An Infrared Study of Intramolecular Hydrogen-bonding in the Histamine H_2-Receptor Antagonists, Burimamide, Metiamide, Cimetidine, and Related Compounds

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The i.r. spectra of *N*-methyl-*N'*-[4-(5-methylimidazol-4-yl)butyl]thiourea (methylburimamide), *N*-(4-imidazol-4-ylbutyl)-*N'*-methylthiourea (burimamide), *N*-methyl-*N'*-{2-[(5-methylimidazol-4-yl)methylthio]ethyl}thiourea (metamide), *N*-{2-[(imidazol-4-yl)methylthio]ethyl}-*N'*-methylthiourea (thiaburimamide), and *N*-cyano-*N'*-methyl-*N''*-[2-(4-methyl-5-imidazolylmethyl)thioethyl]guanidine (cimetidine) in bromoform have been recorded in the 3 500—3 200 cm^{-1} region and compared with those of some closely related model compounds. The results show that all five compounds can form intramolecular hydrogen bonds in solution. Several possible hydrogen-bonded conformations are considered. Metiamide and thiaburimamide probably adopt an eight-membered ring conformation in which the basic imidazole nitrogen atom is hydrogen-bonded to the thiourea NH group nearer to the imidazole ring. The population of the hydrogen-bonded conformations increases when CH_2 is replaced by S in the side chain.

THE histamine H_2-receptor antagonists are a new class of drug which *in vitro* antagonise the effects of histamine on cardiac and uterine muscle and which *in vivo* antagonise histamine-stimulated gastric acid secretion.[1] One of the antagonists, cimetidine (1), is now widely used for the treatment of peptic ulcers and associated gastrointestinal disorders.

Cimetidine, which is a cyanoguanidine, was preceded by the thiourea antagonists, methylburimamide (2), burimamide (3), metiamide (4), and thiaburimamide (5).[2,3] The molecular conformations of four of these compounds in the crystalline state are known. Burimamide [4] adopts an open-chain conformation whereas thiaburimamide,[5] metiamide,[5] and cimetidine [6] adopt a ten-membered ring conformation in which the basic imidazole nitrogen atom is intramolecularly hydrogen

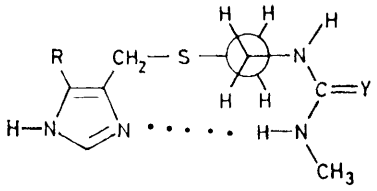


FIGURE 1 Molecular conformation of thiaburimamide, metiamide, and cimetidine in the crystalline state

bonded to the NH group furthest from the imidazole ring (Figure 1). In order to establish whether intramolecularly hydrogen-bonded conformations exist in solution the above and some closely related model compounds have been studied in an aprotic solvent by i.r. spectroscopy.

EXPERIMENTAL

I.r. spectra were recorded in the NH stretching region (3 500—3 200 cm^{-1}) on a Pye-Unicam SP700 UV-VIS-NIR spectrophotometer using 1 cm Infrasil cells. The positions of the sharpest bands are probably accurate to within 2 cm^{-1} and those of the broadest bands to within 5 cm^{-1}. The bromoform was supplied by B.D.H., specially for i.r. spectroscopy. The solutions were made sufficiently dilute (≤ 0.005 mol dm^{-3}) to prevent any significant intermolecular hydrogen bonding. Partition coefficients were measured by the conventional shake-flask technique.[7]

RESULTS AND DISCUSSION

The ten compounds studied are listed in Table 1 together with the frequencies and assignments of the NH stretching modes.

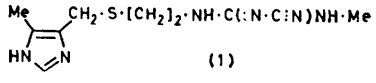
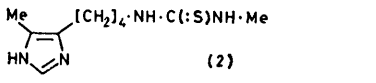
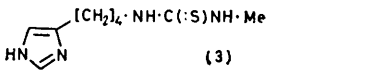
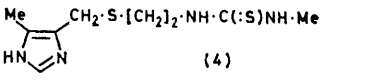
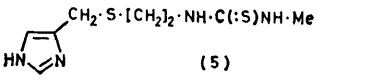
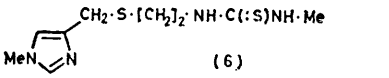
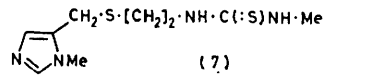
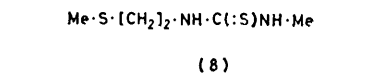
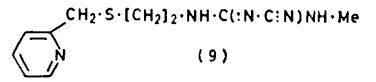
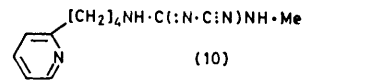
The Thioureas.—The spectra of the thioureas (2)—(5) are very similar; all have a sharp high frequency band near 3 440 cm^{-1} and a broad lower frequency band near 3 240 cm^{-1}. The former band will be composed of overlapping bands from non-associated imidazole and thiourea NH groups whilst the latter band must be due to intramolecularly hydrogen-bonded NH groups since all the solutions were dilute enough to eliminate bands due to intermolecular hydrogen bonding.

Three model thioureas (6)—(8) have been examined in order to establish which groups are involved in the intramolecular hydrogen bonding; compounds (6) and (7) are the methyl analogues of the N^{τ}–H and N^{π}–H tautomeric forms of thiaburimamide (5), respectively. The spectra of compounds (7) and (8) are almost identical. Based on the work of Walter and Ruess,[8] who have studied a large number of substituted thioureas, the lower frequency component of the doublet can be assigned to an NH group in the *E* configuration of the HN·C:S group (NH_E) and the higher frequency component to an NH group in the *Z* configuration of the HN·C:S group (NH_Z). The weak shoulder at *ca.* 3 370 cm^{-1} is probably due to an NH group which is hydrogen bonded to the sulphide linkage, giving a five-membered ring conformation if the NH group nearest to the imidazole ring is involved and a seven-membered ring conformation if the NH group furthest from the imidazole ring is involved. The spectrum of compound (6) is strikingly different from those of compounds (7) and (8); the NH_E component of the doublet is very weak and is replaced by a broad band at 3 235 cm^{-1} which is at almost the same position as the broad low frequency band in the spectra of compounds (2)—(5) and probably originates from the same hydrogen-bonded conformation.

Figure 2 shows four possible hydrogen-bonded conformations of compound (6) involving the three stable rotamers * of the planar *NN'*-disubstituted thiourea group. Only the eight-membered ring conformation of the *E–Z* rotamer contains a bonded NH_E group which suggests that it is the preferred hydrogen-bonded conformation in solution. It is also likely that metiamide (4) and thiaburimamide (5) adopt this conformation in solution which contrasts with the ten-membered ring conformation of the 2-pyridyl analogue (9) has been examined in order to determine which of the cyanoguanidine NH groups is involved in the hydrogen-bonding. The low frequency NH band at **3 275** cm^{-1} is at a higher frequency than the corresponding band in cimetidine (1) presumably because the pyridyl ring is less basic than the imidazolyl ring and forms a weaker hydrogen bond. The bands at **3 453** and **3 411** cm^{-1} can be assigned to NH groups in the *Z* and *E* configurations of the HN·C:N

TABLE 1

Frequencies and assignments of the NH stretching modes of compounds (1)—(10) in bromoform

Compound	Frequency (cm^{-1})	Assignment
 (1)	3 440 } d, sh 3 416 } 3 258br	Free NH (imidazole, cyanoguanidine) Free NH (cyanoguanidine) Intrabonded NH (cyanoguanidine)
 (2)	3 441sh 3 240br	Free NH (imidazole, thourea) Intrabonded NH (thiourea)
 (3)	3 444sh 3 246br	As (2) As (2)
 (4)	3 438sh 3 237br	As (2)
 (5)	3 442sh 3 244br	As (2)
 (6)	3 433sh 3 413w shoulder 3 235br	Free NH_Z (thiourea) Free NH_E (thiourea) Intrabonded NH_E (thiourea)
 (7)	3 430 } d, sh 3 413 } 3370w shoulder	Free NH_Z (thiourea) Free NH_E (thiourea) Intrabonded NH (thiourea)
 (8)	3 432 } d, sh 3 413 } 3 370w shoulder	As (7)
 (9)	3 453w 3 411sh 3 275br	Free NH_Z (cyanoguanidine) Free NH_E (cyanoguanidine) Intrabonded NH (cyanoguanidine)
 (10)	3 460sh 3 411sh 3 289br	As (9)

formation of the *E–Z* rotamer found in the crystalline state.

The Cyanoguanidines.—The spectrum of cimetidine (1) has sharp NH bands between **3 400** and **3 460** cm^{-1}, due to non-associated imidazole and cyanoguanidine NH groups, and a broad low frequency band at **3 258** cm^{-1} which indicates that cimetidine (1), like the corresponding thiourea, metiamide (4), can adopt an intramolecularly hydrogen-bonded conformation in solution. The spectrum of the 2-pyridyl analogue (9) has been examined in order to determine which of the cyanoguanidine NH groups is involved in the hydrogen-bonding. The low frequency NH band at **3 275** cm^{-1} is at a higher frequency than the corresponding band in cimetidine (1) presumably because the pyridyl ring is less basic than the imidazolyl ring and forms a weaker hydrogen bond. The bands at **3 453** and **3 411** cm^{-1} can be assigned to NH groups in the *Z* and *E* configurations of the HN·C:N group respectively (NH_Z and NH_E). The NH_Z band is much weaker than the NH_E band suggesting that an NH_Z group is involved in the hydrogen bonding. CPK molecular models indicate that the NH_E group can interact with the π-electrons of the cyano group.

Three possible intramolecularly hydrogen-bonded conformations of the 2-pyridyl compound (9), involving the two most probable rotamers † of the planar *NN'*-disubstituted cyanoguanidine group, are shown in

* An *NN'*-disubstituted thiourea in solution normally exists as an equilibrium mixture of three planar rotamers (*E–Z*, *Z–E*, and *Z–Z*).[8b,9] The *E–E* rotamer is thought to be unstable due to steric hindrance

† An *NN'*-disubstituted cyanoguanidine in solution normally exists as an equilibrium mixture of two planar rotamers (*Z–E* and *E–Z*).[10] The symmetrical rotamers (*E–E* and *Z–Z*) are presumably unstable due to steric hindrance.

Figure 3. The eight-membered ring conformation of the *Z–E* rotamer and the ten-membered ring conformation of the *E–Z* rotamer both contain a bonded NH_Z group

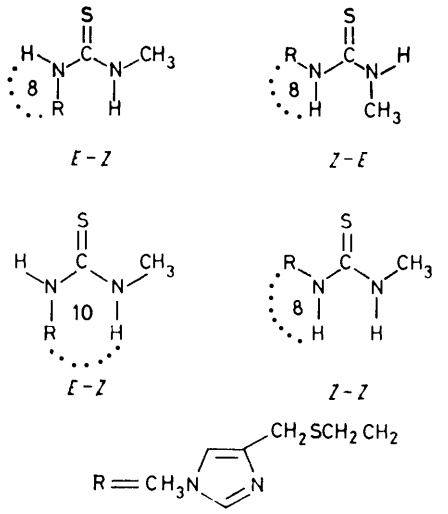


FIGURE 2 Four possible intramolecular hydrogen-bonded conformations of compound (6). The dotted line represents a hydrogen bond between the basic imidazole nitrogen atom and the NH group. The enclosed number is the size of the hydrogen-bonded ring

and, therefore, either of them could be the preferred hydrogen-bonded conformation in solution.

The spectrum of the tetramethylene compound (10) is similar to that of the sulphide analogue (9) except that there is an increase in the intensity of the NH_Z band with a concomitant decrease in the intensity of the bonded NH band, indicating that replacing the sulphide linkage in

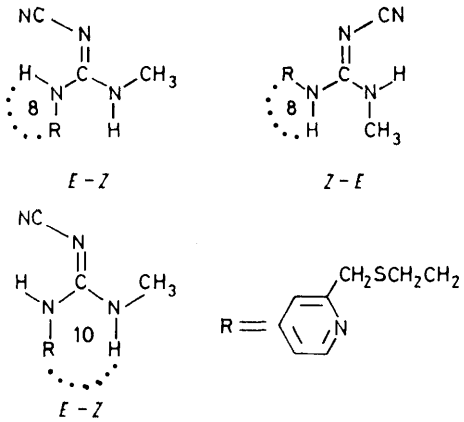


FIGURE 3 Three possible intramolecularly hydrogen-bonded conformations of compound (9). The dotted line represents a hydrogen bond between the basic pyridyl nitrogen atom and the NH group. The enclosed number is the size of the hydrogen-bonded ring

the chain by a methylene group discourages intramolecular hydrogen bonding. This cannot be due to an inductive effect because replacing S by CH_2 in the chain will increase the basicity of the ring * which should encourage rather than discourage hydrogen bonding. It is, therefore, probably a steric effect which adversely affects either the enthalpy or entropy of hydrogen bond formation. In fact, an inspection of CPK molecular models indicates that replacing S by CH_2 in any of the folded conformations in Figures 2 and 3 leads to unfavourable steric interactions between the methylene groups.

Biological Significance.—The ability of an H_2-receptor antagonist to form an intramolecular hydrogen bond means that it can adopt a compact folded structure which will be more lipophilic than the extended non-hydrogen-bonded form. This probably influences the membrane permeability and distribution of the antagonist. It is also possible that a folded structure is the preferred conformation for interaction with the H_2-receptor site.

The increase in lipophilicity afforded by intramolecular hydrogen bonding is illustrated by the partition coefficients in Table 2. The chloroform partition coefficient of compound (6), which can form an intramolecular hydrogen bond is almost four times greater than that of compound (7), which is unable to form an intramolecular hydrogen bond. However, the octanol partition coefficients of compounds (6) and (7) are almost the same indicating that the former compound probably does not form an intramolecular hydrogen bond in the polar octanol phase.

TABLE 2

Partition coefficients of compounds (6) and (7) at pH 9 and 37.5 °C

	Partition coefficient	
	n-Octanol/water [a]	Chloroform/water [a]
(6)	1.7	4.7
(7)	2.0	1.2

[a] 0.1 mol dm^{-3} borax.

The physicochemical and pharmacological consequences of replacing CH_2 by S in an H_2-receptor antagonist have already been discussed.[2,5] The present work supports the suggestion that this replacement could influence biological activity by altering conformational flexibility.

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* The pK_a of burimamide is 1 unit higher than that of thiaburimamide at 37 °C.[2]

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