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Crystal Structure of 3-[4-(2-Ethoxy-2-phenylethyl)-1-piperazinyl]-2-methyl-1-phenyl-1-propanone (Eprazinone) dihydrochloride, $C_{24}H_{32}N_2O_2 \cdot 2HCl$

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The crystal structure of eprazinone dihydrochloride, $C_{24}H_{32}N_2O_2 \cdot 2HCl$, has been determined from 2102 independent reflections collected on an automated Nonious CAD-4 diffractometer using graphite-monochromated Mo-Kα radiation. The crystals are monoclinic, space group $P2_1/n$, with unit cell dimensions $a=11.381(2)$, $b=28.318(2)$, $c=7.840(1)$ Å, $\beta=92.45(2)°$, $\mu=2.37$ cm^{-1}, $F(000)=968$, and $Z=4$. Final R value is 0.071 for independent 2102 observed reflections. The molecule assumes an extended conformation. The piperazine ring has a normal chair conformation and the four carbon atom are planar with a maximum displacement of 0.004 Å for C(18) atom. The two chloride ions are hydrogen bonded to the two piperazine nitrogen atoms [N(14)···Cl(1); 2.986(6) Å, N(17)···Cl(2); 3.084(8) Å].

Introduction

Eprazinone dihydrochloride is a well known antitussive agent[1,2]. We performed the crystal structure determinations of the title compound to gain an understanding of the conformational properties of the compounds containing a piperazine ring in the solid state.

Experimental

The colourless rectangular crystals were grown from a methyl alcohol solution by slow evaporation. The density was determined by flotation methods in a mixture of carbon tetrachloride and acetone. The oscillation and Weissenberg photographs with Cu-Kα radiation ($\lambda=1.5418$ Å) showed the monoclinic symmetry of the crystals and yielded approximate lattice constants. A crystal with approximate dimensions of $0.3\times0.45\times0.25$ mm was selected for data collection. The intensity data were collected on an Enraf-Nonious CAD-4 diffractometer with graphite monochromated Mo-Kα radiation. The intensity of 2136 unique reflections were collected by the ω-2θ scan mode with $\Delta\omega=(0.8+0.34\ \tan\theta)°$ in indices range of $0\leq h\leq 10$, $0\leq k\leq 27$, $-7\leq l\leq 7$. Three standard reflection (0 12 −2), (1 −2 3), (5 2 1) were measured after every 150 reflections during the data collection and showed only small random deviations about their mean intensities. The lattice constants were refined by least-squares refinement from the measured θ values for 25 well centered reflections in the 2θ range of 16-24°. The intensity data were converted to structure factors by the application of Lorentz and polarization factors, and no absorption corrections were applied.

Of the total of 2136 independent intensities measured in the rnge of $3<2\theta<48°$, 2102 reflection with $F_o>3\sigma(F_o)$ were used in the solution and refinement of the structure. The structure was solved by direct method **(SHELXS)**[3] and refined by full-matrix least-squares method **(SHELX)**[4] with anisotropic temperature factors for non-hydrogen atoms and isotropic temperature factors for hydrogen atoms. The unit weight scheme was used throughout the refinement procedure. The hydrogen atoms were located from a difference Fourier synthesis and the positional parameters were refined. The positions of six hydrogen atoms of two methyl groups were calculated assuming an idealized geometry and C-H distances of 1.08 Å. The refinement converged at the final residuals $R=0.071$ and $R_W=0.065$. The maximum residual density in the final difference map is 0.44 eÅ^{-3} near the chloride anion. The atomic scattering factors were taken from *International Tables for X-ray Crystallography*(1974)[5]. All computations were performed on a CYBER 930 NOS/VE computer at Dongguk University.

Results and Discussion

The atomic fractional coordinates for non-hydrogen atoms with equivalent isotropic thermal parameters and the molecular dimensions are listed in Tables 1 and 2, respectively. An **ORTEP**[6] drawing of eprazinone dihydrochloride with atomic numbering scheme is shown in Figure 1 and the **PLUTO**[7] stereoscopic drawing of the crystal packing is shown in Figure 2. The selected torsion angles and the hydrogen bond data are given in Table 3. The C-H bond lengths range from 0.75(8) to 1.14(7) Å. The C-C bond lengths in the two benzene rings vary from 1.344(17) to 1.429(12) Å. The two benzene rings are planar with maximum deviations of 0.012(12) and 0.015(10) Å.

The piperazine ring has a normal chair conformation (average of the absolute values of the intracyclic torsion angle; 58.4(7)°). The four carbon atoms, C(15), C(16), C(18) and C(19), of the piperazine ring form a good plane with a maximum deviation of 0.004(2) Å for C(18). The N(14) and N(17) atoms are displaced from this plane by 0.695 and −0.683 Å, respectively. In the piperazine ring, the mean C-N bond length, 1.496(10) Å, is larger (3σ) than 1.467 Å in PZ[a], 1.464 Å in *cis*-DDP[b], 1.459 Å in *trans*-DDP[c], 1.450 Å in DNP[d] and 1.467 Å in COR-3441[e] [9-13]. The average bond length of

*Tables of anisotropic thermal parameters, H atom parameters, distances and angles involving H atoms, least-squares and the observed and calculated structure amplitudes are available as supplementary materials from the authors (total p. 20).

[a] PZ=piperazine, [b] *cis*-DDP=*cis*-1,4-dibenzoyl-2,5-dimethylpiperazine, [c] *trans*-DDP=*trans*-1,4-dibenzoyl-2,5-dimethylpiperazine, [d] DNP=1,4-nitrosopiperazine, [e] COR-3441=({[(o-methoxyphenyl)-4-piperazinyl-1]-2ethyl}-2-anilino)-3-isobenzofurannone-1(3H)[9-13].

1.516(12) Å for the C-C bonds is in good arreement with 1.512 Å in COR-3441, 1.515 Å in DNP and 1.517 Å in *trans*-DDP.

The N···N distance of 2.905(8) Å is slightly longer (2σ)

Table 1. Atomic Fractional Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Parameters ($Å^2 \times 10^3$) for Non-H Atoms with e.s.d. in Parentheses

Atom	*x*	*y*	*z*	U_{eq}
Cl(1)	4576(2)	−328(1)	2335(2)	57
Cl(2)	10257(2)	431(1)	2639(3)	57
C (3)	6228(10)	1824(4)	−1132(13)	107
C (4)	5424(8)	1517(4)	−231(14)	71
O (5)	6007(4)	1319(2)	1224(6)	51
C (6)	5287(7)	1022(3)	2228(10)	45
C (7)	4347(7)	1305(3)	3096(11)	51
C (8)	3168(8)	1200(3)	2767(12)	64
C (9)	2305(9)	1454(4)	3577(15)	80
C (10)	2628(11)	1805(4)	4650(17)	92
C (11)	3786(10)	1918(3)	5037(13)	78
C (12)	4634(8)	1658(4)	4194(13)	68
C (13)	6103(7)	793(3)	3518(10)	46
N (14)	6598(5)	333(2)	2929(7)	37
C (15)	7244(7)	361(3)	1332(10)	43
C (16)	7628(7)	−130(3)	796(10)	47
N (17)	8396(5)	−356(2)	2180(7)	40
C (18)	7747(7)	−374(3)	3789(11)	45
C (19)	7378(7)	115(3)	4315(10)	46
C (20)	8775(7)	−846(3)	1646(10)	47
C (21)	9811(6)	−1020(3)	2731(10)	44
C (22)	10996(6)	−836(3)	2102(12)	62
C (23)	9861(7)	−1561(3)	2711(11)	53
O (24)	9290(6)	−1771(2)	1604(9)	88
C (25)	10667(7)	−1800(3)	3955(11)	49
C (26)	10980(7)	−1626(3)	5530(13)	60
C (27)	11739(9)	−1865(4)	6620(15)	97
C (28)	12208(10)	−2294(5)	6155(21)	83
C (29)	11896(11)	−2468(4)	4606(23)	99
C (30)	11129(9)	−2246(3)	3504(15)	76

Table 2. The Bond Lengths (Å) and angles(°) for Non-H Atoms

(a) Bond length

C(3)-C(4)	1.465(15)	C(4)-O(5)	1.412(12)
O(5)-C(6)	1.433(10)	C(6)-C(7)	1.520(12)
C(6)-C(13)	1.492(11)	C(6)-C(8)	1.386(12)
C(7)-C(12)	1.351(14)	C(8)-C(9)	1.392(14)
C(9)-C(10)	1.344(17)	C(10)-C(11)	1.376(17)
C(11)-C(12)	1.401(14)	C(13)-N(14)	1.500(10)
N(14)-C(15)	1.481(10)	N(14)-C(19)	1.506(10)
C(15)-C(16)	1.523(12)	C(16)-N(17)	1.507(10)
N(17)-C(18)	1.490(10)	N(17)-C(20)	1.518(10)
C(18)-C(19)	1.510(12)	C(20)-C(21)	1.506(11)
C(21)-C(22)	1.545(10)	C(21)-C(23)	1.534(12)
C(23)-O(24)	1.217(11)	C(23)-C(25)	1.475(12)
C(25)-C(26)	1.364(13)	C(25)-C(30)	1.419(12)
C(26)-C(27)	1.368(14)	C(27)-C(28)	1.383(18)
C(28)-C(29)	1.345(23)	C(29)-C(30)	1.356(18)

(b) Bond angle

O(5)-C(4)-C(3)	110.2(8)	C(6)-O(5)-C(4)	114.7(6)
C(7)-C(6)-O(5)	111.4(7)	C(8)-C(7)-C(6)	119.7(8)
C(9)-C(8)-C(7)	119.9(9)	C(10)-C(9)-C(8)	119.3(10)
C(11)-C(10)-C(9)	122.9(11)	C(11)-C(12)-C(7)	122.6(9)
C(12)-C(7)-C(6)	121.4(7)	C(12)-C(7)-C(8)	118.9(9)
C(12)-C(11)-C(10)	116.4(9)	C(13)-C(6)-O(5)	106.0(6)
C(13)-C(6)-C(7)	110.7(7)	N(14)-C(13)-C(6)	110.1(6)
C(15)-N(14)-C(13)	114.9(6)	C(16)-C(15)-N(14)	110.1(6)
N(17)-C(16)-C(15)	110.7(6)	C(18)-N(17)-C(16)	109.4(6)
C(18)-C(19)-N(14)	109.9(6)	C(19)-N(14)-C(13)	110.5(6)
C(19)-N(14)-C(15)	109.6(6)	C(19)-C(18)-N(17)	110.7(7)
C(20)-N(17)-C(16)	110.6(6)	C(20)-N(17)-C(18)	111.1(6)
C(21)-C(20)-N(17)	111.6(6)	C(22)-C(21)-C(20)	112.4(7)
C(23)-C(21)-C(20)	110.5(7)	C(23)-C(21)-C(22)	107.5(6)
O(24)-C(23)-C(21)	118.5(7)	C(25)-C(23)-C(21)	118.3(7)
C(25)-C(23)-O(24)	123.0(8)	C(26)-C(25)-C(23)	124.4(8)
C(27)-C(26)-C(25)	121.4(9)	C(28)-C(27)-C(26)	120.7(11)
C(29)-C(28)-C(27)	118.1(12)	C(29)-C(30)-C(25)	119.3(11)
C(30)-C(25)-C(23)	118.0(8)	C(30)-C(25)-C(26)	117.6(8)
C(30)-C(29)-C(28)	122.9(12)		

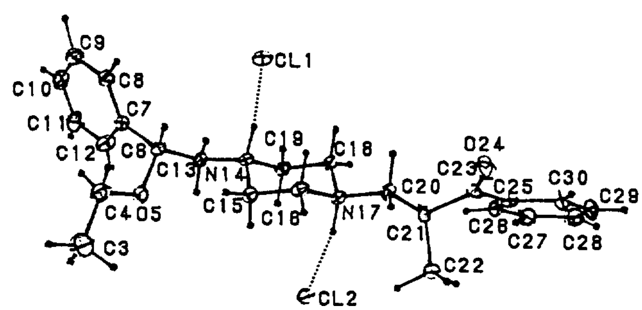

Figure 1. An ORTEP drawing of eprazinone dihydrochloride with atomic numbering scheme. The dotted line denotes the hydrogen bond.

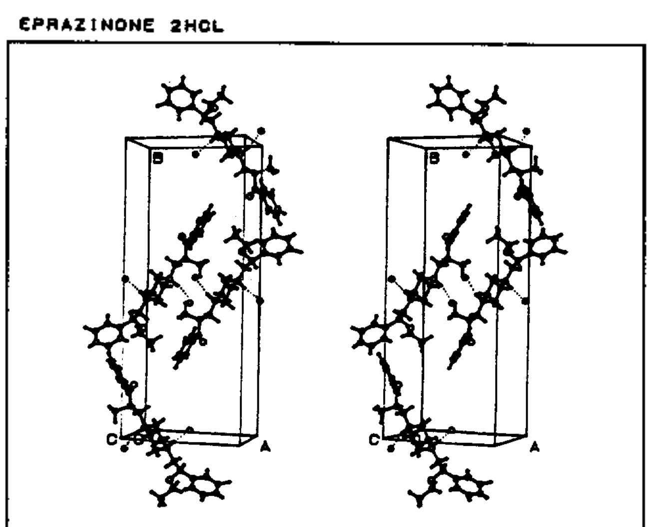

Figure 2. A stereoscopic molecular packing drawing.

Table 3. The Selected Torsion Angles (°), Hydrogen Bond Length (Å) and Angles (°) in the title Compound

C(4)-O(5)-C(6)-C(7)	−68.1(8)	O(5)-C(6)-C(7)-C(8)	120.7(10)
C(13)-C(6)-C(7)-C(8)	−121.6(10)	O(5)-C(6)-C(13)-N(14)	−90.0(7)
C(7)-C(6)-C(13)-N(14)	149.0(9)	C(6)-C(13)-N(14)-C(15)	57.4(7)
C(6)-C(13)-N(14)-C(19)	−178.0(9)	C(13)-N(14)-C(15)-C(16)	−176.0(9)
C(15)-C(16)-N(17)-C(20)	178.8(8)	C(16)-N(17)-C(20)-C(21)	162.9(8)
C(18)-N(17)-C(20)-C(21)	−75.4(7)	N(17)-C(20)-C(21)-C(22)	−83.4(7)
N(17)-C(20)-C(21)-C(23)	156.5(9)	C(20)-C(21)-C(23)-C(25)	−168.2(10)
C(22)-C(21)-C(23)-C(25)	68.9(8)	C(21)-C(23)-C(25)-C(26)	29.9(8)
O(24)-C(23)-C(25)-C(26)	−154.8(14)		
	N···Cl	H···Cl	∠N-H···Cl
N(14)-H(14)···Cl(1)	2.986(6)	2.00(6)	174(5)
N(17)-H(17)···Cl(2)	3.084(6)	2.10(6)	166(5)

than 2.746 Å in DNP and 2.806 Å in *trans*-DDP. The average C-N-C bond angle of 109.5° is in good agreement with 109.8° in COR-3441. But this is slightly smaller than 116.6° in DNP, 115.7° in *cis*-DDP and 113.8° in *trans*-DDP. These differences in the molecular dimensions of the piperazine ring may be attributed to the fact that the two nitrogen atoms are hydrogen-bonded to the two chloride anions [N(14)···Cl(1); 2.986 (6) Å, N(17)···Cl(2); 3.084(8) Å]. There are only these two hydrogen bonds in the crystal lattice.

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Optically Active Intermediate from the Degradation of (−)-Laudanosine, a Benzylisoquinoline Alkaloid, with Ethyl Chloroformate

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Degradation of (−)-laudanosine, a 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloid, with ethyl chloroformate (ECF) afforded an optically active chloro-carbamate as an intermediate. The reason why this intermediate exhibits an optical activity was investigated by comparison with the reactions of some model compounds with ECF. It may be supposed that the chloride group in a hypothetic carbenium ion intermediate stands very closely to the chiral center, so conserving optical activity. However, a neighboring group effect can not be excluded.

Introduction

Gadamer and Knoch[1] have reported that (−)-laudanosine (**1**), a 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloid, was treated with ethyl chloroformate (ECF) and KOH in ether at room temperature to give a (+)-rotating organic phase,