/$Å^3$
1681 reflections	Extinction correction: none
210 parameters	Atomic scattering factors from *International Tables for X-ray Crystallography*
All H-atom parameters refined	

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

$$U_{eq}=(1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i\cdot\mathbf{a}_j$$

Atom	x	y	z	U_{eq}
CL	.5640(2)	.2357(1)	.4814(0)	.076(0)
O(1)	.1166(4)	.5189(2)	.1429(2)	.070(1)
O(2)	-.2548(4)	.3989(2)	.0238(1)	.069(1)
N(1)	.5585(5)	.0004(2)	.2584(2)	.056(1)
C(1)	.0194(5)	.2926(2)	.2297(2)	.042(1)
C(2)	.1891(5)	.3011(2)	.3327(2)	.044(1)
C(3)	.3698(5)	.2064(2)	.3442(2)	.044(1)
C(4)	.3932(5)	.0999(2)	.2550(2)	.044(1)
C(5)	.2199(6)	.0956(2)	.1506(2)	.050(1)
C(6)	.0423(5)	.1888(2)	.1396(2)	.048(1)
C(7)	.7553(7)	-.0148(3)	.3557(2)	.063(1)
C(8)	.8615(7)	-.1401(3)	.3039(3)	.086(1)
C(9)	.7513(7)	-.1918(3)	.1976(3)	.076(1)
C(10)	.5460(7)	-.1079(2)	.1561(2)	.065(1)
C(11)	-.1889(5)	.3936(2)	.2150(2)	.046(1)
C(12)	-.1026(5)	.4417(2)	.1213(2)	.047(1)
C(13)	-.1909(7)	.5029(2)	.3227(2)	.060(1)

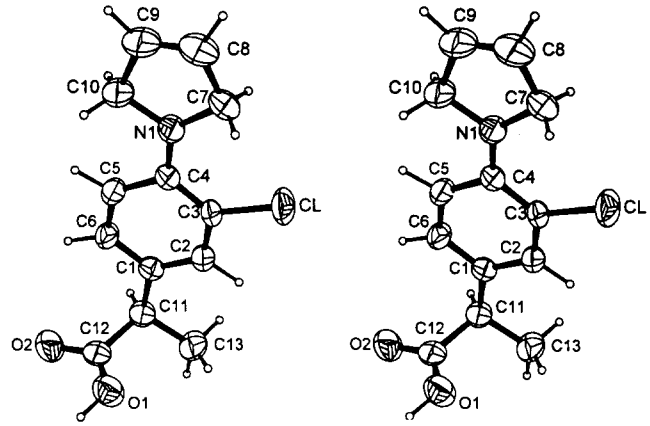

Fig. 2. Stereoscopic view of the molecule drawn by ORTEP (Johnson, 1976) with the atomic numbering scheme. The displacement ellipsoids are drawn at the 50% probability level. H atoms are drawn as small circles of arbitrary radii.

Table III. Selected geometric parameters (Å, °).

C(3)--CL	1.750(2)	C(3)--C(4)	1.387(3)
C(4)--N(1)	1.377(3)	C(7)--C(8)	1.490(4)
C(7)--N(1)	1.469(3)	C(9)--C(8)	1.300(4)
C(10)--N(1)	1.468(3)	N(1)--C(10)	1.468(3)
H(O1)--O(1)	0.85(3)	C(9)--C(10)	1.503(3)
C(7)-N(1)-C(4)	127.9(2)	C(4)-C(3)-CL	123.5(2)
C(10)-N(1)-C(4)	119.9(2)	C(9)-C(8)-C(7)	114.0(2)
C(10)-N(1)-C(7)	112.2(2)	C(9)-C(10)-N(1)	102.1(2)

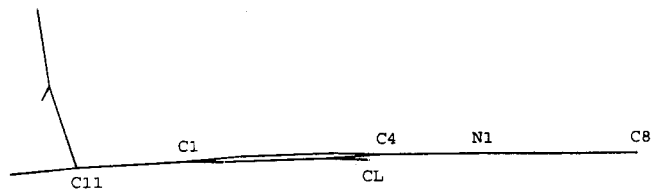

Fig. 3. Side view of the molecule (viewing down from C(7) to C(10)).

tropic temperature factors are listed in Table II. The list of structure factors, anisotropic displacement parameters, hydrogen atomic coordinates and complete geometry are available upon request.

The stereoscopic view of the molecule drawn by *ORTEPII* (Johnson, 1976) together with the atomic numbering scheme is shown in Fig. 2. All of the molecular dimensions are in the reasonable range, and some selected geometric parameters are collected in Table III. The dihydropyrrol group, that is non-aromatic, is quite planar itself ($\sum(\Delta_i)^2$= 2.9×10^{-5} $Å^2$), and which in turn, is nearly coplanar to chlorophenyl ring with the dihedral angle of 2.7°. Fig. 3 shows the planar shape of the molecule clearly. The atoms around the nitrogen also have planar arrangement ($\sum(\Delta_i)^2$= 2.4×10^{-5} $Å^2$) rather than py-

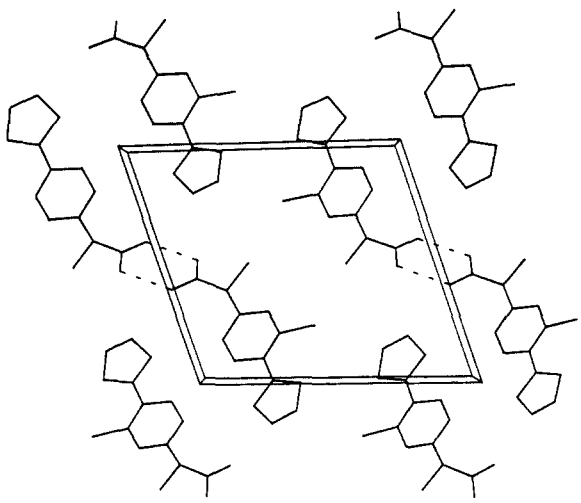

Fig. 4. Crystal packing for pirprofen. The broken lines indicate OH···O type hydrogen bonds.

ramidal, which indicates having more sp^2 character than sp^3 on the nitrogen atom.

The molecular packing is presented in Fig. 4. In the crystal, the molecules are dimerized through the intermolecular hydrogen bonds between the carboxyl groups each other. The distance between O(1) and O(2) at (-x, 1-y, -z) is 2.654(3) Å (H(O1)···O'(2): 1.86(4) Å), and the interatomic angle of ∠O(1)-H(O1)···O'(2) is 156(3)°. The other interatomic distances are in the range of normal *van der Waals'* contacts.

ACKNOWLEDGEMENTS

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