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Conformational Study of a Histamine H₂-Receptor Antagonist: Crystal Structures of 2-Acetoxy-*N*-[3-[*m*-(1-piperidinomethyl)-phenoxy]propyl]acetamide (Roxatidine Acetate) and Its Hydrochloride Salt

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As a part of studies aimed at elucidating the stereostructure-inhibitory activity relationship of histamine H₂-receptor antagonists, the crystal structures of 2-acetoxy-*N*-[3-[*m*-(1-piperidinomethyl)phenoxy]propyl]acetamide (roxatidine acetate) and its hydrochloride salt have been analyzed by the X-ray diffraction method. The neutral and cationic molecules both have similar extended conformations, implying that the molecular conformation of roxatidine acetate is little affected by the hydrochloride salt formation. This is an important difference compared with other H₂-antagonists such as cimetidine and famotidine, where a drastic change has been observed between the neutral and cationic molecular conformations. Based on the present X-ray and related data, the possibility of multiple binding sites on the H₂-receptor is discussed.

Keywords—roxatidine acetate; roxatidine acetate hydrochloride; crystal structure; X-ray analysis; molecular conformation

The therapeutic success of cimetidine as a histamine H₂-receptor antagonist has stimulated the development of more potent and/or long-lasting antagonists such as ranitidine and famotidine. Some potent antagonists have nonimidazole structures and possess a longer side chain than the aminoethyl one of histamine. Based on the stereostructure-inhibitory activity relationship of a series of cimetidine^{1,2)} and famotidine³⁾ analogues, it has been shown that the molecular conformation of neutral antagonists revealed by X-ray crystal analysis reflects, to some extent, the folded form suitable for binding to the receptor, although the crystal structure of the cationic molecule such as the hydrochloride salt always shows the nonactive extended conformation. The large conformational change caused by the formation of the acid (*i.e.*, by the protonation of the polar atom) appears to be a common feature of the antagonists shown in Chart 1: they all have three fundamental substructures: (1) the substituted heteroaromatic ring, (2) the connection *via* a methylthioethyl chain to an end group, and (3) an essentially neutral urea-like end group.

Recently, 2-acetoxy-*N*-[3-[*m*-(1-piperidinomethyl)phenoxy]propyl]acetamide (roxatidine

TABLE I. Summary of Crystal Data and Intensity Measurement Conditions

	1	2
Formula	$C_{19}H_{28}N_2O_4$	$C_{19}H_{28}N_2O_4 \cdot HCl$
F_w	348.44	384.90
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/a$	$Pbca$
Cell constant		
a (Å)	10.677 (7)	7.028 (1)
b (Å)	9.582 (5)	9.486 (1)
c (Å)	18.571 (9)	60.030 (9)
β (deg)	91.00 (5)	—
V (Å ³)	1900 (5)	4002 (1)
Z	4	8
D (measd) (g·cm ⁻³)	1.210 (2)	1.268 (1)
D (Calcd) (g·cm ⁻³)	1.218	1.278
μ (CuK α) (cm ⁻¹)	4.87	19.10
$F(000)$	752	1648
Crystal size (mm ³)	0.3 × 0.2 × 0.3	0.3 × 0.2 × 0.4
Obsd data range	2° < 2 θ < 130°	2° < 2 θ < 130°
Scan speed (in 2 θ) (deg·min ⁻¹)	4	4
Scan range (in θ) (deg)	(1.10 + 0.15 tan θ)	(1.35 + 0.15 tan θ)
No. of obsd data	3032	3225
No. of data with $F_o > 3\sigma(F_o)$	2756	2924
R	0.072	0.091
R_w	0.088	0.126
S	2.785	1.085

Results

Molecular Structure

Bond lengths and angles of roxatidine acetate (**1**) and its hydrochloride salt (**2**) are given in Table III. Compared with the accepted data,⁹ these values are all in the usual region within their estimated standard deviations. A characteristic difference between **1** and **2** can be seen in the bonding parameters around the piperidine N5 atom (N5–C6, N5–C7 and C7–C8 lengths and C4–N5–C7 angle), and this is mainly a result of the difference of N5 binding environment: the tertiary N in **1** and the quaternary one in **2**. Another notable difference observed between the C11–C12–O14 and C13–C12–O14 bond angles would be due to the reverse orientation of the side chain with respect to the benzene ring in **1** and **2**.

Stereoscopic drawings of **1** and **2** are shown in Fig. 1. The relevant torsion angles are given in Table IV. The most significant difference between the **1** and **2** molecular conformations is the ω_3 torsion angle: the C12–C13 bond of **1** takes a *cis* orientation with respect to O14–C15, while that of **2** takes a *trans* one. The torsion angles of ω_4 – ω_{11} in **1** are all in the *trans* region and consequently form a plane consisting of the C12–O14–C15–C16–C17–N18–C19–C21–O22–C23–C25 bond sequence. This plane is almost coplanar with the benzene ring: their dihedral angle = 4.7(2)°. On the other hand, the ω_5 torsion angle of **2** takes a *-syn.clinal* conformation, consequently folding over the extended acetoxypyrrolacetamide side chain at the C15–C16 bond. The C15–C16–C17–N18–C19–C21 bond sequence is nearly planar and takes a dihedral angle of 63.5(3)° to the benzene ring.

The orientations of the piperidine ring with respect to the benzene ring are nearly the same. The piperidine ring, which takes a chair form and is equatorially connected to the C7 atom, is linked to the benzene ring with (ω_1 , ω_2) torsion angles of (*-syn.clinal*, *anti.clinal*) for **1** and **2**; the angle between the benzene ring and the C2–N5 bond vector is –38.5° for **1** and

TABLE II. Final Atomic Coordinates of **1** (Upper) and **2** (Lower)
(e.s.d.s in Parentheses)

Atom	x	y	z	$B_{eq}^{a)}$
C(1)	0.2982 (4)	0.5512 (4)	0.0350 (2)	6.7 (2)
C(2)	0.2391 (4)	0.6924 (4)	0.0196 (2)	7.0 (2)
C(3)	0.0982 (4)	0.6829 (4)	0.0305 (2)	6.2 (2)
C(4)	0.0716 (3)	0.6272 (4)	0.1054 (2)	5.8 (2)
N(5)	0.1308 (2)	0.4915 (3)	0.1175 (1)	4.2 (1)
C(6)	0.2654 (3)	0.4999 (4)	0.1093 (2)	4.9 (2)
C(7)	0.1005 (3)	0.4382 (4)	0.1891 (2)	5.3 (2)
C(8)	0.1368 (3)	0.2870 (4)	0.1980 (2)	4.4 (2)
C(9)	0.0767 (3)	0.1856 (4)	0.1578 (2)	5.6 (2)
C(10)	0.1080 (4)	0.0469 (4)	0.1678 (2)	6.2 (2)
C(11)	0.2003 (3)	0.0069 (4)	0.2174 (2)	5.2 (2)
C(12)	0.2591 (3)	0.1096 (3)	0.2585 (2)	3.9 (1)
C(13)	0.2299 (3)	0.2497 (3)	0.2489 (2)	4.0 (1)
O(14)	0.3475 (2)	0.0617 (2)	0.3070 (1)	4.6 (1)
C(15)	0.4186 (3)	0.1620 (3)	0.3469 (2)	3.8 (1)
C(16)	0.5154 (3)	0.0839 (3)	0.3907 (2)	4.0 (1)
C(17)	0.5909 (3)	0.1853 (3)	0.4355 (2)	4.1 (1)
N(18)	0.6891 (2)	0.1148 (2)	0.4773 (1)	3.7 (1)
C(19)	0.7669 (3)	0.1845 (3)	0.5210 (2)	3.4 (1)
O(20)	0.7638 (2)	0.3114 (2)	0.5279 (1)	4.9 (1)
C(21)	0.8579 (3)	0.0919 (3)	0.5609 (2)	4.2 (2)
O(22)	0.9351 (2)	0.1753 (2)	0.6071 (1)	4.6 (1)
C(23)	1.0313 (3)	0.1091 (3)	0.6397 (2)	4.5 (2)
O(24)	1.0550 (2)	-0.0104 (2)	0.6284 (1)	6.3 (1)
C(25)	1.1017 (4)	0.2043 (4)	0.6881 (2)	6.5 (2)

Atom	x	y	z	$B_{eq}^{a)}$
C(1)	0.5094 (7)	1.1183 (5)	0.77889 (8)	4.2 (2)
C(2)	0.4368 (7)	0.9990 (6)	0.76452 (8)	5.0 (2)
C(3)	0.5174 (7)	0.8621 (4)	0.77325 (7)	4.7 (2)
C(4)	0.4694 (6)	0.8403 (4)	0.79774 (6)	4.1 (2)
N(5)	0.5349 (4)	0.9596 (3)	0.81149 (5)	3.0 (1)
C(6)	0.4566 (6)	1.0968 (4)	0.80345 (8)	3.4 (2)
C(7)	0.4774 (6)	0.9308 (4)	0.83547 (7)	4.0 (2)
C(8)	0.5294 (6)	1.0464 (4)	0.85109 (7)	3.8 (2)
C(9)	0.7179 (6)	1.0727 (5)	0.85709 (7)	4.3 (2)
C(10)	0.7569 (7)	1.1778 (5)	0.87244 (7)	4.8 (2)
C(11)	0.6154 (6)	1.2577 (5)	0.88227 (7)	4.3 (2)
C(12)	0.4267 (6)	1.2300 (4)	0.87630 (6)	3.8 (2)
C(13)	0.3839 (6)	1.1276 (4)	0.86097 (6)	3.7 (2)
O(14)	0.2707 (4)	1.2967 (3)	0.88567 (5)	4.8 (1)
C(15)	0.3040 (6)	1.3991 (5)	0.90252 (7)	4.4 (2)
C(16)	0.1133 (6)	1.4279 (4)	0.91330 (7)	4.2 (2)
C(17)	0.0503 (7)	1.2975 (4)	0.92613 (7)	4.2 (2)
N(18)	-0.1240 (5)	1.3250 (3)	0.93861 (6)	3.8 (1)
C(19)	-0.2286 (6)	1.2210 (4)	0.94721 (7)	3.8 (2)
O(20)	-0.1915 (5)	1.0946 (3)	0.94425 (6)	5.1 (1)
C(21)	-0.3913 (7)	1.2722 (5)	0.96141 (9)	4.9 (2)
O(22)	-0.5374 (5)	1.1668 (3)	0.96159 (5)	4.8 (1)
C(23)	-0.6112 (6)	1.1343 (5)	0.98148 (7)	4.2 (2)
O(24)	-0.5571 (6)	1.1836 (4)	0.99839 (6)	5.8 (2)
C(25)	-0.7698 (7)	1.0285 (6)	0.9789 (1)	5.8 (3)
CL(26)	0.9689 (1)	0.9638 (1)	0.80858 (2)	4.99 (5)

a) $B_{eq} = 4/3(B_{11}a^2 + B_{22}b^2 + B_{33}c^2 + B_{13}ac \cos \beta)$.

TABLE III. Bond Lengths and Bond Angles

	1	2		1	2
Bond lengths (Å)					
1-2	1.518 (6)	1.509 (7)	1-6	1.511 (5)	1.533 (6)
2-3	1.524 (6)	1.513 (7)	3-4	1.521 (5)	1.523 (7)
4-5	1.462 (4)	1.474 (5)	5-6	1.450 (4)	1.493 (5)
5-7	1.465 (4)	1.521 (5)	7-8	1.509 (5)	1.487 (6)
8-9	1.378 (5)	1.396 (6)	8-13	1.406 (5)	1.415 (6)
9-10	1.382 (5)	1.394 (7)	10-11	1.391 (5)	1.379 (7)
11-12	1.389 (4)	1.400 (6)	12-13	1.388 (4)	1.371 (6)
12-14	1.373 (4)	1.385 (5)	14-15	1.424 (4)	1.424 (6)
15-16	1.504 (4)	1.515 (6)	16-17	1.503 (4)	1.527 (6)
17-18	1.460 (4)	1.461 (6)	18-19	1.331 (4)	1.333 (5)
19-20	1.223 (3)	1.240 (6)	19-21	1.502 (4)	1.510 (7)
21-22	1.425 (4)	1.434 (6)	22-23	1.342 (4)	1.340 (5)
23-24	1.192 (4)	1.177 (6)	23-25	1.477 (5)	1.514 (7)
Bond angles (°)					
2-1-6	111.1 (3)	111.5 (4)	1-2-3	109.3 (3)	108.6 (4)
2-3-4	110.1 (3)	111.5 (4)	3-4-5	111.4 (3)	111.6 (4)
4-5-6	111.1 (3)	111.8 (3)	4-5-7	110.3 (3)	107.9 (3)
6-5-7	110.5 (3)	111.5 (3)	1-6-5	111.1 (3)	109.7 (3)
5-7-8	112.0 (3)	113.4 (3)	7-8-9	120.1 (3)	113.4 (3)
7-8-13	119.7 (3)	119.3 (4)	9-8-13	120.2 (3)	118.9 (4)
8-9-10	119.7 (3)	119.0 (4)	9-10-11	121.4 (3)	122.4 (4)
10-11-12	118.5 (3)	118.2 (4)	11-12-13	121.1 (3)	120.9 (4)
11-12-14	115.0 (3)	124.2 (4)	13-12-14	123.9 (3)	114.8 (4)
8-13-12	119.1 (3)	120.6 (4)	12-14-15	118.0 (2)	118.0 (3)
14-15-16	107.5 (2)	106.3 (4)	15-16-17	109.5 (2)	108.8 (4)
16-17-18	111.6 (2)	110.9 (4)	17-18-19	121.8 (2)	121.9 (4)
18-19-20	123.0 (3)	123.1 (4)	18-19-21	113.4 (2)	113.4 (4)
20-19-21	123.6 (3)	123.5 (4)	19-21-22	109.2 (2)	108.7 (4)
21-22-23	115.9 (2)	116.1 (4)	22-23-24	122.6 (3)	123.6 (4)
22-23-25	111.1 (3)	110.1 (4)	24-23-25	126.4 (3)	126.3 (5)

– 38.7° for **2**.

In spite of the above-mentioned individual conformational difference between the **1** and **2** molecules, however, it is of interest to note that, as is clear from Fig. 1, the overall conformations of both molecules are similar and are characterized as the kinked and extended form.

Crystal Structure

Crystal packings of **1** and **2**, viewed along the *a*-axis, are shown in Fig. 2, where the dotted lines represent possible hydrogen bonds, and the filled circles in **2** indicate chloride ions. Although they seem to show different molecular packings at a glance, a common characteristic can be observed in their crystal structures; the neighboring hydrophobic piperidine rings are aggregated to one another and form an infinite column along the *a*- (**1**) or *b*-axis (**2**), which is maintained by the van der Waals contacts. On the other hand, the acetoxypyrrolacetamide side chains themselves form a layered sheet structure prolonged along the *b*-direction. This structure is stabilized by an N–H···O hydrogen bond [N18(*x*, *y*, *z*)···O20(1.5–*x*, *y*–0.5, 1–*z*)=2.952(3) Å for **1** and N18(*x*, *y*, *z*)···O20(2.5–*x*, *y*–0.5, *z*)=2.887(5) Å for **2**] and by the van der Waals interactions among the neighboring atoms.

The hydrogen atom of HCl in **2** was transferred to the piperidine N5 atom. This

Fig. 1. Stereoscopic Drawings of 1 and 2

TABLE IV. Selected Torsion Angles (in Degree)

		1	2			1	2
$\omega 1$	(6-5-7-8)	-68.5 (3)	-54.7 (4)	$\omega 5$	(14-15-16-17)	-178.4 (2)	68.3 (4)
$\omega 1'$	(4-5-7-8)	168.2 (3)	-177.9 (4)	$\omega 6$	(15-16-17-18)	-178.1 (2)	174.4 (4)
$\omega 2$	(5-7-8-13)	115.7 (3)	111.8 (4)	$\omega 7$	(16-17-18-19)	-179.7 (2)	165.5 (4)
$\omega 2'$	(5-7-8-9)	-66.0 (4)	-71.3 (5)	$\omega 8$	(17-18-19-21)	178.0 (2)	174.1 (4)
$\omega 3$	(13-12-14-15)	-3.9 (4)	176.9 (4)	$\omega 9$	(18-19-21-22)	-178.8 (2)	154.7 (4)
$\omega 3'$	(11-12-14-15)	175.0 (3)	-0.4 (6)	$\omega 10$	(19-21-22-23)	-172.0 (2)	133.2 (4)
$\omega 4$	(12-14-15-16)	-175.1 (2)	-166.9 (4)	$\omega 11$	(21-22-23-25)	-177.9 (3)	176.9 (4)

piperidinium ring formation leads to dimensional and conformational changes of roxatidine acetate, and already stated. The chloride anion is interposed among the piperidinium rings stacking along the a -axis, and neutralizes the positive charge by an ionic and hydrogen-bonded $\text{NH}^+ \cdots \text{Cl}^-$ interaction [$\text{N15}(x, y, z) \cdots \text{Cl}(x, y, z) = 3.056(3) \text{ \AA}$].

Discussion

In a series of structural investigations of cimetidine and famotidine analogues, large

Fig. 2. Crystal Packings of 1 and 2, Viewed along the *a*-Direction

Fig. 3. Conformational Comparison between Neutral (a) and Cationic (b) Cimetidine Molecules

conformational changes have been observed between their neutral and cationic molecules.^{2,3,10,11)} Figure 3 shows the molecular conformations of cimetidine observed in crystals of its free form (a)¹⁰⁾ and HCl salt (b).²⁾ The folded conformation of cimetidine neutral form (Fig. 3a), which could be the active form for the H₂-receptor inhibitory activity,³⁾ is drastically changed into an extended one (Fig. 3b) by the salt formation with hydrochloride.²⁾ A similar conformational change has also been observed between the crystal structures of famotidine¹¹⁾ and its HCl salt.³⁾ For H₂-receptor antagonists such as cimetidine, ranitidine and famotidine, therefore, the acid appears to act to diminish the interaction between the heteroatoms of the aromatic ring and side chain.

Contrary to our expectation, on the other hand, roxatidine acetate did not show such

behavior: the effect of HCl on the molecular conformation is not significant, and both the free and cationic molecules, as a whole, take similar extended forms. Since this molecule itself does not have a proton-acceptor atom within the central aromatic ring, the extended conformation observed in **1** could be the energetically stable form.¹²⁾ Therefore, it is supposed from the present X-ray results that roxatidine acetate may be classified as a new type of H₂-receptor antagonist different from cimetidine, ranitidine and famotidine.

Tanaka *et al.*¹³⁾ has reported, based on the effect of H₂-receptor antagonists on ³H-cimetidine binding and histamine stimulated adenosine 3',5'-cyclic monophosphate (cAMP) production in isolated gastric glands, that in contrast to cimetidine, ranitidine and famotidine, roxatidine acetate shows no competitive inhibition of ³H-cimetidine binding with the H₂-receptor, while all of these H₂ antagonists exhibit an inhibitory effect on the cAMP accumulation. Considering these facts and the present X-ray results, it seems possible that the binding site for roxatidine acetate on the H₂-receptor is different from that of cimetidine, ranitidine or famotidine. To investigate further the conformational characteristics of the roxatidine molecule, structural studies on related compounds are in progress.

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