The Crystal Structure of Tolfenamic Acid (C14H12ClNO2), An Antiinflammatory Fenamate

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The structural analysis of tolfenamic acid, 2-[(3-chloro-2-methylphenyl)-amino]benzoic acid, was performed by single crystal X-ray diffraction technique. The compound was recrystallized from a mixture of ether and toluene in triclinic, space group $P2_1/c$, with a=3.914(1), b=22. 020(2), c=14.271(1) Å, β=94.68(1)°, and Z=4. The calculated density is 1.418 g/cm³. The structure was solved by the direct method and refined by full matrix least-squares procedure to the final R value of 0.039 for 1773 independent reflections. In the molecule, carboxyl group at the anthranilic acid is coplanar to the phenyl ring. The dihedral angle between the two aromatic rings of the molecule is 44.2°. The molecules are dimerized through the intermolecular hydrogen bonds at the carboxyl group in the crystal.

INTRODUCTION

Tolfenamic acid (Fig. 1) is a non-steroidal antiinflammatory drug (NSAID), related structurally to drugs such as mefenamic acid, flufenamic acid, and meclofenamic acid. The compound has a modest antiinflammatory activity and mainly used as a short term analgesic. Notable side effects are gastrointestinal complaints and occational hematological complications as in cases of other NSAIDs (Korolkovas, 1988).

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; 1995). And in this paper, we are reporting the structure of the titled compound to provide precise and useful informations necessary for the understanding and designing of a more useful NSAID.

MATERIALS AND METHODS

Yellow prismatic crystals were grown by the slow evaporation from a mixture of ether and toluene at room temperature. A crystal of suitable size was mounted on an Enraf-Nonius CAD4 diffractometer. Lattice parameters were obtained by angular positions of randomly-detected diffraction spots, and intensity data within range of $\theta \le 60°$ were collected using the informations obtained previously. 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. 039 (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).
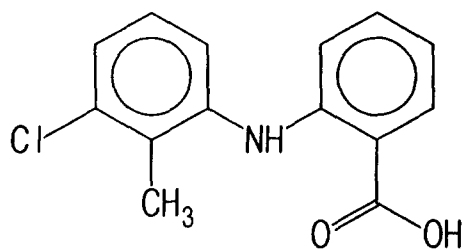

Fig. 1. Tolfenamic acid.

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Table I. Descriptors for the experimental procedure

CRYSTAL DATA

$C_{14}H_{12}ClNO_2$	CuKα radiation
Mr=261.71	λ= 1.5418 Å
Monoclinic	Cell parameters
$P2_1/c$	from 25 reflections
a=3.914(1) Å	θ=13.1-40.6°
b=22.020(2) Å	μ= 2.58 mm^{-1}
c=14.271(1) Å	T=293°K
β=94.68(1)	Yellow prism
V=1225.9(2) Å^3	0.24×0.30×0.26 mm
Z=4	
Dx=1.418 g/cm^3	
Dm=1.42 g/cm^3 by flotation in KI solution	

DATA COLLECTION

Enraf-Nonius CAD-4	R_{int}=0.028
diffractometer	θmax = 60.0°
$\omega/2\theta$ scans	h=-4 → 4
Absorption correction:	k=0 → 14
none	l=0 → 16
1822 measured reflections	3 standard reflections
1797 independent reflections	frequency: 60 min
1773 observed reflections	intensity decay: none
[F>3σ (F)]	

REFINEMENT

Refinement on F	Unit weights applied
R=0.039	$(\Delta/\sigma)_{max}$=0.015
wR=0.036	$\Delta\rho_{max}$=0.173 e/Å^3
S=0.672	$\Delta\rho_{min}$=-0.186 e/Å^3
1773 reflections	Extinction correction: none
211 parameters	Atomic scattering factors
All H-atom parameters	from *International Tables*
refined	*for X-ray Crystallography*

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

$$U_{eq}=(1/3)\sum_i\sum_j U_{ij}{}^*a_i{}^*a_j{}^*a_i a_j$$

| Atom	x	y	z	Ueq
CL	.1682(2)	.1645(0)	.4764(0)	.047(0)
N1	.5449(6)	.3614(1)	.3260(1)	.042(1)
O1	.8923(5)	.5378(1)	.3863(1)	.051(1)
O2	.8155(5)	.4451(1)	.4421(1)	.051(1)
C1	.4776(6)	.2983(1)	.3149(2)	.033(1)
C2	.3585(5)	.2683(1)	.3919(1)	.032(1)
C3	.3130(5)	.2053(1)	.3818(2)	.033(1)
C4	.3768(6)	.1736(1)	.3028(2)	.041(1)
C5	.4983(6)	.2047(1)	.2275(2)	.042(1)
C6	.5523(6)	.2676(1)	.2338(2)	.038(1)
C7	.4891(5)	.4070(1)	.2599(1)	.030(1)
C8	.3122(6)	.3978(1)	.1724(2)	.033(1)
C9	.2685(6)	.4443(1)	.1079(2)	.038(1)
C10	.3974(6)	.5027(1)	.1293(2)	.042(1)
C11	.5633(6)	.5131(1)	.2164(2)	.037(1)
C12	.6119(5)	.4666(1)	.2835(1)	.030(1)
C13	.7760(5)	.4811(1)	.3753(1)	.030(1)
C14	.2826(8)	.3008(1)	.4814(2)	.045(1)

RESULTS AND DISCUSSION

The final atomic coordinates and equivalent isotropic temperature factors are listed in Table II. The
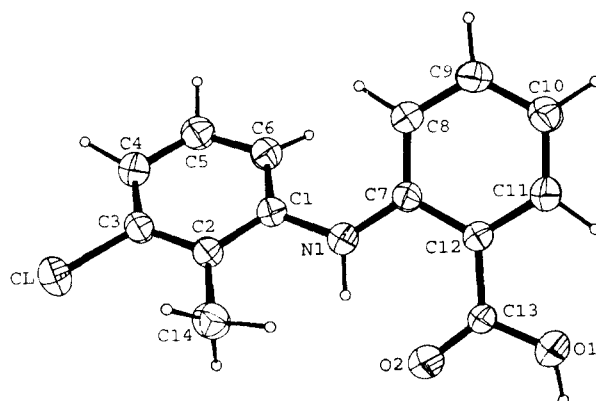
Fig. 2. Perspective view of the molecule drawn by *ORTEP* (Johnson, 1976) with the atomic numbering scheme. The displacement ellipsoids are drawn at the 50% probability level. H atoms are drawn as small circles of arbitrary radii.

Table III. Selected geometric parameters (Å,°)

N(1)--C(1)	1.421(3)	N(1)--C(7)	1.382(3)
C(3)--CL	1.754(2)	C(7)--C(12)	1.430(3)
C(12)--C(13)	1.448(3)	C(13)--O(1)	1.332(3)
C(13)--O(2)	1.240(3)	H(O1)--O(1)	1.03(4)
C(1)-N(1)-C(7)	128.0(2)	C(2)-C(3)-CL	118.2(2)
C(7)-C(12)-C(13)	122.1(2)	O(1)-C(13)-O(2)	119.3(2)
C(7)-N(1)-C(1)-C(6)	41.8(3)		
C(8)-C(7)-N(1)-C(1)	8.5(3)		
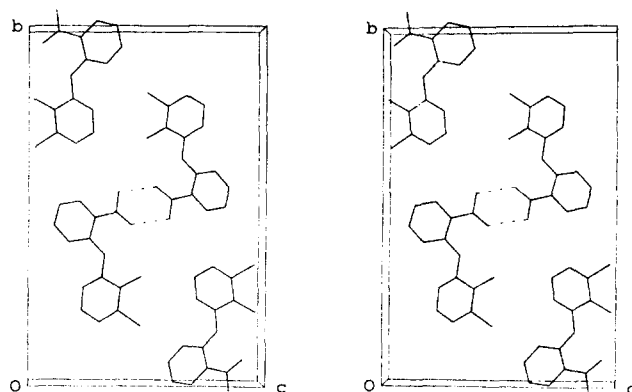
Fig. 3. Crystal packing for tolfenamic acid viewing down along the a-axis. The broken lines indicate OH···O type hydrogen bonds.

list of structure factors, anisotropic displacement parameters, hydrogen atomic coordinates and complete geometry are available upon request.

The atomic numbering scheme and a perspective view of the molecule drawn by *ORTEPII* (Johnson, 1976) 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 carboxyl group at the anthranilic acid is nearly coplanar to phenyl ring with the dihedral angle of

4.3°. The aromatic rings in the molecule are tilted to each other by the dihedral angle of 44.2°. The stereoscopic molecular packing is presented in Fig. 3. In the crystal, the molecules are dimerized through the intermolecular hydrogen bonds between the carboxyl groups. The distance between O(1) and O(2) at (2-x, 1-y, 1-z) is 2.645(3)Å (H(O1)···O'(2): 1.77(4)Å). The other interatomic distances are in the range of normal *van der Waals'* contacts.

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REFERENCES CITED

Bray, M. A. and Gordon, D., Prostaglandin production by macrophages and the effect of antiinflammatory drugs, *Br. J. Pharmac.*, 63, 635-642 (1978).

Fair, C. K., *MolEN: Structure Determination System*, Delft Instruments, The Netherlands, 1990.

Johnson, C. K., *ORTEPII: A FORTRAN Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations (ORNL-5138)*, Oak Ridge National Laboratory, Tennessee, 1976.

Kim, Y. B., Kim, S. J. and Koo, J. H., Refinement of the structure of alclofenac, 4-allyloxy-3-chlorophenylacetic acid ($C_{11}H_{11}O_3Cl$), *Arch. Pharm. Res.*, 9(4), 223-227 (1986).

Kim, Y. B., Song, H. J. and Park, I. Y., Refinement of the structure of naproxen, (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid, *Arch. Pharm. Res.*, 10(4), 232-238 (1987).

Kim, Y. B., Park, I. Y. and Park, Y. H., The crystal structure of fenbufen, 3-(4-biphenylylcarbonyl)propionic acid ($C_{16}H_{14}O_3$), a non-steroidal antiinflammatory agent, *Arch. Pharm. Res.*, 11(2), 127-

133 (1988).

Kim, Y. B., Park, I. Y. and Park, Y. H., The crystal structure of cinmetacin ($C_{21}H_{19}NO_4$), a non-steroidal antiinflammatory agent, *Arch. Pharm. Res.*, 12(1), 52-57 (1989).

Kim, Y. B., Park, I. Y. and Lah, W. R., The crystal structure of naproxen sodium, ($C_{14}H_{13}O_3Na$), a non-steroidal antiinflammatory agent, *Arch. Pharm. Res.*, 13(2), 166-173 (1990).

Kim, Y. B., Kim, J. A. and Park, I. Y., The crystal structure of acemetacin monohydrate ($C_{21}H_{18}NO_6Cl \cdot H_2O$), a non-steroidal antiinflammatory agent. *Arch. Pharm. Res.*, 16(2), 134-139 (1993a).

Kim, Y. B., Kwon, Y. H., Park, I. Y., Lee, B. J. and Kim, C.-K., The crystal structure of tenoxicam (C$_{13}H_{11}N_3O_4S_2$), a non-steroidal antiinflammatory agent, *Seoul Univ. J. Pharm. Sci.*, 18, 1-12, (1993b).

Kim, Y. B. and Park, I. Y.: The crystal structure of pirprofen ($C_{13}H_{14}ClNO_2$), a non-steroidal antiinflammatory agent. *Arch. Pharm. Res.*, 19(1), 71-73 (1996).

Korolkovas, A., Antiphilogistics, In Korolkovas, A. (Eds.), *Essentials of Medicinal Chemistry*, Wiley, New York, 1988, pp. 1091-1103.

Main, P., Germain, G. and Woolfson, M. M., *MULTAN84: A System of Computer Program for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*, Univ. of York, England, 1984.

Sheldrick, G. M., *SHELX76: Program for Crystal Structure Determination*, Univ. of Cambridge, England, 1976.

The International Union of Crystallography, *International Tables for X-ray Crystallography, Vol. III*, Kynoch Press, Birmingham, England, 1974.

Tomlinson, R. V., Ringold, N. J., Qureshi, M. C. and Forchielli, E., Relationship between inhibition of prostaglandin synthesis and drug efficacy: Support for current theory on mode of action of asprin-like drugs, *Biochem. Biophys. Res.*, 46(2), 552-559 (1972).