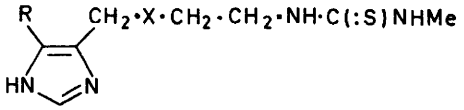
Crystal and Molecular Structure of the Histamine H_2-Receptor Antagonists, *N*-Methyl-*N'*-{2-[(5-methylimidazol-4-yl)methylthio]ethyl}thiourea (Metiamide) and *N*-{2-[(Imidazol-4-yl)methylthio]ethyl}-*N'*-methylthiourea (Thiaburimamide)

By **Keith Prout** * and **Stephen R. Critchley**, Chemical Crystallography Laboratory, 9 Parks Road, Oxford OX1 3PD
C. Robin Ganellin and **Robert C. Mitchell**, Research Institute, Smith, Kline, and French Laboratories Limited, Welwyn Garden City, Hertfordshire AL7 1EY

The crystal and molecular structures of the title compounds have been determined from three-dimensional *X*-ray diffractometer data by direct methods. Metiamide (Ia) is monoclinic. $P2_1/n$ (*b* unique). $Z = 4$. $a = 10.229 \pm 0.008$. $b = 19.045 \pm 0.009$. $c = 6.701 \pm 0.003$ Å. $\beta = 107.76° \pm 0.004$. Thiaburimamide (Ic) is also monoclinic. space goup $P2_1/c$ (*b* unique) $Z = 4$. $a = 9.981 \pm 0.003$. $b = 5.928 \pm 0.003$. $c = 20.396 \pm 0.007$ Å. $\beta = 105.36 \pm 0.02°$. Data were refined by least-squares to $R = 4.4\%$ in both cases (2 226 and 2 903 independent reflections). Both molecules are internally hydrogen bonded by an N • • • H—N bond between the imidazole and thiourea residues. forming a ten-membered ring system. These molecules are further agglomerated in continuous hydrogen-bonded networks. In (Ic) the molecules are linked in pairs by S • • • H—N bonds and further into infinite ribbons parallel to *c*. (Ia) is similarly involved in a complex hydrogen-bonding pattern. to form sheets. These differences are reflected in the relative crystal stabilities. as judged from m.p.s and aqueous solubilities. The compounds are compared with those having CH_2 in place of the thioether S linkage. *viz.* burimamide (Ib) and its 5-methyl derivative (Id). Solid-state i.r. spectra indicate that (Id). like (Ib) does not form the intramolecular hydrogen-bond in the crystal. Thus it appears that the thioether linkage may increase conformational flexibility and favour folding of the side-chain; these effects may contribute to the increased activity of the title compounds as histamine H_2-receptor antagonists.

METIAMIDE, *N*-methyl-*N'*-{2-[(5-methylimidazol-4-yl)-methylthio]ethyl}thiourea (Ia) is a specific competitive histamine H_2-receptor antagonist [1] (a new type of drug



	R	X			R	X	
(Ia)	Me	S	Metiamide	(Ic)	H	S	Thiaburimamide
(Ib)	H	CH_2	Burimamide	(Id)	Me	CH_2	Methylburimamide

which blocks responses to histamine not antagonised by conventional antihistamines such as mepyramine [2,3]); it inhibits histamine-stimulated gastric acid secretion in man [1] and has been investigated clinically for the treatment of duodenal ulcers.[4] Metiamide was developed from burimamide (Ib), the prototype H_2-receptor antagonist,[2] and *in vitro* is 8—9 times more active than the latter;[5] structurally it differs in two ways, *viz.* 'isosteric' replacement of S for CH_2 in the side-chain, and substitution of CH_3 in the imidazole ring. Modifying burimamide in only one of these respective ways affords two other compounds, *viz.* thiaburimamide (Ic) and methylburimamide (Id). The *in vitro* activity of methylburimamide is similar to that of burimamide, but thiaburimamide is 4—5 times more active.[5] It seems possible, therefore, that introduction of the side-chain thioether linkage is more important for increasing antagonist activity than is introduction of the methyl group. These structural changes may affect activity through altering imidazole pK_a and tautomerism as has previously been discussed,[5] but it is possible that they also exert an effect through altering drug conformation. The crystal and molecular structures of metiamide and thiaburimamide have therefore been determined and compared with that of burimamide.[6] Additional information is provided from the solid-state i.r. spectra of the four compounds.

EXPERIMENTAL

Crystal Data.—(i) *Metiamide* (Ia). $C_9H_{16}N_4S_2$, $M = 244.3$. Monoclinic, $a = 10.229 \pm 0.008$, $b = 19.045 \pm 0.009$, $c = 6.701 \pm 0.003$ Å, $\beta = 107.76 \pm 0.004°$, $U = 1\,243.2$ Å^3, $D_m = 1.31$ (by flotation), $Z = 4$, $D_c = 1.305$ g cm^{-3}. Space group $P2_1/n$ [C_{2h}^5, No. 14, non-standard setting. $\pm(x, y, z; \frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z)$]. Mo-$K_\alpha$ radiation $\lambda = 0.710\,7$ Å; $\mu = 3.94$ cm^{-1}. Crystals from methanol.

Approximate cell dimensions were determined from oscillation and Weissenberg photographs. A diamond-

[1] J. W. Black, W. A. M. Duncan, J. C. Emmett, C. R. Ganellin, T. Hesselbo, M. E. Parsons, and J. H. Wyllie, *Agents and Actions*, 1973, **3**, 133.
[2] J. W. Black, W. A. M. Duncan, G. J. Durant, C. R. Ganellin, and M. E. Parsons, *Nature*, 1972, **236**, 385.
[3] A. S. F. Ash and H. O. Schild, *Brit. J. Pharmacol. Chemotherapy*, 1966, **27**, 427.
[4] R. E. Pounder, J. G. Williams, G. J. Milton-Thompson, and J. J. Misiewicz, *Brit. Med. J.*, 1975, **2**, 307.
[5] J. W. Black, G. J. Durant, J. C. Emmett, and C. R. Ganellin, *Nature*, 1974, **248**, 65.
[6] B. Kamenar, K. Prout, and C. R. Ganellin, *J.C.S. Perkin II*, 1973, 1734.

shaped crystal (0.4 × 0.5 × 0.3 mm) was mounted about its c axis on a Hilger and Watts four-circle diffractometer and accurate cell dimensions and orientation matrix obtained by a least-squares fit [7] to the setting angles of 20 reflections. The intensity of one equivalent of each independent reflection with $2\theta \leqslant 54°$ was measured by an ω—2θ scan with ordinate analysis [8] with 50 steps of 0.02°. The 30 consecutive steps giving the highest total count were treated as peak and the remaining 20 as background. The count time at each step was 1.0 s; 2 226 reflections with $I > 3\sigma$ were collected. Lorentz and polarisation corrections were applied but no correction was made for absorption. All non-hydrogen atoms in the molecule were located from an E map based on the best phase set after weighted, multi-solution tangent refinement,[9] with three origin-defining phases ($\bar{5}44$, 621, $\bar{8}32$) and two multi-solution phases five-term Chebychev series with a_0 115.1, a_1 188.2, a_2 113.8, a_3 519.2, and a_4 152.4. Refinement was terminated at R 0.043. There were no unexplained features on a difference-Fourier map calculated at this stage.

(ii) *Thiaburimamide* (Ic). $C_8H_{14}N_4S_2$, M = 230.3. Monoclinic, a = 9.981 ± 0.003, b = 5.928 ± 0.003, c = 20.396 ± 0.007 Å, β = 105.36 ± 0.02°, U = 1 163.6 Å^3, D_m = 1.32 (by flotation), Z = 4, D_c = 1.314 g cm^{-3}. Space group $P2_1/c$ (C_{2h}^5, No. 14, second setting). Mo-K_α radiation, μ = 4.16 cm^{-1}. Crystals from water.

Preliminary unit-cell dimensions were determined from oscillation, Weissenberg and precession photographs. Accurate cell parameters were obtained by a least-squares fit [7] to the setting angles of 24 reflections determined on a Hilger and Watts four-circle diffractometer for a crystal (hexagonal plate, 0.6 × 0.8 × 0.2 mm) mounted about c.

TABLE 1

Metiamide: atomic and thermal parameters * with standard deviations of the last digit in parentheses

	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S(1)	0.504 02(6)	0.083 91(4)	0.808 8(1)	0.038 2(3)	0.072 8(5)	0.065 4(4)	0.026 1(4)	0.011 1(3)	0.004 7(3)
S(2)	−0.151 71(6)	0.060 28(3)	0.743 9(1)	0.041 3(3)	0.044 3(3)	0.055 2(4)	0.002 1(3)	0.020 2(3)	−0.002 7(2)
N(1)	0.329 7(2)	0.272 3(1)	0.358 6(4)	0.064(1)	0.042(1)	0.058(1)	0.015(1)	0.021(1)	0.003(1)
N(2)	0.245 3(2)	0.177 1(1)	0.456 2(4)	0.048(1)	0.052(1)	0.070(1)	0.021(1)	0.026(1)	0.008 8(9)
N(3)	0.115 5(2)	0.043 8(1)	0.831 4(4)	0.043(1)	0.068(1)	0.053(1)	0.022(1)	0.017 7(9)	0.002(1)
N(4)	0.015 4(2)	0.106 1(1)	0.532 9(3)	0.041(1)	0.053(1)	0.049(1)	0.011 7(9)	0.015 8(9)	0.002 6(9)
C(1)	0.221 8(3)	0.243 1(1)	0.398 8(5)	0.058(1)	0.057(2)	0.073(2)	0.024(1)	0.031(1)	0.016(1)
C(2)	0.378 3(2)	0.164 5(1)	0.456 9(4)	0.044(1)	0.046(1)	0.044(1)	0.008(1)	0.017(1)	0.003(1)
C(3)	0.431 1(2)	0.223 2(1)	0.394 1(4)	0.047(1)	0.053(1)	0.044(1)	0.012(1)	0.013(1)	−0.000(1)
C(4)	0.565 2(4)	0.237 2(2)	0.359 5(7)	0.056(2)	0.100(3)	0.101(3)	0.047(2)	0.030(2)	−0.001(2)
C(5)	0.444 6(3)	0.095 6(1)	0.524 5(4)	0.054(1)	0.048(1)	0.063(2)	0.009(1)	0.025(1)	0.008(1)
C(6)	0.346 7(3)	0.094 4(2)	0.879 6(4)	0.054(1)	0.058(2)	0.050(1)	0.004(1)	0.012(1)	−0.001(1)
C(7)	0.248 6(3)	0.035 1(1)	0.792 1(4)	0.050(1)	0.047(1)	0.058(2)	0.010(1)	0.016(1)	0.003(1)
C(8)	0.002 4(2)	0.071 5(1)	0.697 5(4)	0.041(1)	0.036(1)	0.046(1)	0.001 8(9)	0.015 9(9)	−0.000 3(9)
C(9)	−0.096 6(3)	0.136 7(2)	0.369 3(5)	0.052(1)	0.064(2)	0.059(2)	0.018(1)	0.010(1)	0.002(1)

	x/a	y/b	z/c	U_{iso}		x/a	y/b	z/c	U_{iso}
H(11)	0.330(3)	0.312(2)	0.319(5)	0.038(9)	H(52)	0.524(3)	0.092(2)	0.490(5)	0.038(8)
H(12)	0.136(3)	0.269(2)	0.383(5)	0.043(8)	H(61)	0.301(3)	0.141(1)	0.836(4)	0.026(7)
H(13)	0.105(3)	0.025(1)	0.942(4)	0.024(7)	H(62)	0.364(3)	0.095(2)	1.041(6)	0.05(1)
H(14)	0.095(3)	0.116(2)	0.525(5)	0.038(8)	H(71)	0.295(3)	−0.011(2)	0.858(4)	0.030(7)
H(41)	0.599(6)	0.286(3)	0.406(9)	0.13(2)	H(72)	0.234(3)	0.028(1)	0.635(4)	0.007(7)
H(42)	0.588(4)	0.246(2)	0.229(6)	0.06(1)	H(91)	−0.104(4)	0.179(2)	0.392(6)	0.07(1)
H(43)	0.628(4)	0.200(2)	0.422(6)	0.08(1)	H(92)	−0.079(4)	0.128(2)	0.239(7)	0.08(1)
H(51)	0.382(3)	0.059(2)	0.451(5)	0.036(8)	H(93)	−0.174(4)	0.112(2)	0.352(6)	0.06(1)

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

(041, 144); 516 phases with normalised structure factors >1.2 were used in this refinement. This model was refined by full-matrix least-squares calculations to R 0.138 with individual isotropic temperature factors and unit weights and then further to R 0.071 when allowance was made for anisotropic vibration. A difference-Fourier map calculated at this stage revealed peaks of density appropriate to all hydrogen atoms which were introduced into the model with individual isotropic temperature factors. For the ensuing refinement, the least-squares matrix was blocked into two parts, one containing positional parameters and the second involving temperature factors and the scale factor. Each reflection was assigned a weight (w) of the type: $w = 1/\{a_0t_0^*(x) + a_1t_1^*(x) + \ldots a_it_i^*(x)\}$ where a_i are the coefficients for Chebychev series in $t_i^*(x)$ with $x = F_o/F_{omax.}$ The coefficients were chosen to minimise the variation of mean $w(|F_o| - |F_c|)^2$ with $|F_o|$. Initially a four-term series was used but for the final two cycles of least-squares, the weights were modified to a

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

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

The intensities of at least two equivalents of each independent reflection with $2\theta \leqslant 60°$ were measured on this instrument by an ω—2θ scan and ordinate analysis [8] with 50 steps of 0.02°. Count times at each step varied between 0.7 and 1.0 s depending on Bragg angle; 2 903 unique reflections with $I > 3\sigma$ remained after merging equivalents (merging R 0.016). Lorentz and polarisation corrections were made and an empirical absorption correction was applied by the method of ref. 10. A subset of data was used for structure solution and the initial stages of refinement. This comprised 2 258 reflections ($I > 3\sigma$) from the first equivalent collected. The phases of 480 reflections with $E > 1.2$ were developed by weighted, multi-solution tangent refinement [9] using three defining phases ($\bar{1}2$,1,10; $\bar{1}3$,0,16; $\bar{1}3$,3,7) and (014; 11,1,2) as multi-solution phases. All non-hydrogen atoms were located from an E map based on the phase set with lowest figure-of-merit after ten cycles

[9] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A24**, 368.

[10] A. C. T. North, D. C. Phillips, and F. S. Mathews, *Acta Cryst.*, 1968, **A24**, 351.

TABLE 2

Thiaburimamide: atomic and thermal parameters * with standard deviations of the last digit in parentheses

	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{23}
S(1)	0.511 88(5)	0.314 8(1)	0.090 64(3)	0.045 5(3)	0.070 8(4)	0.081 1(4)	0.028 1(3)	0.028 4(2)	0.020 1(2)
S(2)	1.151 76(4)	0.240 36(8)	0.057 99(2)	0.034 1(2)	0.056 4(3)	0.040 6(2)	0.002 1(2)	0.010 1(1)	0.004 4(2)
N(1)	0.716 9(2)	−0.135 0(4)	0.281 02(9)	0.089(1)	0.063(1)	0.039 4(8)	0.008 8(7)	0.013 6(8)	−0.004 (1)
N(2)	0.754 9(2)	−0.091 8(3)	0.180 58(7)	0.048 6(8)	0.055 4(9)	0.042 1(7)	0.005 6(6)	0.008 1(6)	0.000 9(7)
N(3)	0.885 5(1)	0.310 7(3)	0.043 96(8)	0.035 1(6)	0.051 5(8)	0.056 2(8)	0.015 3(7)	0.012 9(6)	0.004 1(6)
N(4)	0.978 0(2)	0.015 4(3)	0.113 77(7)	0.041 6(7)	0.046 2(8)	0.045 9(7)	0.007 0(6)	0.010 5(6)	0.004 1(6)
C(1)	0,810 0(2)	−0.142 8(4)	0.245 0(1)	0.061(1)	0.061(1)	0.047 6(9)	0.010 7(9)	0.002 2(8)	−0.001 9(9)
C(2)	0.616 8(2)	−0.049 0(3)	0.175 76(9)	0.048 5(8)	0.043 6(9)	0.044 2(8)	0.003 3(7)	0.013 3(7)	−0.003 0(7
C(3)	0.592 7(3)	−0.075 2(4)	0.238 0(1)	0.074(1)	0.057(1)	0.056(1)	0.009 0(9)	0.030(1)	0.001(1)
C(5)	0.517 8(2)	0.013 0(4)	0.109 8(1)	0.041 8(8)	0.065(1)	0.054(1)	0.009 9(9)	0.009 9(7)	−0.000 2(8)
C(6)	0.692 6(2)	0.375 3(3)	0.096 4(1)	0.049 3(9)	0.046 6(9)	0.060(1)	0.003 7(8)	0.118 2(8)	0.006 2(7)
C(7)	0.740 3(2)	0.260 8(3)	0.039 90(9)	0.035 2(7)	0.056(1)	0.045 6(8)	0.005 1(7)	0.077(6)	0.001 2(7)
C(8)	0.995 3(2)	0.183 0(3)	0.073 39(8)	0.035 6(7)	0.042 7(8)	0.036 1(7)	−0.002 3(6)	0.007 3(5)	0.001 2(6)
C(9)	1.080 2(2)	−0.157 9(4)	0.139 8(1)	0.059(1)	0.050(1)	0.065(1)	0.012 2(9)	0.011(1)	0.012 7(9)

	x/a	y/b	z/c	U_{iso}		x/a	y/b	z/c	U_{iso}
H(11)	0.731(3)	−0.155(5)	0.321(1)	0.049(8)	H(61)	0.762(2)	0.325(4)	0.143(1)	0.037(6)
H(12)	0.904(3)	−0.184(5)	0.264(1)	0.047(7)	H(62)	0.704(2)	0.546(4)	0.095(1)	0.036(6)
H(13)	0.900(2)	0.425(5)	0.023(1)	0.040(7)	H(71)	0.673(2)	0.313(4)	−0.007(1)	0.037(6)
H(14)	0.904(2)	−0.003(4)	0.126(1)	0.032(6)	H(72)	0.724(2)	0.094(4)	0.039(1)	0.020(5)
H(31)	0.510(3)	−0.060(5)	0.252(1)	0.051(7)	H(91)	0.142(4)	−0.112(8)	0.170(2)	0.10(1)
H(51)	0.536(2)	−0.079(4)	0.069(1)	0.035(6)	H(92)	1.039(3)	−0.291(6)	0.151(2)	0.07(1)
H(52)	0.427(3)	−0.040(5)	0.111(1)	0.044(7)	H(93)	1.130(4)	−0.219(6)	0.109(2)	0.08(1)

* See footnote to Table 1.

of refinement. This model was refined to R 0.163 by full-matrix least-squares (isotropic vibration) and further to R 0.099 with anisotropic temperature factors. A difference-Fourier map now revealed all hydrogen atoms. At this stage, the full set of data became available and refinement was continued with the hydrogen atoms incorporated into the model with isotropic temperature factors and the least-squares matrix blocked. Thermal parameters were put in one block, together with the scale factor, and positional parameters in a second block. In the later stages of refinement each reflection was assigned a weight (w) where $w = \{1 + [(F_o - 31)/37]^2\}^{-1}$; refinement converged at R 0.045. A final difference map revealed one area of density >0.4 eÅ^{-3}, 0.9 Å from sulphur atom S(1). Reflections 014, $\bar{2}02$, and 012 appear to be significantly affected by extinction.

All calculations were performed on the Oxford University Computing Laboratory's ICL 1906A using the CRYSTALS program series.[11] Scattering factors for hydrogen were taken from ref. 12 and for other atoms from ref. 13. In the final stages of refinement, account was taken of anomalous dispersion effects for sulphur.[14] Observed structure amplitudes and structure factors calculated from the final atomic co-ordinates in Tables 1 and 2 are listed in Supplementary Publication No. SUP 21779 (46 pp., 1 microfiche).*

DISCUSSION AND DESCRIPTION OF STRUCTURES

For each compound, interatomic distances and inter-bond angles with their standard deviations are given in Tables 3 and 4 and torsion angles in Table 5. The atom numbering corresponds to that shown in Figures 1 and 2, projections of the two molecules down the bonds C(5)–C(2) and C(6)–C(7). Figures 3 and 4 show the two crystal structures in projection, down the z-axis for metiamide and down the y-axis for thiaburimamide. These projections were chosen because they show the

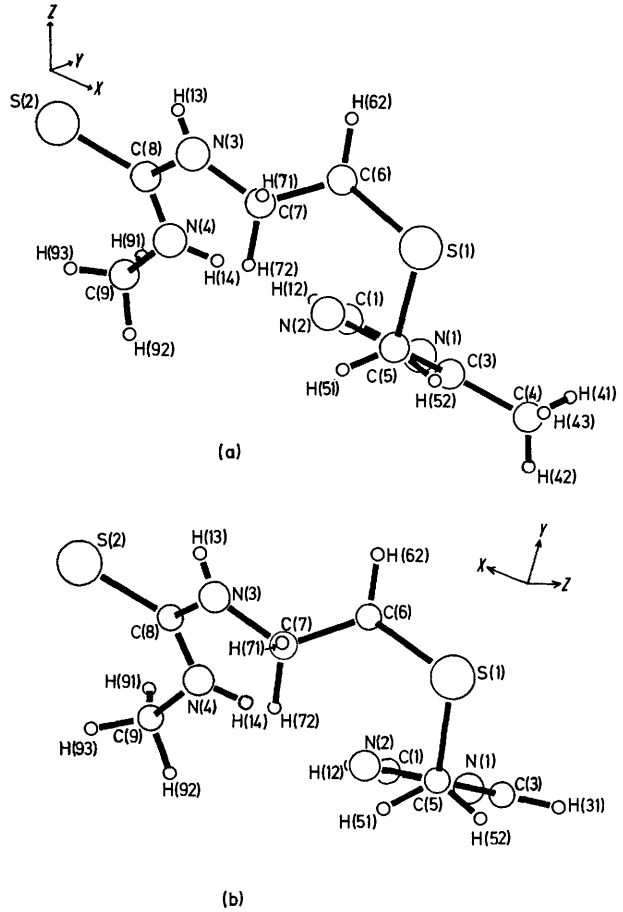


FIGURE 1 The molecules viewed down the bond C(5)–C(2) looking from C(5) to C(2): (a) metiamide, (b) thiaburimamide

* See note about Supplementary Publication in Notice to Authors, No. 7 in *J.C.S. Perkin II*, 1975, Index issue.

[11] J. R. Carruthers, 1975, personal communication.

[12] 'International Tables for X-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962, p. 202

[13] D. T. Cromer and J. B. Mann, Los Alamos Scientific Laboratory Report LA 3816, 1968.

[14] D. T. Cromer and D. Liberman, *J. Chem. Phys.*, 1970, **53**, 1891.

molecules similarly oriented with respect to the axis of projection.

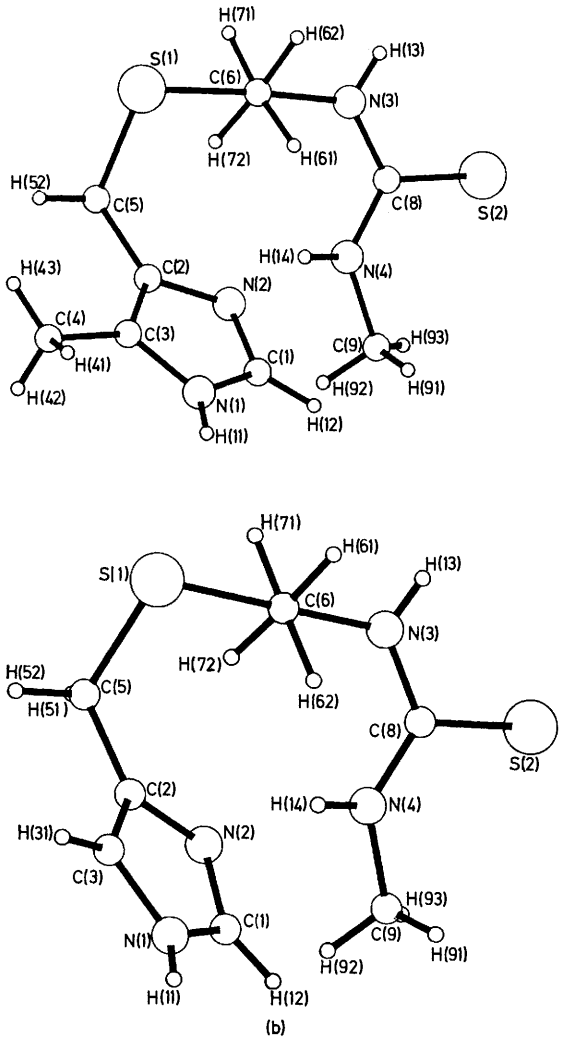


FIGURE 2 The molecules viewed down the bond C(6)–C(7) looking from C(6) to C(7): (a) metiamide, (b) thiaburimamide

Molecular Dimensions.—The bond lengths and angles are well determined but have not been corrected for thermal motion. The molecular dimensions are very similar. The only possibly significant dimensional difference between the two compounds is in the thioether linkage, C(6)–S(1) which is 1.823 in metiamide and 1.812 Å in thiaburimamide. The dimensions of the thiourea and imidazole residues do not differ significantly from those reported for burimamide [6] and other related compounds. The imidazole residue is strictly planar in both compounds but the mirror symmetry which is apparent in burimamide is not found for either metiamide or thiaburimamide and is now thought to be accidental. As in burimamide, the imidazole residues in both metiamide and thiaburimamide exist in the N^{τ}–H tautomeric form * in which the non-protonated nitrogen is adjacent to the side-chain.

Molecular Conformation.—The molecular conformations of metiamide and thiaburimamide are similar. In each molecule, a ten-membered ring is formed by the hydrogen-bonded linkage N(2) · · · H(14)–N(4). This contrasts sharply with the open-chain conformation of burimamide.

Examination of Corey–Pauling–Koltun (CPK) space-filling molecular models indicates that it should be

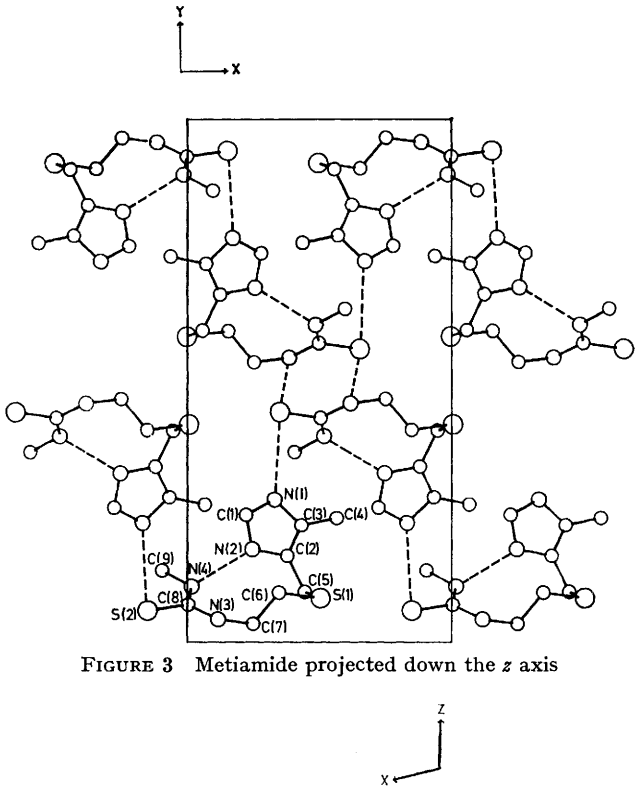


FIGURE 3 Metiamide projected down the *z* axis

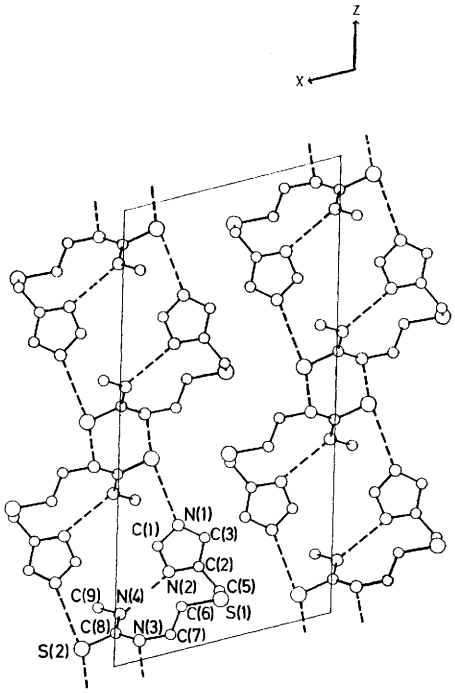


FIGURE 4 Thiaburimamide projected down the *y* axis

* Following the IUPAC–IUB Commission on Biochemical Nomenclature, 1972, recommendations for histidine, the imidazole N nearer the side-chain is designated [15] N^{π}, and the one further away is N^{τ}.

[15] J. W. Black and C. R. Ganellin, *Experientia*, 1974, **30**, 111.

possible to form two sizes of intramolecular H-bonded rings, containing 8 or 10 atoms (Figure 5). The eight-membered ring imposes a *gauche* conformation about the $-CH_2CH_2-$ bond, but does not restrict the thiourea

TABLE 3

Interatomic distances (Å) and interbond angles (°) for metiamide, with standard deviations in parentheses

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

(i) Distances

S(1)–C(5)	1.828(3)	N(3)–H(13)	0.86(3)
S(1)–C(6)	1.823(3)	N(4)–H(14)	0.85(3)
S(2)–C(8)	1.711(2)	C(1)–H(12)	0.98(3)
N(1)–C(1)	1.335(3)	C(4)–H(41)	1.01(6)
N(1)–C(3)	1.364(3)	C(4)–H(42)	0.87(4)
N(2)–C(1)	1.315(3)	C(4)–H(43)	0.96(4)
N(2)–C(2)	1.381(3)	C(5)–H(51)	0.98(3)
N(3)–C(7)	1.472(3)	C(5)–H(52)	0.91(3)
N(3)–C(8)	1.338(3)	C(6)–H(61)	1.01(3)
N(4)–C(8)	1.325(3)	C(6)–H(62)	1.04(3)
N(4)–C(9)	1.445(3)	C(7)–H(71)	1.02(3)
C(2)–C(3)	1.362(4)	C(7)–H(72)	1.03(3)
C(2)–C(5)	1.483(3)	C(9)–H(91)	0.82(4)
C(3)–C(4)	1.484(4)	C(9)–H(92)	0.96(4)
C(6)–C(7)	1.506(4)	C(9)–H(93)	0.90(4)
N(1)–H(11)	0.80(3)		

(ii) Angles

C(5)–S(1)–C(6)	102.6(1)	N(1)–C(3)–C(4)	122.7(3)
C(1)–N(1)–C(3)	108.1(2)	N(1)–C(3)–C(2)	105.4(2)
C(1)–N(2)–C(2)	105.0(2)	C(2)–C(3)–C(4)	132.0(3)
C(7)–N(3)–C(8)	125.6(2)	C(2)–C(5)–S(1)	113.7(2)
C(8)–N(4)–C(9)	125.1(2)	S(1)–C(6)–C(7)	110.7(2)
N(1)–C(1)–N(2)	111.7(2)	C(6)–C(7)–N(3)	112.9(2)
N(2)–C(2)–C(3)	109.9(2)	S(2)–C(8)–N(3)	119.0(2)
N(2)–C(2)–C(5)	120.9(2)	S(2)–C(8)–N(4)	123.0(2)
C(3)–C(2)–C(5)	129.2(2)	N(3)–C(8)–N(4)	118.0(2)

(*b*) Some intramolecular contacts

N(2) · · · N(4)	2.891	H(51) · · · H(72)	2.30
N(2) · · · H(14)	2.089	H(72) · · · H(14)	2.18

(*c*) Some intermolecular contacts *

$N(1^{I}) \cdots S(2)$	2.891	$N(3^{II}) \cdots S(2)$	3.394
$S(2) \cdots H(11^{I})$	2.500	$S(2) \cdots H(13^{II})$	2.581

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

I $x - \frac{1}{2}, \frac{1}{2} - y, \frac{1}{2} + z$ II $-x, -y, 2 - z$

configuration [Figure 5(a)]. The ten-membered ring, however, requires that the thiourea group be in *E,Z*-configuration [16] but can accommodate either *trans*- or *gauche*-conformations about the $-CH_2CH_2-$ bond [Figure 5(c) and (b)]; the CPK models indicate that the *trans*-arrangement is sterically preferred. In this preferred arrangement, more than one overall conformation of the side-chain is possible.

As found in the crystal, each molecule can be described in terms of four planes, the imidazole ring, C(2)–C(5)–S(1), the S–CH_2–CH_2–NH group, and the thiourea residue. The five atoms of the imidazole ring are planar to within 0.01 Å in metiamide and to 0.002 Å in thiaburimamide. The carbon atom C(5) lies slightly out of the plane of the ring in both cases (0.06 Å below, *i.e.* on the same side of the ring as the sulphur atom, in metiamide and 0.02 Å above in thiaburimamide). Similarly, the methyl-carbon, C(4), in metiamide lies above the ring by 0.05 Å.

The C(5)–S(1) bond is almost perpendicular to the imidazole plane, but leans slightly towards N(2) as found in burimamide. If Figure 1(a) and (b) are superimposed then the degree of tilt of the imidazole ring with respect to the rest of the molecule is virtually the only conformational difference between them. The values of the torsion angles about the bond C(2)–C(5) (86.5 in thiaburimamide and 78.2° in metiamide) suggest

TABLE 4

Interatomic distances (Å) and interbond angles (°) for thiaburimamide, with standard deviations in parentheses

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

(i) Distances

S(1)–C(5)	1.829(2)	N(1)–H(11)	0.80(3)
S(1)–C(6)	1.812(2)	N(3)–H(13)	0.83(3)
S(2)–C(8)	1.707(2)	N(4)–H(14)	0.84(2)
N(1)–C(1)	1.330(3)	C(1)–H(12)	0.95(3)
N(1)–C(3)	1.362(3)	C(3)–H(31)	0.94(3)
N(2)–C(1)	1.317(2)	C(5)–H(51)	1.04(2)
N(2)–C(2)	1.380(2)	C(5)–H(52)	0.97(3)
N(3)–C(7)	1.460(2)	C(6)–H(61)	1.06(2)
N(3)–C(8)	1.337(2)	C(6)–H(62)	1.02(3)
N(4)–C(8)	1.330(2)	C(7)–H(71)	1.06(2)
N(4)–C(9)	1.446(2)	C(7)–H(72)	1.00(2)
C(2)–C(3)	1.362(3)	C(9)–H(91)	0.80(4)
C(2)–C(5)	1.489(3)	C(9)–H(92)	0.95(4)
C(6)–C(7)	1.518(3)	C(9)–H(93)	0.96(4)

(ii) Angles

C(5)–S(1)–C(6)	101.8(1)	C(3)–C(2)–C(5)	129.2(2)
C(1)–N(1)–C(3)	107.6(2)	N(1)–C(3)–C(2)	106.0(2)
C(1)–N(2)–C(2)	105.0(2)	C(2)–C(5)–S(1)	114.2(2)
C(7)–N(3)–C(8)	126.5(2)	S(1)–C(6)–C(7)	111.7(1)
C(8)–N(4)–C(9)	124.3(2)	C(6)–C(7)–N(3)	111.9(2)
N(1)–C(1)–N(2)	112.0(2)	S(2)–C(8)–N(3)	119.1(1)
N(2)–C(2)–C(3)	109.4(2)	S(2)–C(8)–N(4)	122.5(1)
N(2)–C(2)–C(5)	121.4(2)	N(3)–C(8)–N(4)	118.4(1)

(*b*) Some intramolecular contacts

N(2) · · · N(4)	2.971	H(51) · · · H(72)	2.36
N(2) · · · H(14)	2.155	H(72) · · · H(14)	2.24

(*c*) Some intermolecular contacts *

$N(1^{I}) \cdots S(2)$	3.281	$N(3^{II}) \cdots S(2)$	3.337
$S(2) \cdots H(11)$	2.516	$S(2) \cdots H(13^{II})$	2.547

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

I $2 - x, \frac{1}{2} + y, \frac{1}{2} - z$ II $2 - x, 1 - y, -z$

TABLE 5

Torsion angles (°) *

I–J–K–L	Thiaburimamide	Metiamide
C(3)–C(2)–C(5)–S(1)	93.9	100.6
N(2)–C(2)–C(5)–S(1)	−86.8	−77.7
C(2)–C(5)–S(1)–C(6)	55.6	58.8
C(5)–S(1)–C(6)–C(7)	67.4	66.7
S(1)–C(6)–C(7)–N(3)	179.5	−175.7
C(6)–C(7)–N(3)–C(8)	95.8	95.8
C(7)–N(3)–C(8)–N(4)	−13.3	−13.5
C(7)–N(3)–C(8)–S(2)	166.7	165.8
N(3)–C(8)–N(4)–C(9)	169.3	177.4
S(2)–C(8)–N(4)–C(9)	−10.7	−1.9

* The torsional angle about the bond J–K is defined as the angle the bond K–L is rotated from the IJK plane. It is positive when on looking from IJ to KL the rotation is clockwise.

that the methylene hydrogens of C(5) are more strongly repelled by the nitrogen lone-pair than by a hydrogen,

[16] J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, 1968, **90**, 509.

H(31), on C(3) and much more strongly than by a methyl group at C(3). The torsional angles at C(5)–S(1) and S(1)–C(6) of *ca.* 60° (thiaburimamide 55.6 and 67.4°, metiamide 58.8 and 66.7°) contrast strongly with the 180° angles of the staggered conformation about the second methylene in burimamide. Models suggest that if the metiamide conformation were adopted by burimamide it would be hindered by repulsions between a pair of hydrogen atoms [H(51) and H(72) in metiamide], one from the first and one from the fourth methylene groups. This repulsion is reduced by the replacement of the

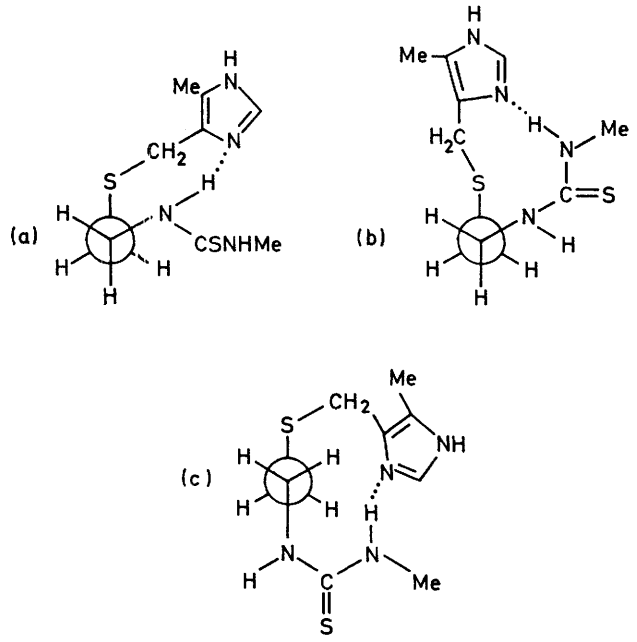


FIGURE 5 Intramolecular hydrogen-bonded structures of metiamide, viewed as Newman projection formulae along CH_2–CH_2 bond [from C(7) to C(6)], showing: (a) eight-membered ring, thiourea group not constrained CH_2·CH_2 *gauche*; (b) ten-membered ring, thiourea group in *E,Z*-configuration, CH_2·CH_2 *gauche*, and (c) ten-membered ring, thiourea group in *E,Z*-configuration, CH_2CH_2 *trans*, as found in the crystal

second methylene by a thioether linkage because the C–S are longer than the C–C bonds, although the reduction of the angle at the second atom of the chain from 111 to 104° tends somewhat to offset this effect. Atoms S(1), C(6), C(7), and N(3) form a group which is planar to within 0.005 Å in thiaburimamide and to within 0.03 Å in metiamide. The group adopts the staggered *trans*-conformation in order to minimise hydrogen–hydrogen repulsions. The torsion angle about the C(7)–N(3) bond approaches 90° (95.8° for each) so as to fold the thiourea residue around towards the imidazole ring. The thiourea group is strictly planar in the *E,Z* configuration with the hydrogen H(13) *cis* with respect to the sulphur atom and the hydrogen H(14) *trans*. This is the same configuration as in the thiourea residue in burimamide, but, because the side-chain is folded, H(14) in thiaburimamide and metiamide is directed towards the imidazole nitrogen N(2) to form the hydrogen bond which completes the ten-membered ring. The hydrogen bond is shorter in metiamide (2.891 Å) than in thiaburimamide (2.971 Å); in metiamide the nitrogen atom N(4) is only 0.1 Å from the imidazole plane whereas in thiaburimamide it is 0.8 Å out of this plane. This suggests that the hydrogen bond will be significantly stronger in metiamide than in thiaburimamide.

It is concluded that the introduction of the thioether linkage into a burimamide molecule eases the hydrogen–hydrogen repulsions in the ten-membered ring conformation and the replacement of the imidazole 4-hydrogen by a 4-methyl group further stabilises this conformation.

Crystal Structure.—The crystal structures of metiamide and thiaburimamide are very different from that of burimamide because the intramolecular hydrogen bond in the former compounds prevents the formation of the hydrogen bonded imidazole chains which are such a significant feature of the latter. In all three crystals the molecules are linked in pairs about symmetry centres by S · · · H–N hydrogen bonds involving the N–H group nearer to the imidazole ring (see Figures 3 and 4 and ref. 6). In thiaburimamide, the overall hydrogen-bond distance S(2) · · · H(13)–N(3) is 3.337, with S(2) · · · H(13) 2.55 Å, and in metiamide the corresponding values are 3.393 and 2.58 Å, all in keeping with Donohue's criteria for S · · · H hydrogen bonds.[17] In these compounds, as in burimamide, there is a second type of S · · · H–N hydrogen bond, but, whereas in burimamide this is to the second thiourea N–H, it is to the N–H of the imidazole in metiamide and thiaburimamide. The bond [S(2) · · · H(11)–N(1) and S(2) · · · H(11) 3.297 and 2.49 Å in metiamide, 3.281 and 2.52 Å in thiaburimamide] links the hydrogen bonded pairs into sheets in metiamide and into chains in thiaburimamide. This appears to be a direct effect of the presence of the 4-methyl group in the former which, if introduced into the chain structure of the latter, would prevent the neat packing of the chains (see Figures 3 and 4).

Solid-state I.r. Spectra (3 400—1 700 cm^{-1}).—The i.r. spectra of compounds (I a—d) and 4(5)-methylimidazole were run as KBr discs (1—100 mg KBr) on a Perkin-Elmer 577 spectrophotometer. Crystal-structure determinations of 4(5)-methylimidazole,[18] and burimamide [6] have shown that in the crystal the imidazole rings of these compounds form hydrogen-bonded chains. Broad intense NH bands which occur in the solid-state i.r. spectra of these compounds in the 3 000—1 700 cm^{-1} region also indicate the presence of hydrogen-bonded chains. In the case of 4(5)-methylimidazole there are prominent features at 2 630 and 1 840 cm^{-1} and, according to Bellocq and Garrigou-Lagrange [19] these are due to Fermi resonance of the NH vibration (which is lowered in frequency due to strong intermolecular

[17] J. Donohue, *J. Mol. Biol.*, 1969, **45**, 231.
[18] H. Zimmermann, *Annalen*, 1958, **612**, 193.
[19] A.-M. Bellocq and C. Garrigou-Lagrange, *J. Chim. phys.*, 1969, **66**, 1511.

N · · · H–N hydrogen-bonding) with overtone and combination bands from lower-frequency fundamentals. Almost identical bands are present in the spectrum of burimamide; in addition, the sharp band at 2 930 cm^{-1} and the strong band at 3 240 cm^{-1}, which are not present in the spectrum of 4(5)-methylimidazole, can be assigned respectively to the asymmetric stretching vibrations of the CH_2 groups and to the stretching vibrations of the thiourea NH groups.

The i.r. spectra of thiaburimamide and metiamide do not have the broad bands at 2 630 and 1 840 cm^{-1}. This is in accord with the crystal structure determinations which show that in these cases the imidazole rings are not self-associated but are involved in intramolecular hydrogen-bonds with the thiourea NH groups.

The i.r. spectrum of methylburimamide also shows the broad bands at 2 630 and 1 840 cm^{-1} indicating that the imidazole rings are self-associated. Thus, although crystal structure data are not available, the i.r. evidence suggests that in the crystal methylburimamide resembles burimamide and is not in the intramolecularly hydrogen-bonded form found with metiamide and thiaburimamide.

Biological Significance.—The three compounds (I a—c) show many structural similarities. The imidazole residues are in the same unique tautomeric form in which the non-protonated (basic) nitrogen atom is adjacent to the side-chain, and the geometries of the imidazole rings are the same within experimental error. The dihedral angle between the planes of the imidazole ring and the side-chain is in the range 78—87°. The thiourea groups have the same staggered *E,Z*-configuration (four planar configurations are possible) and form pairs held together by two S · · · H–N hydrogen bonds. The dihedral angle about the bond connecting the thiourea group to the side-chain is in the range 89—96°.

The feature of the molecular structure of thiaburimamide and metiamide which distinguishes them from that of burimamide is the folding of the side-chains with the formation of a ten-membered ring, and intramolecular hydrogen-bond from a thiourea N–H to the imidazole-ring basic nitrogen atom. This is in contrast with crystalline burimamide where the side-chain is extended and there is a complete absence of contact between the imidazole rings and the thiourea groups.[6] Comparison of the solid-state i.r. data indicates that methylburimamide (Id), also forms no intramolecular hydrogen bond in the crystal. These findings suggest that the thioether linkage may increase the conformational flexibility of the side-chain and favour the formation of the folded side-chain. The ring-methyl substituent in metiamide does not appear to alter the molecular dimensions [compare (Ia) and (Ic)] in any way which might account for the greater antagonist activity of metiamide. It gives rise to the same molecular structure although it slightly alters the ring orientation which tends to produce a more satisfactory intramolecular hydrogen bond co-planar with the imidazole ring. However, the methyl group has a pronounced effect on the crystal structure. In metiamide, the molecules combine to form N–H · · · S hydrogen bonded sheets rather than the chains found in the thiaburimamide crystal This is reflected in the lower stability of the thiaburimamide crystal, *e.g.* (Ic) has a lower m.p. and is more than twenty times more soluble in water than is metiamide (see Table 6).

Replacement of CH_2 by S in burimamide was made initially as an 'isosteric' substitution which would modify the electronic properties of the side-chain; however, it was pointed out that the replacement may slightly lengthen the chain and increase conformational flexibility.[5] It is pertinent, therefore, to establish from the crystal structure the extent of the isosterism. Data in Table 7 confirm that the S and CH_2 links in these molecules are sterically similar.

TABLE 6

Physical characteristics of compounds (I a—d)

	M.p./°C [a]	H-bonding [b]	Aqueous solubility [c] g l^{-1}	molar
(Ia)	150—152	Intra.	3.2	0.013
(Ib)	129—130	Inter.	14.7	0.069
(Ic)	96—98	Intra.	70.4	0.306
(Id)	110—112	Inter.	25.4	0.112

[a] M.p.s, determined in capillary tubes in an electrothermal electrically-heated copper block, are corrected for stem-emergence. [b] From i.r. spectra as KBr discs. Intra. = intramolecular, inter. = intermolecular. [c] Solubilities measured as follows. An excess of the sample was tumbled with distilled water in a sealed glass ampoule in a bath at 37.5 ± 0.04 °C for at least 2 days. After allowing the contents to settle, the tip of the ampoule was snapped off and an aliquot of the supernatant drawn into a warm pipette, through a glass-wool plug, and analysed by u.v. spectrometry. The pH of the supernatant remaining in the ampoule was measured and finally the residue was filtered off, dried, and its i.r. spectrum recorded. In each case, the pH of the supernatant was at least 2 log units above the pK_a of the compound, and the i.r. spectrum of the residue was identical to that of the starting material. The values given are the means of two determinations.

TABLE 7

Comparison of methylene and thioether linkages: $R^1C^1H_2–X–C^2H_2R^2$

	X	
	CH_2 [a]	S
$C^1–X$/Å	1.515	1.829
$C^2–X$/Å	1.528	1.812
$C^1–X–C^2$/(°)	113.7	101.8
$C^1 \cdots C^2$/Å [b]	2.55	2.83
Van der Waals radius of X	2.0	1.8

R^1 = 4(5)-imidazolyl, R^2 = CH_2·NH·C(:S)NHMe.

[a] Ref. 6. [b] Interatomic distance between centres.

In summary, the crystal structures provide evidence for the formation of a cyclic intramolecularly hydrogen-bonded conformation in these compounds with a thioether side-chain. It is interesting that a ten-membered ring should form and one must consider that this may contribute to the greater activity of these molecules. It is not known whether the molecule has to achieve this configuration in order to be biologically active, or whether the thioether link simply functions to increase molecular flexibility in a way that is biologically ad-

vantageous. Thus, in addition to the electronic effects of the thioether previously reported,[5] the present work suggests that conformational effects of the thioether linkage may also contribute to the activity of these compounds as histamine antagonists.

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