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X-ray Structure Analysis Online

Crystal Structure of (±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolidine-1-carboxylic acid, Ketorolac

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The title compound, (±)-5-benzoyl-2,3-dihydro-1H-pyrrolidine-1-carboxylic acid, $C_{15}H_{13}NO_3$, also known as Ketorolac, crystallizes in the orthorhombic space group *Pbca* with unit-cell parameters: a = 7.0857(2), b = 8.0605(3), c = 43.9209(13)Å, $\alpha = \beta = \gamma$ 90.0000°, Z = 8. The dihedral angle between the mean planes of the benzyl and pyrrolidine groups is 45.7(9)°. Intermolecular hydrogen bonding C–H···O interactions and π-π stacking interactions between nearby pyrrolidine rings influence the twist angle between these two groups as well as crystal packing effects.

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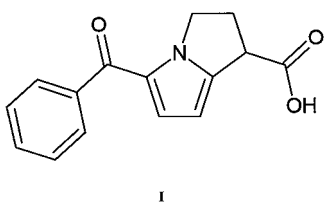
Ketorolac or ketorolac tromethamine (marketed as Toradol—generics have been approved) is a non-steroidal anti-inflammatory drug (NSAID) in the family of propionic acids, often used as an analgesic, antipyretic (fever reducer), and anti-inflammatory agent. Ketorolac acts by inhibiting bodily synthesis of prostaglandins. Ketorolac in its oral and intramuscular preparations is a racemic mixture of (*S*)-(–)-ketorolac, the active isomer, and (*R*)-(+)-ketorolac. An ophthalmic solution of ketorolac is available under the name Acular, and is used to treat eye pain and to relieve the itchiness and burning of seasonal allergies. One of the important features of the non-steroidal anti-inflammatory drug is the presence of a carboxylic acid moiety.[1] Another important structural characteristic is the presence of two aromatic rings spaced by a heteroatom or central ring such as heterocyclic, carbocylic, or aromatic. Studies on carboxylic acid bearing non-steroidal anti-inflammatory drugs reveal that the presence of a carboxylic acid moiety can lead to gastrointestinal problems.[2] In view of the importance of these findings, we report the crystal structure of the title compound, $C_{15}H_{13}NO_3$,

A pure sample of Ketorolac was obtained from CAD Pharma, Bangalore and was crystallized by slow evaporation of the alcoholic solution (M.P.: 425 K). X-ray data were collected with an Oxford Diffraction Gemini R CCD area detector using CrysAlisPro software and graphite-monochromated Mo-K_α (λ = 0.71073 Å) at 296(2)K. The structure was solved by direct methods using SHELXS97.[3] All of the non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2 using SHELXL97.[3] All H atoms were placed in their calculated



I

Fig. 1 Chemical structure of (±)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid (I).

Table 1 Crystal and experimental data

Formula	$C_{15}H_{13}NO_3$
Formula weight	255.26
Crystal color, habit	colorless, prism
Crystal size/mm	0.45 × 0.41 × 0.33
Crystal system	orthorhombic
Space group, Z	*Pbca*, 8
Temperature/K	200(2)
a/Å	7.0857(2)
b/Å	8.0605(3)
c/Å	43.9209(13)
V/Å^3	258.51(14)
D_{calc}/Mg m^{-3}	1.352
No. of reflections [$I > 2\sigma(I)$]	4365
$2\theta_{max}$/° with Mo K_α	65.1
R, R_w [$I > 2\sigma(I)$]	0.0518/0.1205
$(\Delta/\sigma)_{max}$	0.000
$(\Delta\rho)_{max}$/e Å^{-3}	0.207
$(\Delta\rho)_{min}$/e Å^{-3}	–0.269
Measurement	GEMINI (Oxford Diffraction, 2007)
Program system	CrysAlisPro
Structure determination	SHELXS97
Refinement	full-matrix least-squares on F^2 (SHELXL97)

CCDC-680340 contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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Table 2 Selected geometric parameters for I [Å, °]

O(1)-C(7)	1.2286(15)	O(2)-C(15)	1.3143(16)
O(3)-C(15)	1.2153(15)	N(1)-C(11)	1.3515(15)
N(1)-C(8)	1.3860(16)	N(1)-C(14)	1.4633(16)
C(11)-N(1)-C(8)	109.72(10)	C(11)-N(1)-C(14)	114.65(10)
C(8)-N(1)-C(14)	135.46(10)	C(6)-C(1)-C(7)	117.64(12)
C(2)-C(1)-C(7)	123.00(12)	N(1)-C(8)-C(9)	105.99(10)
N(1)-C(8)-C(7)	121.23(11)	C(9)-C(8)-C(7)	132.46(12)
C(14)-N(1)-C(8)-C(9)	176.84(13)	C(14)-N(1)-C(8)-C(7)	-8.8(2)
O(1)-C(7)-C(8)-N(1)	-9.71(19)	C(1)-C(7)-C(8)-N(1)	170.61(11)
O(1)-C(7)-C(8)-C(9)	162.90(14)	C(2)-C(1)-C(7)-O(1)	143.64(14)
C(11)-C(12)-C(15)-O(3)	-99.81(14)	C(13)-C(12)-C(15)-O(3)	16.02(18)
C(13)-C(12)-C(15)-O(2)	-166.87(11)	C(11)-C(12)-C(15)-O(2)	77.31(14)

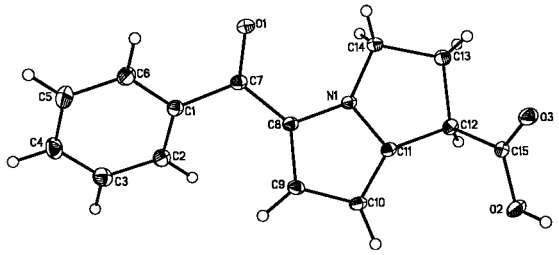

Fig. 2 ORTEP drawing of $C_{18}H_{17}NO_3$ showing the atom numbering scheme and 50% probability displacement ellipsoids.

positions and included in the refinement using the riding model. An absorption correction was performed using CrysAlis RED and all calculations were performed using SHELXTL.[4] A scheme for the molecular structure of I is shown in Fig. 1. Crystal and experimental data are listed in Table 1. Bond lengths, bond angles are all within normal expected ranges. Selected geometric parameters for I are listed in Table 2.

The dihedral angle between the mean planes of the benzyl and pyrrolidine groups is 45.7(9)° (Fig. 2). The mean planes of the carboxyl group and the pyrrolidine ring are separated by a dihedral of 65.9(4)°. Torsion angles of C(13)-C(12)-C(15)-O(3) and C(13)-C(12)-C(15)-O(2) measure 16.02(18)° and –166.87(11)°, respectively. The mean plane of the keto group lies between the mean planes of the pyrrolizine and 5-benzoyl groups with dihedral angles of 13.0(1)° and 35.1(8)°, respectively. The O(1)-C(7)-C(8)-C(9) torsion angle [162.90(14)°] indicates that there is a closer interaction of the *keto* group with the pyrrolidine ring than with the 5-benzoyl group whose torsion angle [C(2)-C(1)-C(7)-O(1)] measures 143.64(14)°.

There are intermolecular C–H···O hydrogen bond interactions (Table 3) between an oxygen atom (O1) from the 5-benzoyl group and a hydrogen atom (H14B) from a nearby pyrrolidine group [C(14)···O(1) (–*x*–1/2, *y*–1/2, *z*) 3.4646(17), C(14)-H14B 0.99, H(14B)···O(1) 2.48 Å, C(14)-H(14B)-O(1) 170.5°] and from an oxygen atom (O3) and a hydrogen atom (H2B) from a nearby carboxylic acid group [O(2)···O(3) (–*x*–1, *y*+1, –*z*) 2.6401(13), O(2)–H2B 0.84, H(2B)···O(3) 1.80 Å, O(2)–H(2B)–O(3) 176.7°] that help stabilize crystal packing in the unit cell. In addition, intermolecular π-π stacking interactions also occur between nearby pyrrolidine rings [Cg1···Cg2 = 3.676(9)Å (1/2–*x*, 1/2+*y*, *z*)] where Cg1 = N1-C8-C9-C10-C11 and Cg2 = N1-C11-C12-C13-C14 providing additional stability to crystal packing.

Table 3 Hydrogen bonds for $C_{15}H_{13}NO_3$ [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2B)...O(3)$^{\#1}$	0.84	1.80	2.6401(13)	176.7
C(14)-H(14B)...O(1)$^{\#2}$	0.99	2.48	3.4646(17)	170.5

Symmetry transformations used to generate equivalent atoms: #1 –*x*+1, –*y*+1, –*z* #2 –*x*–1/2, *y*–1/2, *z*.

MOPAC calculations were performed with MOPAC Pro™ as implemented by WeMO.[5] The AM1 (Austin Model 1) approximation together with the Hartree–Fock closed-shell (restricted) wavefunction was used and minimizations were teminnated at an r.m.s. gradient of less than 0.01 kJ mol^{-1} A^{-1}. When the refined atom coordinates in I are subjected to a MOPAC calculation the angle between the mean planes of the benzyl and pyrrolidine groups becomes 49.3(3)° in the local minimized structure. The dihedral angle between the mean planes of the carboxyl group and the pyrrolidine ring becomes 66.3(9)°, and the dihedral angle between the mean planes of the *keto* group with that of the pyrrolidine and 5-benzoyl groups is 10.9(2)° and 42.6(1)°, respectively. It is clear that intermolecular hydrogen bonding and π-π ring stacking interactions influence this twist angle value for the molecule in this crystal. The repulsion of the H atoms at C2 and C9 is balanced by the π conjugation of the carbonyl and aryl groups as well as from intermolecular hydrogen bonding effects. The difference between the C7-O1 bond length (1.228(6) Å crystal *vs*. 1.24(1) Å MOPAC) indicates slightly different degrees of conjugation of the sp^2 hybridized C7 atom.

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