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Crystal structure and spectroscopic study of 2-[(2,6-dichlorophenyl)amino]phenylacetoxyacetic acid (Aceclofenac)

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The crystal structure of the title compound has been determined. The crystals are monoclinic: $P2_1/n$ (*NO.* 14), $a = 12.279(7)$, $b = 8.223(1)$, $c = 15.504(7)$ Å, $\beta = 96.16(2)°$, $V_c = 1556(2)$ Å^3, $Z = 4$, $D_x = 1.511$ g cm^{-3}, λ = (Mo $K\alpha$) = 0.71069 Å. The structure was solved by direct methods and refined with 1970 reflections to a final R value of 0.057. Analytical, mass, spectral, and physicochemical data are also reported.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDS) are of interest because of their wide therapeutical uses in the treatment of inflammatory and painful diseases of rheumatic and nonrheumatic origin. However, several adverse side effects limit their clinical usefulness, the most frequent being the cause of gastrointestinal disturbances that may lead to discontinuation of the treatment.

2-[(2,6-Dichlorophenyl)amino]phenylacetoxyacetic acid (Aceclofenac, 4) (Vila Casas, 1984) is a recently developed NSAID of arylacetic acid type and structurally related to Diclofenac (1) (Skoutakis *et al.*, 1988), which shows a potent antiinflammatory and analgesic activity, with an improved gastrointestinal tolerance (Grau *et al.*, 1991) well demonstrated in clinical studies (Ballesteros *et al.*, 1990; Cecchettin *et al.*, 1988; Diaz *et al.*, 1988; Movilia, 1989; Torri, 1987).

NSAID mechanism of action seems to proceed through inhibition of the synthesis of prostaglandins from arachidonic acid at the level of cyclooxygenase. From the study of many of the NSAID drugs available, there are some common structural and physicochemical features that appear to be responsible for the activity of this kind of molecules.

From the structural point of view, most of them are carboxylic acids with two aromatic rings capable of adopting a twisted conformation relative to each other (Moser *et al.*, 1990).

Regarding physicochemical properties of these drugs, their acidities (pK values between 4 and 5) and octanol/water distribution coefficients at physiological pH (log P in the range 0.7 to 2.0) are considered optimal for their transport through biological membranes (Dearden, 1985).

The aim of the present paper is to present a better insight on the three-dimensional structural properties of Aceclofenac (4), based on the X-ray determination of its crystal structure and spectroscopic data as well as to relate it to that of other NSAIDs, particularly to Diclofenac free acid (5).

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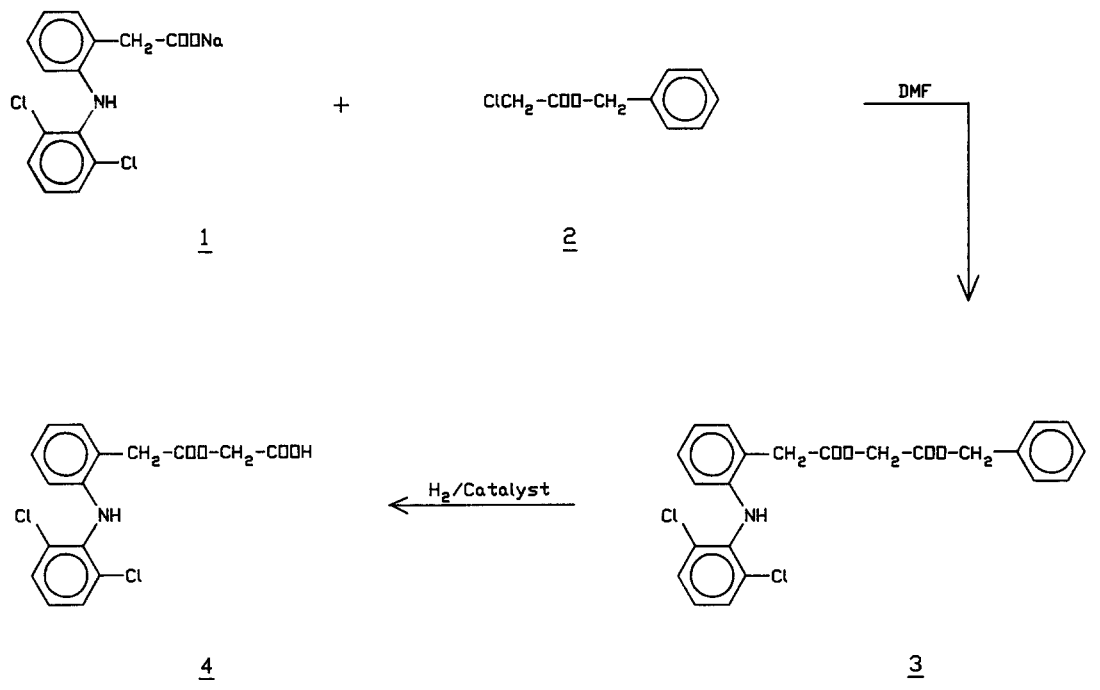


Scheme 1

Experimental

Preparation of crystals

Reaction of sodium Diclofenac (1) with benzyl 2-chloroacetate (2) in dimethylformamide yields Aceclofenac benzyl ester (3). Subsequent catalytic hydrogenolysis of 3 over carbon/palladium under pressure conditions leads to Aceclofenac (4) in good yield (Scheme 1). Purification is carried out by crystallization from toluene.

Colorless monocrystals suitable for X-ray analysis were obtained from a toluene solution (melting point 150–151 °C)

Spectral and microanalytical measurements

The Mass spectrum was obtained using a Hewlett-Packard 5995A instrument at 70 eV. The ir spectrum (KBr disk) was recorded in a 1320 Perkin-Elmer spectrometer. The uv spectrum (MeOH) was determined on a 124 Perkin-Elmer spectrophotometer. The ^{1}H-NMR spectrum (deuterated DMSO) was registered on a Bruker AC-80 operating at 80.1 MHz. The ^{13}C-NMR (deuterated DMSO) was measured on a Varian Geminis 200 operating at 50.3 MHz. CHONCl microanalysis was carried out on a Carlo Erba 1106 instrument. A monocrystal of 0.3 × 0.2 × 0.2 mm was used for the crystal data collection; the monocrystal was mounted on an Enraf–Nonius CAD4 automatic diffractometer. The unit cell parameters were determined by centering 25 reflections ($4 < \theta < 16°$) and refining the orientation matrix by least-squares. A summary of crystal and measurement parameters is shown in Table 1. The intensities

Table 1. Crystal and measurement parameters

$C_{16}H_{13}O_4NCl_2$	M_r = 354.19
a = 12.279(7) Å	Space group $P2_1/n$
b = 8.223(1)	Z = 4
c = 15.504(7)	D_x = 1.511 g · cm^{-3}
β = 96.16(2)°	μ = 4.39 cm^{-1}
V = 1556(2) Å^3	$F(000)$ = 728
Crystal size	0.3 × 0.2 × 0.2 mm
Radiation	Mo $K\alpha$ (λ = 0.71069 Å)
No. of collected reflections	2688
No. of unique reflections	2651
No. of observed reflections	1970 ($I \geq 2.5\sigma(I)$)
Data collection range (θ)	1–25°
Scan method	$\omega/2\theta$
Range of *hkl*	0 14; 0 9; −18 18
Standard reflection decay	0.5%

were corrected for Lorentz and polarization effects but not for absorption.

Physicochemical measurements

Dissociation constant K_a was determined at 25° by potentiometric titration of a 0.05 M methanol/water solution (1:1 v/v) of Aceclofenac (4) with 0.01 M NaOH solution. 1-Octanol/water distribution coefficient was determined at 25° C at physiological pH = 7.4, according to standard procedure (Wang and Lien, 1980).

Determination and refinement of structure

The crystal structure was solved by direct methods using the SHELXS86 program (Sheldrick, 1986). All non-H-atoms were located. The refinement of the structure was carried out by full-matrix least-squares methods using the program SHELX76 (Sheldrick, 1976). The H atoms bonded to carbons were calculated riding on the adjacent atoms assuming C–H = 1.08 Å. The H atoms belonging to the amino and carboxylic groups were found in difference Fourier syntheses. All H were refined with an overall isotropic temperature factor. The anisotropic refinement converged to a conventional $R = 0.057$; $R_w = 0.069$ with $R_w = \Sigma_w(\Delta F^2)/wF_o^2)^{1/2}$; $w = 1/(\sigma^2(F_o) + 1.16 \times 10^{-2}F_o^2))$. $\sigma(F_o)$ were derived from counting statistics. Max. shift/esd = 0.05; $S = 0.75$. Final maximum and minimum heights in the final ΔF map were 0.42 and -0.42 e Å^{-3}. The scattering factors were taken from the *International Tables for X-ray Crystallography* (1974).

Table 2. Final fractional atomic coordinates and equivalent isotropic temperature factors (Å^2) with esd's in parentheses

Atom	X/A	Y/B	Z/C	B^a_{eq}
CL1	0.1686(1)	0.1934(1)	0.9644(1)	3.88
CL2	0.2941(1)	0.8167(1)	1.0222(1)	4.10
C11	0.2224(2)	0.5093(4)	0.9926(2)	2.69
C12	0.1476(3)	0.4014(4)	0.9494(2)	2.97
C13	0.0563(3)	0.4521(4)	0.8968(2)	3.55
C14	0.0372(3)	0.6157(4)	0.8863(2)	3.90
C15	0.1090(3)	0.7276(4)	0.9262(2)	3.78
C16	0.2019(3)	0.6723(4)	0.9779(2)	3.18
N	0.3164(2)	0.4525(3)	1.0424(2)	3.20
C21	0.3344(3)	0.4822(3)	1.1333(2)	2.82
C22	0.4364(3)	0.4377(3)	1.1768(2)	2.68
C23	0.4525(3)	0.4588(4)	1.2660(2)	3.72
C24	0.3744(4)	0.5234(5)	1.3110(2)	4.94
C25	0.2760(4)	0.5768(6)	1.2685(3)	4.89
C26	0.2567(3)	0.5524(5)	1.1797(2)	3.96
C31	0.5249(2)	0.3668(4)	1.1285(2)	3.06
C32	0.5059(3)	0.1873(4)	1.1146(2)	2.92
O33	0.5782(2)	0.0992(2)	1.1644(2)	3.56
O33B	0.4340(2)	0.1305(3)	1.0650(2)	3.74
C34	0.5687(3)	−0.0744(4)	1.1527(2)	3.54
C35	0.6659(3)	−0.1504(4)	1.2016(2)	2.80
O36B	0.7389(2)	−0.0783(3)	1.2415(2)	3.90
H1	0.3377(37)	0.3450(59)	1.0332(28)	5.19
H2	0.7229(36)	−.3686(59)	1.2360(27)	5.19

$^a B_{eq} = \frac{8}{3}\pi^2 \Sigma_i \Sigma_j u_{ij} a_i^* a_j^* \vec{a}_i \cdot \vec{a}_j$

Discussion

Atomic parameters and geometrical data are given in Tables 2 and 3. The molecular structure with the atom numbering is presented in Fig. 1. The bond lengths and

Table 3. Bond lengths (Å) and bond angles (°) with esd's in parentheses

C12–CL1	1.742(3)	C16–C11–C12	116.1(2)
C16–CL2	1.731(3)	N–C11–C12	121.0(3)
C12–C11	1.396(4)	N–C11–C16	122.8(3)
C16–C11	1.378(4)	C11–C12–CL1	118.6(2)
N–C11	1.398(4)	C13–C12–CL1	118.4(2)
C13–C12	1.377(4)	C13–C12–C11	122.9(3)
C14–C13	1.372(5)	C14–C13–C12	119.0(3)
C15–C14	1.374(5)	C15–C14–C13	120.6(3)
C16–C15	1.397(4)	C16–C15–C14	119.0(3)
C21–N	1.424(4)	C11–C16–CL2	120.1(2)
C22–C21	1.406(4)	C15–C16–CL2	117.6(3)
C26–C21	1.381(5)	C15–C16–C11	122.3(3)
C23–C22	1.387(4)	C21–N–C11	121.4(3)
C31–C22	1.502(5)	C22–C21–N	117.8(3)
C24–C23	1.354(6)	C26–C21–N	123.0(3)
C25–C24	1.384(6)	C26–C21–C22	119.3(3)
C26–C25	1.387(5)	C23–C22–C21	118.0(3)
C32–C31	1.507(4)	C31–C22–C21	121.1(3)
O33–C32	1.327(3)	C31–C22–C23	120.8(3)
O33B–C32	1.202(4)	C24–C23–C22	122.0(3)
C34–O33	1.442(4)	C25–C24–C23	120.6(3)
C35–C34	1.482(4)	C26–C25–C24	118.4(4)
O36B–C35	1.191(3)	C25–C26–C21	121.5(3)
O36–C35	1.313(3)	C32–C31–C22	110.0(3)
H1–N	0.937(49)	O33–C32–C31	111.6(2)
H2–O36	1.080(41)	O33B–C32–C31	124.4(2)
		O33B–C32–O33	124.0(3)
		C34–O33–C32	115.3(2)
		C35–C34–O33	107.7(2)
		O36B–C35–C34	125.2(3)
		O36–C35–C34	109.5(2)
		O36–C35–O36B	125.3(3)
		H1–N–C11	117.2(24)
		C21–N–H1	107.2(26)

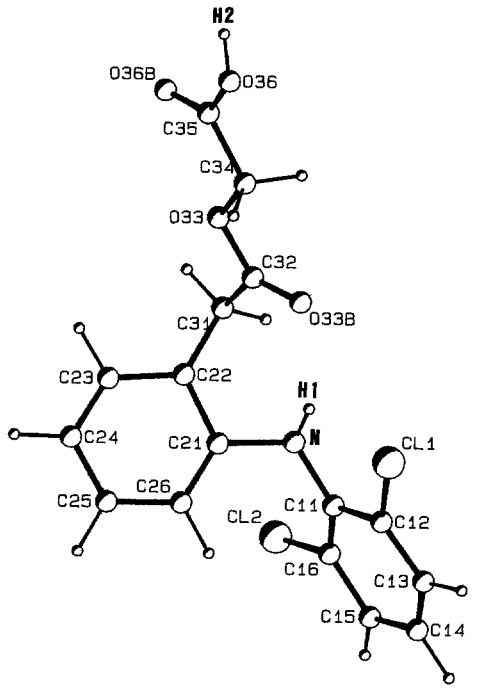


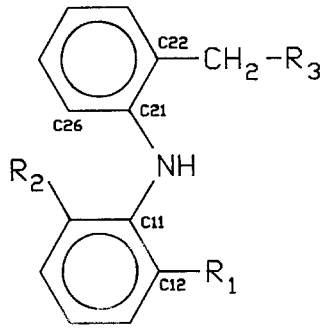
Fig. 1. View of Aceclofenac (4) with atom numbering (PLUTO; Motherwell and Clegg, 1978).

angles found for the title compound are normal for this kind of molecules (Lipka, 1978, 1980). Aceclofenac (4) structural features are compared with those of related compounds in Table 4. In this group of molecules the bond distances and angles as well as the overall conformation are very close to each other; even though Aceclofenac (4) exhibits a longer acid chain (acetoxyacetic instead of acetic) such structural characteristics are in fair coincidence particularly to Diclofenac free acid (5) (Moser *et al.*, 1990). Table 5 shows the comparison of bond distances and angles around the aminic N atom. The angle C—N—C lies in a narrow range near 120° suggesting an sp^2 hybridization for the N atom; however, the aminic H atom is far from planarity as indicated by the angle P (Table 4). The N—H bond is pointing to the carbonilic O33B indicating an intramolecular hydrogen bond. On the other hand, the difference between angles C21—N—H1 and C11—N—H1 is related to the difference between distances N—C21 and N—C11; the greater is the difference in angles, the greater is the difference in bond distances. In Aceclofenac (4), as in 5 and 7, the distance N—C21 is longer than N—C11 suggesting a greater delocalization of the N lone pair toward the chlorinated ring.

All the structures shown in Table 4 related to Aceclofenac (4) present intramolecular hydrogen bonding N—H···O=C; furthermore, all of them except 8, exhibit intermolecular hydrogen bond between carboxylic groups forming dimers; in this association, the carbonylic oxygen is also involved in the intramolecular N—H···O=C quoted above.

In Aceclofenac (4) The situation is different because of the longer lateral chain and the presence of two carbonylic groups; the carbonyl of the ester is exclusively devoted to the intramolecular hydrogen bond; whereas the carboxylic group is exclusively devoted to intermolecular interaction forming infinite chains along the b axis instead of dimers (Table 6).

Table 4. Comparison of aceclofenac (4) with related molecules



	R_1	R_2	R_3	Reference
1[a]	Cl	Cl	COONa	Reck (1988)
5	Cl	Cl	COOH	Rihs (1991)
6	CH_3	CH_3	COOH	Rihs (1991)
7	Cl	H	COOH	Rihs (1991)
8	F	F	COOH	Rihs (1991)
9	H	H	COOH	Rihs (1991)
4	Cl	Cl	$COOCH_2COOH$	This paper

Ranges of structural data for 5 6 7 8 and 9		Aceclofenac (4)
N—C11	1.396—1.424 Å	1.399 Å
N—C21	1.390—1.424 Å	1.441 Å
C21—N—C11	121.7—125.8°	121.4°
Angle P[b]	60 to 74°	51°
T.A. ϕ_1[c]	3 to 16°	6°
T.A. ϕ_2[d]	−114 to −132°	−116°
T.A. ϕ_3[e]	−79 to −83°	−82°
T.A. ϕ_4[f]	64 to 79°	72°
Angle α	58 to 69°	70°

[a] 1 Not included because of poor resolution data (R = 0.18).
[b] Angle P: Angle between the line N—H1 and the plane defined by C21—N—C11.
[c] Torsion angle C26—C21—N—C11.
[d] Torsion angle C12—C11—N—C21.
[e] Torsion angle C21—C22—C31—C32.
[f] Torsion angle C22—C31—C32—O33B.

Table 5. Geometry around N atom

	5	6	7	8	9	4
C21—N—C11	122.1	120.7	121.8	124.3	125.8	121.4°
C21—N—H1	110	120	111	113	122	107°
C11—N—H1	119	114	125	115	107	117°
N—C21	1.423	1.424	1.417	1.404	1.390	1.441 Å
N—C11	1.396	1.424	1.404	1.406	1.407	1.399 Å

Table 6. Hydrogen bonds

(A) Intramolecular N—H···O=C ranges for 5, 6, 7, 8, and 9		Aceclofenac 4
N···O	2.901 to 2.995 Å	3.019 Å
N—H	0.77 to 1.09 Å	0.94 Å
H···O	2.00 to 2.33 Å	2.15 Å
N—H—O	136 to 152°	153°

(B) Intermolecular hydrogen bond	O···O	Symmetry code
5	2.648 Å	$-X+1, -Y-1, -Z+1$
6	2.631 Å	$-X, -Y+1, -Z+2$
7	2.650 Å	$-X+2, -Y+2, -Z+1$
8	No hydrogen bond	
9	2.602 Å	$-X+2, -Y, -Z+1$
Aceclofenac	(4)	
O36···O36B	2.683 Å	$1.5-X, -0.5+Y, 2.5-Z$
O36B···O36	2.683 Å	$1.5-X, 0.5-Y, 2.5-Z$

In the title compound (4), spectral and analytical data are consistent with the proposed structure. Elemental analysis (found: C, 54.29%; H, 3.72%; O, 18.10%; N, 3.91%; Cl, 19.98%) agrees with the empirical formula $C_{16}H_{13}O_4NCl_2$ (Calcd.: C, 54.23%; H, 3.70%; O, 18.07%; N, 3.97%; Cl, 20.02%). The mass spectrum exhibits the molecular ion (M^+) at $m/z = 353$ (according to Aceclofenac empirical formula) and peaks at $M^+ + 2$ and $M^+ + 4$ with abundances in agreement with the presence of two chlorine atoms.

The UV spectrum was registered in two different solvents, both showing only one band: methanolic solution $\lambda_{max} = 274$ nm $\epsilon = 12120$; HCl 0.1N solution $\lambda_{max} = 272$ nm $\epsilon = 9573$.

The IR spectrum recorded in KBr pellet reveals as main information the presence of two carbonyl groups: an ester group (C=O stretching 1770 cm^{-1}) a carboxylic acid group (C=O stretching 1720 cm^{-1}), and associated OH stretching vibration (3400–2500 cm^{-1}). Other important bands are 3320 (N—H stretching) and 1500, 1580, 1590 cm^{-1} (C=C stretching).

Table 7. ^{13}C nmr spectral data (values in δ scale).

C=O	171.0, 169.0
C_{ar}—N	142.9, 137.2
C_{ar}—H[a]	131.0, 129.2, 127.9, 126.0, 120.8, 116.1
C_{ar}—Cl,[a] C_{ar}—C[a]	130.7, 123.1
C—CH_2—O	61.1
C—CH_2—C	36.7

[a]Based on DEPT experiment.

The ^1H nmr peaks (values in δ scale) are compatible with the structure 4: 3.92 ppm (s, 2H, Ar—CH_2—COO); 4.65 ppm (s, 2H, COO—CH_2—COO); 6.30–6.80ppm (broad abs, 1H, NH) exchangeable with D_2O; 6.80–7.58 ppm (m, 7H, aromatic H); 8.60–8.90 ppm (broad abs, 1H, COOH) exchangeable with D_2O. The ^{13}C-nmr spectral data are given in Table 7. The physicochemical measurements carried out on Aceclofenac also are in the range found for other NSAIDS drugs; concretely the pK was 4.7 and the distribution coefficient 1-octanol/water gave a log P = 1.23.

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Structure factor data have been deposited with the British Library, Boston Spa, Wetherby, West Yorkshire, UK as supplementary publication No. 63176 (16 pages).