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Structures of Nine Histamine H_2 Antagonists Related to *N*-Cyano-*N'*-methyl-*N''*-[4-(2-pyridyl)butyl]guanidine

BY KEITH PROUT*, KEITH BURNS AND DAVID J. WATKIN

Chemical Crystallography Laboratory, Oxford University, 9 Parks Road, Oxford OX1 3PD, England

AND DAVID G. COOPER,† GRAHAM J. DURANT,‡ C. ROBIN GANELLIN§ AND GEORGE S. SACH

SmithKline Beecham Research, The Frythe, Welwyn, Herts AL6 9AR, England

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Abstract

The crystal and molecular structures of the following compounds showing histamine H_2-antagonist activity have been determined: (1) *N*-Cyano-*N'*-methyl-*N''*-{2-[(2-pyridyl)methylthio]ethyl}guanidine, $C_{11}H_{15}N_5S$, M_r = 249.33, triclinic, $P\bar{1}$, a = 7.482(2), b = 9.775(2), c = 10.019(1) Å, α = 116.00(1), β = 102.00(2), γ = 96.78(2)°, V = 625.7 Å^3, Z = 2, D_x = 1.32 g cm^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, μ = 21.21 cm^{-1}, F(000) = 264, R = 4.98% for 2490 observed reflexions. (2) *N*-Cyano-*N'*-methyl-*N''*-{2-[(3-methoxy-2-pyridyl)methylthio]ethyl}guanidine, $C_{12}H_{17}N_5OS$, M_r = 279.36, monoclinic, $P2_1/a$, a = 8.670(4), b = 14.095(4), c = 11.682(2) Å, β = 99.32(7)°, V = 1408.7 Å^3, Z = 4, D_x = 1.32 g cm^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, μ = 2.3 cm^{-1}, F(000) = 592, R = 3.72% for 1880 observed reflexions. (3) *N*-Cyano-*N'*-methyl-*N''*-{2-[(3-bromo-2-pyridyl)methylthio]ethyl}guanidine, $C_{11}H_{14}BrN_5S$, M_r = 328.23, monoclinic, $P2_1/c$, a = 10.928(4), b = 9.183(2), c = 14.229(8) Å, β = 100.4(8)°, V = 1404.42 Å^3, Z = 4, D_x = 1.55 g cm^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, μ = 32.3 cm^{-1}, F(000) = 664, R = 4.43% for 1952 observed reflexions. (4) *N*-Cyano-*N'*-methyl-*N''*-[4-(2-pyridyl)butyl]guanidine monohydrate, $C_{12}H_{17}N_5.H_2O$, M_r = 249.31, monoclinic, $I2/c$, a = 15.570(8), b = 10.390(3), c = 17.383(4) Å, β = 99.38(2)°, V = 2774.3 Å^3, Z = 8, D_x = 1.19 g cm^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, μ = 6.62 cm^{-1}, F(000) = 1072, R = 4.00% for 2116 observed reflexions. (5) *N*-Cyano-*N'*-methyl-*N''*-[4-(3-methyl-2-pyridyl)butyl]guanidine monohydrate, $C_{13}H_{19}N_5.H_2O$, M_r = 263.34, triclinic, $P\bar{1}$, a = 7.860(2), b = 9.388(1), c = 9.706(1) Å, α = 92.96(1), β = 95.89(1), γ = 91.49(1)°, V = 708.45 Å^3, Z = 2, D_x = 1.23 g cm^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, μ = 6.72 cm^{-1}, F(000) = 284, R = 5.16% for 2697 observed reflexions. (6) *N*-Cyano-*N'*-methyl-*N''*-[4-(3-methoxy-2-pyridyl)butyl]guanidine, $C_{13}H_{19}N_5O$, M_r = 261.33, monoclinic, $I2/c$, a = 23.780(4), b = 9.162(2), c = 28.144(5) Å, β = 111.47(1)°, V = 5706.8 Å^3, Z = 16, D_x = 1.22 g cm^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, μ = 0.88 cm^{-1}, F(000) = 2240, R = 3.75% for 3554 observed reflexions. (7) *N*-Cyano-*N'*-methyl-*N''*-[4-(3-fluoro-2-pyridyl)butyl]guanidine, $C_{12}H_{16}FN_5$, M_r = 249.29, monoclinic, $P2_1/n$, a = 4.6267(3), b = 13.846(1), c = 19.828(2) Å, β = 93.14(1)°, V = 1268.95 Å^3, Z = 4, D_x = 1.31 g cm^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, μ = 7.89 cm^{-1}, F(000) = 528, R = 6.19% for 2303 observed reflexions. (8) *N*-Cyano-*N'*-methyl-*N''*-[4-(3-bromo-2-pyridyl)butyl]guanidine, $C_{12}H_{16}BrN_5$, M_r = 310.2, monoclinic, $P2_1/c$, a = 14.104(8), b = 12.678(4), c = 7.812(3) Å, β = 101.92(4)°, V = 1366.7 Å^3, Z = 4, D_x = 1.51 g cm^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, μ = 31.77 cm^{-1}, F(000) = 632, R = 3.7% for 1463 observed reflexions. (9) *N*-Cyano-*N'*-methyl-*N''*-[4-(5-methoxy-2-pyridyl)butyl]guanidine monohydrate, $C_{13}H_{19}N_5O.H_2O$, M_r = 279.34, triclinic, $P\bar{1}$, a = 7.700(1), b = 9.331(1), c = 10.767(1) Å, α = 78.52(1), β = 85.56(1), γ = 76.46(1)°, V = 736.56 Å^3, Z = 2, D_x = 1.26 g cm^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, μ = 0.95 cm^{-1}, F(000) = 300, R = 4.19% for 3687 observed reflexions. The molecular dimensions and environments in the crystal are reported, together with the molecular conformations from the structure analyses and modelling studies. It is concluded that biological activity is maximized for molecules in which there is a prevalence of low-energy molecular conformations with the aromatic N-atom to N''-atom distance between 3 and 5 Å.

Introduction

The compounds (1)–(9) are among a group of compounds which have been studied at SmithKline Beecham following the observation that replacing the imidazole ring of cimetidine by a pyridine ring makes little difference to the activity of the molecule as a histamine H_2-receptor antagonist (Cooper, 1986). For (1)–(9) Table 1 gives the chemical formula, pA_2 values obtained from the guinea pig atrium, log$P$(octanol/water) and pK_a values. (3) was also measured on the rat uterus (pA_2 6.1).

* To whom all correspondence should be addressed.

† Present address: SmithKline Beecham Research, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD, England.

‡ Present address: Department of Medicinal and Biological Chemistry, College of Pharmacy, University of Toledo, 2801W Bancroft Street, Toledo, Ohio 43606, USA.

§ Present address: Department of Chemistry, University College London, 20 Gordon Street, London WC1H OAJ, England.

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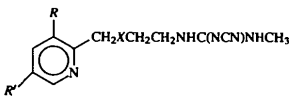
Table 1. *Chemical formulae*, pA_2, log*P*(*octanol/water*) *and* pK_a *values of compounds* (1)–(9)



The pA_2 values were obtained from the guinea pig atrium. (3) was also measured on the rat uterus (pA_2 = 6.1). log *P*(octanol/water) and pK_a values are calculated except for those marked with an asterisk which were measured at SmithKline and French.

	R	*R'*	*X*	pA_2	log *P*(octanol/water)	pK_a
(1)	H	H	S	6.0	0.79*	4.43*
(2)	OCH_3	H	S	6.67	0.97*	4.2*
(3)	Br	H	S	6.6	1.48*	2.1
(4)	H	H	CH_2	5.64	1.4	5.8
(5)	CH_3	H	CH_2	4.94	1.9	6.2
(6)	OCH_3	H	CH_2	6.77	1.6	5.6
(7)	F	H	CH_2	6.17	1.4	3.6
(8)	Br	H	CH_2	5.41	2.1	3.5
(9)	H	OCH_3	CH_2	4.82	1.6	5.6

This substitution of imidazole by pyridine eliminates the possibility of tautomerism, reduces the ring pK_a (imidazole pK_a = 7.1, pyridine pK_a = 4.98) and increases the lipophilicity of the molecule [log*P*(octanol/water) imidazole = 0.4, pyridine = 1.3]. By varying the identity of the 3-pyridyl substituent and by the introduction of a 5-substituent on the pyridyl ring significant changes in activity can be made. These changes in biological activity do not correlate with either the changes in basicity (pK_a) or lipophilicity [log*P*(octanol/water)] induced by the substituent. The pattern of activity *versus* substituent is the same for the *X* = S and *X* = CH_2 series of compounds and, although there is a general trend for compounds with *X* = S to be somewhat more active than the corresponding compound with *X* = CH_2, the most active compounds, the 3-methoxy-2-pyridyl compounds (2) and (6), have approximately the same activity. There is some correlation of biological activity with substituent size suggesting an optimal substituent size for *R* = OCH_3.

In an attempt to define factors relating the H_2-receptor antagonist activity to steric bulk and conformation, the conformational space of a range of molecules has been investigated and the crystal and molecular structures of compounds (1)–(9) have been determined. The compounds (1)–(9) were chosen to represent both the methylthioethyl and butyl series of antagonists and to have substituent groups that lead to a wide range of biological activities. The compounds were difficult to obtain as single crystals of a quality suitable for X-ray diffraction and this placed an undesirable constraint on choice of substituent.

Results

General

The numbering scheme used in the text describing the crystallographic results is defined in Table 2 which also presents a summary of the significant dimensions of the molecular skeletons. For compound (3), for purposes of comparison with (1) and (2), the torsion angles given in Table 2 are for a molecule related to that defined by the parameters in Table 3 by a centre of inversion. The H-atom coordinates are not quoted in Table 3 because the observed positions do not differ significantly from the computer-predicted positions that may be generated from the atomic parameters and crystal data given in Tables 3 and 4.* Figs. 1(*a*)–1(*i*) show the numbered asymmetric unit and the crystal packing in each compound. The location of the asymmetric unit in the crystal packing is indicated by the heavy arrow. For clarity in some diagrams the asymmetric unit has been rotated through a small angle so that all atoms are clearly visible. In each diagram the extent to which the crystal packing is illustrated is confined to that required to show the molecular environment. The details of the structure analyses are given in the *Experimental* section.

Molecular dimensions

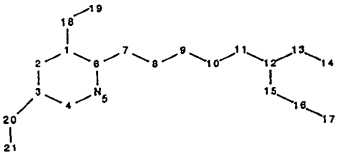
An examination of the bond lengths and interbond angles in Table 2 reveals no surprises. Indeed Table 2 records a satisfying consistency between equivalent lengths and angles. Those variations that are significant follow well established patterns. In the pyridyl group the variation in endocyclic ring angle at the substituent groups may be predicted by extrapolation of the results for benzenoid systems (Domenicano, Vaciago & Coulson, 1975; Domenicano & Murray-Rust, 1979) so that the variation of the endocyclic angle, 6—1—2, parallels the variation in the substituent group electronegativity. The endocyclic angle 5—6—1 at the carbon carrying the major side chain is generally somewhat larger for the methylthioethyl series than for the butyl series indicating the enhancement of the group electronegativity of C(7). The reason for the introduction of the S atom into the side chain was to enhance the electronegativity of C(7) (Black, Durant, Emmett & Ganellin, 1974). This change in group electronegativity also influences the 6—7 bond length which is just significantly shorter in the methylthioethyl series. Bonding to the sulfur is asymmetric with the bond 8—9 significantly shorter than 9—10, a general feature of the structures of methylthioethyl chains in H_2 antagonists. The variations in the dimensions of the guanidine residues rarely exceed three standard deviations and show no significant trends.

Molecular conformations

The molecules (1)–(9) do show very significant variations in conformation. The molecules contain a planar pyridyl group linked by a four-atom (butyl or methylthioethyl) flexible chain to a planar cyanoguanidine group. The crystals of the compounds (1)–(9) that were studied showed a wide variety of molecular conformations and crystal structures.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55888 (252 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF Reference: HA0114]

Table 2. *Comparison of bond lengths, interbond angles and selected torsion angles for compounds* (1)–(9)



The numbering scheme is indicated above. Atoms 5, 11, 13, 15 and 17 are N atoms. Distances are in Å, angles in °.

	(1)	(2)	(3)	(4)	(5)	(6*a*)	(6*b*)	(7)	(8)	(9)
1—2	1.379 (3)	1.384 (3)	1.385 (7)	1.376 (3)	1.384 (2)	1.375 (3)	1.384 (3)	1.379 (4)	1.360 (7)	1.378 (2)
2—3	1.370 (3)	1.362 (5)	1.373 (8)	1.345 (4)	1.377 (2)	1.369 (3)	1.380 (3)	1.367 (4)	1.360 (8)	1.379 (2)
3—4	1.377 (3)	1.366 (5)	1.373 (8)	1.366 (3)	1.373 (2)	1.365 (3)	1.364 (3)	1.371 (4)	1.380 (8)	1.376 (2)
4—5	1.340 (3)	1.350 (4)	1.341 (7)	1.344 (2)	1.342 (2)	1.345 (3)	1.342 (3)	1.337 (3)	1.325 (7)	1.343 (1)
5—6	1.339 (2)	1.330 (3)	1.345 (6)	1.322 (2)	1.338 (2)	1.332 (2)	1.335 (2)	1.331 (3)	1.334 (6)	1.331 (1)
1—6	1.388 (2)	1.398 (3)	1.408 (6)	1.380 (2)	1.409 (2)	1.404 (3)	1.401 (2)	1.381 (3)	1.402 (7)	1.385 (2)
6—7	1.497 (3)	1.491 (3)	1.481 (7)	1.508 (2)	1.503 (2)	1.500 (2)	1.501 (3)	1.499 (3)	1.504 (6)	1.508 (2)
7—8	1.816 (2)	1.822 (3)	1.829 (5)	1.521 (2)	1.516 (2)	1.521 (3)	1.527 (3)	1.524 (3)	1.523 (6)	1.503 (2)
8—9	1.811 (2)	1.807 (2)	1.809 (5)	1.527 (2)	1.519 (2)	1.522 (2)	1.521 (2)	1.517 (3)	1.501 (7)	1.524 (2)
9—10	1.516 (3)	1.517 (3)	1.518 (7)	1.513 (2)	1.530 (2)	1.512 (3)	1.518 (3)	1.518 (3)	1.521 (7)	1.514 (2)
10—11	1.456 (2)	1.444 (3)	1.456 (6)	1.466 (2)	1.459 (2)	1.457 (2)	1.457 (2)	1.455 (3)	1.452 (6)	1.458 (1)
11—12	1.347 (2)	1.344 (3)	1.343 (6)	1.334 (2)	1.333 (2)	1.342 (2)	1.336 (2)	1.345 (3)	1.343 (6)	1.332 (1)
12—13	1.324 (3)	1.325 (3)	1.327 (6)	1.339 (2)	1.337 (2)	1.332 (2)	1.329 (2)	1.336 (3)	1.323 (6)	1.339 (1)
13—14	1.452 (2)	1.446 (3)	1.454 (7)	1.441 (2)	1.445 (2)	1.446 (2)	1.439 (2)	1.431 (3)	1.448 (7)	1.442 (1)
12—15	1.333 (3)	1.334 (3)	1.339 (6)	1.332 (2)	1.338 (2)	1.331 (2)	1.340 (2)	1.325 (3)	1.331 (6)	1.342 (1)
15—16	1.308 (2)	1.309 (3)	1.304 (7)	1.308 (2)	1.308 (2)	1.307 (3)	1.313 (3)	1.315 (3)	1.315 (7)	1.315 (1)
16—17	1.152 (2)	1.151 (3)	1.145 (7)	1.150 (2)	1.156 (2)	1.155 (3)	1.154 (3)	1.149 (3)	1.140 (7)	1.152 (1)
1—18	—	1.354 (3)	1.896 (5)	—	1.499 (2)	1.358 (2)	1.361 (2)	1.354 (3)	1.902 (5)	—
18—19	—	1.427 (3)	—	—	—	1.425 (3)	1.426 (2)	—	—	—
3—20	—	—	—	—	—	—	—	—	—	1.364 (1)
20—21	—	—	—	—	—	—	—	—	—	1.422 (2)
6—1—2	118.7 (2)	119.0 (2)	120.7 (4)	119.7 (2)	117.8 (1)	119.6 (2)	119.4 (2)	122.4 (2)	121.2 (5)	120.2 (1)
1—2—3	119.2 (2)	118.2 (3)	117.8 (5)	119.2 (2)	120.3 (1)	118.3 (2)	118.4 (2)	117.0 (2)	118.3 (5)	119.0 (1)
2—3—4	118.8 (2)	119.9 (3)	119.4 (5)	118.4 (2)	118.2 (1)	119.6 (2)	119.1 (2)	118.4 (2)	118.7 (5)	117.9 (1)
3—4—5	123.2 (2)	123.2 (3)	123.4 (5)	123.4 (2)	123.4 (2)	123.2 (2)	123.2 (2)	124.4 (2)	123.4 (5)	123.0 (1)
4—5—6	117.6 (2)	117.2 (2)	118.7 (4)	118.0 (2)	118.5 (1)	117.9 (2)	118.7 (2)	118.1 (2)	118.9 (4)	119.3 (1)
5—6—1	122.5 (2)	122.5 (3)	120.0 (6)	121.2 (2)	121.9 (1)	121.4 (2)	121.1 (2)	119.7 (2)	119.5 (4)	120.6 (1)
1—6—7	120.5 (2)	120.1 (2)	122.7 (4)	122.2 (2)	120.0 (1)	—	—	121.1 (2)	121.7 (4)	123.1 (1)
5—6—7	117.0 (2)	117.5 (2)	117.3 (4)	115.6 (2)	118.1 (1)	118.1 (2)	117.5 (1)	119.1 (2)	118.8 (4)	116.2 (1)
6—7—8	113.8 (1)	112.6 (2)	110.8 (3)	112.6 (1)	116.6 (1)	113.4 (2)	111.2 (2)	112.7 (2)	115.6 (4)	116.4 (1)
7—8—9	102.8 (1)	101.2 (1)	101.0 (2)	113.2 (1)	111.3 (1)	112.8 (2)	113.9 (2)	112.8 (2)	110.6 (4)	113.6 (1)
8—9—10	113.6 (1)	114.9 (2)	111.0 (3)	113.5 (1)	114.1 (1)	111.8 (2)	112.0 (2)	112.5 (2)	112.9 (4)	111.1 (1)
9—10—11	111.9 (2)	110.7 (2)	110.7 (4)	112.1 (1)	113.5 (1)	114.8 (2)	114.3 (2)	113.7 (2)	109.9 (4)	113.1 (1)
10—11—12	123.3 (2)	125.4 (2)	120.8 (4)	122.2 (1)	125.4 (1)	122.2 (2)	122.6 (2)	121.9 (2)	122.4 (4)	123.5 (1)
11—12—13	118.3 (2)	119.1 (2)	119.5 (4)	118.8 (1)	119.8 (1)	118.9 (2)	119.2 (2)	118.6 (2)	118.9 (4)	118.6 (1)
12—13—14	124.3 (2)	122.2 (2)	124.5 (4)	125.1 (1)	122.8 (1)	124.4 (2)	124.4 (2)	125.6 (2)	123.7 (4)	124.6 (1)
11—12—15	116.9 (2)	123.3 (2)	116.6 (4)	117.8 (1)	123.8 (1)	117.2 (2)	117.7 (2)	117.5 (2)	116.5 (4)	118.5 (1)
13—12—15	124.8 (2)	117.6 (2)	123.9 (4)	123.4 (1)	116.4 (1)	123.9 (2)	123.1 (2)	124.0 (2)	124.6 (4)	122.9 (1)
12—15—16	120.4 (2)	118.8 (2)	119.8 (4)	119.0 (1)	122.8 (1)	118.7 (2)	117.9 (2)	117.9 (2)	116.9 (4)	116.2 (1)
15—16—17	172.4 (2)	174.8 (2)	172.9 (5)	173.7 (2)	173.6 (2)	173.4 (2)	174.5 (2)	174.8 (2)	175.6 (6)	176.0 (1)
2—1—18	—	125.4 (2)	119.8 (4)	—	120.8 (1)	124.7 (2)	125.2 (2)	119.0 (2)	119.7 (4)	—
6—1—18	—	115.6 (2)	119.5 (4)	—	121.4 (1)	115.7 (2)	115.4 (2)	118.6 (2)	119.1 (4)	—
1—18—19	—	118.5 (2)	—	—	—	117.2 (2)	117.5 (2)	—	—	—
2—3—20	—	—	—	—	—	—	—	—	—	116.9 (1)
4—3—20	—	—	—	—	—	—	—	—	—	125.2 (1)
3—20—21	—	—	—	—	—	—	—	—	—	117.0 (1)
1—6—7—8	93.4 (2)	−85.5 (4)	78 (1)	100.3 (3)	−176.1 (2)	−79.3 (4)	93.9 (3)	−89.6 (2)	179.9 (6)	−4.3 (2)
5—6—7—8	−86 (2)	94.2 (4)	−97 (1)	−78.8 (3)	3.8 (2)	100.7 (4)	−82.5 (4)	88.4 (2)	−0.8 (6)	176.1 (2)
6—7—8—9	−76.4 (2)	73.9 (4)	83.4 (7)	172.5 (3)	179.2 (2)	177.1 (4)	−179.3 (4)	179.7 (4)	−177.6 (5)	−176.4 (2)
7—8—9—10	98.5 (3)	−77.7 (4)	79.5 (7)	72 (3)	179.2 (2)	−176.5 (4)	−179.4 (4)	179.4 (4)	−178.4 (6)	−178.6 (2)
8—9—10—11	175.1 (3)	−51.4 (3)	172.6 (6)	−175.8 (3)	−63.1 (2)	−173.6 (4)	174.9 (3)	178.9 (2)	−178.7 (6)	−174.2 (2)
9—10—11—12	93.8 (3)	−167.7 (4)	170.4 (7)	88.3 (3)	−77.4 (2)	−77.3 (4)	81.2 (4)	−80.6 (2)	177.2 (5)	−93 (2)
10—11—12—13	176.9 (3)	9.5 (4)	174.2 (6)	−177 (3)	1.2 (2)	−175.5 (4)	175.1 (3)	178.2 (4)	−178.4 (5)	176.8 (2)
11—12—13—14	−3.6 (3)	178.7 (5)	−2 (1)	−6.7 (3)	−179.9 (2)	8 (4)	−5.6 (4)	5 (1)	1.1 (6)	−2.1 (2)
11—12—15—16	171 (3)	0.7 (4)	−179.4 (7)	174.2 (3)	7.3 (2)	−179.1 (4)	179 (4)	−174.2 (4)	173.7 (6)	179.9 (1)

In all the compounds the pyridyl ring is, as expected, strictly planar and in (2), (6*a*), (6*b*) and (9) the OCH_3 substituent at the 3- or 5-position is almost coplanar with the ring [6—1—18—19 is -174.2° in (2), -170.9° in (6*a*), 173.5° in (6*b*) and 4—3—20—21 is 0.8(2)° in (9)] with the methoxy group at the 3-position turned away from the major side chain and that at the 5-position turned towards the pyridine N atom.

The bond 7—8 is either almost coplanar with the pyridyl ring in (5), (8) and (9) or approximately perpendicular to the pyridyl ring in the remainder (Table 2). Thus for all the methylthioethyl side chains 7—8 is approximately perpendicular to the pyridyl plane but the butyl chains are equally divided between the coplanar and perpendicular conformations. For compounds in which 7—8 is coplanar with the pyridyl group, 7—8 is *trans* to bulky 3-substituents [(3), CH_3 and (8), Br] and *cis* to H. If the 7—8 bond is approximately perpendicular to the pyridyl plane for bulky 3-substituents there is some tendency [with the exception of (6*b*)] for 5—6—7—8 to be >90° perhaps

Table 3. *Positional parameters with e.s.d.'s in parenthesis and equivalent isotropic temperature factors*

The equivalent isotropic temperature factor is calculated as $U_{eq} = (U_{11}U_{22}U_{33})^{1/3}$, where U_{11}, U_{22}, U_{33} are the mean-square displacements (Å^2) along each of the principal axes of the thermal ellipsoid.

	x	y	z	U_{iso}/U_{eq}
Compound (1)				
C(1)	0.5542 (3)	0.2887 (2)	0.6785 (3)	0.0417
C(2)	0.4662 (3)	0.3395 (2)	0.7936 (3)	0.0458
C(3)	0.4727 (3)	0.2716 (2)	0.8881 (3)	0.0492
C(4)	0.5680 (3)	0.1548 (2)	0.8652 (2)	0.0480
N(5)	0.6570 (2)	0.1049 (2)	0.7558 (2)	0.0413
C(6)	0.6504 (2)	0.1724 (2)	0.6644 (2)	0.0353
C(7)	0.7541 (3)	0.1179 (2)	0.5450 (2)	0.0412
S(8)	1.00091 (6)	0.21906 (5)	0.61716 (6)	0.0395
C(9)	0.9929 (3)	0.4064 (2)	0.6240 (2)	0.0421
C(10)	1.0086 (3)	0.5360 (2)	0.7842 (2)	0.0403
N(11)	1.0179 (2)	0.6872 (2)	0.7875 (2)	0.0393
C(12)	0.8656 (2)	0.7451 (2)	0.7675 (2)	0.0355
N(13)	0.8911 (2)	0.8870 (2)	0.7798 (2)	0.0368
C(14)	1.0739 (3)	0.9889 (2)	0.8223 (3)	0.0430
N(15)	0.6999 (2)	0.6560 (2)	0.7416 (2)	0.0431
C(16)	0.5495 (2)	0.7121 (2)	0.7413 (2)	0.0399
N(17)	0.4076 (2)	0.7468 (2)	0.7409 (2)	0.0510
Compound (2)				
C(1)	0.9070 (2)	0.2883 (2)	0.4286 (2)	0.0405
C(2)	0.9775 (3)	0.2543 (2)	0.3386 (2)	0.0515
C(3)	0.9939 (4)	0.1587 (3)	0.3287 (2)	0.0616
C(4)	0.9408 (4)	0.0993 (2)	0.4062 (3)	0.0655
N(5)	0.8710 (3)	0.1304 (2)	0.4943 (2)	0.0553
C(6)	0.8549 (2)	0.2237 (2)	0.5047 (2)	0.0381
C(7)	0.7785 (3)	0.2585 (2)	0.6022 (2)	0.0443
S(8)	0.9189 (1)	0.2886 (1)	0.7305 (1)	0.0412
C(9)	0.9799 (3)	0.1721 (2)	0.7843 (2)	0.0409
C(10)	0.8652 (3)	0.1215 (2)	0.8485 (2)	0.0397
N(11)	0.8210 (2)	0.1817 (1)	0.9378 (2)	0.0353
C(12)	0.7436 (2)	0.1532 (1)	1.0226 (2)	0.0333
N(13)	0.7225 (2)	0.0613 (1)	1.0377 (2)	0.0412
C(14)	0.6434 (4)	0.0254 (2)	1.1286 (3)	0.0534
N(15)	0.6861 (2)	0.2132 (1)	1.0933 (2)	0.0381
C(16)	0.7040 (3)	0.3045 (1)	1.0795 (2)	0.0359
N(17)	0.7124 (3)	0.3858 (1)	1.0735 (2)	0.0502
O(18)	0.8837 (2)	0.3809 (1)	0.4510 (2)	0.0567
C(19)	0.9201 (5)	0.4503 (3)	0.3704 (3)	0.0689
Compound (3)				
C(1)	0.5463 (4)	0.0675 (5)	0.1295 (3)	0.0348
C(2)	0.5871 (5)	−0.0585 (6)	0.1789 (4)	0.0426
C(3)	0.7078 (6)	−0.1011 (6)	0.1804 (4)	0.0494
C(4)	0.7837 (5)	−0.0168 (6)	0.1355 (5)	0.0473
N(5)	0.7451 (4)	0.1046 (4)	0.0866 (3)	0.0394
C(6)	0.6269 (4)	0.1486 (5)	0.0828 (3)	0.0306
C(7)	0.5906 (5)	0.2894 (5)	0.0351 (3)	0.0367
S(8)	0.5991 (1)	0.4365 (1)	0.1227 (1)	0.0391
C(9)	0.7628 (5)	0.4818 (6)	0.1401 (3)	0.0368
C(10)	0.7907 (4)	0.5770 (6)	0.0593 (3)	0.0366
N(11)	0.9188 (4)	0.6287 (5)	0.0798 (3)	0.0351
C(12)	0.9689 (4)	0.6972 (5)	0.0125 (3)	0.0308
N(13)	1.0820 (4)	0.7542 (5)	0.0353 (3)	0.0381
C(14)	1.1569 (6)	0.7523 (10)	0.1308 (4)	0.0566
N(15)	0.9002 (4)	0.7011 (6)	−0.0755 (3)	0.0400
C(16)	0.9437 (4)	0.7649 (6)	−0.1445 (3)	0.0395
N(17)	0.9699 (4)	0.8188 (7)	−0.2107 (3)	0.0507
Br(18)	0.38019 (5)	0.13124 (6)	0.12388 (4)	0.0472
Compound (4)				
C(1)	1.0803 (1)	0.0343 (2)	0.1570 (1)	0.0658
C(2)	1.1658 (1)	−0.0047 (3)	0.1649 (1)	0.0727
C(3)	1.1844 (1)	−0.1321 (3)	0.1687 (1)	0.0703
C(4)	1.1170 (1)	−0.2175 (3)	0.1638 (1)	0.0696
N(5)	1.0330 (1)	−0.1818 (1)	0.1551 (1)	0.0548
C(6)	1.0150 (1)	−0.0565 (2)	0.1514 (1)	0.0462
C(7)	0.9200 (1)	−0.0198 (2)	0.1397 (1)	0.0538
C(8)	0.8760 (1)	−0.0337 (2)	0.0553 (1)	0.0464
C(9)	0.7776 (1)	−0.0140 (2)	0.0441 (1)	0.0489
C(10)	0.7512 (1)	0.1246 (2)	0.0531 (1)	0.0454
N(11)	0.6568 (1)	0.1389 (1)	0.0478 (1)	0.0452
C(12)	0.6172 (1)	0.1287 (1)	0.1101 (1)	0.0427
N(13)	0.5303 (1)	0.1370 (1)	0.1002 (1)	0.0456
C(14)	0.4749 (1)	0.1695 (2)	0.0280 (1)	0.0515
N(15)	0.6669 (1)	0.1122 (1)	0.1793 (1)	0.0518
C(16)	0.6304 (1)	0.1128 (2)	0.2420 (1)	0.0503
N(17)	0.6059 (1)	0.1121 (2)	0.3010 (1)	0.0648
O(1*w*)	0.8961 (1)	0.6393 (1)	0.1163 (1)	0.0662
Compound (5)				
C(1)	−0.0652 (2)	0.2669 (1)	0.0355 (1)	0.0409
C(2)	−0.2299 (2)	0.2243 (2)	−0.0174 (2)	0.0486
C(3)	−0.3682 (2)	0.2926 (2)	0.0284 (2)	0.0519
C(4)	−0.3373 (2)	0.4030 (2)	0.1270 (2)	0.0505
N(5)	−0.1796 (1)	0.4468 (1)	0.1815 (1)	0.0434
C(6)	−0.0453 (2)	0.3809 (1)	0.1366 (1)	0.0370
C(7)	0.1307 (2)	0.4317 (1)	0.1974 (2)	0.0393
C(8)	0.1402 (2)	0.5483 (2)	0.3121 (1)	0.0390
C(9)	0.3245 (2)	0.5885 (1)	0.3657 (2)	0.0398
C(10)	0.3437 (2)	0.7072 (2)	0.4806 (1)	0.0403
N(11)	0.2770 (1)	0.8429 (1)	0.4364 (1)	0.0400
C(12)	0.3555 (2)	0.9338 (1)	0.3608 (1)	0.0373
N(13)	0.5066 (1)	0.9017 (1)	0.3174 (1)	0.0439
C(14)	0.5988 (2)	0.9952 (2)	0.2353 (2)	0.0529
N(15)	0.2904 (2)	1.0576 (1)	0.3219 (1)	0.0441
C(16)	0.1507 (2)	1.0992 (2)	0.3721 (2)	0.0436
N(17)	0.0303 (2)	1.1484 (2)	0.4121 (2)	0.0586
C(18)	0.0865 (2)	0.1959 (2)	−0.0162 (2)	0.0540
O(1*w*)	0.2595 (2)	0.3247 (2)	0.6338 (2)	0.0625
Compound (6)				
Molecule (*a*)				
C(1*a*)	0.4386 (1)	0.8698 (2)	1.0904 (1)	0.0486
C(2*a*)	0.4800 (1)	0.9340 (3)	1.1330 (1)	0.0585
C(3*a*)	0.4626 (1)	0.9648 (3)	1.1732 (1)	0.0646
C(4*a*)	0.4053 (1)	0.9322 (3)	1.1699 (1)	0.0630
N(5*a*)	0.3639 (1)	0.8704 (2)	1.1284 (1)	0.0524
C(6*a*)	0.3803 (1)	0.8389 (2)	1.0891 (1)	0.0424
C(7*a*)	0.3344 (1)	0.7690 (2)	1.0430 (1)	0.0471
C(8*a*)	0.3048 (1)	0.8758 (2)	0.9996 (1)	0.0451
C(9*a*)	0.2607 (1)	0.8023 (2)	0.9521 (1)	0.0446
C(10*a*)	0.2348 (1)	0.9092 (2)	0.9086 (1)	0.0479
N(11*a*)	0.1873 (1)	0.8503 (2)	0.8636 (1)	0.0470
C(12*a*)	0.1994 (1)	0.7633 (2)	0.8302 (1)	0.0444
N(13*a*)	0.1541 (1)	0.7214 (2)	0.7881 (1)	0.0502
C(14*a*)	0.0931 (1)	0.7772 (3)	0.7722 (1)	0.0613
N(15*a*)	0.2567 (1)	0.7236 (2)	0.8416 (1)	0.0523
C(16*a*)	0.2700 (1)	0.6395 (3)	0.8097 (1)	0.0533
N(17*a*)	0.2874 (1)	0.5643 (3)	0.7851 (1)	0.0693
O(18*a*)	0.4497 (1)	0.8319 (2)	1.0480 (1)	0.0664
C(19*a*)	0.5106 (1)	0.8413 (4)	1.0507 (1)	0.0814
Molecule (*b*)				
C(1*b*)	−0.0149 (1)	0.1373 (2)	0.3944 (1)	0.0492
C(2*b*)	−0.0518 (1)	0.0424 (3)	0.3581 (1)	0.0579
C(3*b*)	−0.0257 (1)	−0.0482 (3)	0.3327 (1)	0.0596
C(4*b*)	0.0348 (1)	−0.0376 (3)	0.3430 (1)	0.0589
N(5*b*)	0.0712 (1)	0.0546 (2)	0.3778 (1)	0.0520
C(6*b*)	0.0472 (1)	0.1402 (2)	0.4038 (1)	0.0438
C(7*b*)	0.0897 (1)	0.2328 (2)	0.4456 (1)	0.0473
C(8*b*)	0.1177 (1)	0.1456 (2)	0.4949 (1)	0.0485
C(9*b*)	0.1608 (1)	0.2338 (2)	0.5391 (1)	0.0440
C(10*b*)	0.1880 (1)	0.1424 (2)	0.5871 (1)	0.0503
N(11*b*)	0.2336 (1)	0.2180 (2)	0.6293 (1)	0.0473
C(12*b*)	0.2194 (1)	0.3095 (2)	0.6601 (1)	0.0448
N(13*b*)	0.2633 (1)	0.3663 (2)	0.7001 (1)	0.0490
C(14*b*)	0.3260 (1)	0.3264 (3)	0.7158 (1)	0.0634
N(15*b*)	0.1608 (1)	0.3412 (2)	0.6485 (1)	0.0539
C(16*b*)	0.1465 (1)	0.4293 (3)	0.6791 (1)	0.0535
N(17*b*)	0.1292 (1)	0.5055 (3)	0.7034 (1)	0.0689
O(18*b*)	−0.0338 (1)	0.2313 (2)	0.4229 (1)	0.0651
C(19*b*)	−0.0972 (1)	0.2438 (3)	0.4111 (1)	0.0751
Compound (7)				
C(1)	0.9202 (5)	−0.6265 (2)	0.0641 (1)	0.0461
C(2)	1.1146 (6)	−0.6997 (2)	0.0538 (1)	0.0530
C(3)	1.2416 (6)	−0.7425 (2)	0.1101 (1)	0.0534
C(4)	1.1653 (6)	−0.7112 (2)	0.1723 (1)	0.0507
N(5)	0.9782 (4)	−0.6397 (1)	0.1820 (1)	0.0439
C(6)	0.8539 (4)	−0.5966 (1)	0.1279 (1)	0.0371
C(7)	0.6509 (5)	−0.5139 (2)	0.1374 (1)	0.0456
C(8)	0.8058 (5)	−0.4168 (2)	0.1421 (1)	0.0407
C(9)	0.6006 (5)	−0.3329 (2)	0.1513 (1)	0.0433
C(10)	0.7559 (5)	−0.2363 (2)	0.1553 (1)	0.0405
N(11)	0.5637 (4)	−0.1543 (1)	0.1628 (1)	0.0414
C(12)	0.4116 (4)	−0.1154 (1)	0.1098 (1)	0.0368
N(13)	0.2332 (4)	−0.0418 (1)	0.1209 (1)	0.0410
C(14)	0.2059 (8)	0.0048 (2)	0.1846 (1)	0.0572
N(15)	0.4455 (4)	−0.1537 (1)	0.0495 (1)	0.0437
C(16)	0.3182 (5)	−0.1109 (2)	−0.0033 (1)	0.0425
N(17)	0.2153 (5)	−0.0789 (2)	−0.0524 (1)	0.0545
F(18)	0.7864 (4)	−0.5828 (1)	0.0098 (1)	0.0690

Table 3 (*cont.*)

	x	*y*	*z*	U_{iso}/U_{eq}
Compound (8)				
C(1)	0.0856 (3)	0.2078 (4)	0.1891 (7)	0.0431
C(2)	0.0009 (4)	0.1667 (4)	0.2166 (9)	0.0551
C(3)	−0.0696 (4)	0.2345 (5)	0.2422 (9)	0.0572
C(4)	−0.0522 (4)	0.3415 (5)	0.2388 (8)	0.0574
N(5)	0.0303 (3)	0.3821 (3)	0.2131 (6)	0.0488
C(6)	0.1006 (3)	0.3171 (4)	0.1880 (6)	0.0409
C(7)	0.1946 (4)	0.3635 (3)	0.1613 (7)	0.0426
C(8)	0.1999 (4)	0.4834 (4)	0.1630 (8)	0.0452
C(9)	0.2952 (4)	0.5200 (4)	0.1276 (8)	0.0462
C(10)	0.3058 (4)	0.6394 (4)	0.1327 (8)	0.0483
N(11)	0.3984 (3)	0.6692 (3)	0.0935 (6)	0.0455
C(12)	0.4248 (3)	0.7702 (4)	0.0821 (7)	0.0406
N(13)	0.5095 (3)	0.7912 (3)	0.0418 (6)	0.0457
C(14)	0.5757 (4)	0.7109 (4)	0.0060 (8)	0.0513
N(15)	0.3628 (3)	0.8429 (3)	0.1146 (6)	0.0490
C(16)	0.3919 (4)	0.9416 (4)	0.1201 (8)	0.0546
N(17)	0.4122 (4)	1.0288 (4)	0.1295 (9)	0.0685
Br(18)	0.18648 (4)	0.11594 (4)	0.15380 (8)	0.0532

	x	*y*	*z*	U_{iso}/U_{eq}
Compound (9)				
C(1)	0.2384 (2)	0.4526 (1)	0.9095 (1)	0.0487
C(2)	0.2435 (2)	0.5838 (1)	0.9482 (1)	0.0510
C(3)	0.2767 (2)	0.5788 (1)	1.0732 (1)	0.0428
C(4)	0.3053 (2)	0.4415 (1)	1.1534 (1)	0.0460
N(5)	0.2994 (2)	0.3139 (1)	1.1159 (1)	0.0461
C(6)	0.2653 (2)	0.3184 (1)	0.9957 (1)	0.0422
C(7)	0.2596 (3)	0.1708 (2)	0.9610 (1)	0.0556
C(8)	0.2093 (2)	0.1766 (1)	0.8277 (1)	0.0454
C(9)	0.1950 (2)	0.0252 (1)	0.8017 (1)	0.0466
C(10)	0.1485 (2)	0.0374 (1)	0.6654 (1)	0.0434
N(11)	0.1157 (1)	−0.1013 (1)	0.6393 (1)	0.0413
C(12)	0.2414 (1)	−0.2055 (1)	0.5955 (1)	0.0353
N(13)	0.1988 (1)	−0.3321 (1)	0.5807 (1)	0.0391
C(14)	0.0261 (2)	−0.3670 (1)	0.6126 (1)	0.0459
N(15)	0.4054 (1)	−0.1790 (1)	0.5686 (1)	0.0431
C(16)	0.5248 (1)	−0.2851 (1)	0.5258 (1)	0.0404
N(17)	0.6368 (1)	−0.3730 (1)	0.4882 (1)	0.0524
O(20)	0.2792 (2)	0.7116 (1)	1.1072 (1)	0.0572
C(21)	0.3166 (3)	0.7064 (2)	1.2355 (2)	0.0623
O(1*w*)	0.2706 (1)	0.0637 (1)	0.3105 (1)	0.0541

Table 4. *Crystal data and experimental parameters*

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Formula	$C_{11}H_{15}N_5S$	$C_{12}H_{17}N_5OS$	$C_{11}H_{14}BrN_5S$	$C_{12}H_{17}N_5.H_2O$	$C_{13}H_{19}N_5.H_2O$	$C_{13}H_{19}N_5O$	$C_{12}H_{16}FN_5$	$C_{12}H_{16}BrN_5$	$C_{13}H_{19}N_5O.H_2O$
M_r	249.33	279.36	328.23	249.31	263.34	261.33	249.29	310.2	279.34
Crystal class	Triclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic
a (Å)	7.482 (2)	8.670 (4)	10.928 (4)	15.570 (8)	7.860 (2)	23.780 (4)	4.6267 (3)	14.104 (8)	7.700 (1)
b (Å)	9.775 (2)	14.095 (4)	9.183 (2)	10.390 (3)	9.388 (1)	9.162 (2)	13.846 (1)	12.678 (4)	9.331 (1)
c (Å)	10.019 (1)	11.682 (2)	14.229 (8)	17.383 (4)	9.706 (1)	28.144 (5)	19.828 (2)	7.812 (3)	10.767 (1)
α (°)	116.00 (1)	90	90	90	92.96 (1)	90	90	90	78.52 (1)
β (°)	102.00 (2)	99.32 (7)	100.4 (8)	99.38 (2)	95.89 (1)	111.47 (1)	93.14 (1)	101.92 (4)	85.56 (1)
γ (°)	96.78 (2)	90	90	90	91.49 (1)	90	90	90	76.46 (1)
V (Å^3)	625.7	1408.7	1404.42	2774.3	708.45	5706.8	1268.95	1366.7	736.56
Space group	$P\bar{1}$	$P2_1/a$	$P2_1/c$	$I2/c$	$P\bar{1}$	$I2/c$	$P2_1/n$	$P2_1/c$	$P\bar{1}$
Z	2	4	4	8	2	16	4	4	2
D_x (Mg m^{-3})	1.32	1.32	1.55	1.19	1.23	1.22	1.31	1.51	1.26
$F(000)$	264	592	664	1072	284	2240	528	632	300
Crystal size (mm)	0.3 × 0.5 × 0.7	1.0 × 0.85 × 0.43	0.5 × 0.5 × 0.4	0.45 × 0.37 × 0.65	0.25 × 0.33 × 0.55	0.65 × 0.6 × 0.45	0.6 × 0.4 × 0.3	0.5 × 0.5 × 0.3	1.0 × 1.0 × 0.8
μ (cm^{-1})	21.21	2.3	32.3	6.62	6.72	0.88	7.89	31.77	0.95
Scan angle (°)	1.2 + 0.14tanθ	1.2 + 0.35tanθ	1.0 + 0.35tanθ	1.15 + 0.14tanθ	1.15 + 0.14tanθ	1.1 + 0.35tanθ	1.1 + 0.14tanθ	1.13 + 0.35tanθ	1.07 + 0.35tanθ
$\sin(\theta/\lambda)_{max}$ (Å^{-1})	0.58	0.64	0.66	0.58	0.58	0.6	0.58	0.62	0.725
$h_{min}, k_{min}, l_{min}$, $h_{max}, k_{max}, l_{max}$	−9, −12, −1 8,11,12	−11, −1, −1 10,17,14	−14, −1, −1 14,11,18	−17, −1, −1 17,11,20	−9, −11, −1 9,11,12	−26, −1, −1 26,10,33	−5, −1, −1 5,17,24	−17, −1, −1 16,15,9	−11, −13, −1 11,13,14
No. of reflexions measured	3434	3733	4222	6632	3851	6915	4747	4022	6341
No. of independent reflexions	2527	2701	3392	2510	2931	5010	2516	2874	5099
R_m (%)	1.83	2.12	5.44	3.63	2.57	1.82	2.31	4.96	1.5
No. of observed [$I > 3\sigma(I)$] reflexions	2490	1880	1952	2116	2697	3554	2303	1463	3687
R (%)	4.98	3.72	4.43	4.00	5.16	3.75	6.19	3.7	4.19
wR (%)	6.2	4.63	6.06	5.18	7.2	4.82	8.22	4.53	5.25
Σ(shift/e.s.d.)^2	2.8	0.21	0.8	0.13	2.9	0.35	0.16	2.41	0.76
$\Delta\rho_{max}$ (e Å^{-3})	0.5	0.25	0.5	0.11	0.23	0.19	0.32	0.84	0.23
Weights	9025, 12604 4158, 497	51, 49, −14 −14	323, 432, 90 −40, −17	134, 153, 21, −5	797, 9342 2874, 302	5361, 455, 123	5361, 8439 4082, 1011	1917, 2590 1188, 206	165, 154

to accommodate steric repulsion between the substituent and the H atoms on 7.

The torsion angle 6—7—8—9 is ≃180° for all the butyl chains but in sharp contrast this angle is ≃±80° in the methylthioethyl chains. Furthermore the torsion angle 7—8—9—10 is ≃180° for all the butyl chains except (4) where it has a value of 72.0° and again in the methylthioethyl compounds the angle is ≃±80°. The two *gauche* torsion angles 6—7—8—9 and 7—8—9—10 in the methylthioethyl chains may be in the same sense or in opposite senses. The overall effect of *gauche* angles 6—7—8—9 and 7—8—9—10 is to shorten the distance between the N atoms 5 and 11. For two *gauche* angles N(5)···N(11) has the value 5.85 Å in (1), 5.32 Å in (2) and 5.18 Å in (3). When one or both of the angles are *trans*, the distances N(5)···N(11) are (4) 6.73, (5) 5.47, (6*a*) 6.87, (6*b*) 7.09, (7) 6.99, (8) 6.56 and (9) 7.41 Å (see Table 5). The short distance in (5) is brought about by two *gauche* angles 8—9—10—11 and 9—10—11—12. The presence of *gauche* linkages at thioether groups is a very general phenomenon in both acyclic systems and macrocycles. With two exceptions [(2) and (5)] 8—9—10—11 is *trans* and with three exceptions [(2), (3) and (8)] 9—10—11—12 is *gauche* with a value of ≃±80°. Thus only in (2) are both these angles *gauche*.

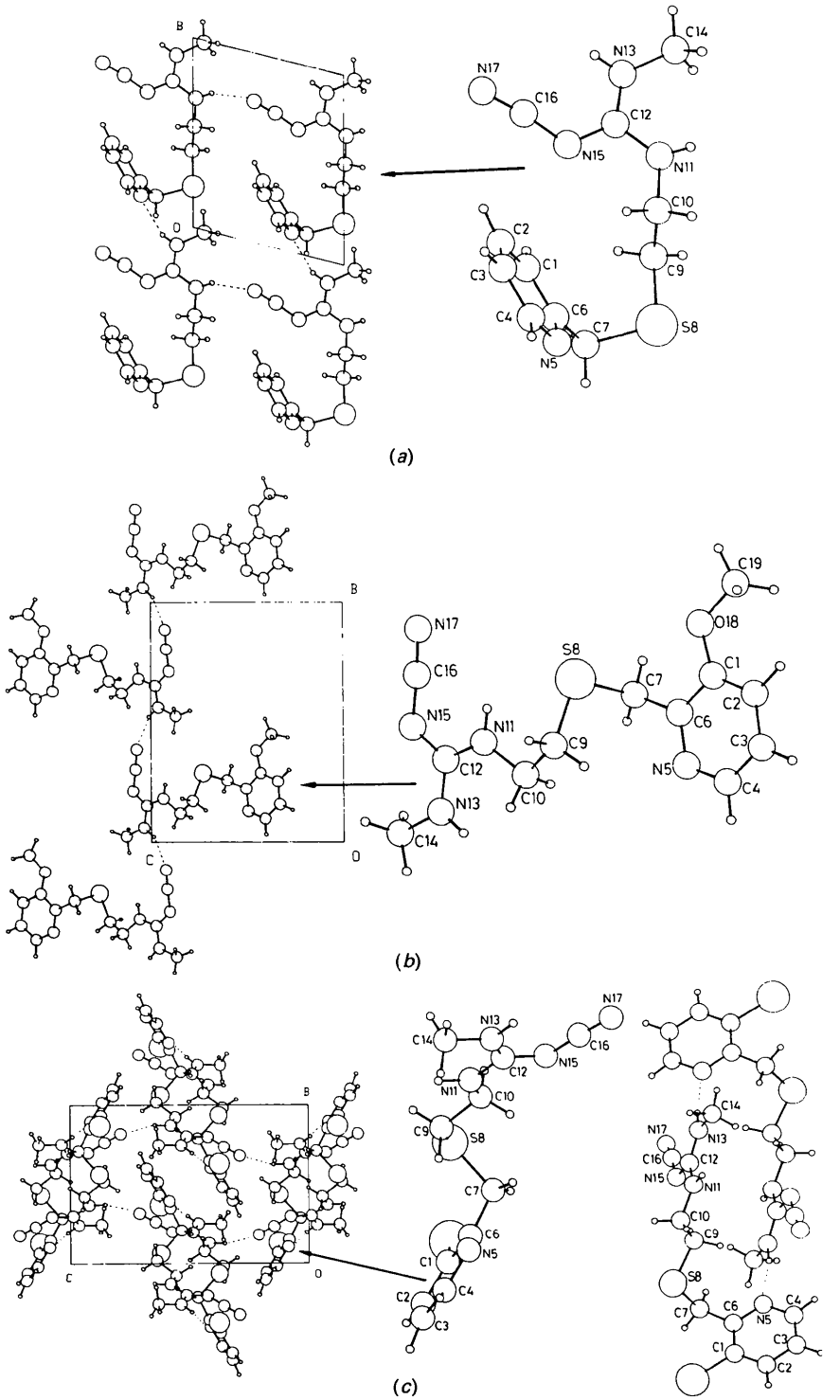
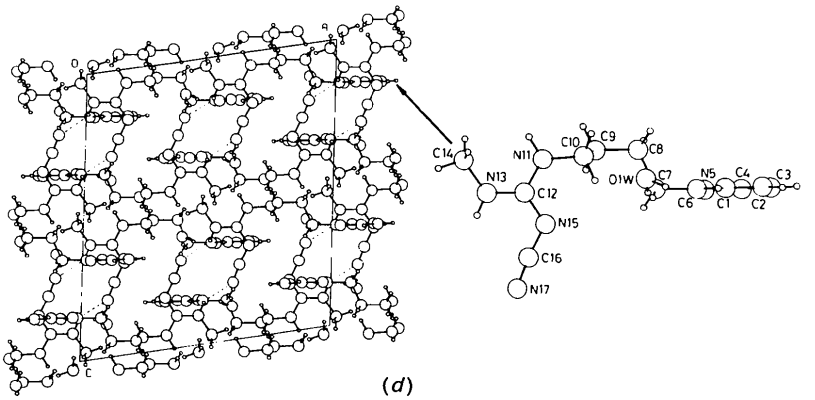
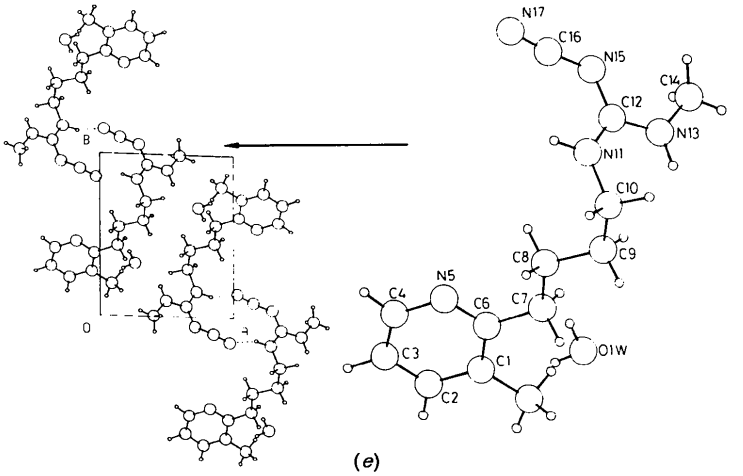


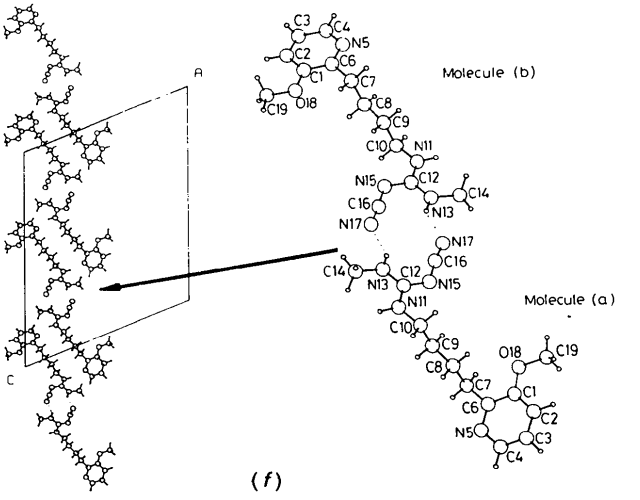
Fig. 1. (*a*) *N*-Cyano-*N'*-methyl-*N''*-{2-[(2-pyridyl)methylthio]ethyl}guanidine, (1), in projection down **c** and showing the *gauche* torsion angles at the S atom. In the crystal the molecules form hydrogen-bonded sheets parallel to the *ab* plane. There is a second hydrogen-bonded sheet related to the one shown by an inversion centre. (*b*) *N*-Cyano-*N'*-methyl-*N''*-{2-[(3-methoxy-2-pyridyl)methylthio]ethyl}guanidine, (2), in projection down **a** and again showing the *gauche* torsion angles of the S atom. The molecules related by a twofold screw axis form hydrogen-bonded chains parallel to *b*. (*c*) *N*-Cyano-*N'*-methyl-*N''*-{2-[(3-bromo-2-pyridyl)methylthio]ethyl}guanidine, (3), in projection down **a** showing the *gauche* torsion angles at the S atom. The molecules form dimers arrowed in the crystal projection bonded by a pair of N(5)···H—N(13) intermolecular hydrogen bonds. The dimer is shown on the right of the diagram in an alternative view. These dimers form hydrogen-bonded sheets.



(*d*)



(*e*)



(*f*)

Fig. 1 (*cont.*) (*d*) *N*-Cyano-*N'*-methyl-*N''*-[4-(2-pyridyl)butyl]guanidine monohydrate, (4), shown in projection down **b** has a complex body-centred crystal structure. The molecules have a folded butyl chain at C(8) and are linked to form centrosymmetric dimers by a pair of intermolecular hydrogen bonds N(17)···H—N(13). Similar dimers are found in (6), (7), (8) and (9). The dimers are then linked by water molecules to form a complex hydrogen-bonded network. (*e*) *N*-Cyano-*N'*-methyl-*N''*-[4-(3-methyl-2-pyridyl)butyl]guanidine, (5), shown in projection down **c** and demonstrating an extended butyl chain in the antiperiplanar conformation at C(8) and the formation of centrosymmetric dimers linked by two intermolecular hydrogen bonds N(17)···H—N(11). These dimers are hydrogen bonded to water of crystallization (Table 5). For clarity the dimers about the origin and the point 110 have been omitted. (*f*) *N*-Cyano-*N'*-methyl-*N''*-[4-(3-methoxy-2-pyridyl)butyl]guanidine, (6), shown in projection down **b**. Two crystallographically distinct molecules (*a*) and (*b*) have extended butyl chains and form pseudo-centrosymmetric hydrogen-bonded dimers similar to those found in (4), (7), (8) and (9). The dimers are then hydrogen bonded to form chains parallel to *c*. The linkage to form sheets suggests alternative dimers similar to those found in (3). The chains are generated by the **c** glide.

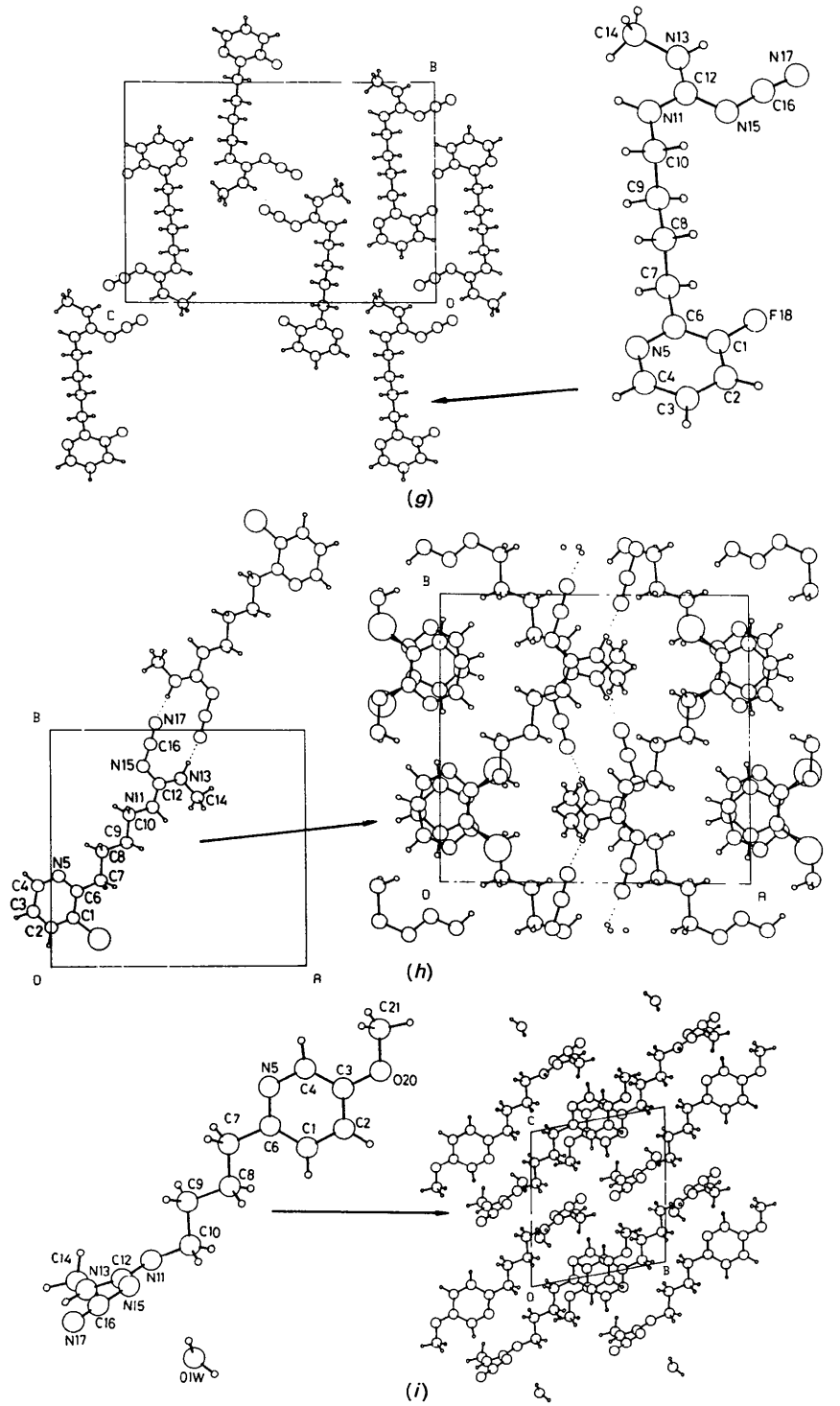


Fig. 1 (*cont.*) (*g*) *N*-Cyano-*N'*-methyl-*N''*-[4-(3-fluoro-2-pyridyl)butyl]guanidine, (7), shown in projection down **a**. The molecular conformation is almost identical to that observed for (4), (6), (8) and (9). The molecules link to form similar hydrogen-bonded dimers about crystallographic symmetry centres and the dimers link to form sheets parallel to the *bc* plane. (*h*) *N*-Cyano-*N'*-methyl-*N''*-[4-(3-bromo-2-pyridyl)butyl]guanidine, (8), shown in projection down **c**. The molecules which have an extended butyl chain and a flat heavy-atom skeleton, link to form centrosymmetric hydrogen-bonded dimers similar to those found in (4), (6), (7) and (9). The crystal has no other hydrogen bonds. (*i*) *N*-Cyano-*N'*-methyl-*N''*-[4-(5-methoxy-2-pyridyl)butyl]guanidine monohydrate, (9), shown in projection down **a**. The molecules have monohydrate extended butyl chains and form hydrogen-bonded centrosymmetric dimers similar to those found in (4), (6), (7) and (8). Water molecules link the dimers to form a complex hydrogen-bonded structure.

For compounds (1)–(9) there are two observed configurations of the cyanoguanidine moiety. Considering only the *N*-methyl group and the four-atom side chain, then (2) and (5) have the *E,Z* configuration and all the others have the *Z,E* configuration. For the *E,Z* configuration the cyanide group is on the opposite side of the C—N bond to the NCH_3 group and in the *Z,E* configuration it is on the same side of the C—N bond as the NCH_3. Molecular-mechanics calculations indicate that the energy barrier to interconversion of the two configurations is in the region of 20 kcal mol^{-1}. There is no relation between the observed configuration of the cyanoguanidine and the conformation of the flexible chain nor is there any relation between the observed configuration and the nature of the solvent from which the crystals were grown, or the type of hydrogen-bonding network in the crystal. It is very tempting to attribute the observed differences of configuration to crystal-packing effects but a pair of compounds (5) and (8) which might well be expected to give isomorphous crystals (thus identical molecular packing) do not do so and have different configurations and conformations, although it must be added that the crystals studied were grown from different solvents. On the other hand it might be suggested that the frequency of the observation of the *Z,E* diastereomer indicates that it is preferred to the *E,Z*; however, molecular-mechanics calculations give very similar energies for the two diastereomers and it may be that *Z,E* leads to higher lattice energies than *E,Z*.

Hydrogen-bonding interactions

The hydrogen-bonded contacts are recorded in Table 5. Compounds (1)–(9) all have two atoms, N(11) and N(13), that can act as hydrogen donors and three atoms, N(5), N(15) and N(17), that can act as hydrogen acceptors in hydrogen bonds. The intramolecular hydrogen bond N(5)···N(13) which is a prominent structural feature of thiaburimamide, metiamide (Prout, Critchley, Ganellin & Mitchell, 1977) and cimetidine (Hadicke, Frickel & Franke, 1978) polymorphs crystallized from methyl cyanide solvent, is not observed in any of these crystals. In each compound a hydrogen bond is formed to N(17) from either atom N(11) [(1), (3) and (5)] or atom N(13) [(2), (4), (6), (7), (8) and (9)] of a neighbouring molecule. These hydrogen bonds show only a small spread in bond length. In compound (4) this hydrogen bond leads to the formation of a hydrogen-bonded dimer with a twofold symmetry axis, in (5), (7), (8) and (9) a dimer with a centre of symmetry and in (6) a dimer with a non-crystallographic pseudo-centre formed from molecules (6*a*) and (6*b*). For (5) the dimer is similar to that found in cimetidine (Hadicke, Frickel & Franke, 1978) crystallized from methyl cyanide, and in (4) and (6)–(9) to that found in burimamide (Kamenar, Prout & Ganellin, 1973) from methyl cyanide. There seems to be some preference for compounds containing the butyl chain to form the burimamide type of end-to-end hydrogen-bonded

Table 5. *Hydrogen-bond lengths* (Å) *and angles* (°) *and non-bonded contact distances* (Å) *of possible relevence to biological activity*

The H atoms are placed in observed positions but these do not differ significantly from those positions that would be calculated from the observed heavy-atom skeleton. Standard deviations are 0.002–0.003 Å, except in compound (8) where they are *ca* 0.007 Å.

Compound (1)

N(5)···N(13^{i})	2.970	N(17)···N(11^{ii})	3.076
N(5)···N(11)	5.851	N(5)···N(17)	6.807
N(5)···N(13)	7.525	N(11)···N(13)	2.295
N(5)···N(15)	5.424	N(11)···(17)	4.626

Symmetry code: (i) $x, y-1, z$; (ii) $x+1, y, z$.

Compound (2)

N(13)···N(17^{i})	2.892		
N(5)···N(11)	5.318	N(5)···N(17)	7.978
N(5)···N(13)	6.746	N(11)···N(13)	2.302
N(5)···N(15)	7.520	N(11)···N(17)	3.484

Symmetry code: (i) $\frac{1}{2}-x, y-\frac{3}{2}, 2-z$.

Compound (3)

N(5)···N(13^{i})	3.074	N(17)···N(11^{ii})	2.972
N(5)···N(11)	5.181	N(5)···N(17)	8.408
N(5)···N(13)	7.117	N(11)···N(13)	2.306
N(5)···N(15)	6.294	N(11)···N(17)	4.612

Symmetry code: (i) $2-x, 1-y, -z$; (ii) $x, \frac{1}{2}-y, z-\frac{1}{2}$.

Compound (4)

N(5)···O(1w^{i})	2.826	N(17)···O(1w^{iii})	2.985
N(17)···N(13^{ii})	2.951	O(1w)···N(11^{iv})	2.837
N(5)···N(11)	6.733	N(5)···N(17)	8.091
N(5)···N(13)	8.409	N(11)···N(13)	2.301
N(5)···N(15)	6.541	N(11)···N(17)	4.605

Symmetry code: (i) $x, y-1, z$; (ii) $-x+1, y, -z+\frac{1}{2}$; (iii) $-x+\frac{3}{2}, -y+\frac{1}{2}, -z+\frac{1}{2}$; (iv) $-x+\frac{3}{2}, y-\frac{1}{2}, -z$.

Compound (5)

N(5)···O(1w^{i})	2.848	N(17)···O(1w^{iii})	3.049
N(17)···N(11^{ii})	2.955	O(1w)···N(13^{iv})	2.872
N(5)···N(11)	5.419	N(5)···N(17)	6.948
N(5)···N(13)	6.770	N(11)···N(13)	2.310
N(5)···N(15)	6.742	N(11)···N(17)	3.508

Symmetry code: (i) $-x, 1-y, 1-z$; (ii) $-x, 2-y, 1-z$; (iii) $x, y+1, z$; (iv) $1-x, 1-y, 1-z$.

Compound (6)

N(5*a*)···N(11*b*^{i})	3.212	N(17*a*)···N(13*b*^{ii})	2.887
N(5*b*)···N(11*a*^{i})	3.058	N(17*b*)···N(13*a*^{ii})	2.986
N(5*a*)···N(11*a*)	7.093	N(5*b*)···N(11*b*)	6.874
N(5*a*)···N(13*a*)	9.139	N(5*b*)···N(13*b*)	8.999
N(5*a*)···N(15*a*)	7.643	N(5*b*)···N(15*b*)	7.589
N(5*a*)···N(17*a*)	9.574	N(5*b*)···N(17*b*)	9.679
N(11*a*)···N(3*a*)	2.303	N(11*b*)···N(13*b*)	2.299
N(11*a*)···N(17*a*)	4.611	N(11*b*)···N(17*b*)	4.608

Symmetry code: (i) $x, 1-y, \frac{1}{2}+z$; (ii) x, y, z.

Compound (7)

N(5)···N(11^{i})	3.100	N(17)···N(13^{ii})	2.938
N(5)···N(11)	6.993	N(5)···N(17)	9.620
N(5)···N(13)	9.023	N(11)···N(13)	2.306
N(5)···N(15)	7.585	N(11)···N(17)	4.599

Symmetry code: (i) $\frac{3}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z$; (ii) $-x, -y, -z$.

Compound (8)

N(17)···N(13^{i})	2.972		
N(5)···N(11)	6.563	N(5)···N(17)	9.906
N(5)···N(13)	8.837	N(11)···N(13)	2.296
N(5)···N(15)	7.630	N(11)···N(17)	4.571

Symmetry code: (i) $1-x, 2-y, -z$.

Compound (9)

N(5)···O(1w^{i})	2.848	O(1w)···N(11^{iii})	2.933
N(17)···N(13^{ii})	2.959		
N(5)···N(11)	7.413	N(5)···N(17)	10.013
N(5)···N(13)	9.319	N(11)···N(13)	2.297
N(5)···N(15)	8.052	N(11)···N(17)	4.587

Symmetry code: (i) $x, y, z-1$; (ii) $1-x, -1-y, 1-z$; (iii) $-x, -y, 1-z$.

dimers but this preference is by no means exclusive. The end-to-end hydrogen-bonded dimer has not been seen as yet in the methylthioethyl compounds. Centrosymmetric hydrogen-bonded dimers are also to be found in (3) but these involve an N(5)···N(13) intermolecular hydrogen bond and the N(11)···N(17) hydrogen bond links these dimers into sheets parallel to the *bc* plane. In (1) the intermolecular hydrogen bonds N(5)···N(13) and N(11)···N(17) link the molecules into sheets parallel to the *ab* plane without dimer formation and in (2) N(13)···N(17) is the only hydrogen bond and links the molecules into chains parallel to [110]. (4), (5) and (9) are hydrates (the water present in wet ethanol) but show no resemblance to cimetidine hydrate. In (4) and (5) the water solvent links the dimers to form a three-dimensional hydrogen-bonded network and in (9) to form sheets. In (6) the dimers are linked by N(5)···N(11) hydrogen bonds into chains by the formation of units of the type found in (3). Molecules (6*a*) and (6*b*) alternate along the chain. In (7) the hydrogen bond N(5)···N(11) links the dimers into chains in the direction of the **n** glide without the formation of the additional dimer units found in (3). In (8) there is no further hydrogen bonding of the dimers.

Discussion and conclusion concerning biological activity

Torsion angles in the chain linkages

The molecular conformations of the H_2 antagonists reported here, together with those of antagonists previously reported, can be described in terms of two rigid planar fragments containing heteroatoms which are connected by a flexible methylthioethyl or butyl linkage. The conformational behaviour of this flexible chain will have a strong influence on the relative dispositions of the functional groups of the pyridyl and cyanoguanidine residues and in turn could have a significant influence on the biological activity.* Further, the steric bulk and disposition of the substituents at the pyridyl residue may influence the conformation of the flexible chain. The replacement of the CH_2 group in the butyl chain of burimamide by S to give the methylthioethyl chain of metiamide and then cimetidine, was described as an isosteric substitution (Black, Durant, Emmett & Ganellin, 1974) that would affect electronic properties without changing the molecular stereochemistries. If the substitution of CH_2 by S were truly isosteric, as first postulated, then it might be expected that the pairs of compounds (1) and (4), (2) and (6), and (3) and (8) would, when crystallized from the same solvents under the same conditions, form isostructural crystals. These conditions were only satisfied by (3) and (8) which are crystallized from the same solvent and the crystals are not isostructural. The crystals obtained for (1) and (4) and (2) and (6) are also not isostructural but they were obtained from different solvents so differences in crystal structure might be expected particularly in view of the prevalence of polymorphism in the cimetidine family of compounds.

In the crystal structures previously reported the distribution of torsion angles for the two types of linkages follows the pattern observed in the present work. In the thioether-chain linkages the first torsion angle (5—6—7—8) spreads 20° or so about 100° suggesting that these molecules have a shallow minimum potential at about this value. In contrast, those antagonists with a butyl chain have torsion angles lying about 0, 90 or 180°. Further contrasts are observed in the torsion angles about the sulfur atoms in the thioether-containing chains and their equivalent in the butyl chains (6—7—8—9 and 7—8—9—10). With the exception of cimetidine monohydrate (Kojić-Prodić, Ružić-Toroš, Bresciani-Pahor & Randaccio, 1980), the moduli of these two torsion angles in the thioether-containing antagonists all lie between 60 and 90°, whereas those for the butyl-containing antagonists almost invariably lie very close to 180°. Infrared studies have shown that in solution intramolecular hydrogen bonds occur in thiaburimamide, metiamide, cimetidine and (1) (Mitchell, 1980). In the reported crystal structures of thiaburimamide, metiamide and cimetidine these molecules may adopt a folded conformation in which an intramolecular hydrogen bond is present. However, in contrast (1) [and (2) and (3)] have more extended conformations in the crystal which show neither intramolecular hydrogen bonding nor the folded structure of cimetidine monohydrate. The methoxy- and bromo-substituted compounds (2) and (3) are very similar in overall shape giving a very good fit when superimposed. (1) is very different in shape to the two substituted compounds primarily because the torsion angle 7—8—9—10 is of a similar magnitude but of opposite sign. However, a van der Waals energy calculation, performed using *MODEL* (Davies, 1983), suggests that the sign of this torsion angle can be reversed with almost no change in energy. Both (6) and (7), which have identical substituent size (*STERIMOL*) parameters (Verloop, Hoogenstraaten & Tipker, 1976), have almost exactly superimposable molecular conformations with the butyl chains at right angles to the ring planes but different crystal structures. For (5) and (8) similar substituent *STERIMOL* parameters are associated with conformational similarities.

The variety of torsion angles found in the molecular structures of H_2 antagonists in the solid state confirms that these are very flexible molecules and suggests that replacing a methylene group by a thioether linkage increases the tendency of the chain to fold. This is also evidence to suggest that the conformations of the antagonists are sensitive to their environment. However, a comparison of molecular conformation in the crystal indicates that there are certain values for torsion angles in the four-atom chain which necessarily occur in low-energy conformations but the crystallography does not suggest any possible active conformations.

* The biological activity was determined from the H_2-antagonist response of the guinea pig atrium.

Use of potential calculations

In order to investigate the possibility that a common low-energy conformation might exist for all active antagonists, van der Waals (VDW) repulsion energy calculations were used. (A prior assessment of the results of these calculations and others using a full molecular-mechanics force field indicated that the latter, though very much more expensive, were not significantly better.) These antagonists have five conformationally flexible torsion angles which all lie in the chain linkage. In order to map out the whole of conformational space accessible to each molecule it is necessary to systematically modify one torsion angle at a time while calculating the VDW energy. A step of 30° about each torsion angle seemed a reasonable compromise allowing an adequate sampling of conformational space with a minimum of increments. Each structure, therefore, would result in 12^5 (248 832) calculations (a computing time in excess of 24 h on a VAX 11/750) and so a further reduction in the complexity of the calculation was sought. Although the presence of the sulfur in the antagonist chain increases the flexibility of the molecule the variation in crystal structure torsion angles about the sulfur is fairly small and well defined. Therefore, as a first approximation, basing the starting geometry on the crystal structures, only the two torsion angles about the sulfur were varied. These calculations suggest that the first sulfur torsion angle prefers to lie at about 60° with a spread of 15° whereas the other sulfur torsion angle in each case lies between 67 and 127°. Furthermore the latter range seems to be subdivided into two groups, one lying around 84.4° with a spread of 12.2° and the other about 117.6° with a spread of 6.0°. These values are consistent with those observed over a wide range of crystal structures. The two sulfur torsion angles were set to their minimum energy values and the other three torsion angles in each molecule were varied.

The resulting 12 lowest energy conformations were then investigated using the *MINIMISE* routine (Davies, 1983) in the program *MODEL*. The most significant feature of this analysis is that after energy minimization there is a very wide variety of conformations which suggest that many conformations attainable by the thioether antagonists may also be achieved by the butyl analogues. Indeed none of the energy-minimized butyl antagonists favoured a completely extended *trans* structure and the thioether-containing (3) minimized to the same conformation as the butyl chain (6).

Unfortunately, in the process of this analysis it became clear that many very different sets of torsion angles could exist for the same molecule with energies differing by less than 1 kcal mol^{-1}. For example (5) could equally adopt either of the following two forms:

1-2-3-4 (°)	3-4-5-6 (°)	4-5-6-7 (°)	5-6-7-8 (°)	6-7-8-9 (°)	Energy (kcal mol^{-1})
106.6	136.5	-164.2	63.4	74.9	571.87
102.2	142.0	-176.1	142.8	-74.7	571.84

The lack of deep energy minima together with the insensitivity of the energy calculations themselves clearly make any attempt to obtain a common low-energy active conformation impossible.

Any potential interaction between receptor and substrate is likely to be as a result of the substrate being of a conformational shape where certain atoms (probably heteroatoms) are orientated so as to interact, possibly by hydrogen bonding, with particular groups at the receptor site. It could be argued, therefore, that the individual torsion angles may not be of overriding importance; rather it may be more important to consider the interatomic distances between heteroatoms and, if followed logically to its conclusion, the direction in which the lone pairs of electrons or H atoms belonging to such heteroatoms are orientated.

In order to pursue this possibility, the variation of potential energy with N(5)···N(11) separation distance was investigated, for each antagonist, by first optimizing the two torsion angles about the sulfur and then rotating about the three remaining chain linkage bonds in steps of 30° and calculating the separation at each step. For each molecule a plot of energy *versus* separation distance was produced where each point represented the energy and N(5)···N(11) separation distance for a specific conformation. A bounding curve was drawn around the points on each plot to separate the accessible conformational space from the inaccessible space as detailed in Fig. 2. The bounding curves only for the conformational space of 14 molecules displaying varying degrees of antagonist activity are shown in Fig. 3.

In the H_2-antagonist crystal structures, many molecules containing butyl-chain linkages assume an extended struc-

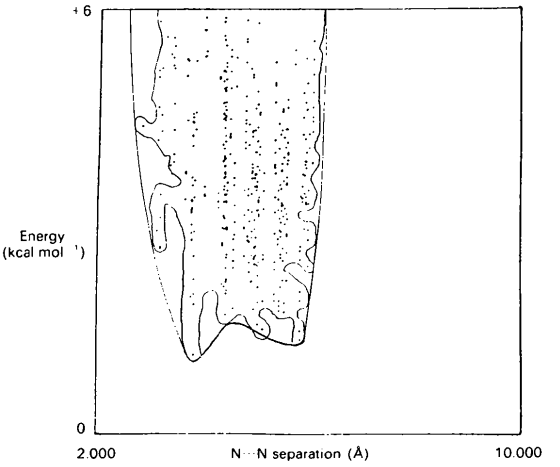


Fig. 2. Points in the low-energy conformational space of (1), with a computer-drawn bounding curve and outside that a simplified hand-drawn curve which attempts to join the principle headlands and smooth out deeply re-entrant features. Each point shows the energy (1 kcal = 4.18 kJ) of a molecular conformation *versus* the N(5)···N(11) separation distance for that conformation. Although the relative energies of the various conformations are significant, the absolute values may be misleading.

ture where the N(5)···N(11) separation for the more active molecules can be as large as 7.09 Å (6). In contrast, the results found from the conformational energy calculations suggest that the most stable antagonist conformations are those where the molecule folds rather than where it assumes an extended structure. Fig. 3 shows that those molecules with high antagonist activity have many low-energy conformations with N(5)···N(11) separations of between 3 and 5 Å, whereas those antagonists with lower activity do not. Indeed some particularly active antagonists such as (3) and (6) appear to have no low-energy conformations where the N(5)···N(11) separation lies outside these limits. In contrast (9), which has a fairly low activity, has almost no low-energy conformations where the separation distance falls below 5 Å. A similar situation is found for the separation distances of N(5) from the hydrogen attached to N(11). Once again the more active compounds have a greater number of low-energy conformations at small separation distances than the less active compounds. This time the majority of energy conformations for active molecules lie between 3 and 6 Å. The range of N(5)···N(11) separation distances available in low-energy conformations of more active H_2 antagonists is the same as the range of N···N separations available to histamine. This suggests that both histamine and the antagonists studied may act at a common site and by a similar mechanism.

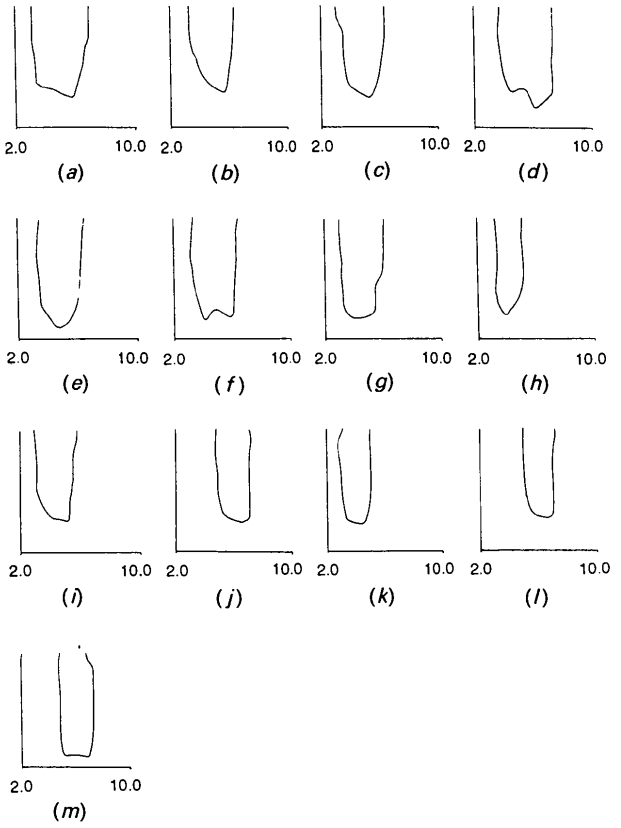


Fig. 3. Hand-drawn bounding curves analogous to that in Fig. 2 for (*a*) thiaburimamide, (*b*) metiamide, (*c*) cimetidine, (*d*) 1-{2-[(4-methyl-5-imidazolyl)methylthio]ethylamino}-1-methylamino-2-nitroethene, (*e*) ranitidine, (*f*) (1), (*g*) (2), (*h*) (3), (*i*) (4), (*j*) (5) (*k*) (6), (*l*) (8) and (*m*) (9).

It is concluded that in any interaction with a biological receptor it is unlikely that the molecule will be present in a conformation with an intramolecular hydrogen bond or in a conformation in which the pyridyl and cyanoguanidine planes are parallel and overlap as observed in cimetidine hydrate. If either of these conformations represented a substantial potential-energy minimum for the molecules it would be expected that they would be represented in the sample of the nine different but closely related compounds whose crystal structures have been determined. Further, it is reasonable to expect that any interaction with the receptor will involve hydrogen bonding to the pyridyl nitrogen N(5) and to N(17) and either N(11) or N(13), and that the hydrogen bonds to N(17) and N(11) or N(13) will be parallel and coplanar. Also it is expected that the active conformation of an H_2 antagonist will require an N(5)···N(11) separation in the region of 5 Å. These conclusions appear to be in conflict with those of Holtje & Batzenschlager (1990).

Experimental

All samples were prepared at SmithKline Beecham Research and were characterized by elemental analysis, proton NMR and infrared and mass spectrometry. The crystals were grown in Oxford and after preliminary X-ray precession and Weissenberg photography the X-ray data were collected with an Enraf-Nonius CAD-4 diffractometer following the manufacturer's recommended procedures. For each of the structures the three reference reflexions showed no significant variation in intensity. Cu $K\alpha$ radiation (1.5418 Å) was used for (1), (4), (5) and (7) and Mo $K\alpha$ (0.71069 Å) for the rest. The crystal data and some details of the data collection and structure solution are given in Table 4. Unit-cell dimensions and the orientation matrix were determined by the least-squares best fit to the setting angles of 25 reflexions with $20 < \theta < 30°$. The intensities were measured using an ω-2θ scan and were taken as observed when $I > 3\sigma(I)$. The data were corrected for Lorentz and polarization effects and for (3), (4), (5), (8) for absorption. All calculations were carried out on a VAX 11/750 computer using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) for direct methods and *CRYSTALS* (Watkin, Carruthers & Betteridge, 1985) for all other calculations. Atomic scattering factors and corrections for anomalous dispersion were taken from Cromer & Waber (1974). The structures of (3) and (4) were determined by Patterson heavy-atom methods and the rest by direct methods. Only in the solution of (7) were any particular problems encountered. Unless stated otherwise the structures were refined by a two-block (space and thermal parameters) approximation to the normal matrix.

$\Sigma w|F_o - F_c|^2$ was minimized. H atoms were located in the difference electron density. Once located they were placed geometrically and in the refinement the shifts in their space parameters were equivalenced to those of the atom to which they were bonded. Their isotropic temperature factors were refined as independent variables. A truncated Chebyshev polynomial weighting scheme (Carruthers & Watkin, 1979) was used and the appropriate coefficients are given in Table 4. Extinction and anomalous dispersion were included.

(1) *N-Cyano-N'-methyl-N''-{2-[(2-pyridyl)methylthio]-ethyl}guanidine.* Crystals were obtained as colourless tablets from cyanomethane.

(2) *N-Cyano-N'-methyl-N''-{2-[(3-methoxy-2-pyridyl)-methylthio]ethyl}guanidine.* Crystals were obtained as colourless tablets by the slow cooling of a saturated solution in ethanol.

(3) *N-Cyano-N'-methyl-N''-{2-[(3-bromo-2-pyridyl)-methylthio]ethyl}guanidine* Crystals were obtained as colourless tablets by the slow cooling of a saturated solution in ethanol. The final electron-density map showed three peaks of 0.5 e $Å^{-3}$ lying 0.85-1.0 Å from the Br atom.

(4) *N-Cyano-N'-methyl-N''-[4-(2-pyridyl)butyl]guanidine.* Colourless crystals were prepared by slowly cooling a saturated solution in dioxane. The subsequent structure analysis showed these crystals to be a monohydrate. The space group *I2/c* was preferred to the alternative *C*-centred space group because the monoclinic angle was closer to 90°. The structure analyses proceeded routinely and the H-atom space parameters were refined. The water molecule was clearly identified and its H atoms located.

(5) *N-Cyano-N'-methyl-N''-[4-(3-methyl-2-pyridyl)-butyl]guanidine.* Colourless crystals were obtained by the slow cooling of a saturated solution in cyanomethane. Again the structure analysis showed the crystals to be a monohydrate. The water molecule was clearly identified from its hydrogen-bonding environment and its H atoms were observed in the difference electron density.

(6) *N-Cyano-N'-methyl-N''-[4-(3-methoxy-2-pyridyl)-butyl]guanidine.* The colourless crystals were obtained by the slow cooling of a saturated solution in cyanomethane. The space group *I2/c* was preferred to its C-centred equivalent because the latter has a monoclinic angle of 137°. The asymmetric unit contains two independent molecules. A *MULTAN*80 calculation gave an *E* map in which all atoms of both molecules could be identified.

(7) *N-Cyano-N'-methyl-N''-[4-(3-fluoro-2-pyridyl)-butyl]guanidine.* Colourless crystals were obtained from a slowly cooled saturated solution in cyanomethane. The systematic absences approximated to space group $P2_1/n$ but there were ten reflexions $20l$ for which $l = 2n + 1$. Intensity statistics suggested a centrosymmetric space group but, although the structure was readily solved by *MULTAN*80 in space group $P2_1$ with two molecules in the asymmetric unit, a solution could not be obtained in space group $P2_1/n$. However, the solution in $P2_1$ had additional symmetry which was an excellent approximation to $P2_1/n$. The structure was refined in $P2_1$ and $P2_1/n$ and the results were indistinguishable by Hamilton's criteria. By comparison with other molecules in this series of structures the bond lengths obtained from the refinement in $P2_1/n$ are chemically much more acceptable than the solution in $P2_1$ and the solution in $P2_1/n$ is regarded as the better approximation. However, by comparison with the other structures it has a noticeably high *R* value. A riding model was used for the H-atom refinement.

(8) *N-Cyano-N'-methyl-N''-[4-(3-bromo-2-pyridyl)-butyl]guanidine.* Yellow crystals were obtained from the slow cooling of a saturated solution in ethanol. The structure was solved with ease. At the end of the refinement there were four peaks between 0.84 and 0.63 e $Å^{-3}$ all about 1 Å from the Br atom but elsewhere there were no significant maxima.

(9) *N-Cyano-N'-methyl-N''-[2-(5-methoxy-2-pyridyl)-butyl]guanidine.* Colourless crystals were obtained by slowly cooling a saturated ethanol solution. Surprisingly, *MULTAN*80 calculations gave the chicken-wire features usually associated with multi-ring aromatics. Eventually a nine-atom fragment was identified that when used to phase an electron-density synthesis revealed the whole molecule. Again the crystals were found to be a monohydrate. The water molecule was characterized by its hydrogen-bonding environment and by the location of its H atoms.

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