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X-Ray Crystallographic Studies of 4,5,6,7-Tetrahydrobenzimidazole and Two Related Semirigid Histamine Analogues

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The hydrochlorides of two semirigid histamine analogues, having a 4,5,6,7-tetrahydrobenzimidazole ring system in common as well as the 4,5,6,7-tetrahydrobenzimidazole hydrochloride itself, have been subjected to crystal structure analysis. The three compounds are of considerable interest as no crystal structure determination has earlier been performed on substances of this kind. In the three structures all nitrogen atoms are fully protonated and there are accordingly extensive hydrogen bonding systems with chloride ions as acceptors. Besides there are C–H···Cl interactions with H···Cl distances ranging from 2.47 to 2.62 Å. These interactions involve only the carbon atom (C1) bonded to the two charged nitrogen atoms (N1 and N2) of the imidazole ring.

The discovery that histamine activates at least two different sets of receptors (H_1 and H_2) producing different physiological responses and with different structural requirements on their agonists and antagonists has given rise to intense interest in the physiologically active conformations of histamine.[1–4] One way to shed light on this problem might be to investigate rigid or semirigid analogues of histamine and as part of a program aiming at selective H_1- and H_2-receptor agonists and antagonists we synthesized a series of tetrahydrobenzimidazolamines, some of which were subjected to X-ray crystallographic studies. However, we soon became aware that a partly identical project was carried out by Schunack and co-workers[5–7] and our studies were abandoned. The crystallographic data collected are, however, of general interest and are therefore reported.

EXPERIMENTAL

4,5,6,7-Tetrahydrobenzimidazole (THBI) was prepared from 2-chlorocyclohexanone and formamide[8] and converted to hydrochloride by dissolving the dry powder in hydrochloric acid. Large crystals were obtained by slow evaporation of the solution. The dihydrochlorides of 5(6)-amino-4,5,6,7-tetrahydrobenzimidazole (ATHBI) and 4(7)-aminomethyl-4,5,6,7-tetrahydrobenzimidazole (AMTHBI) were obtained by hydrogenation of 5-aminobenzimidazole and 4-cyanobenzimidazole in hydrochloric acid, essentially as later described by Lebenstedt and Schunack.[5] Good crystals were produced from these two compounds by slow evaporation of solutions in water and ethanol respectively.

Preliminary crystal data and space groups for the three compounds were derived from Weissenberg photographs while accurate unit cell dimensions were calculated from measurements on an automatic diffractometer. The integrated intensities within $\sin\theta/\lambda < 0.65$ were recorded on this diffractometer (Philips PAILRED) using graphite monochromated Mo$K\alpha$ radiation ($\lambda = 0.7107$ Å). The fainter reflexions were scanned up to three times and the background was measured for one min on each side. Scan range 1.8–2.3°. Reference reflexions recorded at regular intervals during the data collection proved that the crystals were perfectly stable. A list of the crystal data and some of the experimental conditions is given in Table 1. The measured intensities were corrected for Lorentz and polarization factors but not for absorption owing to the low μ-values. The net amplitudes were placed on an approximately absolute scale by Wilson statistics.

Structure determination and refinement. The three crystal structures were partially solved by direct methods. Subsequent Fourier refinement gave coordinates for all non-hydrogen atoms. The further refinement was carried out by full-matrix least-squares techniques. In all three cases the hydrogen

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Table 1. Crystal data and some experimental conditions.

Compound	4,5,6,7-Tetrahydrobenzimidazole · HCl	5(6)-Amino-4,5,6,7-tetrahydrobenzimidazole · 2HCl	4(7)-Aminomethyl-4,5,6,7-tetrahydrobenzimidazole · 2HCl
Abbreviated name	THBI	ATHBI	AMTHBI
Stoichiometry	$C_7H_{10}N_2 \cdot HCl$	$C_7H_{11}N_3 \cdot 2HCl$	$C_8H_{13}N_3 \cdot 2HCl$
Formula weight	158.63	210.11	224.14
Z	8	4	4
$F(000)$	672	440	472
Space group	$P2_1/c$	$Pna2_1$	$P2_1/a$
a (Å)	8.922	9.629	9.129
b (Å)	11.005	15.315	10.194
c (Å)	17.421	6.854	13.129
β (°)	97.19	90.00	111.15
Cell volume (Å^3)	1697.06	1010.75	1139.50
D_x (g cm^{-3})	1.227	1.381	1.307
D_m (flotation) (g cm^{-3})	1.22	1.38	1.31
μ(Mo$K\alpha$) (cm^{-1})	3.73	5.97	5.34
Crystal size (mm)	0.22 × 0.23 × 0.26	0.13 × 0.27 × 0.40	0.32 × 0.35 × 0.40
Number of independent reflexions	3962	1274	2658
Number of observed reflexions	2105	960	1821

atoms were located in three-dimensional difference electron density maps except for the amino hydrogen atoms of the ATHBI molecule. In this case the hydrogen atoms were placed at positions most favourable with regard to the hydrogen bonding system. In the ATHBI structure the heavy chloride ions as well as most of the lighter non-hydrogen atoms have almost the same z-coordinates and the structure thus approaches a Pnam symmetry having mirror planes perpendicular to the c axis. The presence of pseudo mirror planes in the ATHBI structure makes the parameters strongly correlated. This is not only reflected in the abnormally large e.s.d.'s of the z-coordinates but also in the difficulties encountered during the refinement procedure to get a reliable z-coordinate of the atom C6. This atom which apparently is located close to a pseudo mirror plane was either found in this plane or at some distance (roughly ±0.1 Å) from it. For this reason it was finally decided to place C6 in a fixed position (z/c=0.1880) which gave the most appropriate interatomic distances and angles. The parameters involving C6 are hence given within parentheses when appearing in the text, tables or figures.

The final cycle of refinement for each structure included one scale factor, positional and anisotropic thermal parameters for the non-hydrogen atoms and positional parameters for the hydrogen atoms. During the refinement a weighting scheme was applied, $w=k/(\sigma^2F+gF^2)$ with the k-values 0.67, 0.94, 0.97 and the g-values 0.005, 0.0003, 0.0005 for the three structures, respectively. It also became obvious that the F_o-values of THBI were affected by secondary extinction. The nine $F_o>100$ were hence excluded from the last refinement cycle of THBI. The final conventional R-values for the three structure determinations were 0.049, 0.042 and 0.049 for THBI, ATHBI, and AMTHBI, respectively.

Our own program system [9] was used for the initial stages of data reduction. The solutions and refinements of the structures were performed on an IBM 370/65 using the SHELX program system.[10] Perspective drawings were produced by the plotting program ORTEP.[11] The scattering factors for the atoms were those listed in International Tables for X-Ray Crystallography.[12] All atoms but Cl^- were treated as uncharged. Lists of the final structure factors are on request available from the authors (D.C. or I.H.).

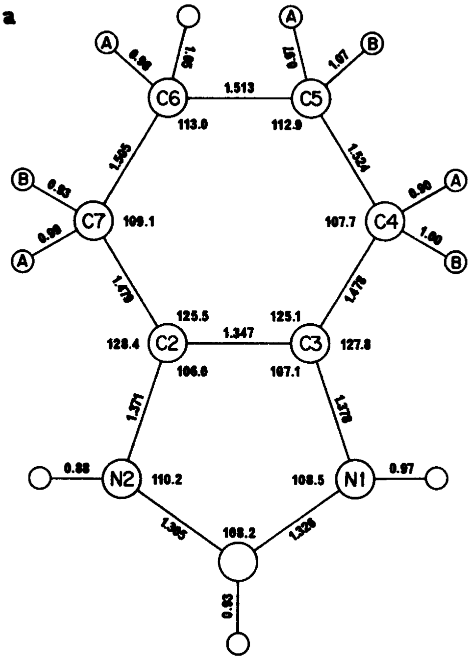
RESULTS AND DISCUSSION

The final parameters of the three structures are given in Tables 2 and 3. The estimated standard deviations of the coordinates for nitrogen and carbon atoms are of the same magnitude (0.003–0.004 Å) in the three structures except those of the

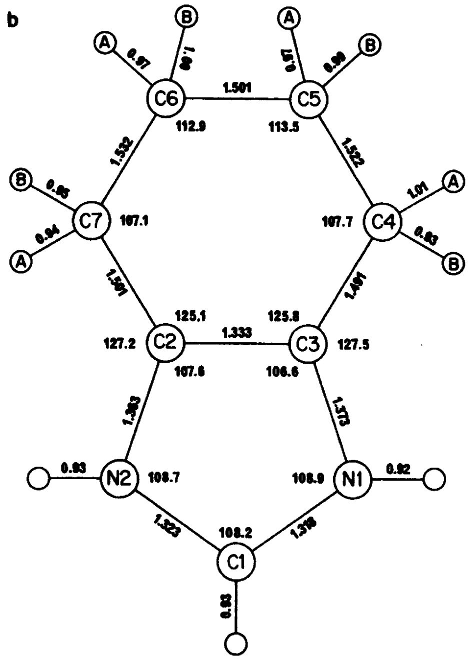
Table 2. Final positional and thermal parameters for non-hydrogen atoms ($\times 10^4$). The e.s.d.'s are given in parentheses. The temperature factors are defined by: $\exp[-2\pi^2(h^2a^{*2}U_{11}+\cdots+2klb^*c^*U_{23}\cdots)]$.

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
4,5,6,7-Tetrahydrobenzimidazole (THBI)									
Cl1	4256(1)	3061(1)	4538(1)	587(6)	672(4)	692(6)	32(4)	163(5)	4(4)
Cl2	914(1)	8660(1)	6269(1)	639(6)	752(4)	591(6)	8(4)	204(5)	28(4)
N1A	3930(4)	−1066(2)	4552(2)	661(21)	571(12)	491(17)	57(13)	−31(15)	−110(14)
C1A	2695(5)	−488(3)	4700(3)	765(29)	705(18)	553(23)	−70(18)	247(21)	−233(20)
N2A	2286(3)	256(2)	4129(2)	501(18)	616(14)	694(20)	−120(15)	139(15)	−18(13)
C2A	3272(4)	180(2)	3587(2)	394(17)	525(13)	468(19)	−46(14)	30(15)	−45(13)
C3A	4310(4)	−657(2)	3854(2)	503(20)	536(15)	425(19)	−33(13)	59(15)	−106(14)
C4A	5576(4)	−1065(3)	3446(2)	524(23)	700(18)	749(26)	−22(19)	122(19)	−3(17)
C5A	5253(5)	−643(4)	2608(3)	874(34)	1095(30)	765(31)	−56(25)	412(26)	26(26)
C6A	4724(5)	663(4)	2536(2)	899(35)	1045(27)	590(26)	178(22)	185(24)	−1(26)
C7A	3256(4)	871(3)	2858(2)	614(25)	742(18)	625(24)	82(18)	−30(20)	−96(17)
N1B	1228(4)	5897(2)	6041(2)	685(21)	624(13)	565(19)	64(14)	21(16)	−46(14)
C1B	2333(4)	5512(4)	5667(2)	539(23)	953(24)	525(23)	170(20)	28(19)	−208(21)
N2B	2172(3)	4327(3)	5560(2)	414(17)	872(18)	551(18)	15(14)	99(14)	47(14)
C2B	946(4)	3950(3)	5890(2)	395(19)	713(17)	418(18)	29(15)	48(15)	2(16)
C3B	340(4)	4925(3)	6184(2)	449(19)	678(16)	402(19)	18(14)	18(15)	−16(15)
C4B	−1012(4)	4929(3)	6608(2)	604(25)	890(20)	544(23)	−35(18)	146(19)	119(19)
C5B	−1749(4)	3680(4)	6531(2)	501(22)	1152(28)	619(25)	−29(22)	142(19)	−214(22)
C6B	−634(4)	2654(3)	6593(2)	707(28)	776(19)	600(25)	−1(19)	75(21)	−249(20)
C7B	388(4)	2670(3)	5949(2)	719(27)	657(17)	634(25)	−96(17)	−6(21)	−38(18)
5(6)-Amino-4,5,6,7-Tetrahydrobenzimidazole (ATHBI)									
Cl1	1401(1)	1879(1)	2000	397(6)	365(5)	657(6)	24(17)	3(15)	44(5)
Cl12	7559(1)	1497(1)	6954(7)	301(5)	383(5)	689(6)	−51(15)	4(16)	−15(4)
N1	741(4)	3844(2)	1953(18)	390(21)	309(16)	562(20)	60(52)	−80(57)	−45(16)
C1	−477(5)	4239(3)	1989(21)	351(25)	453(23)	596(24)	62(62)	242(50)	−46(20)
N2	−268(3)	5090(2)	2029(16)	253(17)	389(18)	555(19)	−155(48)	182(38)	−5(15)
C2	1141(4)	5248(2)	1926(16)	251(20)	333(20)	408(20)	118(47)	103(40)	32(15)
C3	1775(4)	4469(3)	1990(18)	310(21)	299(20)	454(19)	211(45)	45(53)	−1(16)
C4	3292(5)	4318(3)	2016(20)	304(22)	339(20)	672(25)	142(54)	188(53)	105(18)
C5	3959(5)	5165(3)	2860(9)	283(24)	388(25)	592(27)	−32(24)	−31(23)	73(21)
C6	3390(5)	5962(3)	1880	282(21)	348(20)	487(21)	−11(44)	74(44)	22(17)
N3	4165(5)	6750(3)	2438(12)	275(19)	334(19)	1228(77)	73(26)	42(28)	−10(17)
C7	1842(4)	6111(2)	1999(24)	260(21)	310(20)	650(25)	3(66)	−10(63)	42(16)
4(7)-Aminomethyl-4,5,6,7-Tetrahydrobenzimidazole (AMTHBI)									
Cl1	1528(1)	−3215(1)	1674(1)	434(5)	405(3)	514(5)	25(3)	61(4)	−8(3)
Cl2	2013(1)	−1679(1)	4805(1)	433(5)	522(4)	484(5)	17(3)	−41(4)	−15(3)
N1	3439(3)	4217(2)	2401(2)	448(17)	348(11)	505(17)	11(11)	91(14)	61(12)
C1	4718(4)	4082(3)	3285(3)	489(20)	422(13)	466(19)	−69(14)	88(17)	−46(15)
N2	5112(3)	2818(2)	3384(2)	356(15)	422(11)	364(14)	6(10)	14(12)	2(11)
C2	4029(3)	2127(2)	2546(2)	322(16)	383(12)	321(16)	−34(11)	73(13)	2(12)
C3	2991(4)	3008(2)	1925(2)	363(17)	375(11)	347(16)	4(11)	70(14)	19(12)
C4	1649(4)	2717(3)	891(3)	417(20)	466(14)	452(20)	−10(15)	−7(16)	74(15)
C5	1776(6)	1327(4)	574(4)	610(26)	552(17)	575(25)	−37(18)	−143(20)	−5(20)
C6	2373(5)	360(3)	1461(3)	637(25)	430(14)	548(23)	−27(16)	−84(20)	9(16)
C7	4007(4)	689(3)	2326(3)	404(18)	366(11)	392(17)	20(12)	104(14)	43(13)
C8	4361(5)	−113(3)	3351(3)	549(22)	404(13)	436(19)	1(13)	87(17)	−63(15)
N3	4444(4)	−1529(2)	3138(3)	425(18)	390(11)	488(18)	66(12)	37(14)	−13(12)

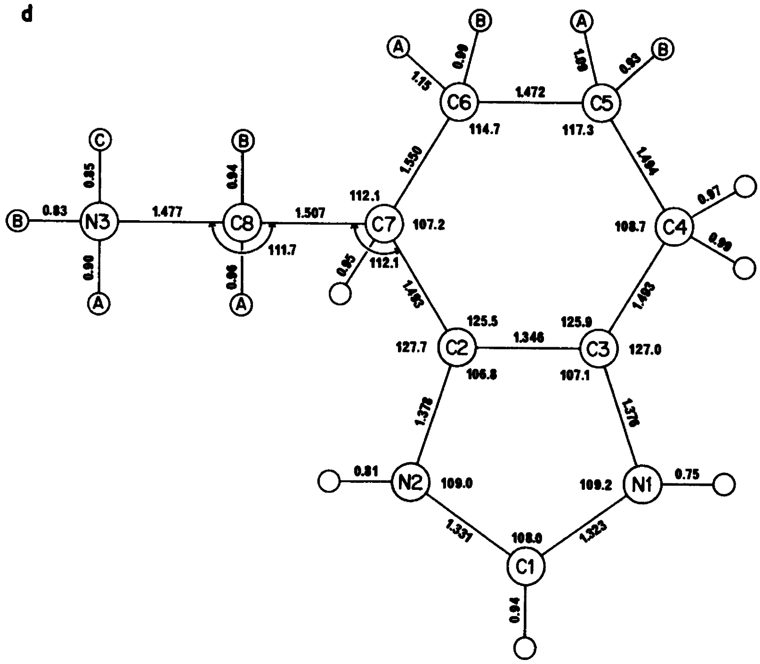
a


C6
C5
C7
C4
C2
C3
N2
N1
1.513
1.347

b


C6
C5
C7
C4
C2
C3
N2
N1
C1
1.501
1.333

d


N3
C8
C7
C6
C5
C4
C2
C3
N2
N1
C1
1.477
1.507
1.472
1.346

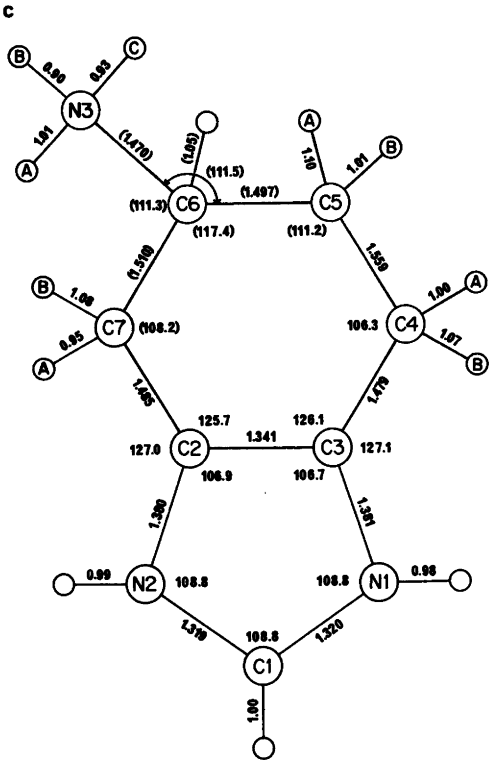


Fig. 1. Numbering scheme, bond distances (Å) and bond angles (degrees) for the A and B ions of 4,5,6,7-tetrahydrobenzimidazole (a and b), for the 5(6)-amino-4,5,6,7-tetrahydrobenzimidazole ion (c) and for the 4(7)-aminomethyl-4,5,6,7-tetrahydrobenzimidazole ion (d).

z-coordinates in the ATHBI structure which are more than three times higher. The bond lengths and bond angles uncorrected for thermal motion are given in Fig. 1. The estimated standard deviations for intramolecular bond lengths and bond angles involving non-hydrogen atoms are in the range of 0.004 – 0.006 Å and 0.3 – 0.4° for THBI, 0.005 – 0.009 Å and 0.3 – 0.5° for ATHBI and 0.003 – 0.005 Å and 0.2 – 0.3° for AMTHBI.

The three structures have a 4,5,6,7-tetrahydrobenzimidazole ring system in common. According to the Cambridge Structural Data Retrieval System, and, to the best of our knowledge, no such ring system or any derivative thereof has earlier been subjected to crystal structure determinations.

The two independent cations (mol A and mol B) in the THBI structure are almost identical. The bond distances and angles are all close to expected values except for the C3 – C4 – C5 and C2 – C7 – C6 angles which are slightly smaller (~108°) and the C4 – C5 – C6 and C5 – C6 – C7 angles which are slightly larger (~113°) than the normal sp^3-hybridized C – C – C angle (~111°) of cyclohexane. In both ions the imidazole ring is planar, the largest deviations being: 0.001 Å (mol A) and 0.007 Å (mol B). When including the atoms C4 and C7 in the least-squares planes it is seen (Table 4) that the two atoms C5 and C6 are on either side of the

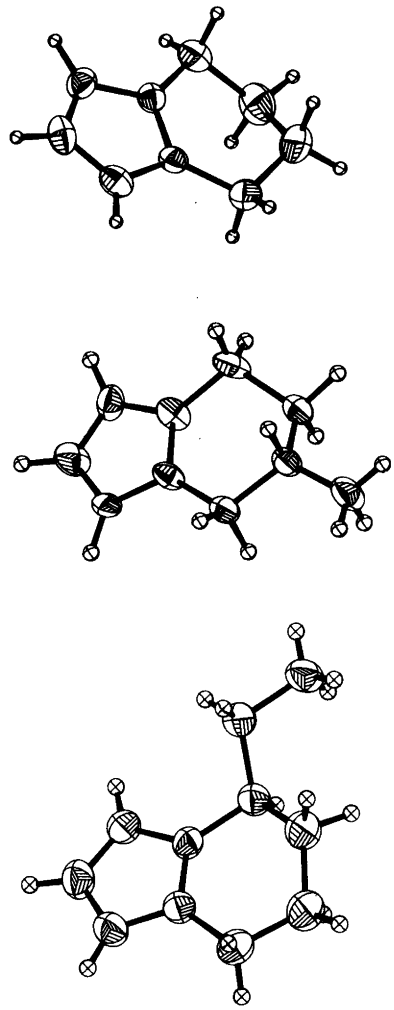


Fig. 2. Perspective drawings of the A ion of THBI (top), the ATHBI ion (middle) and the AMTHBI ion (bottom).

Table 3. Final positional parameters for hydrogen atoms ($\times 10^3$). The e.s.d.'s are given in parentheses. Temperature factor $U = 0.05$.

Atom	*x/a*	*y/b*	*z/c*	Atom	*x/a*	*y/b*	*z/c*
4,5,6,7-Tetrahydrobenzimidazole (THBI) Molecule A				4,5,6,7-Tetrahydrobenzimidazole (THBI) Molecule B			
HN1	453(4)	−167(4)	486(2)	HN1	102(4)	667(3)	620(2)
HN2	148(4)	72(3)	408(2)	HN2	283(4)	384(4)	533(3)
HC1	221(4)	−62(3)	514(2)	HC1	304(4)	602(3)	548(2)
HC4A	568(4)	−188(4)	348(3)	HC4A	−172(4)	561(4)	640(3)
HC4B	653(4)	−67(4)	368(2)	HC4B	−71(4)	511(4)	712(2)
HC5A	613(4)	−75(3)	234(2)	HC5A	−231(4)	359(3)	602(2)
HC5B	438(4)	−123(4)	235(3)	HC5B	−249(4)	361(4)	691(2)
HC6A	468(4)	95(4)	200(2)	HC6A	−6(5)	267(4)	711(3)
HC6B	559(4)	115(3)	287(2)	HC6B	−117(4)	186(3)	659(2)
HC7A	314(4)	176(4)	294(3)	HC7A	120(5)	215(4)	611(3)
HC7B	240(4)	56(3)	256(2)	HC7B	−13(4)	244(4)	546(2)
5(6)-Amino-4,5,6,7-Tetrahydrobenzimidazole (ATHBI)							
HN1	87(5)	323(3)	153(19)	HC4B	381(10)	385(7)	289(14)
HN2	−99(4)	551(3)	242(20)	HC5A	509(6)	511(3)	266(8)
HN3A	400	686	387	HC5B	382(5)	527(3)	431(9)
HN3B	375	725	205	HC6	356(5)	591(3)	37(9)
HN3C	512	673	220	HC7A	149(12)	637(6)	84(18)
HC1	−140(4)	395(3)	187(20)	HC7B	171(12)	649(6)	333(18)
HC4A	340(11)	413(7)	62(13)				
4(7)-Aminomethyl-4,5,6,7-Tetrahydrobenzimidazole (AMTHBI)							
HN1	299(4)	484(4)	219(3)	HC5A	268(4)	121(4)	22(3)
HN2	585(4)	249(4)	287(3)	HC5B	85(4)	105(4)	4(3)
HN3A	349(4)	−183(4)	272(3)	HC6A	136(4)	24(4)	177(3)
HN3B	486(4)	−162(3)	267(3)	HC6B	255(4)	−47(4)	114(3)
HN3C	483(4)	−192(4)	375(3)	HC7	477(4)	46(4)	203(3)
HC1	524(4)	478(4)	374(3)	HC8A	351(4)	−11(4)	361(3)
HC4A	65(4)	288(4)	97(3)	HC8B	533(4)	15(4)	387(3)
HC4B	153(4)	335(4)	29(3)				

planes. Although not quite symmetrical the six-membered rings thus have the normal half-chair conformation of cyclohexene.

In the ATHBI and AMTHBI ions comparable bond distances and bond angles are, disregarding those involving the atoms C5 and C6, nearly the same as in the THBI ions. The imidazole rings of ATHBI and AMTHBI are planar within the limits of error, the maximal deviations being 0.029 and 0.007 Å, respectively. The larger deviations in the ATHBI ion is explained by the large e.s.d.'s of its *z*-coordinates. From Table 4 it is evident that the cyclohexene ring of ATHBI is heavily distorted. However, owing to the difficulties already mentioned in obtaining a completely reliable structure determination, a detailed discussion of the bond lengths, bond angles and conformation of the cyclohexene ring of ATHBI is not meaningful. Nevertheless, it seems as if the position chosen for the atom C6 in ATHBI is realistic. Similar distorted bond lengths and bond angles are found in the cation of AMTHBI where no pseudo mirror planes or other intrinsic properties of the structure have disturbed the accuracy of the positional parameters. In the AMTHBI structure the cyclohexene ring has an almost normal conformation (Table 4) but the C5−C6 bond is about 0.03 Å shorter and the C4−C5−C6 angle is about 4° wider than in the unsubstituted THBI ions. We have found no really good explanation for these discrepancies.

The two substituted molecules can be regarded as histamine analogues. In ATHBI the amino

Table 4. Least-squares planes and deviations in Å ($\times 10^3$) of the atoms of the ring system, C5 and C6 are not included in the calculations. The equations of the planes are in the form $AX+BY+CZ=D$ where X, Y and Z are coordinates in orthogonal Ångström space.

Equations

THBI (A): $0.5188X+0.7088Y+0.4779Z=4.2169$
THBI (B): $0.4764X-0.1392Y+0.8681Z=8.0392$
ATHBI: $-0.0015X-0.0020Y+0.9999Z=1.3453$
AMTHBI: $0.8284X+0.1393Y-0.5425Z=0.6724$

	THBI Mol A	THBI Mol B	ATHBI	AMTHBI
N1	+12	+11	−19	−10
C1	−1	+18	+6	+4
N2	−14	−18	+30	+19
C2	−4	−20	−42	−13
C3	+11	−16	+3	−17
C4	−14	+1	+19	+19
C7	+11	+23	+4	−2
C5	−430	−227	+594	+252
C6	+298	+490	(−79)	−371

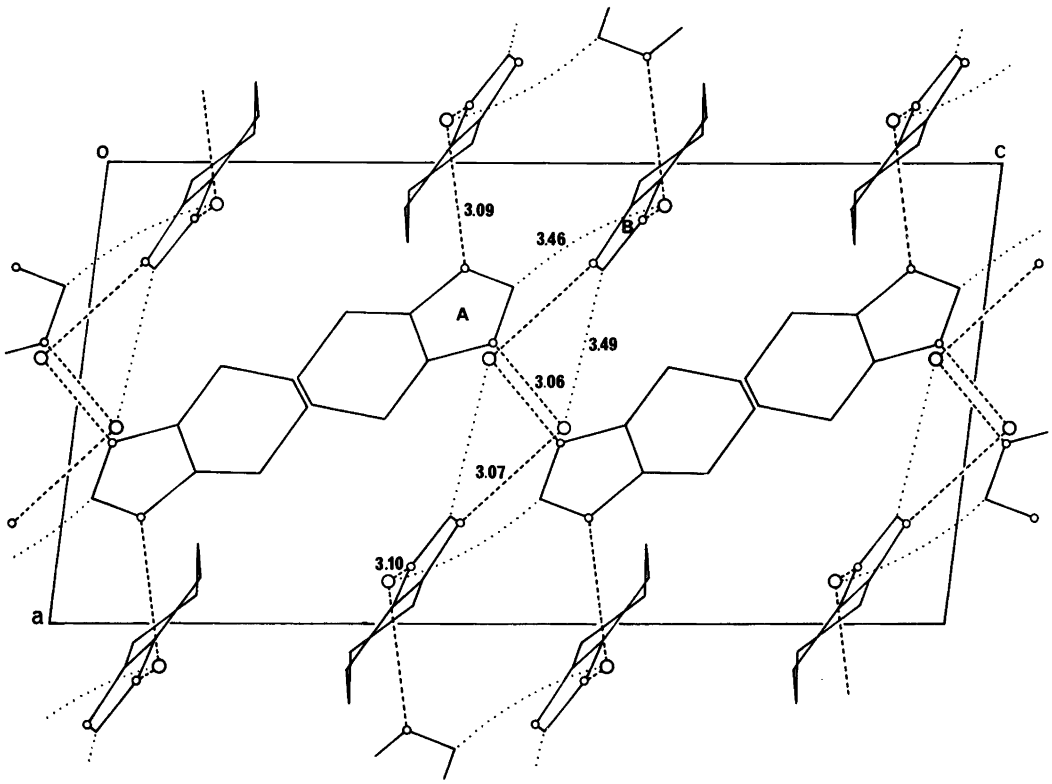


Fig. 3. The crystal structure of 4,5,6,7-tetrahydrobenzimidazole (THBI) hydrochloride seen along the *b* axis. Nitrogen atoms are drawn as small open circles, chloride ions as larger open circles. Hydrogen bonds are represented by broken lines and C−H···Cl interactions by dotted lines. Distances in Å.

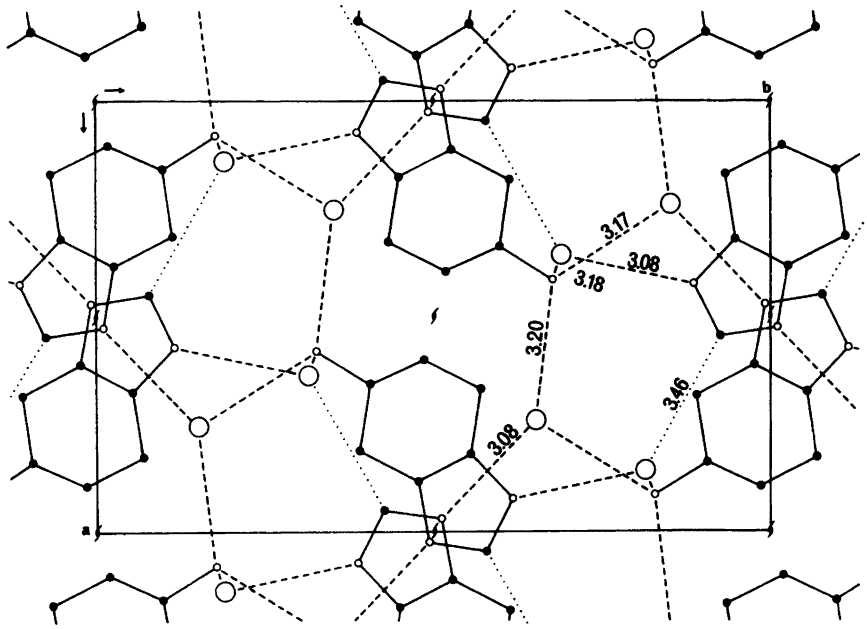


Fig. 4. The crystal structure of 5(6)-amino-4,5,6,7-tetrahydrobenzimidazole (ATHBI) dihydrochloride seen along the *c* axis. Carbon atoms are represented by filled circles, nitrogen atoms by small open circles and chloride ions as larger open circles. Hydrogen bonds are represented by broken lines and C–H···Cl interactions by dotted lines. Distances in Å.

Table 5. Intermolecular interactions of the type D–H···Cl. Reference molecule in *x*, *y*, *z*. The symmetry of the acceptor atom (Cl) is given in parenthesis.

				D–H Å	H···Cl Å	D···Cl Å	D–H···Cl °
4,5,6,7-Tetrahydrobenzimidazole HCl (THBI)							
N1A	HN1A	Cl1	$(1-x,-y,1-z)$	0.97	2.09	3.06	175.6
N2A	HN2A	Cl2	$(-x,1-y,1-z)$	0.88	2.25	3.09	160.8
N1B	HN1B	Cl2	(x,y,z)	0.92	2.21	3.10	161.8
N2B	HN2B	Cl1	(x,y,z)	0.93	2.16	3.07	164.6
C1A	HC1A	Cl2	$(x,y-1,z)$	0.94	2.53	3.46	170.6
C1B	HC1B	Cl1	$(1-x,1-y,1-z)$	0.93	2.62	3.49	154.5
5(6)-Amino-4,5,6,7-tetrahydrobenzimidazole 2HCl (ATHBI)							
N1	HN1	Cl1	(x,y,z)	0.98	2.17	3.08	153.8
N2	HN2	Cl2	$(1/2-x,1/2+y,-1/2+z)$	0.99	2.16	3.08	155.4
N3	HN3A	Cl1	$(1/2-x,1/2+y,1/2+z)$	1.01	2.18	3.18	171.6
N3	HN3B	Cl2	$(1-x,1-y,-1/2+z)$	0.90	2.30	3.17	163.5
N3	HN3C	Cl2	$(1\ 1/2-x,1/2+y,-1/2+z)$	0.93	2.27	3.20	170.8
C1	HC1	Cl1	$(-1/2+x,1/2-y,z)$	1.00	2.47	3.46	172.3
4(7)-Aminomethyl-4,5,6,7-tetrahydrobenzimidazole 2HCl (AMTHBI)							
N1	HN1	Cl1	$(x,1+y,z)$	0.75	2.35	3.10	174.7
N2	HN2	Cl2	$(1-x,-y,1-z)$	0.81	2.25	3.06	176.8
N3	HN3A	Cl1	(x,y,z)	0.90	2.30	3.17	161.5
N3	HN3B	Cl2	$(1/2+x,-1/2-y,z)$	0.83	2.44	3.15	141.8
N3	HN3C	Cl1	$(1/2+x,-1/2-y,z)$	0.85	2.35	3.17	167.7
C1	HC1	Cl2	$(1/2+x,1/2-y,z)$	0.94	2.58	3.52	170.4

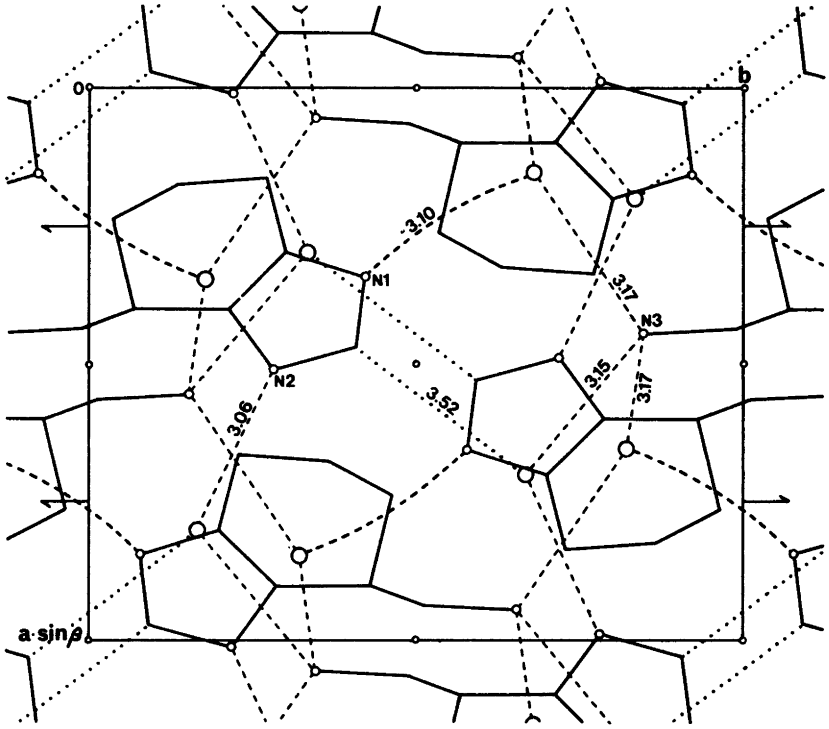


Fig. 5. The crystal structure of 4(7)-aminomethyl-4,5,6,7-tetrahydrobenzimidazole (AMTHBI) dihydrochloride seen along the *c* axis. Nitrogen atoms are represented by small open circles and chloride ions as larger open circles. Hydrogen bonds are represented by broken lines and C–H···Cl interactions by dotted lines. Distances in Å.

nitrogen atom is connected *via* C6 and C7 to the C2 atom of the imidazole ring. The conformation of the ethylamine side chain of histamine can be described by two torsion angles τ_1 and τ_2. In the case of the ATHBI ion τ_1(N2–C2–C7–C6) is 178.8° and τ_2 (C2–C7–C6–N3) is −165.6°, showing that the rigid "ethylamine side chain" of the histamine part of the ATHBI ion is nearly planar with its plane almost in the plane of the imidazole ring. In the AMTHBI ion the "ethylamine side chain" is also nearly planar but the plane of the chain is inclined to the imidazole plane as shown by the torsion angles τ_1(N2–C2–C7–C8)=44.0° and τ_2 (C2–C7–C8–N3)=−176.1°. It is noteworthy that while the ethylamine side chain in histidine structures always has been found to be in a *gauche* conformation, *i.e.* with a τ_2-angle around 60°, the *trans* conformation, *i.e.* with a τ_2-angle around 180°, has invariably been found in structure determinations of histamine.[13] Perspective drawings of the molecules are shown in Fig. 2.

In the three structures all nitrogens are protonated and the molecules thus appear as cations making full use of possible hydrogen bondings to the chloride ions. However, the nitrogen atoms of the imidazole ring make stronger hydrogen bonds (3.06–3.10 Å) with the chloride ions than do the amino nitrogen atoms (3.15–3.20 Å). The hydrogen bonding systems and the packing of the molecules are illustrated in Figs 3, 4 and 5. In addition, in each of the three structures there are C1–HC1···Cl interactions with H···Cl contacts ranging from 2.47 to 2.62 Å which is appreciably shorter than the sum of van der Waals radii (2.8 Å). This interaction may be attributed to the strong polarization of HCl caused by the protonation of the two neighbouring nitrogen atoms of the imidazole ring. A similar situation is found *e.g.* in the structure of 1,9-dimethyladeninium chloride where H···Cl distances of 2.54 and 2.58 Å were observed.[14] Bond

lengths and angles involving hydrogen bonds and C–H···Cl interactions are given in Table 5. No other short contacts violating ordinary packing requirements were found in the three structures.

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