advice. Crystallographic programs used were those of XRAY70.[37] The crystallographic figures were drawn with the aid of the ORTEP[38] program. We also thank Miss Jo Anne Backstrom for programming the PDP-8E. This work was supported by U. S. Public Health Grants GM-14292 and GM-10828 from the National Institutes of Health.

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The Structure of Histamine

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Abstract: The structure of histamine free base has been determined from three-dimensional X-ray data, collected by counter methods. The tautomer obtained in the solid state by recrystallization from benzene is 5-(2-aminoethyl)imidazole, with no evidence for the coexistence of 4-(2-aminoethyl)imidazole. The imidazole and NH_2 groups are trans to one another across the C–C bond of the ethyl group. The nitrogen and carbon atoms of the imidazole ring are coplanar. The dihedral angle between this plane and the plane of the carbon and nitrogen atoms of the aminoethyl side chain is 66.3°. Distances within the molecule are in good agreement with recent X-ray and neutron diffraction results on the orthorhombic form of L-histidine, despite the fact that orthorhombic L-histidine is a derivative of 4-ethylimidiazole, rather than 5-ethylimidazole. In histamine free base there is an N–H···N hydrogen bond involving the N–H function of the imidazole ring with the NH_2 group on the side chain of an adjacent molecule. In this way infinite zig-zag chains of imidazole molecules are formed in the crystal. Histamine free base crystallizes in space group C_2^2-$P2_1$ of the monoclinic system, in a cell of dimensions a = 7.249 (2), b = 7.634 (3), c = 5.698 (2) Å, and β = 104.96 (2)°. A density of 1.218 g/cm³ calculated for two molecules in the unit cell agrees with that of 1.20 (1) g/cm³ observed by flotation in an ethyl benzoate–iodobenzene medium. A total of 548 unique reflections was collected using Cu Kα X-radiation, prefiltered with Ni foil. The structure was solved by direct methods and refined by least-squares methods to a final agreement index on F of 3.1%.

The cooperation of endopeptidases, which break the proteins at certain places into large fragments, and of exopeptidases, which hydrolyze these fragments, results in a mixture of amino acids. Some of these amino acids are used to build new endogenous proteins. Most, however, are degraded further and included in these degradations is the well known enzymic decarboxylation of the amino acids which gives rise to primary amines. Many amines of this type possess a strong pharmacological activity. This is true for histamine, the product of the decarboxylation of histidine.[2]

For histamine, which is present in mammal tissue (lung, muscle, etc.) and blood, ponderous volumes have been written. Its primordial activity at the central nervous system level and in regulation of insomia[3–5] led many authors to consider histamine as the third chemical mediator, following adrenaline and acetylcholine. Furthermore, histamine is a powerful vasodilator and a stimulator of gastric secretion in higher animals.[6–10]

Free histamine, obtained by the enzymic decarboxylation of histidine, forms complexes with metals of biological interest and it is well known that the majority of active compounds are those capable of forming a a six-membered ring between a 2-amino side chain nitrogen, a tertiary nitrogen of an aromatic nucleus, and some polar center. Indeed, in order to be involved in the binding between small molecules and proteins, a metal must be capable of forming an independent complex with the small molecule.[11] The crystal structures of some metal complex of histamine are already known,[12–15] but surprisingly the crystal structure of histamine free base was unknown until the present work. Niemann and Hays[16] considered three possible tautomeric structures (Figure 1) and, from a consideration of the possible resonance forms of each tautomer and from bond energies, concluded that only structures I and II are possible. They further concluded that tautomer I is the structure responsible for the histamine-like activity of histamine. Although structure I, 4-(2-aminoethyl)imidazole, may exist in solution and, in fact, has the same tautomeric form as

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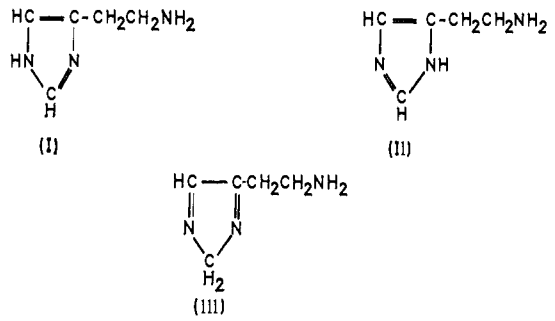

Figure 1. Three possible tautomeric structures for histamine considered by Niemann and Hays.[16] Structure I is 4-(2-aminoethyl)-imidazole while structure II is 5-(2-aminoethyl)imidazole.

orthorhombic L-histidine,[17,18] the tautomer found here is structure II, 5-(2-aminoethyl)imidazole.

Experimental Section

Histamine was obtained from Sigma Chemical Co. It was recrystallized from dry benzene as long, colorless needles elongated along c. The crystal used for the X-ray study was mounted inside a capillary under dry nitrogen.

Examination of this crystal by precession methods using Mo Kα radiation showed that histamine crystallizes in the monoclinic system. The systematic absence ($0k0$, $k = 2n + 1$) leads to the two possible space groups, $P2_1$ and $P2_1/m$.

Cell constants and corresponding standard deviations at 22° were obtained from a least-squares refinement[19] of 14 reflections centered on a Picker FACS-1 computer controlled diffractometer. These 14 reflections were in the range $30 < 2\theta < 60°$. Cell constants thus obtained are $a = 7.249\ (2)$, $b = 7.634\ (3)$, $c = 5.698\ (2)$ Å, and $\beta = 104.96\ (2)°$ (λ(Cu Kα_1) 1.540562 Å).

Based on a calculated volume of 304.6 Å^3 and two $C_5N_3H_9$ formula units in the cell, the calculated density of 1.218 g/cm^3 is in good agreement with that of 1.20 (1) g/cm^3 obtained by flotation in an ethyl benzoate–iodobenzene medium.

The crystal selected for data collection was roughly a parallelepiped with bonding faces of the forms {100}, {010}, and {001}. The distances between the faces of these forms are 0.205, 0.025, and 0.350 mm. The crystal was mounted with [001] approximately along the spindle axis.

Data were collected at 22° in shells of 2θ by the θ–2θ scan mode of the diffractometer using the Ni prefiltered Cu Kα radiation and a pulse height analyzer set to admit about 90% of the Kα peak. Copper foil attenuators were automatically inserted if the intensity of the diffracted beam exceeded about 7000 counts/sec during the scan. The X-ray tube was set at a 3.3° takeoff angle and a scintillation detector was placed 32 cm from the crystal with an aperture 6.0 mm square. The scan speed was 2°/min in 2θ from 1.5° below the Kα_1 peak to 1.5° above the Kα_2 peak. Stationary crystal, stationary counter background counts of 20 sec were taken at each end of the scan range. A total of 637 reflections was collected out to $2\theta = 128°$. Three standard reflections, measured periodically during the data collection, showed no significant trend in intensity.

The data were processed in the normal manner[19] using a value of p of 0.04. Of the 637 reflections obtained, 547 reflections are unique and have $F^2 > 3\sigma(F^2)$.

Structure Determination. Normalized structure factors (E's) were calculated, whose distribution[20] indicated clearly that the space group is noncentric and therefore $P2_1$ rather than $P2_1/m$.

The structure was solved by direct methods and refined by full-matrix least-squares techniques.[21] The quantity minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $|F_o|$ and $|F_c|$ are the observed and calculated structure amplitudes and where the weights w are taken as $4F_o^2/\sigma^2(F_o^2)$. The agreement indices are defined as $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_w = (\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2)^{1/2}$. Values of the atomic scattering factors[22] and the anomalous terms[23] for the nitrogen atoms were from the usual sources and the effects of anomalous dispersion were included in F_c.[24]

A three-dimensional E map based on the 103 highest E's ($E > 1.28$) was computed corresponding to phases suggested by the program MULTAN.[21] In this E map, the highest features corresponded to the eight heavy atoms of histamine, *i.e.*, three nitrogen and five carbon atoms.

A least-squares refinement with these eight atoms involving isotropic thermal parameters led to values of R and R_w of 0.13 and 0.18.

As shown in Figure 2 two conformations corresponding to a rotation of the imidazole ring around the C(3)–C(4) axis of the ethyl group must be considered. From a refinement of both conformations (Table I) it is clear that the conformation II is the true one.

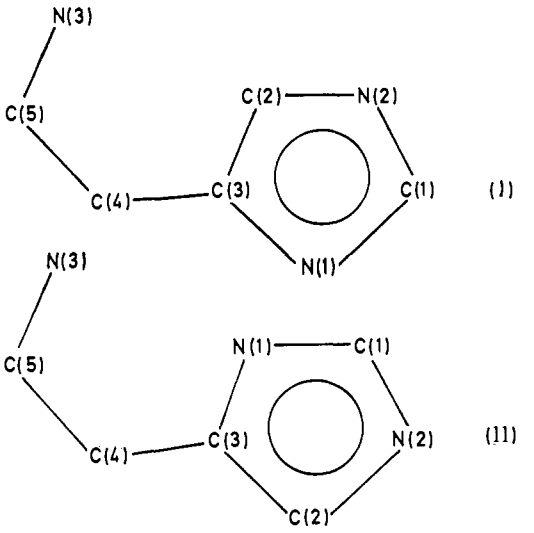

Figure 2. Possible conformations for the histamine molecule at a stage of refinement when only the heavy atoms were being considered and allowed to vibrate isotropically.

Table I. Results of Refinements of the Two Conformations Shown in Figure 2

	1st conform	2nd conform
R	0.125	0.102
R_w	0.182	0.140
B N(1)	2.4 Å^2	3.4 Å^2
B C(1)	4.9	3.7
B N(2)	3.0	4.0
B C(2)	4.8	3.8

In the next cycle variable anisotropic thermal parameters were added and the refinement converged to values of R and R_w of 0.075 and 0.085. A three-dimensional difference Fourier map clearly revealed the positions of the nine hydrogen atoms and provided the first evidence that the present structure corresponds to tautomer II of Figure 1. The positions of the hydrogen atoms were refined in a next cycle using fixed isotropic thermal parameters equal to those of the heavy atoms to which the hydrogen atoms are attached. The values of R and R_w were now 0.033 and 0.042.

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Table III. Atomic Parameters for Histamine

Atom	x	y	z	B (Å^2) or β_{11}[a]	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	−0.1263 (3)	−0.2360[b]	−0.2155 (3)	0.0138 (4)	0.0166 (4)	0.0316 (7)	0.0009 (3)	0.0039 (4)	0.0010 (5)
N(2)	0.1800 (3)	−0.3010 (4)	−0.1065 (4)	0.0150 (4)	0.0193 (4)	0.0405 (8)	−0.0002 (4)	0.0015 (5)	0.0019 (5)
N(3)	−0.5268 (3)	−0.5661 (5)	−0.7997 (4)	0.0132 (4)	0.0194 (5)	0.0381 (8)	−0.0019 (4)	0.0002 (5)	0.0016 (5)
C(1)	0.0404 (3)	−0.2230 (5)	−0.0433 (5)	0.0162 (5)	0.0197 (5)	0.0307 (8)	−0.0001 (5)	0.0019 (5)	0.0004 (7)
C(2)	0.0968 (4)	−0.3699 (4)	−0.3331 (5)	0.0164 (5)	0.0155 (5)	0.0425 (9)	0.0009 (4)	0.0092 (6)	−0.0004 (6)
C(3)	−0.0918 (3)	−0.3303 (4)	−0.4032 (4)	0.0157 (5)	0.0137 (5)	0.0301 (8)	−0.0007 (4)	0.0071 (5)	0.0017 (4)
C(4)	−0.2423 (4)	−0.3772 (5)	−0.6246 (4)	0.0185 (5)	0.0178 (5)	0.0311 (8)	−0.0029 (4)	0.0043 (5)	0.0009 (6)
C(5)	−0.3970 (3)	−0.4984 (5)	−0.5812 (4)	0.0156 (5)	0.0187 (5)	0.0334 (5)	−0.0009 (4)	0.0051 (6)	0.0022 (6)
H(1)	−0.239 (5)	−0.177 (5)	−0.212 (5)	4.8[c]					
H(2)	0.051 (4)	−0.159 (4)	0.107 (4)	3.7					
H(3)	0.167 (3)	−0.426 (4)	−0.421 (4)	3.8					
H(4)	−0.187 (3)	−0.432 (4)	−0.756 (4)	3.8					
H(5)	−0.306 (4)	−0.270 (4)	−0.705 (4)	3.8					
H(6)	−0.339 (4)	−0.584 (4)	−0.483 (5)	3.8					
H(7)	−0.470 (4)	−0.431 (4)	−0.487 (5)	3.8					
H(8)	−0.597 (4)	−0.475 (4)	−0.903 (5)	4.1					
H(9)	−0.455 (4)	−0.623 (4)	−0.895 (4)	4.1					

[a] The form of the anisotropic thermal ellipsoid is $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$. [b] The y coordinate of N(1) fixes the origin. [c] The isotropic temperature factor for a given hydrogen atom is that of the heavy atom to which it is attached.

At this point an absorption correction was made. Based on a linear absorption coefficient of 2.04 cm^{-1}, the resultant transmission factors were found to range from 0.89 to 0.99. A final cycle of least-squares refinement led to values of R and R_w of 0.031 and 0.039. The final error in an observation of unit weight is 1.61 e. Up to this point a specific enantiomer of the molecule had been considered. This enantiomer, which we may designate A, has atomic parameters x, y, and z. Enantiomer B then has atomic parameters $\bar{x}$, $\bar{y}$, and $\bar{z}$. Since $P2_1$ is a polar space group it is important to test the effects of refining enantiomer B, rather than enantiomer A, using the imaginary dispersion term $\Delta f''$ for N of 0.018. Such a refinement for enantiomer B leads to the same R indices as above. More important, although there were some shifts, as expected in the y coordinates of the C atoms, none of these shifts was significant. Hence, it is not possible in the present instance to determine the enantiomer in the crystal selected, but the errors resulting from our inability to do so are small compared with the errors on the derived bond distances and angles. It has been shown[25] that at least in some instances the absolute configurations of molecules containing C, N, and O may be determined from data collected with Cu radiation. But the $\Delta f''$ term for O is about twice that for N.

On a final difference Fourier map the electron density is less than 0.3 e/A^3 and hence the map is essentially featureless. An analysis of $\Sigma w(|F_o| - |F_c|)^2$ as a function of $|F_o|$, setting angles, and Miller indices shows no unusual trends that would suggest an unreasonable, relative weighing scheme.

In Table II[26] we present the values of $50|F_o|$ and $50|F_c|$ for the reflections used in the refinements. Structure factor calculations for those reflections having $F_o^2 < 3\,\sigma(F_o^2)$ revealed none for which $|F_o^2 - F_c^2| > 3\sigma(F_o^2)$. The final atomic parameters for enantiomer A, together with standard deviations as derived from the inverse matrix, are collected in Table III. The root-mean-square amplitudes of vibration for those atoms refined anisotropically are presented in Table IV.

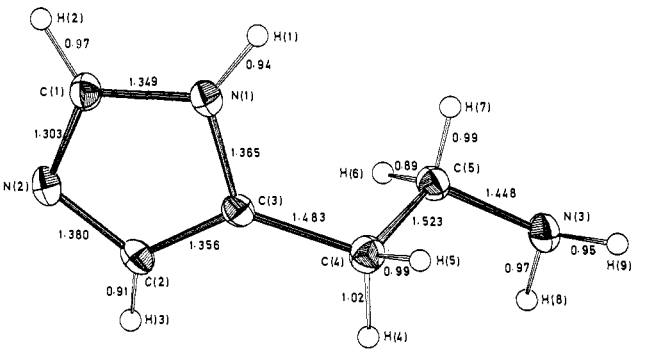

Figure 3. A drawing of the histamine free base molecule. The thermal ellipsoids for the heavy atoms correspond to 50% probability ellipsoids. The circles corresponding to the hydrogen atoms are at an arbitrary scale.

Table IV. Root-Mean-Square Amplitude of Vibration (Å)

Atom	Min	Inter	Max
N(1)	0.184 (3)	0.220 (3)	0.226 (3)
N(2)	0.189 (3)	0.236 (3)	0.266 (3)
N(3)	0.174 (3)	0.234 (3)	0.264 (3)
C(1)	0.192 (3)	0.233 (3)	0.242 (3)
C(2)	0.194 (3)	0.216 (3)	0.256 (3)
C(3)	0.186 (3)	0.204 (3)	0.219 (3)
C(4)	0.201 (3)	0.217 (3)	0.246 (3)
C(5)	0.196 (3)	0.220 (3)	0.244 (3)

Results and Discussion

In Figure 3 we present a drawing of the molecule along with the labeling scheme used. Bond distances are shown in Figure 3; distances and angles are presented in Table V. Figure 4 is a stereoscopic view of the unit cell.

Adopting the usual system of nomenclature for heterocyclic rings wherein the H substituted N atom in the ring is position 1 and numbering proceeds in a direction to give the next non-C atom the smaller number, the structure in Figure 3 is that of 5-(2-aminoethyl)imidazole. Although histamine is a degradation product of histidine, L-histidine has the side chain attached to the 4 position on the imidazole ring.[17,18,27] Presumably the tautomerism between 4 and 5 substitution on the imidazole, which is formally the result of a proton transfer from one ring N atom to the other, is a facile process in solution. Of course, there is no way of knowing the relation of possible tautomeric forms in solution to the products obtained by crystallization under specific conditions. It is interesting to note that when histamine acts as bidentate ligand with

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(26) Table II, a listing of observed and calculated structure amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to the code number JACS-73-4829. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(27) J. J. Madden, E. L. McGandy, and N. C. Seeman, *Acta Crystallogr., Sect. B*, **28**, 2382 (1972).

Table V. Selected Bond Distances (Å) and Angles (deg)

Distances	Bond angles	Bond angles
C(3)-N(1) 1.365 (3)	C(2)-C(3)-N(1) 105.1 (2)	C(3)-C(4)-H(4) 112.3 (1.3)
N(1)-C(1) 1.349 (3)	C(3)-N(1)-C(1) 107.3 (2)	C(3)-C(4)-H(5) 110.4 (1.3)
C(1)-N(2) 1.303 (4)	N(1)-C(1)-N(2) 112.3 (2)	C(5)-C(4)-H(4) 108.1 (1.5)
N(2)-C(2) 1.380 (3)	C(1)-N(2)-C(2) 104.5 (2)	C(5)-C(4)-H(5) 107.4 (1.5)
C(2)-C(3) 1.356 (3)	N(2)-C(2)-C(3) 110.8 (2)	H(4)-C(4)-H(5) 102.9 (1.9)
C(3)-C(4) 1.483 (3)	C(2)-C(3)-C(4) 131.4 (2)	C(4)-C(5)-H(6) 107.4 (1.7)
C(4)-C(5) 1.523 (4)	N(1)-C(3)-C(4) 123.4 (2)	C(4)-C(5)-H(7) 106.7 (1.6)
C(5)-N(3) 1.448 (3)	C(3)-C(4)-C(5) 114.8 (2)	N(3)-C(5)-H(6) 112.0 (1.8)
N(1)-H(1) 0.94 (3)	C(4)-C(5)-N(3) 114.8 (2)	N(3)-C(5)-H(7) 109.5 (1.5)
C(1)-H(2) 0.97 (2)	C(3)-N(1)-H(1) 127.3 (1.7)	H(6)-C(5)-H(7) 106.0 (2.3)
C(2)-H(3) 0.91 (3)	C(1)-N(1)-H(1) 124.8 (1.8)	C(5)-N(3)-H(8) 112.8 (1.7)
C(4)-H(4) 1.02 (3)	N(1)-C(1)-H(2) 121.8 (1.5)	C(5)-N(3)-H(9) 108.9 (1.5)
C(4)-H(5) 0.99 (3)	N(2)-C(1)-H(2) 125.9 (1.5)	H(8)-N(3)-H(9) 105.3 (2.1)
C(5)-H(6) 0.89 (3)	N(2)-C(2)-H(3) 121.7 (1.5)	Torsion angle
C(5)-H(7) 0.99 (3)	C(3)-C(2)-H(3) 127.4 (1.5)	C(3)-C(4)-C(5)-N(3) −170.8 (2)
N(3)-H(8) 0.97 (3)		
N(3)-H(9) 0.95 (3)		

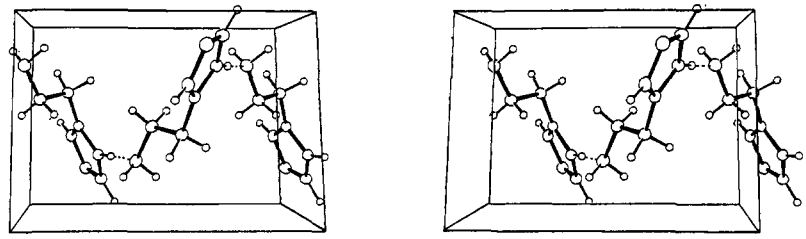

Figure 4. A stereoscopic view of the cell showing the intermolecular hydrogen bonding scheme. The view is down z, with y horizontal and x vertical.

a metal, then again these complexes are derivatives of 4-substituted imidazoles,[12-15] or in terms of the notation of Figure 3 the metal complexes have an H on N(2), and N(1) and N(3) are coordinated to the metal. In the histaminium cation, of course, all three N atoms are protonated.[28-30] The action of antihistaminic drugs has been ascribed to the successful competition with histamine for various receptor sites on muscle tissue.[31] How this simple picture is complicated by possible tautomerism is unclear.

Veidis, *et al.*,[28] have discussed in detail the differences between the conformations of histidine and histamine ions, a point of considerable interest in the biological activity of these chemicals. The conformation of the histaminium cation is such that the amino nitrogen atom is trans to the imidazole ring, while the histidine cation has the gauche conformation.[32] Similarly the histamine free base has the trans configuration, the torsion angle C(3)-C(4)-C(5)-N(3) being −170.8 (2)° while orthorhombic L-histidine[17,18] again shows the gauche configuration, the corresponding torsion angle being 58.3 (6)°. The trans conformation was predicted[33] in an MO study of the conformations of histamine.

As discussed below the imidazole ring is planar. It is therefore possible to describe a dihedral angle between this plane and the plane of the aminoethyl group. This angle is 66.3 (2)° The distribution of atoms into two planes—imidazole and side chain—is general for the histaminium cation and for histamine as a ligand, as well as for histamine free base. However, the dihedral angle between the two planes varies considerably from one compound to another. It has been suggested[30,34] that for the histaminium cation the value of this angle is correlated with the presence and the strength of intermolecular hydrogen bonds involving the nitrogen atom of the amino group of the side chain. Indeed, in the histaminium tetrachlorocobaltate(II),[30] no hydrogen bond is present and the dihedral angle is 7°. In histaminium bromide[29] a weak N-H···Br bond (N···Br = 3.29 Å) leads to a dihedral angle of 30°, while this same angle is 82.5° in histaminium diphosphate monohydrate[28] in which there is a N-H···O bond of modest strength (N···O = 2.77 Å) involving an O atom of the $H_2PO_4^{2-}$ ion. In histamine free base an intermolecular hydrogen bond is also present, as shown in Figure 5. This N-H···N bond (N···N = 2.851 (3) Å) is intermediate in strength between the N-H···Br and N-H···O bonds discussed above, and the dihedral angle is also intermediate. This hydrogen bond in histamine free base (Figure 5) completes an approximately tetrahedral environment around N(3), the amino nitrogen atom, with two of the angles deviating significantly from the tetrahedral value. In orthorhombic L-histidine[17,18] there is, in addition to an intermolecular hydrogen bonding arrangement, a rather bent N-H···N intramolecular hydrogen bond between the NH_3 group of the side chain and the unprotonated N atom of the imidazole ring.

The geometry of the imidazole ring found here is of

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Table VI. Distances (Å) and Angles (deg) in the Imidazole Ring for Different Compounds

Type of bond	Histamine ligand	Histaminium compound	Imidazole	Orthorhombic L-histidine		Histamine free base
N(1)–C(1)	1.34 (3)[a]	1.22 (2)[b]	1.396[c]	1.349 (7)[d]	1.339 (3)[e]	1.349 (3)[f]
C(1)–N(2)	1.34 (1)	1.31 (2)	1.349	1.309 (6)	1.327 (3)	1.303 (4)
N(2)–C(2)	1.38 (1)	1.39 (1)	1.369	1.376 (6)	1.382 (2)	1.380 (3)
C(2)–C(3)	1.37 (2)	1.36 (2)	1.358	1.372 (7)	1.361 (3)	1.356 (3)
C(3)–N(1)	1.39 (2)	1.36 (2)	1.378	1.376 (7)	1.374 (3)	1.365 (2)
C(3)–N(1)–C(1)	107 (1)	109 (1)	105.4	106.8 (5)	106.9 (2)	107.2 (2)
N(1)–C(1)–N(2)	110 (1)	109 (1)	108.7	112.4 (5)	112.2 (2)	112.3 (2)
C(1)–N(2)–C(2)	108 (1)	109 (1)	107.2	105.4 (4)	104.9 (2)	104.5 (2)
N(2)–C(2)–C(3)	106 (1)	106 (1)	106.3	109.8 (4)	109.6 (2)	110.8 (2)
C(2)–C(3)–N(1)	109 (2)	107 (1)	109.8	105.7 (5)	106.4 (2)	105.1 (2)

[a] Average values from ref 12–15 with maximum deviations. [b] Average values from ref 28 and 30 with maximum deviations. [c] S. Martinez-Carrera, *Acta Crystallogr.*, **20**, 783 (1966). Standard deviations were not given. [d] Reference 18 (neutron diffraction results). [e] Reference 17 (X-ray results). [f] Present work.

interest. The ring is rigorously planar. The best weighted least-squares plane through the ring has the equation $2.374x + 6.452y - 2.808z = -1.218$ and the deviations from this plane are 0.000 (1), 0.002 (3), −0.003 (3), −0.003 (3), and 0.001 (3) Å for N(1), N(2), C(1), C(2), and C(3), respectively. Atom C(4) of the side chain is significantly out of this plane by 0.047 (3) Å. In Table VI we compare distances and angles within the imidazole ring as found in a variety of compounds. Despite the differences in the side chains (if any) and in the position of substitution of side chains on the ring, the agreement is very good, particularly among the more recent investigations. It thus appears that the geometry of the ring is rather insensitive to the position of substitution. The results found here for the imidazole ring are consistent with the charge densities estimated for histidine using an INDO approximation.[35]

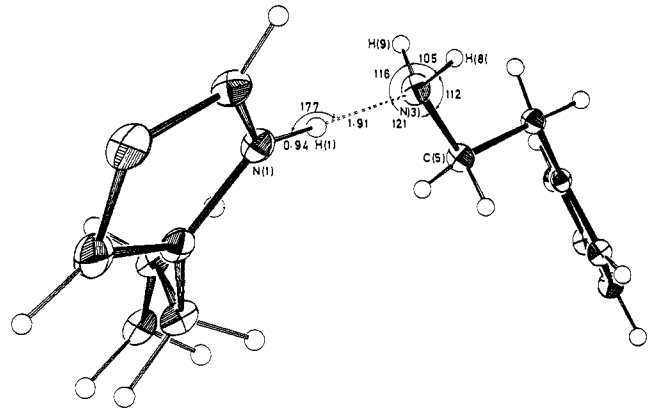

Figure 5. A drawing of two molecules of histamine showing the environment about the N(3) atom and the details of the N–H···N bond.

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