Crystal and Molecular Structure of the Histamine H_2-Receptor Antagonist *N*-(4-Imidazol-4-ylbutyl)-*N'*-methylthiourea (Burimamide)

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The crystal and molecular structure of the title compound has been determined from three-dimensional *X*-ray diffractometer data by Patterson and Fourier methods. Crystals are orthorhombic, space group *Pccn*, $Z = 8$, $a = 10{\cdot}71 \pm 0{\cdot}01$, $b = 22{\cdot}84 \pm 0{\cdot}02$, $c = 9{\cdot}51 \pm 0{\cdot}01$ Å. Data were refined by least-squares methods to *R* 4·8% for 1507 independent reflections. The crystals are built up from isolated molecules linked together by hydrogen bonds between imidazole rings and thiourea residues. The molecular conformation may be described in terms of three planes, those of the imidazole ring, alkyl chain, and thiourea residue. The imidazole and thiourea planes make angles of 83·6 and −109·5° respectively with the plane of the alkyl chain. There are no imidazole–thiourea contacts. The overall configuration is determined by a combination of intramolecular repulsion and crystal-packing factors.

BURIMAMIDE [*N*-(4-imidazol-4-ylbutyl)-*N'*-methylthiourea] (I), has recently been defined [1] as a specific competitive histamine H_2-receptor antagonist, a new type of drug which blocks those responses to histamine not antagonised by mepyramine,[2] and is active in man in inhibiting histamine-stimulated gastric acid secretion. Burimamide (I) and histamine (II) have an obvious superficial resemblance in that both substances possess an imidazole ring and which, in view of the biological properties, suggests a common site of action. It is therefore pertinent to examine the extent of the structural similarity between the natural transmitter substance, histamine, and its inhibitor, burimamide.

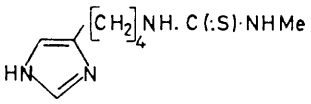
Another point of interest derives from the suggestion by Kier [3] that H_2-receptor activity of histamine is

[1] J. W. Black, W. A. M. Duncan, G. J. Durant, C. R. Ganellin, and M. E. Parsons, *Nature*, 1972, **236**, 385.

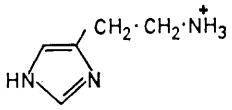
[2] A. S. F. Ash and H. O. Schild, *Brit. J. Pharmacol. Chemotherapy*, 1966, **27**, 427.

[3] L. B. Kier, *J. Medicin. Chem.*, 1968, **11**, 441.

associated with a molecular conformation of the agonist in which the distance between the nitrogen atom of the ring (in the position *ortho* to the side-chain) and that of the ammonium group is 3·6 Å, and his prediction that an



(I)



(II)

antagonist should also be able to achieve this feature. Although burimamide differs from histamine in having an uncharged side-chain one may note that it is similar in possessing NH functionality (in the thiourea group) and in this sense the side-chain nitrogen atoms of these two compounds can be considered as comparable. By folding of the side-chain, which could occur in several ways, burimamide can achieve a distance of 3·6 Å between the nitrogen atoms of the ring and thiourea group, and one may envisage that such a form would possibly be stabilised by intramolecular attraction through hydrogen bonding or by stacking interactions (of the type found in nucleotide bases).[4] The crystal structure was investigated as a potential source of evidence.

EXPERIMENTAL

The compound was recrystallised from water.

Crystal Data.—$C_9H_{16}N_4S$, $M = 212·3$. Orthorhombic, $a = 10·71 \pm 0·01$, $b = 22·84 \pm 0·02$, $c = 9·51 \pm 0·01$ Å, $U = 2326·23$ Å^3, $D_m = 1·21$, $Z = 8$, $D_c = 1·212$. Space group $Pccn$ (D_{2h}^{10}, No. 56). Cu-K_α Radiation $\lambda = 1·5418$ Å; $\mu = 17·81$ cm^{-1}. 1507 Independent reflections, four-circle diffractometer.

Unit cell dimensions were determined from oscillation and Weissenberg photographs and subsequently refined by a least-squares procedure [5] with a Hilger and Watts four-circle diffractometer which was also used for the measurement of the intensities of the reflections by an ω—2θ step scan procedure together with an ordinate analysis.[6] There were 1507 independent reflections with $I \geqslant 3\sigma(I)$. Lorentz and polarisation corrections were applied but not absorption corrections.

The most prominent maxima in the unsharpened Patterson function were consistent with a sulphur atom in an eight-fold general position. A sulphur phased F_o synthesis gave a trial structure for all atoms except hydrogen. The trial structure with individual isotropic temperature factors for each atom and unit weight for the F_o was refined by full-matrix least-squares analysis. At convergence R was 11% and the hydrogen atoms were located from a difference-Fourier synthesis. The refinement of all atomic parameters except those of hydrogen was then continued with anisotropic temperature factors and the weighting scheme: $w = (5·87 + |F_o| + 0·011|F_o|^2)^{-1}$. At R 5·1% hydrogen atoms were included in the refinement with isotropic temperature factors. Convergence was reached at R 4·8%. Observed structure amplitudes and structure factors calculated from the final atomic parameters in Table 1 are

TABLE 1

Atomic parameters and thermal parameters * with standard deviations in parentheses

	x/a	y/b	z/c	U_{11} or U_{iso}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S	0·0637(1)	0·4075(0)	0·4542(1)	0·0533(6)	0·0480(5)	0·0487(6)	−0·0030(4)	−0·0062(4)	−0·0068(4)
C(1)	0·2346(6)	0·3295(2)	0·6326(8)	0·077(3)	0·049(2)	0·111(5)	−0·003(3)	−0·019(3)	0·013(2)
C(2)	0·1506(3)	0·4287(2)	0·5960(4)	0·043(2)	0·043(2)	0·047(2)	0·004(2)	0·005(2)	−0·006(1)
C(3)	0·2055(4)	0·5092(2)	0·7619(4)	0·056(2)	0·048(2)	0·042(2)	0·001(2)	0·001(2)	−0·006(2)
C(4)	0·3316(4)	0·5352(2)	0·7254(5)	0·053(2)	0·048(2)	0·053(2)	0·008(2)	−0·013(2)	−0·006(2)
C(5)	0·3217(4)	0·5893(2)	0·6314(4)	0·051(2)	0·048(2)	0·056(2)	0·005(2)	−0·004(2)	0·001(2)
C(6)	0·4466(4)	0·6119(2)	0·5804(5)	0·053(2)	0·059(2)	0·065(3)	0·012(2)	−0·002(2)	−0·006(2)
C(7)	0·4350(3)	0·6667(2)	0·4961(4)	0·048(2)	0·053(2)	0·039(2)	0·000(2)	0·003(1)	−0·007(2)
C(8)	0·4343(4)	0·6744(2)	0·3550(5)	0·067(5)	0·060(2)	0·044(2)	−0·008(2)	0·007(2)	−0·006(2)
C(9)	0·4077(5)	0·7582(2)	0·4554(5)	0·112(4)	0·051(3)	0·046(2)	−0·003(2)	0·004(2)	−0·018(2)
N(1)	0·2267(3)	0·3922(1)	0·6624(4)	0·051(2)	0·046(2)	0·068(2)	0·003(2)	−0·007(2)	0·002(1)
N(2)	0·1421(3)	0·4838(1)	0·6423(3)	0·046(2)	0·042(2)	0·045(2)	0·002(1)	−0·008(1)	−0·001(1)
N(3)	0·4166(4)	0·7329(2)	0·3306(4)	0·080(2)	0·062(2)	0·036(2)	0·003(2)	0·004(2)	−0·012(2)
N(4)	0·4178(4)	0·7203(2)	0·5591(3)	0·105(3)	0·057(2)	0·033(2)	−0·002(1)	0·002(2)	−0·011(2)
H(11)	0·263(9)	0·321(4)	0·540(10)	0·05(3)					
H(12)	0·292(7)	0·308(3)	0·687(9)	0·08(3)					
H(13)	0·135(11)	0·310(6)	0·658(14)	0·19(5)					
H(21)	0·282(7)	0·412(3)	0·738(8)	0·06(2)					
H(22)	0·088(3)	0·505(2)	0·592(4)	0·02(1)					
H(31)	0·214(4)	0·480(2)	0·837(5)	0·02(1)					
H(32)	0·148(3)	0·539(1)	0·812(4)	0·01(1)					
H(41)	0·381(4)	0·503(2)	0·674(5)	0·04(1)					
H(42)	0·377(6)	0·548(2)	0·812(7)	0·04(2)					
H(51)	0·260(4)	0·580(2)	0·544(5)	0·03(1)					
H(52)	0·273(4)	0·621(2)	0·675(5)	0·03(1)					
H(61)	0·480(6)	0·576(3)	0·523(7)	0·07(2)					
H(62)	0·501(5)	0·621(2)	0·682(6)	0·06(2)					
H(81)	0·461(6)	0·644(3)	0·301(8)	0·07(2)					
H(82)	0·419(6)	0·750(3)	0·239(9)	0·08(2)					
H(91)	0·400(4)	0·801(2)	0·473(5)	0·02(1)					

* The temperature factor T is given by the expression: $T = \exp[-2\pi^2(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + 2U_{23}b^*c^*kl + 2U_{13}a^*c^*hl + 2U_{12}a^*b^*hk)]$.

[5] M. Dobler and B. Duerr, personal communication.

[6] H. C. Watson, D. M. Shotton, J. M. Cox, and H. Muirhead, *Nature*, 1970, **225**, 806.

[4] 'Molecular Associations in Biology,' ed. B. Pullman, Academic Press, New York, 1968.

listed in Supplementary Publication No. SUP 20766 (9 pp.).† Atomic scattering factors for neutral atoms were taken from ref. 7. All calculations were carried out on the Oxford University ICL 1906A computer with a program kindly provided by Dr. Sheldrick.

RESULTS AND DISCUSSION

Interatomic distances and interbond angles with their standard deviations are given in Table 2. The atom numbering corresponds to that in Figure 1, the projection of the molecule onto the least-squares best plane of the imidazole residue. Figure 2 shows the molecule viewed down the C(4)–C(5) bond looking towards C(5), and Figure 3 the crystal structure projected down the *a* axis.

TABLE 2

Interatomic distances (Å) and interbond angles (deg.) with standard deviations in parentheses

(*a*) Bond lengths and angles within the molecule.

(i) Distances

S–C(2)	1·709(4)	C(1)–H(12)	0·94(8)
C(1)–N(1)	1·461(6)	C(1)–H(13)	1·18(12)
C(2)–N(1)	1·326(5)	N(1)–H(21)	1·03(7)
C(2)–N(2)	1·336(5)	N(2)–H(22)	0·90(4)
C(3)–N(2)	1·446(5)	C(3)–H(31)	0·97(4)
C(3)–C(4)	1·517(5)	C(3)–H(32)	1·04(3)
C(4)–C(5)	1·528(5)	C(4)–H(21)	1·03(5)
C(5)–C(6)	1·515(6)	C(4)–H(42)	1·00(7)
C(6)–C(7)	1·491(6)	C(5)–H(51)	1·08(4)
C(7)–C(8)	1·353(6)	C(5)–H(52)	0·99(4)
C(7)–N(4)	1·375(5)	C(6)–H(61)	1·06(6)
C(8)–N(3)	1·371(6)	C(6)–H(62)	1·15(6)
C(9)–N(3)	1·323(6)	C(8)–H(81)	0·91(7)
C(9)–N(4)	1·317(6)	C(9)–H(91)	0·99(5)
C(1)–H(11)	0·95(9)	N(3)–H(82)	0·95(8)

(ii) Angles

C(1)–N(1)–C(2)	124·0(4)	C(5)–C(6)–C(7)	112·7(3)
N(1)–C(2)–S	122·2(3)	C(6)–C(7)–C(8)	129·9(4)
N(2)–C(2)–S	119·3(3)	C(6)–C(7)–N(4)	121·6(4)
N(2)–C(2)–N(1)	118·5(3)	C(8)–C(7)–N(4)	108·4(4)
C(2)–N(2)–C(3)	127·2(3)	C(7)–C(8)–N(3)	107·1(4)
N(2)–C(3)–C(4)	113·3(3)	C(8)–N(3)–C(9)	106·5(4)
C(3)–C(4)–C(5)	112·9(3)	N(3)–C(9)–N(4)	112·3(4)
C(4)–C(5)–C(6)	113·7(3)	C(7)–N(4)–C(9)	105·7(3)

(*b*) Some interesting intramolecular contacts

S · · · H(22)	2·596	C(4) · · · H(62)	2·703
C(2) · · · H(31)	2·662	C(5) · · · H(32)	2·770
C(3) · · · H(21)	2·382	C(6) · · · H(41)	2·736
C(3) · · · H(51)	2·697	C(6) · · · H(42)	2·746
C(3) · · · H(52)	2·781	C(6) · · · H(81)	2·761
C(4) · · · H(21)	2·870	C(7) · · · H(51)	2·761
C(4) · · · H(22)	2·985	C(7) · · · H(52)	2·645
C(4) · · · H(61)	2·665	C(8) · · · H(61)	2·804

(*c*) Some interesting intermolecular contacts *

S · · · H(21^{I})	2·640	S · · · N(1^{III})	3·587
S · · · H(22^{II})	2·609	N(4) · · · H(82^{IV})	1·843
S · · · N(2^{II})	3·444	N(3) · · · N(4^{IV})	2·793

* Roman numeral superscripts denote the following equivalent positions relative to the reference molecule at x, y, z:

I $\frac{1}{2} - x, y, 1 - z$ III $\frac{1}{2} - x, y, z - \frac{1}{2}$
II $1 - x, 1 - y, 1 - z$ IV $x, 3/2 - y, \frac{1}{2} + z$

Molecular Dimensions.—The bond lengths and interbond angles are well determined but have not been corrected for thermal motion. They do not differ significantly from those previously observed in related compounds. The imidazole residue is strictly planar and although the hydrogen atom H(82) is unambiguously attached to N(3), the bond lengths and angles within the imidazole ring are symmetrical with the pairs of bonds C(9)–N(3), C(9)–N(4) and N(3)–C(8), N(4)–C(7) equivalent in length at the 50% probability level. This is contrary to prediction from empirical quantum mechanical calculations [8] but in reasonable agreement with the better *X*-ray analyses of related compounds

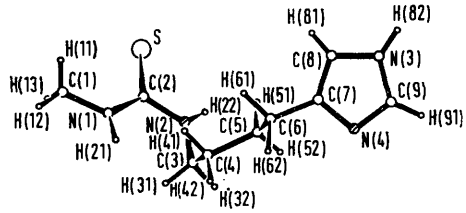


FIGURE 1 The burimamide molecule projected on the least-squares best plane of the imidazole group

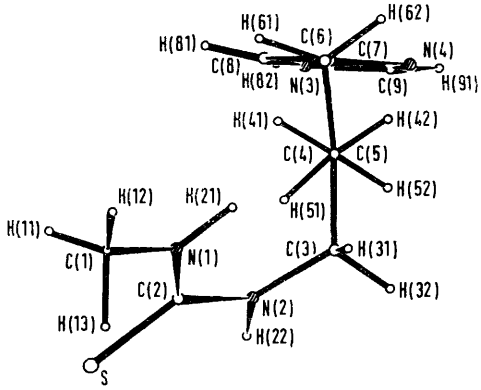


FIGURE 2 The burimamide molecule viewed down the C(4)–C(5) bond looking from C(4) towards C(5)

(*e.g.* imidazole,‡ [9] L-histidine [10]). The dimensions of the $[CH_2]_4$ chain do not differ significantly from those found in other alkane [11] derivatives. The thiourea also has no remarkable feature and its dimensions agree well with those found for thiourea [12] itself.

Molecular Conformation.—The molecule may be described in terms of three planes: the imidazole ring, the alkyl side-chain, and the thiourea residue (Figures 1 and 2). The planes of the imidazole group and thiourea residue make angles of 83·6 and −109·5° respectively with the plane of the alkyl side-chain. The carbon and nitrogen atoms of the imidazole group are coplanar to within ±0·001 Å. The alkyl side-chain is perpendicular

† See note about Supplementary Publications in Notice to Authors, No. 7, in *J.C.S. Dalton*, 1972. Index issue.

‡ We have refined the published imidazole structure by full-matrix least-squares analysis and have confirmed the published results.

[7] D. T. Cromer and I. T. Waber, *Acta Cryst.*, 1965, **18**, 104.
[8] B. and A. Pullman, 'Quantum Biochemistry,' Wiley, New York, 1963.
[9] S. Martinez-Carrera, *Acta Cryst.*, 1966, **20**, 783.
[10] J. J. Madden, E. L. McGandy, N. C. Seeman, M. M. Harding, and A. Hoy, *Acta Cryst.*, 1972, *B*, **28**, 2382; J. J. Madden, E. L. McGandy, and N. C. Seeman, *ibid.*, p. 2377.
[11] L. Pauling, 'The Nature of the Chemical Bond,' Cornell University Press, Ithaca, New York, 1960.
[12] M. R. Truter, *Acta Cryst.*, 1967, **22**, 556.

to the imidazole ring to minimise the hydrogen–hydrogen repulsions between hydrogens of the imidazole and those of the side-chain. Similarly, the *trans*-configuration of the side-chain also minimises hydrogen–hydrogen interactions. The first side-chain carbon atom attached to C(7) of the imidazole atom C(6) is significantly (0·043 Å) out of the imidazole plane (Figure 2) and on the same side of the imidazole plane as the rest of the side-chain. H(81) attached to C(8) is also significantly out of the imidazole plane on the opposite side of C(6). However, C(5) is twisted slightly towards N(4) so that H(61) tends to approach the imidazole plane, but not such that the C(5)–C(6) bond is substantially moved away from the H(31) or H(32). However, other positions of N(2) seem unlikely on the ground of intramolecular repulsion.

From the known thiourea structures [12] it is expected that the atoms of the thiourea group [*i.e.* C(3), N(2), H(22), C(2), S, H(21), N(1), and C(1)] would be coplanar. For the atoms of this group, other than hydrogen, the maximum and mean deviations from the best plane are 0·060 and 0·027 Å respectively. Of the methyl group hydrogen atoms at C(1), H(12) lies close to the thiourea plane. At N(1) and N(2) respectively H(21) is *trans* with respect to sulphur and H(22) *cis*. Consideration of intramolecular repulsions appears to impose only minor constraints at C(3) and to require that H(21) should be

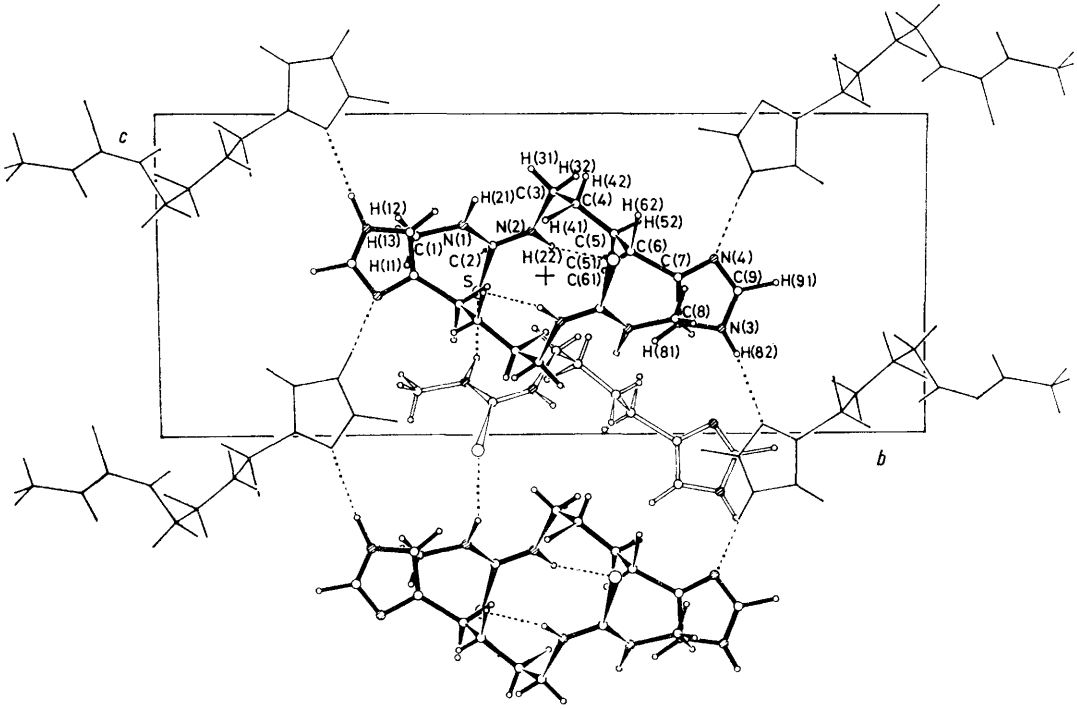


FIGURE 3 Part of the crystal structure burimamide projected down *a*. The hydrogen bonded sheet at $x = \frac{1}{2}$ (ball and stick molecules) is complete showing the N–H · · · N and N–H · · · S hydrogen bonds. Only one molecule of the layer at $x = 0$ (open lines) is shown to indicate the N–H · · · S hydrogen bonds. The positions of the molecules in this layer are related to those in the plane at $z = \frac{1}{2}$ by the *c* glide plane at $x = \frac{1}{4}$

plane perpendicular to the imidazole ring (Figure 2). It seems, therefore, that although the major structural features of this part of the molecule are determined by intramolecular repulsion between the atoms of the imidazole and those of the side-chain, the final detail does not appear to be so determined unless the repulsion of the N(4) lone-pair by H(62) is greater than the H(61) · · · H(81) interaction.

The alkyl chain has the expected *trans*-configuration about the C(6)–C(5) and C(5)–C(4) bonds but at C(3) it is H(31) which lies approximately in the C(3)—(7) plane and N(2) occupies a half *cis*-position on the same side of the C(3)—(7) plane as C(8) of the imidazole (Figures 1 and 2). Examination of a model of the molecule suggests that the observed configuration is little more satisfactory than that with N(2) interchanged with *trans* if H(22) is *cis*. The configuration with both H(21) and H(22) *trans* does not appear to be sterically inhibited.

Intramolecular packing forces do not appear to determine even the major features of the configuration of this part of the molecule. However, any of the possible configurations will lead to short non-bonded hydrogen–hydrogen contacts such as those found in the observed structure (Table 2).

Crystal Structure.—The crystals are built up from burimamide molecules linked by a complex network of N–H · · · N and N–H · · · S hydrogen bonds. The short N(3)–H(82) · · · N(4), 2·79 Å [N(3)–H(82) · · · N(4) 176°; N(3)–H(82), 0·95, H(82) · · · N(4) 1·84 Å], hydrogen bond links the imidazole residues to form ribbons parallel to *c*. Within the ribbon the imidazole rings lie almost

exactly in the *bc* plane and at the same height along *a*. The alkyl side-chains lie alternately in the $+b$ and $-b$ directions (Figure 3). Hydrogen-bonded imidazole chains are a feature of the crystal structure of imidazole [9] itself and similar hydrogen-bonded linear oligomers of imidazoles have been observed for carbon tetrachloride solutions.[13] The vertical separation between the ribbons is $a/2$ (5·35 Å) and is much larger than that found in other crystals *e.g.* imidazolium dihydrogen orthophosphate [14] (3·29 Å) because in the burimamide crystal the *N*-methyl groups of molecules of neighbouring chains are intercalated into the stacks of ribbons of imidazole residues.

At each thiourea group there are two S · · · H–N contacts of 3·444 and 3·587 Å with S · · · H(21) 2·640 and S · · · H(22) 2·609 Å [Figure 3 and Table 2(*b*)] significantly <2·75 Å, the sum of the van der Waals radii. The systems S · · · H(21)–N(1) and S · · · H(22)–N(2) deviate from linearity by 28 and 25° and are in keeping with the criteria suggested by Donohue [15] for classifying S · · · H interactions as hydrogen bonds. Pairs of S · · · H(22)–N(2) bonds about symmetry centres (*e.g.* that at $\frac{1}{2},\frac{1}{2},\frac{1}{2}$ in Figure 3) link the N–H · · · N bonded imidazole ribbons to form sheets with mean heights 0 and $\frac{1}{2}$ along *a*. The arrangement is similar to that found in thiourea.[12] The pairs of N–H · · · S hydrogen bonds require the sulphur and hydrogen to be *cis* about a C–N bond. If H(21) and S were *cis* then the imidazole side-chains would meet end to end (Figure 4b) leaving large spaces in the crystals; but if, as is found in the crystal, H(22) and S are *cis* the side-chains meet side by side (Figure 4a and Figure 3) interleaving to form a compact structure which effectively fills space. That H(22) and S are *cis* appears, therefore, to be a crystal packing requirement. However, it follows from consideration of intramolecular overcrowding that H(21) and S must then be *trans*. The sheets at 0 and $\frac{1}{2}$ along *a* are linked by further S · · · H(21)–N(1) hydrogen bonds (Figure 3). Therefore, all the hydrogen atoms covalently bonded to nitrogen participate in hydrogen bonding.

It is concluded that the molecular conformation of burimamide in the crystal is determined by a combination of intramolecular repulsion and crystal packing factors.

Biological Significance.—A feature of importance to biological considerations is the complete absence of contact between the imidazole rings and thiourea groups. The two residues are widely separated and the shortest nitrogen–nitrogen intramolecular distance is >6 Å. Thus the crystal structure, while not disproving Kier's suggestion [3] that an H_2-receptor antagonist should have an internitrogen distance of 3·6 Å, does not provide evidence in support of it.

The imidazole residues are notably in a unique tautomeric form in which the non-protonated nitrogen atom is adjacent to the side-chain. The same form is found in the crystal of L-histidine [8] and 6-histaminopurine dihydrate.[16] The tautomeric form of crystalline histamine is unavailable for comparison since the only structure reported is of the diprotonated species. The dihedral angle between the planes of the ring and the alkyl side-chain in burimamide is 83·6°, closely comparable to that found in histamine dication [17] (82·5°).

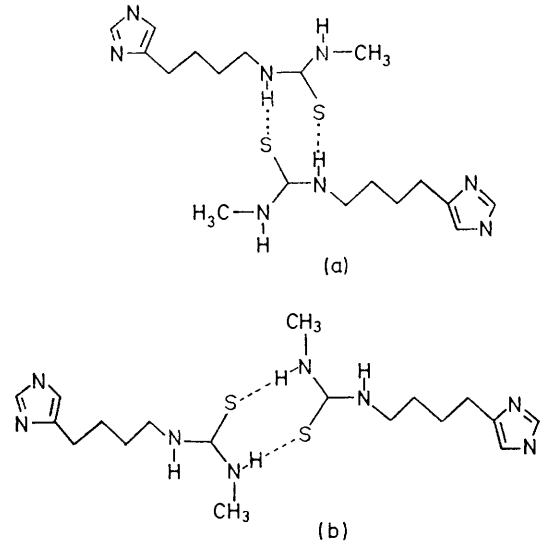


FIGURE 4 Two possible pairings of burimamide molecules about a centre of symmetry: (a) the imidazole and side-chains meet side-by-side giving the more compact structure which is found in the crystal structure, and (b) the imidazole and side-chains meet end-to-end

The configuration adopted by the thiourea group is of especial interest. An *NN'*-unsymmetrical disubstituted thiourea has four possible different planar configurations but the burimamide crystal shows only one of these. This could be the biologically active form but it is necessary to be cautious in drawing conclusions since hydrogen bonding and packing factors may determine the outcome in the crystal. Indeed, in solution there is evidence from n.m.r. spectroscopy of three different configurational forms in equilibrium, none of which is apparently particularly more stable than the others.[18]

In summary, the crystal structure provides tangible evidence of a preferred configuration under one set of circumstances. There is no abnormal feature in the structure of burimamide that would raise the question of its possible contribution to the biological properties of the molecule.

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