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Structures of Histamine H_1-Receptor Antagonists Derived from the Cimetidine Group of Histamine H_2-Receptor Antagonists

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Abstract

The crystal and molecular structures of ten compounds with strong structural resemblances to the cimetidine group of histamine H_2-receptor antagonists, but exhibiting selective H_1-receptor antagonist activity, (1)–(7), or H_1 and H_2 activity (8)–(10), have been determined: (1) 2-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone trihydrobromide (temalastine), $C_{21}H_{27}BrN_5O^{3+}.3Br^-$, $M_r = 685.09$, triclinic, $P\bar{1}$, $a = 6.314$ (2), $b = 11.192$ (2), $c = 19.441$ (5) Å, $\alpha = 102.47$ (2), $\beta = 92.77$ (2), $\gamma = 103.28$ (2)°, $V = 1298.51$ Å^3, $Z = 2$, $D_x = 1.75$ g cm^{-3}, $\mu = 61.6$ cm^{-1}, $F(000) = 672$, $R = 2.93\%$ for 3208 independent reflexions. (2) 2-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-4-pyrimidone, $C_{14}H_{19}BrN_4O_2$, $M_r = 355.23$, monoclinic, $I2/a$, $a = 16.359$ (3), $b = 10.469$ (6), $c = 18.339$ (4) Å, $\beta = 90.90$ (2)°, $V = 3140.49$ Å^3, $Z = 8$, $D_x = 1.503$ g cm^{-3}, $\mu = 26.0$ cm^{-1}, $F(000) = 1176$, $R = 4.2\%$ for 1872 independent reflexions. (3) 3-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-4-amino-1,2,5-thiadiazole-1-oxide, $C_{12}H_{16}BrN_5OS$, $M_r = 358.26$, triclinic, $P\bar{1}$, $a = 14.295$ (2), $b = 12.447$ (2), $c = 9.917$ (2) Å, $\alpha = 95.77$ (2), $\beta = 113.86$ (2), $\gamma = 106.91$ (1)°, $V = 1495.18$ Å^3, $Z = 4$, $D_x = 1.59$ g cm^{-3}, $\mu = 50.96$ cm^{-1}, $F(000) = 728$, $R = 5.98\%$ for 5674 independent reflexions. (4) 3-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-4-benzylamino-1,2,5-thiadiazole-1-oxide, $C_{19}H_{22}BrN_5OS$, $M_r = 448.38$, monoclinic, $P2_1/c$, $a = 36.293$ (7), $b = 4.826$ (2), $c = 11.528$ (3) Å, $\beta = 96.91$ (2)°, $V = 2004.27$ Å^3, $Z = 4$, $D_x = 1.49$ g cm^{-3}, $\mu = 39.2$ cm^{-1}, $F(000) = 920$, $R = 12.1\%$ for 1945 independent reflexions. (5) 2-[3-(*N*-Benzyl-*N*-2-pyridylamino)propylamino]-4-pyrimidone, $C_{19}H_{21}N_5O$, $M_r = 335.4$, orthorhombic, *Pbna*, $a = 7.082$ (1), $b = 19.889$ (3), $c = 24.899$ (3) Å, $V = 3507.16$ Å^3, $Z = 8$, $D_x = 1.27$ g cm^{-3}, $\mu = 6.24$ cm^{-1}, $F(000) = 1424$, $R = 4.05\%$ from 2470 independent reflexions. (6) 3-[3-(*N*-4-Fluorobenzyl-*N*-2-pyridylamino)propylamino]-4-ethylamino-1,2,5-thiadiazole-1-oxide, $C_{19}H_{23}FN_6OS$, $M_r = 402.5$, monoclinic, $P2_1/n$, $a = 6.686$ (2), $b = 14.717$ (3), $c = 20.850$ (5) Å, $\beta = 97.83$ (2)°, $V = 2032.47$ Å^3, $Z = 4$, $D_x = 1.32$ g cm^{-3}, $\mu = 16.41$ cm^{-1}, $F(000) = 848$, $R = 8.5\%$ from 2484 independent reflexions. (7) 5-(6-Methyl-3-pyridylmethyl)-2-[3-(5,6,7,8-tetrahydro-8-quinolyl)propylamino]-4-pyrimidone, $C_{23}H_{29}N_5O_2$, $M_r = 407.5$, monoclinic, $P2_1/c$, $a = 14.966$ (2), $b = 16.075$ (2), $c = 9.1608$ (9) Å, $\beta = 99.158$ (8)°, $V = 2175.83$ Å^3, $Z = 4$, $D_x = 1.24$ g cm^{-3}, $\mu = 6.19$ cm^{-1}, $F(000) = 872$, $R = 5.3\%$ from 2784 independent reflexions. (8) 2-(4-Phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone, $C_{20}H_{26}N_4O_3$, $M_r = 370.5$, monoclinic, $P2_1/c$, $a = 8.040$ (4), $b = 21.279$ (4), $c = 11.404$ (2) Å, $\beta = 92.08$ (5)°, $V = 1949.68$ Å^3, $Z = 4$, $D_x = 1.26$ g cm^{-3}, $\mu = 0.93$ cm^{-1}, $F(000) = 792$, $R = 4.05\%$ from 3816 independent reflexions. (9) 2-[2-(3-Pyridylmethylthio)ethylamino]-5-(3-pyridylmethyl)-4-pyrimidone, $C_{18}H_{19}N_5OS$, $M_r = 353.4$, triclinic, $P1$, $a = 8.577$ (3), $b = 9.197$ (2), $c = 11.830$ (2) Å, $\alpha = 86.57$ (2), $\beta = 81.88$ (2), $\gamma = 69.83$ (2)°, $V = 867.2$ Å^3, $Z = 2$, $D_x = 1.35$ g cm^{-3}, $\mu = 2.04$ cm^{-1}, $F(000) = 372$, $R = 7.46\%$ from 3673 independent reflexions. (10) 2-[4-(3-Ethoxy-2-pyridyl)butylamino]-5-(3-pyridylmethyl)-4-pyrimidone, $C_{21}H_{25}N_5O_2$, $M_r = 379.5$, monoclinic, $P2_1/c$, $a = 8.451$ (2), $b = 19.522$ (4), $c = 12.564$ Å, $\beta = 106.78$ (3)°, $V = 1984.51$ Å^3, $Z = 4$, $D_x = 1.27$ g cm^{-3}, $\mu = 0.91$ cm^{-1}, $F(000) = 808$, $R = 4.36\%$ from 3908 independent reflexions. The relationship between activity as H_1-receptor histamine antagonists and conformation has been examined and it has been found that a predominance of low-energy conformations with distances between

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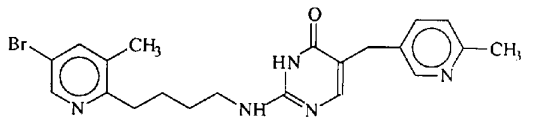
'aromatic' N atoms and those in the isocytosine or thiadiazole-1-oxide groups in the region 5.2–6.0 Å tend to correlate with H_1 activity in agreement with work by others on established H_1 antagonists.

Introduction

Since the identification of the histamine H_2 receptor (Black, Duncan, Durant, Ganellin & Parsons, 1972), a variety of compounds have been shown to be specific histamine H_2-receptor antagonists. Of these compounds a significant number, cimetidine (Brimblecombe, Duncan, Durant, Emmett, Ganellin & Parsons, 1975), ranitidine (Bradshaw, Brittain, Clitherow, Daly, Jack, Price & Stables, 1979), tiotidine (Yellin, Buck, Gilman, Jones & Wardleworth, 1979), famotidine (Yanagisawa, Hirata & Ishii, 1984) and oxmetidine (Brown, Blakemore, Durant, Emmett, Ganellin, Parsons, Rawlings & Walker, 1988) have the general form of a heterocyclic 'head' linked by a four-atom chain, often methylthioethyl, to a dipolar 'tail'. These compounds are both potent and highly selective in their action. Certain closely related compounds in which the heterocyclic 'head' is pyridine, the dipolar group is an isocytosine, as in oxmetidine, and the four-atom chain butyl, are active as both H_1 and H_2 antagonists (Cooper, Durant, Ganellin, Ife, Meeson & Sach, 1991). Exploitation of QSAR (quantitative structure activity relationships) studies on these compounds has lead to the generation of a series of compounds which have the same general characteristics, (heterocyclic head, four-atom chain and dipolar tail), but are specific and potent H_1 antagonists (Cooper *et al.*, 1991).

Here we report the crystal and molecular structures of a selection of these compounds, some, temalastine (1) and (2)–(7), are specific H_1 antagonists and others, (8)–(10), are active as both H_1 and H_2 antagonists.



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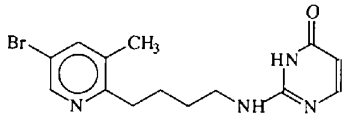

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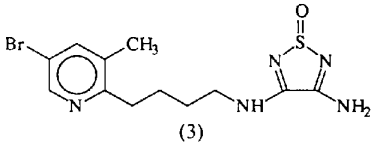

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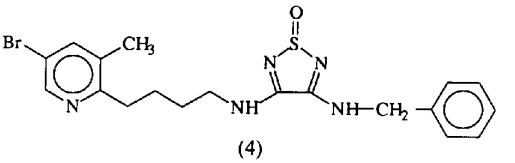

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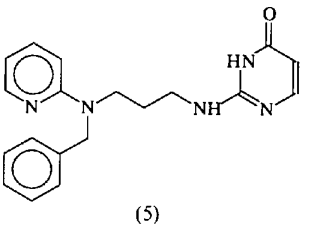

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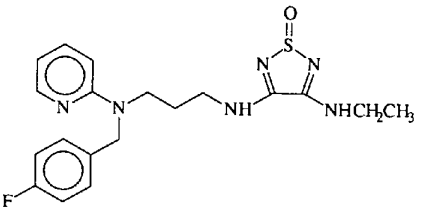

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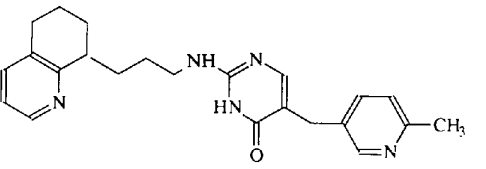

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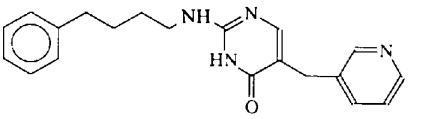

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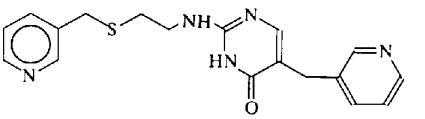

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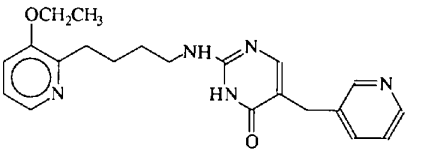


(10)

These structures, which were determined to gain insight into their conformational space and intermolecular interactions, are discussed together with an analysis of the conformations of these and other related H_1 antagonists, including the long established H_1 antagonists of the promethazine group. The selection of molecules for X-ray structure analysis was constrained by the availability of crystals of the required quality and is thus somewhat arbitrary. With the exception of (1), which is the hydrobromide

salt, all the molecules studied are the free bases. The free base is believed to be the biologically active form. In each molecule the heterocycle is a subst.-tuted pyridine and the dipolar groups are either isocytosines [also found in the H_2 antagonist oxmetidine (Brown *et al.*, 1988)] or 1,2,5-thiadiazole-1-oxides found in H_2 antagonists (Lumma, Anderson, Baldwin, Bolhofer, Habecker, Hirshfield, Pietruszkiewicz, Randall, Torchiana, Britcher, Clineschmidt, Denny, Hirschmann, Hoffman, Philips & Streeter, 1982; Algieri, Luke, Standridge, Brown, Partyka & Crenshaw, 1982). Compounds (1)–(4) and (7) have a four-C atom connecting chain, which in (7) is conformationally restricted, and (5) and (6) have propylamino connecting chains, and show a greater formal analogy to the 'classical' H_1 antagonists. These molecules contrast with the *N*-cyano-*N'*-methyl-*N''*-[4-(2-pyridyl)butyl]guanidines which are selective H_2 antagonists.

Experimental

All samples were prepared by SmithKline and French Research Ltd, and were characterized by elemental analysis, proton NMR and infrared and mass spectrometry. A guinea-pig ileum *in vitro* assay for H_1-receptor histamine antagonism and guinea-pig atrium *in vitro* assay for H_2-receptor histamine antagonism were carried out using the procedure described in Cooper *et al.* (1991).

X-ray structure analysis

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. The crystal data and some details of the data collection and structure solution are given in Table 1. The data were corrected for Lorentz and polarization effects and for (1), (2) and (4) also for absorption. All calculations were carried out on a VAX 11/750 computer using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) or *DIRDIF* (Beurskens, Bosman, Doesburg, Gould, van den Hark, Prick, Noordik, Beurskens, Parthasarathi, Bruins Slott & Haltiwanger, 1985) [for (3)] 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) and (9) were any particular problems encountered. Unless stated otherwise: (*a*) The structures were refined by the full-matrix least-squares method using only observed reflections (Table 1) and minimizing $\sum w(F_{obs} - F_{calc})^2$ for the observed reflections. (*b*) The H atoms were located in the difference electron-density syntheses then either placed geometrically or at the position indicated by the electron-density maximum. (*c*) H-atom space parameters were refined with a riding model except where stated otherwise, and the distance from the H to the heavy atom to which it is bonded was fixed at 1.0 Å. (*d*) The H-atom isotropic temperature factors were refined as independent variables. (*e*) A truncated Chebyshev polynomial weighting scheme (Carruthers & Watkin, 1979) was used and the appropriate coefficients are given in Table 1. (*f*) Extinction and anomalous dispersion were included. (*g*) Atomic scattering factors and corrections for anomalous dispersion were taken from *International Tables for X-ray Crystallography*, Volume IV (Cromer & Waber, 1974).

(1) 2-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-5-(6-methyl-3-pyridylmethyl])4-pyrimidone (Temalastine). Crystals of (1) were grown from a methanolic solution of the free base with hydrobromic acid. Direct methods (*MULTAN*80, Main *et al.*, 1980) in $P\bar{1}$ located four heavy atoms, assumed to be Br, and the other non-H atoms were located by a difference electron-density synthesis. A final difference Fourier revealed a number of peaks of 0.38–0.58 e $Å^{-3}$, close (~ 1 Å) to Br atoms. All the peaks not close to Br atoms were of lesser height.

(2) 2-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-4-pyrimidone. Pyrimidal crystals of (2) were grown by slow cooling of an ethanolic solution. The position of the Br atom was determined using a Patterson map in *I*2/*a* (No. 15). A difference Fourier located all other non-H atoms, including one some distance from the main molecule, which was assumed to be the O atom of a water molecule. Some of the H atoms were input in found positions, others in calculated positions. Intermolecular distances indicated there was a hydrogen bond across the centre of inversion, between equivalent N atoms in the isocytosine ring so necessarily both tautomers of isocytosine are present in the crystal, and H atoms were placed on both isocytosine ring N atoms with occupancies of 0.5.

(3) 3-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-4-amino-1,2,5-thiadiazole-1-oxide. Brick-shaped crystals of (3) were grown by slow evaporation of a solution in acetonitrile. A Patterson map revealed the Br atom positions, and these were input into *DIRDIF* (Beurskens *et al.*, 1985), assuming the space group to be $P\bar{1}$. Full-matrix least-squares refinement of positions and anisotropic temperature factors on Br atoms, isotropic on other atoms, converged at $R = 0.139$, $wR = 0.136$. There are two molecules in the asymmetric unit. When the model was made fully

Table 1. *Crystallographic data and experimental parameters*

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Formula	$C_{21}H_{27}BrN_5O^{3+}.3Br^+$	$C_{14}H_{19}BrN_4O_2$	$C_{12}H_{16}BrN_5OS$	$C_{19}H_{22}BrN_5OS$	$C_{19}H_{21}N_5O$	$C_{19}H_{23}FN_6OS$	$C_{23}H_{29}N_5O_{2.7}$	$C_{20}H_{26}N_4O_3$	$C_{18}H_{19}N_5OS$	$C_{21}H_{25}H_5O_2$
M_r	685.09	355.23	358.26	448.38	335.4	402.5	407.5	370.5	353.4	379.5
Crystal class	Triclinic	Monoclinic	Triclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic
a (Å)	6.314 (2)	16.359 (3)	14.295 (2)	36.293 (7)	7.082 (1)	6.686 (2)	14.966 (2)	8.040 (4)	8.577 (3)	8.451 (2)
b (Å)	11.192 (2)	10.469 (6)	12.447 (2)	4.826 (2)	19.889 (3)	14.717 (3)	16.075 (2)	21.279 (4)	9.197 (2)	19.522 (4)
c (Å)	19.441 (5)	18.339 (4)	9.917 (2)	11.528 (3)	24.899 (3)	20.850 (5)	9.1608 (9)	11.404 (2)	11.830 (2)	12.564 (5)
α (°)	102.47 (2)	90	95.77 (2)	90	90	90	90	90	86.57 (2)	90
β (°)	92.77 (2)	90.90 (2)	113.86 (2)	96.91 (2)	90	97.83 (2)	99.158 (8)	92.08 (5)	81.88 (2)	106.78 (3)
γ (°)	103.28 (2)	90	106.91 (1)	90	90	90	90	90	69.83 (2)	90
V (Å^3)	1298.51	3140.49	1495.18	2004.27	3507.16	2032.47	2175.83	1949.68	867.2	1984.51
Space group	$P\bar{1}$	$I2/a$	$P\bar{1}$	$P2_1/c$	$Pbna$	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P1$	$P2_1/c$
Z	2	8	4	4	8	4	4	4	2	4
D_x (g cm^{-3})	1.75	1.503	1.59	1.49	1.27	1.32	1.24	1.26	1.35	1.27
$F(000)$	672	1176	728	920	1424	848	872	792	372	808
Crystal size (mm)	0.5 × 0.25 × 0.15	0.75 × 0.5 × 0.4	0.75 × 0.5 × 0.4	0.15 × 0.1 × 0.6	0.5 × 0.3 × 0.1	0.45 × 0.3 × 0.1	0.4 × 0.25 × 0.13	1.1 × 0.67 × 0.35	0.6 × 0.5 × 0.4	0.3 × 0.4 × 0.7
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (cm^{-1})	61.6	26.0	50.96	39.2	6.24	16.41	6.19	0.93	2.04	0.91
$\sin(\theta/\lambda)_{max}$ (Å^{-1})	0.628	0.65	0.626	0.61	0.63	0.62	0.6	0.62	0.639	0.617
No. of reflexions measured	6121	5073	7674	3743	5738	5633	4960	5195	4786	5474
No. of independent reflexions	3208	1872	5674	1945	2470	2484	2784	3816	3673	3908
h_{min}–h_{max}	−7–7	−18–20	−17–15	−44–43	−1–8	−8–8	−17–17	−9–9	−10–10	−10–9
k_{min}–k_{max}	−13–13	−1–13	−15–15	−1–5	−1–24	−1–17	−1–19	−1–26	−11–11	−1–23
l_{min}–l_{max}	−1–23	−1–23	−1–12	−1–14	−1–31	−1–25	−1–10	−1–26	−1–15	−1–14
R_σ (%)	1.35	1.96	1.68	7.74	1.6	2.23	2.1	3.26	1.27	4.34
R (%)	2.93	4.2	5.98	12.1	4.05	8.5	5.3	4.05	7.46	4.36
wR (%)	3.67	5	6.86	12.8	5.48	10.5	6.9	5.02	5.84	5.38
Σ (shift/e.s.d.)^2	0	0	0.52	0.03	0	0.16	0.17	1.06	2.1	2.2
$\Delta\rho_{max}$ (e Å^{-3})	0.58	0.44	0.13	0.29	0.25	0.23	0.44	0.14	0.4	0.17
Weights	51,65,21	574,789,241	11,5.9,7.8,1.4	10,3.1,7.6,0.47	107,139,34.7	7.7,4.2,5.2	88.7,107,23.8	13.5,16.2,2.4	-	11.9,15.7,4.5
No. of parameters	285	206	414	250	249	260	290	293	340	355
No. of restraints	12	0	20	77	0	83	13	7	150	46

anisotropic, the thermal ellipsoids of the atoms in the thiadiazole ring of each molecule became very elongated perpendicular to the ring planes. This appeared to indicate the presence of two conformations of thiadiazole ring for each molecule in the asymmetric unit. This disorder was modelled by splitting the S, O and N atom sites in each ring and inputting an atom with occupancy 0.5 at the foci of each thermal ellipsoid. For each molecule the atomic sites within each distinct conformation were given equal occupancies and the sum of occupancies of the two conformations was unity so that there was only one least-squares occupancy parameter for each disordered pair of thiadiazole rings. H atoms were input in calculated positions and the shifts in H atom positions were restrained to equal those of the atoms they were attached to. Refinement of positions and temperature factors for all atoms, and occupancies of the disordered atoms was continued. All non-H atoms were refined anisotropically, except for the fractional N and O atoms. As the refinement progressed the different conformations of the thiadiazole ring showed differences in bond lengths within the ring. Since there seemed to be no chemical reason for these differences, restraints were applied to make corresponding bond lengths equal. Isotropic temperature factors on H atoms were included and chemically similar H atoms were given equivalent temperature factors when some values became rather large.

(4) 3[4-(5-Bromo-3-methylpyrid-2-yl)butylamino]-4-(benzylamino)-1,2,5-thiadiazole-1-oxide. Crystals, thin needles, of (4) were grown by slow evaporation of a solution in ethanol. These crystals were poor diffracters and the average intensity of the data set collected was undesirably low. *MULTAN*80 (Main *et al.*, 1980), using default options, revealed most of the non-H atoms and after a cycle of Fourier refinement the remaining atoms were obtained. The model was refined isotropically to $R = 0.171$, $wR = 0.187$, then anisotropically to convergence at $R = 0.127$, $wR = 0.152$. The geometry of the phenyl and pyridyl rings was examined and appeared to be markedly different from that found in better resolved structures. In an attempt to improve the structure, restraints were applied, making the rings planar and restraining the thermal-vibration components along each bond to be equal for both atoms in the bond. The phenyl ring was made symmetrical by restraining opposite angles to be equal. In addition, restraints on bond lengths of 1.39 Å for phenyl C—C, 1.38 Å for pyridyl C—C and 1.34 Å for pyridyl C—N bonds were input. Isotropic temperature factors on H atoms were included in refinement and chemically similar H atoms were given equivalent temperature factors when some values became rather large. An alternative absorption correction, *DIFABS* (Walker & Stuart, 1983) was applied to the structure factors from the best isotropic model. However, there was little improvement and final residuals were $R = 0.115$ and $wR = 0.123$.

(5) 2-[3-(*N*-Benzyl-*N*-2-pyridylamino)propylamino]-4-pyrimidone. Crystals, thin plates, of (5) were grown by slow evaporation of a solution in ethanol. H atoms were placed in calculated positions. Calculated intermolecular distances revealed a hydrogen-bond contact between equivalent N atoms in isocytosine rings so that both tautomers of isocytosine were present in the crystal. H atoms were placed on both N atoms and given an occupancy of 0.5.

(6) 3-[3-(*N*-4-Fluorobenzyl-*N*-2-pyridylamino)propylamino]-4-ethylamino-1,2,5-thiadiazole-1-oxide. The platy crystals were grown by slow evaporation of a solution in ethanol. Full-matrix anisotropic refinement converged to $R = 0.126$, $wR = 0.138$.

(7) 5-(6-Methyl-3-pyridylmethyl)-2-[3-(5,6,7,8-tetrahydro-8-quinolyl)propylamino]-4-pyrimidone. Crystals of (7) were grown by slow evaporation of a solution in acetonitrile. *MULTAN*80 (Main *et al.*, 1980) gave most of the non-H atoms and one cycle of Fourier refinement revealed the missing non-H atoms, including the O atom of a water of crystallization. It became apparent there was disorder in the saturated section of the fused ring system with at least two conformations of the ring present. To model this disorder the sites concerned were split, inputting an atom with occupancy 0.5 at each focus of the ellipsoids. Refinement of positions and temperature factors of all atoms, and occupancies of the disordered atoms, was continued with the disordered atoms handled as for (3). Bond length and angle restraints based on the observed structure of methyl-(15*S*)-7,8,16-trihydroxy-serrulatan-19-oate (Hall, Raston, Skelton & White, 1981) were applied.

(8) 2-(4-Phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone. Needle-shaped crystals of (8) were prepared by slow evaporation from ethanol. At $R = 8.6\%$ a difference Fourier revealed the positions of all the H atoms, including 'half' atoms at N(13) and N(18), respectively. After refinement the temperature factors of the H atoms attached to N(13) and N(18) were 0.12, which seemed not unreasonable since both N atoms could not be protonated at the same time if the molecule was to remain neutral. The sum of the occupancies of the two H atoms attached to N(13) and N(18) was fixed at unity and further refinement gave final values close to 0.5. During the final stages of refinement the data were corrected for an extinction effect.

(9) 2-[2-(3-pyridylmethylthio)ethylamino]-5-(3-pyridylmethyl)-4-pyrimidone. Crystals of (9) were obtained by slowly cooling a saturated solution in *n*-propanol. Using default values, *MULTAN*80

(Main *et al.*, 1980) produced a solution in $P\bar{1}$ which contained peaks for all the atoms in the molecule. A cycle of Fourier refinement was followed by four cycles of full-matrix isotropic refinement until the model converged at $R = 25.1\%$. An agreement analysis at this point indicated that the low-angle data agreed fairly well (approximately 15%) but that agreement within the high-angle data was much poorer (about 30%). All atoms in the thioether chain had large isotropic temperature factors, the most extreme being C(9) where the temperature factor had risen to 0.154. Despite the evidence suggesting that there was something wrong with the isotropic model the molecule was gradualy turned anisotropic and refined until convergence at 0.156. By this point the thermal ellipsoids belonging to the atoms in the thioether chain had become unreasonably elongated normal to the chain. In particular, the magnitude of the three principal axes of the ellipsoids in C(9) and C(10) became 0.04, 0.06, 0.75 and 0.04, 0.06, 0.34, respectively. Various constrained anisotropic refinements failed to improve the model significantly.

The structure was assumed to be either disordered in $P\bar{1}$ or in $P1$ with a pseudo-symmetry centre between the two molecules. In an attempt to keep the model as simple as possible the latter possibility was considered first. The model chosen was derived by generating two molecules for which all atoms except those in the thioether chain were related by a pseudo-inversion centre. The differing thioether chains were derived from examination of the difference electron density synthesis for the model in $P\bar{1}$. After several cycles, alternating constrained least-squares and Fourier refinement of the chain, the difference electron density suggested that in $P1$ the S atoms in both molecules were still disordered between two sites with occupancies of 0.8 and 0.2. Again, the thioether chains were refined alternating cycles of constrained least-squares and Fourier refinement. Individual isotropic temperature factors were assigned except for the S atoms of 0.8 occupancy which were given a common anisotropic temperature factor and the 0.2 occupancy S atoms which were given a common isotropic temperature factor. When the refinement converged at $R = 15.1\%$ the H atoms were placed geometrically and, as refinement progressed, more of the non-H atoms were given anisotropic temperature factors until all were anisotropic except the two S atoms of 0.2 occupancy. In the final refinement the H atoms were given one overall temperature factor and during the last cycle of refinement corrections were made for extinction effects. Restraints were included in all cycles of refinement; however, when they were removed (except for those fixing the origin), a further cycle of refinement produced little change in the model. The final model gave an agreement with the low-angle data which was substantially better than the agreement at high angles. The choice of spacegroup $P1$ is believed to be justified because it leads to a self-consistent pattern of hydrogen bonds and to a self-consistent pattern of bond lengths and angles within the isocytosine residues.

Further marginal improvements might have been possible but perhaps the best description is in terms of a rigidly held pyridyl group linked to a rigidly held isocytosine group by a flexible three-atom chain, —S—CH_2—CH_2—, with a number of different conformations randomly distributed between different molecules in the crystal.

(10) 2-[4-(3-Ethoxy-2-pyridyl)butylamino]-5-(3-pyridylmethyl)-4-pyrimidone. Colourless crystals of (10) were obtained by slowly cooling a solution of the sample in methyl cyanide. All H atoms were found in a difference electron-density synthesis and treated as riding. A secondary extinction correction was applied.

Energy calculations

Most of the calculations used the molecular-modelling package *COSMIC* (Vinter, Davis & Saunders, 1987). The input conformations came from the crystal structures where available, or were built up using the *COSMIC DRAW* facility. First, each molecule was input to a molecular-mechanics energy minimizer to relieve any strain in the initial conformation. The conformational space of the molecules was then searched by the sequential bond-rotation minimizer. This changes the torsion angles about each bond in turn by a specified increment and evaluates the energy at each step. No relaxation of the molecule is allowed. Conformations are rejected by the program if they are higher in energy than the lowest energy conformation by a specified amount. When all the torsion angles have been adjusted, a new initial conformation is selected at random and the process repeated. The number of 'randomizations' can also be chosen by the user. When the whole procedure is finished, the 100 lowest-energy conformations are retained.

In general, the method gives good results for unstrained molecular systems. In this treatment, the energy limit above minimum was 5 kcal mol^{-1}, the number of randomizations was 20 and the increment for bond rotation was 15°. The program's arbitrary maximum of 100 conformations within the energy limits was generated for all the molecules, except triprolidine (15), for which 43 were generated, *cis*-triprolidine, which produced 53, and cyproheptadine, for which only two were output. The *COSMIC* sequential bond-rotation routine does not rotate about bonds within ring systems and consequently, in cyproheptadine, only the torsion angle about the

double bond attached to the piperidine ring was altered.

A more representative picture of conformational space might be obtained if only the local-energy minimum conformers are studied. If the 100 conformations output by *COSMIC* were minimized, far fewer different conformers result, since some conformations would relax to common geometries. Slightly higher energy conformations might then be retained in the low-energy group and the range of conformations increased. However, any arbitrary limit on the numbers of conformations is undesirable.

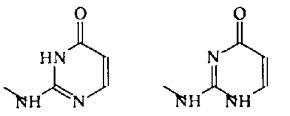
Results and discussion

X-ray structure analysis

For (1)–(10) the crystal data, atomic coordinates and molecular geometries are reported in Tables 1–5.* Figs. 1–10 show for each compound the atomic numbered asymmetric unit, molecular conformation and crystal packing. The location of the asymmetric unit, as defined by the parameters in Table 2, is indicated by the arrow. For clarity, in some diagrams the asymmetric unit has been rotated through a small angle so that the atoms are more clearly visible. The molecular structures are sufficiently diverse that a common atomic numbering scheme offered little advantage and some inconvenience. For each structure the refined H-atom positions do not differ significantly from those positions calculated from the skeletal geometry and atom type, and therefore the observed atomic coordinates for the H atoms are not given.

In compound (1), the antihistamine is present as the tripositive cation, that is protonated at all possible protonation sites, both pyridine groups and the isocytosine. The counter-ion is Br^- and each Br^- anion is in a proton/hydrogen-bond environment. Br(1) and Br(2) hydrogen bond only to one molecule and Br(3) hydrogen bonds to one molecule at x, y, z and a second at $1 + x, 1 + y, z$. There is no hydrogen bonding in the crystal other than the N—H···Br interactions.

The compounds (2), (5), (7), (8), (9) and (10) all contain neutral isocytosine groups, and have complex intermolecular hydrogen-bonded networks in which the formation of hydrogen-bonded isocytosine dimers is a common feature. Frequently in these structures the proposed centrosymmetric space groups fail to take into account the hydrogen bonding and the true structures must be either of lower symmetry or disordered. In (2) the isocytosine residue forms, through N(13), N(15) and O(17), hydrogen-bonded dimers with three hydrogen bonds, about pseudo-inversion centres at $\frac{3}{4},\frac{3}{4},\frac{3}{4}$, *etc.*, in space group *I*2/*a*. The dimers are formed from one molecule of each of the two tautomeric forms (11) and (12).



(11) (12)

Each solvent water forms three hydrogen bonds to give a pseudo-centrosymmetric arrangement in which the water binds a second water across the pseudo-inversion centres, $0,\frac{1}{2},0$, *etc.* and an O(17) and an N(20) of two neighbouring molecules (Table 3), thus linking the dimers into hydrogen-bonded sheets *via* the solvent water. While any sheet must be non-centrosymmetric, the sheets are so nearly symmetrical that they pack in a disordered array so that, on average, there is an apparent symmetry centre. The unsolvated crystals of (5) also are found to have similar pseudo-centrosymmetric dimeric pairs of molecules in which the two molecules, one in each tautomeric form, are held together across pseudo-inversion centres at $\frac{1}{2},0,\frac{1}{2}$, by three hydrogen bonds. These dimers are then linked to form chains by a hydrogen bond between two isocytosine N(25) atoms of molecules related by a pseudo-twofold axis parallel to *b* relating two molecules, one in each tautomeric form. Although each discrete chain must contain an ordered array of alternating tautomers, the chains pack in a random fashion to give the averaged structure seen by the X-ray diffraction experiment.

The crystal of (7) is a monohydrate in which four antihistamine molecules form hydrogen bonds to the water solvate. Two hydrogen bonds are to the pyridine N(1) and N(25) atoms of two different pyridine residues in two symmetry-related molecules, two are to the isocytosine N(14) and N(16) atoms of a third molecule. In this arrangement, N(1) and N(25) are necessarily unprotonated and N(14) and N(16) must be protonated so that the isocytosine residue must be in the cyclic-amide tautomeric form (11). N(21) does not partake in hydrogen bonding. Hydrogen-bonded dimers are not formed.

In crystals of (8), as in (2) and (5), the isocytosine residues again form hydrogen-bonded dimers through N(11), N(13) and O(15), about pseudo-inversion centres (0,0,0 *etc.* in $P2_1/c$) where again the two molecules of the dimers must be one in each of the two tautomeric forms, (11) and (12), of the

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71520 (272 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: HA0121]

Table 2. *Positional parameters and equivalent isotropic temperature factors with e.s.d.'s in parentheses*

U_{eq} is the square of the radius of the sphere that has the same volume as the thermal ellipsoid.

	x	y	z	U_{iso}/U_{eq}
Compound (1)				
Br(1)	0.82099 (8)	0.24977 (5)	0.59896 (3)	0.0434
Br(2)	1.52722 (9)	0.28295 (5)	0.94384 (3)	0.0430
Br(3)	1.2902 (1)	−0.24361 (6)	0.76472 (3)	0.0561
N(1)	0.8710 (6)	−0.2984 (3)	0.6473 (1)	0.0381
C(2)	0.6869 (8)	−0.3882 (4)	0.6455 (2)	0.0420
C(3)	0.5119 (7)	−0.3938 (3)	0.5991 (2)	0.0339
Br(4)	0.25241 (9)	−0.52110 (5)	0.59423 (3)	0.0463
C(5)	0.5279 (7)	−0.3103 (3)	0.5569 (2)	0.0363
C(6)	0.7204 (7)	−0.2180 (3)	0.5598 (2)	0.0341
C(7)	0.7351 (9)	−0.1232 (5)	0.5154 (3)	0.0482
C(8)	0.8968 (7)	−0.2134 (3)	0.6070 (2)	0.0316
C(9)	1.1158 (7)	−0.1221 (4)	0.6156 (2)	0.0363
C(10)	1.1282 (7)	−0.0050 (4)	0.6746 (3)	0.0351
C(11)	1.3485 (7)	0.0899 (4)	0.6824 (3)	0.0379
C(12)	1.3770 (8)	0.2066 (5)	0.7413 (3)	0.0390
N(13)	1.2071 (6)	0.2730 (4)	0.7301 (2)	0.0359
C(14)	1.1511 (7)	0.3584 (4)	0.7791 (2)	0.0312
N(15)	0.9809 (6)	0.4042 (4)	0.7624 (2)	0.0336
C(16)	0.8911 (8)	0.4856 (4)	0.8103 (3)	0.0339
O(17)	0.7238 (5)	0.5117 (3)	0.7907 (2)	0.0429
C(18)	1.0060 (7)	0.5296 (4)	0.8810 (2)	0.0315
C(19)	1.1791 (7)	0.4841 (4)	0.8954 (2)	0.0328
N(20)	1.2493 (6)	0.3986 (3)	0.8451 (2)	0.0326
C(21)	0.9195 (8)	0.6169 (5)	0.9368 (3)	0.0383
C(22)	0.9221 (7)	0.7418 (4)	0.9193 (1)	0.0347
C(23)	0.7405 (7)	0.7576 (4)	0.8830 (1)	0.0396
N(24)	0.7421 (6)	0.8664 (4)	0.8658 (1)	0.0433
C(25)	0.9136 (9)	0.9683 (5)	0.8813 (2)	0.0437
C(26)	0.894 (1)	1.0832 (6)	0.8579 (4)	0.0613
C(27)	1.0981 (8)	0.9558 (5)	0.9177 (2)	0.0464
C(28)	1.1019 (7)	0.8444 (4)	0.9363 (1)	0.0415
Compound (2)				
N(1)	0.1090 (3)	−0.1572 (4)	−0.0101 (2)	0.0540
C(2)	0.1357 (3)	−0.1813 (5)	0.0579 (2)	0.0534
C(3)	0.1632 (3)	−0.0874 (5)	0.1037 (2)	0.0453
Br(4)	0.20371 (3)	−0.13069 (5)	0.19780 (2)	0.0598
C(5)	0.1608 (3)	0.0379 (5)	0.0813 (2)	0.0491
C(6)	0.1320 (3)	0.0656 (4)	0.0116 (2)	0.0453
C(7)	0.1276 (4)	0.2024 (5)	−0.0146 (3)	0.0665
C(8)	0.1077 (3)	−0.0364 (4)	−0.0331 (2)	0.0442
C(9)	0.0798 (3)	−0.0124 (4)	−0.1107 (2)	0.0501
C(10)	0.0509 (3)	−0.1282 (5)	−0.1530 (2)	0.0471
C(11)	0.0395 (3)	−0.0985 (4)	−0.2337 (2)	0.0465
C(12)	0.0008 (2)	−0.2069 (4)	−0.2770 (2)	0.0428
N(13)	−0.0880 (2)	−0.2133 (3)	−0.2712 (2)	0.0416
C(14)	−0.1389 (2)	−0.1435 (4)	−0.3115 (2)	0.0374
N(15)	−0.21[illegible] (2)	−0.1648 (3)	−0.3049 (2)	0.0395
C(16)	−0.2763 (3)	−0.0994 (4)	−0.3462 (2)	0.0400
O(17)	−0.3503 (2)	−0.1264 (3)	−0.3407 (2)	0.0510
C(18)	−0.2459 (3)	−0.0049 (5)	−0.3948 (2)	0.0511
C(19)	−0.1647 (3)	0.0128 (5)	−0.3980 (2)	0.0515
N(20)	−0.1095 (2)	−0.0556 (4)	−0.3578 (2)	0.0431
O(21)	0.0360 (2)	0.5127 (4)	0.0709 (2)	0.0730
Compound (3)				
N(1)	−0.1057 (2)	0.0350 (3)	−0.2581 (3)	0.0486
C(2)	−0.1603 (3)	0.0174 (4)	−0.1751 (4)	0.0480
C(3)	−0.1146 (3)	0.0762 (3)	−0.0260 (4)	0.0402
Br(4)	−0.19840 (3)	0.05224 (4)	0.08231 (5)	0.0564
C(5)	−0.0069 (3)	0.1529 (3)	0.0445 (4)	0.0445
C(6)	0.0509 (3)	0.1717 (3)	−0.0395 (4)	0.0437
C(7)	0.1683 (3)	0.2552 (4)	0.0372 (6)	0.0639
C(8)	−0.0026 (3)	0.1112 (3)	−0.1933 (4)	0.0398
C(9)	0.0502 (3)	0.1277 (4)	−0.2981 (5)	0.0513
C(10)	−0.0136 (3)	0.1672 (3)	−0.4349 (4)	0.0453
C(11)	−0.0201 (3)	0.2840 (3)	−0.3904 (3)	0.0375
C(12)	−0.0953 (3)	0.3187 (4)	−0.5240 (4)	0.0377
N(13)	−0.0429 (2)	0.3579 (3)	−0.6185 (3)	0.0332
C(14)	−0.0968 (2)	0.3835 (3)	−0.7445 (3)	0.0341
S(16)	−0.2472 (1)	0.3684 (1)	−0.9875 (1)	0.0390
S(26)	−0.2166 (1)	0.4686 (2)	−0.9136 (2)	0.0350
N(15)	−0.2056 (3)	0.3545 (7)	−0.8102 (4)	0.0359
N(25)	−0.1913 (5)	0.3991 (9)	−0.7765 (9)	0.0356
O(27)	−0.3138 (4)	0.3888 (6)	−1.0541 (5)	0.0480
O(17)	−0.2971 (4)	0.4587 (4)	−1.0029 (6)	0.0431
N(18)	−0.1222 (2)	0.4298 (7)	−0.9787 (5)	0.0352
N(28)	−0.1056 (5)	0.4795 (9)	−0.94165 (9)	0.0362
C(19)	−0.0467 (2)	0.4301 (3)	−0.8434 (3)	0.0343
N(20)	0.0573 (2)	0.4517 (3)	−0.8094 (3)	0.0363
N(101)	−0.4169 (2)	−0.1559 (3)	0.5539 (3)	0.0420
C(102)	−0.3832 (3)	−0.1017 (3)	0.4620 (4)	0.0444
C(103)	−0.4569 (3)	−0.0863 (3)	0.3312 (3)	0.0389
Br(104)	−0.40567 (4)	−0.01079 (4)	0.20454 (5)	0.0591
C(105)	−0.5664 (3)	−0.1237 (3)	0.2944 (4)	0.0415
C(106)	−0.6023 (3)	−0.1796 (3)	0.3878 (3)	0.0397
C(107)	−0.7211 (3)	−0.2230 (5)	0.3497 (5)	0.0564
C(108)	−0.5233 (2)	−0.1937 (3)	0.5190 (3)	0.0342
C(109)	−0.5580 (3)	−0.2542 (3)	0.6252 (3)	0.0402
C(110)	−0.4646 (3)	0.2483 (3)	0.7744 (3)	0.0372
C(111)	−0.5079 (2)	−0.3023 (3)	0.8783 (3)	0.0357
C(112)	−0.4169 (2)	−0.3060 (3)	1.0237 (3)	0.0338
N(113)	−0.4622 (2)	−0.3550 (3)	1.1213 (3)	0.0326
C(114)	−0.4015 (2)	−0.3626 (3)	1.2570 (3)	0.0342
S(116)	−0.25321 (8)	−0.3298 (1)	1.5073 (1)	0.0411
S(126)	−0.2655 (2)	−0.4293 (3)	1.4355 (3)	0.0335
N(115)	−0.2926 (2)	−0.3139 (4)	1.3307 (3)	0.0401 (8)
N(125)	−0.2997 (4)	−0.3605 (7)	1.2978 (8)	0.014 (1)
O(127)	−0.1690 (4)	−0.3493 (5)	1.5754 (5)	0.016 (1)
O(117)	−0.1886 (3)	−0.4072 (3)	1.5289 (5)	0.0601 (9)
N(118)	−0.3758 (2)	−0.4097 (3)	1.4919 (3)	0.0359 (7)
N(128)	−0.3803 (4)	−0.4530 (7)	1.4581 (7)	0.013 (1)
C(119)	−0.4502 (2)	−0.4179 (3)	1.3535 (3)	0.0332
N(120)	−0.5567 (2)	−0.4604 (3)	1.3086 (3)	0.0370
Compound (4)				
N(1)	0.1355 (3)	0.149 (1)	0.1324 (6)	0.0623
C(2)	0.1047 (3)	0.258 (2)	0.1660 (7)	0.0559
C(3)	0.0698 (3)	0.181 (1)	0.1155 (5)	0.0475
Br(4)	0.02784 (5)	0.3423 (3)	0.1701 (1)	0.0703
C(5)	0.0665 (3)	−0.016 (1)	0.0276 (5)	0.0506
C(6)	0.0985 (3)	−0.128 (1)	−0.0066 (6)	0.0498
C(7)	0.0965 (5)	−0.347 (3)	−0.100 (1)	0.0706
C(8)	0.1327 (3)	−0.042 (1)	0.0473 (5)	0.0475
C(9)	0.1702 (4)	−0.147 (3)	0.021 (1)	0.0551
C(10)	0.1836 (4)	−0.015 (3)	−0.086 (1)	0.0586
C(11)	0.2194 (4)	−0.138 (3)	−0.114 (1)	0.0590
C(12)	0.2333 (4)	−0.012 (3)	−0.219 (1)	0.0570
N(13)	0.2690 (2)	−0.139 (2)	−0.2383 (7)	0.0425
C(14)	0.2881 (3)	−0.051 (2)	−0.3188 (8)	0.0399
N(15)	0.2777 (3)	0.131 (2)	−0.3987 (7)	0.0472
S(16)	0.31260 (9)	0.2037 (6)	−0.4749 (2)	0.0473
O(17)	0.3028 (2)	0.103 (2)	−0.5957 (5)	0.0519
N(18)	0.3443 (3)	−0.029 (2)	−0.4087 (7)	0.0464
C(19)	0.3278 (3)	−0.142 (2)	−0.3254 (8)	0.0397
N(20)	0.3442 (3)	−0.329 (2)	−0.2525 (7)	0.0458
C(21)	0.3840 (3)	−0.409 (2)	−0.2541 (9)	0.0460
C(22)	0.4100 (2)	−0.1946 (9)	−0.2036 (6)	0.0428
C(23)	0.4086 (2)	−0.097 (1)	−0.0907 (6)	0.0627
C(24)	0.4347 (2)	0.093 (1)	−0.0418 (5)	0.0743
C(25)	0.4636 (2)	0.2003 (9)	−0.0972 (8)	0.0773
C(26)	0.4637 (1)	0.096 (1)	−0.2095 (8)	0.0641
C(27)	0.4384 (2)	−0.093 (1)	−0.2629 (5)	0.0587
Compound (5)				
N(1)	−0.3058 (2)	0.1804 (1)	0.3542 (1)	0.0476
C(2)	−0.4164 (3)	0.2154 (1)	0.3198 (1)	0.0575
C(3)	−0.5419 (3)	0.1856 (1)	0.2854 (1)	0.0627
C(4)	−0.5575 (3)	0.1163 (1)	0.2865 (1)	0.0582
C(5)	−0.4473 (3)	0.0792 (1)	0.3206 (1)	0.0504
C(6)	−0.3192 (3)	0.1130 (1)	0.3544 (1)	0.0401
N(7)	−0.2009 (2)	0.0792 (1)	0.3888 (1)	0.0422
C(8)	−0.2315 (3)	0.0079 (1)	0.3989 (1)	0.0463
C(9)	−0.1549 (3)	−0.0403 (1)	0.3571 (1)	0.0409
C(10)	−0.2196 (3)	−0.1064 (1)	0.3571 (1)	0.0522

Table 2 (*cont.*)

	x	*y*	*z*	U_{iso}/U_{eq}
C(11)	−0.1433 (4)	−0.1534 (1)	0.3225 (1)	0.0583
C(12)	−0.0043 (4)	−0.1352 (1)	0.2869 (1)	0.0615
C(13)	0.0590 (4)	−0.0699 (1)	0.2859 (1)	0.0608
C(14)	−0.0152 (3)	−0.0228 (1)	0.3208 (1)	0.0490
C(15)	−0.0769 (3)	0.1166 (1)	0.4252 (1)	0.0448
C(16)	0.0928 (3)	0.1470 (1)	0.3975 (1)	0.0485
C(17)	0.2376 (3)	0.1735 (1)	0.4383 (1)	0.0466
N(18)	0.3343 (2)	0.1174 (1)	0.4633 (1)	0.0395
C(19)	0.4720 (2)	0.1231 (1)	0.4994 (1)	0.0340
N(20)	0.5558 (2)	0.0661 (1)	0.5163 (1)	0.0349
C(21)	0.6993 (3)	0.0666 (1)	0.5531 (1)	0.0407
O(22)	0.7737 (2)	0.0128 (1)	0.5664 (1)	0.0530
C(23)	0.7528 (3)	0.1313 (1)	0.5738 (1)	0.0447
C(24)	0.6637 (3)	0.1860 (1)	0.5555 (1)	0.0414
N(25)	0.5233 (2)	0.1838 (1)	0.5180 (1)	0.0370
Compound (6)				
N(1)	0.3001 (5)	0.5504 (2)	0.2580 (2)	0.0706
C(2)	0.3655 (7)	0.6127 (2)	0.3032 (2)	0.0767
C(3)	0.2592 (8)	0.6376 (3)	0.3528 (2)	0.0884
C(4)	0.0770 (8)	0.5951 (2)	0.3548 (2)	0.0823
C(5)	0.0042 (6)	0.5309 (2)	0.3095 (2)	0.0680
C(6)	0.1210 (5)	0.5103 (2)	0.2615 (2)	0.0580
N(7)	0.0530 (7)	0.4486 (3)	0.2146 (2)	0.0650
C(8)	−0.1419 (9)	0.4070 (4)	0.2118 (3)	0.0703
C(9)	−0.1484 (5)	0.3263 (2)	0.2576 (1)	0.0569
C(10)	0.0184 (5)	0.2969 (2)	0.2990 (1)	0.0641
C(11)	0.0109 (5)	0.2237 (2)	0.3405 (1)	0.0723
C(12)	−0.1746 (5)	0.1816 (2)	0.3380 (1)	0.0738
F(13)	−0.1884 (6)	0.1091 (3)	0.3792 (2)	0.1037
C(14)	−0.3481 (5)	0.2067 (2)	0.2981 (1)	0.0879
C(15)	−0.3290 (5)	0.2804 (2)	0.2580 (1)	0.0779
C(16)	0.1805 (8)	0.4229 (3)	0.1653 (2)	0.0628
C(17)	0.1431 (7)	0.4812 (3)	0.1052 (2)	0.0537
C(18)	0.2986 (7)	0.4636 (3)	0.0593 (2)	0.0587
N(19)	0.2836 (5)	0.3711 (2)	0.0342 (2)	0.0506
C(20)	0.4453 (5)	0.3210 (3)	0.0279 (2)	0.0450
N(21)	0.6288 (5)	0.3479 (3)	0.0477 (2)	0.0614
S(22)	0.7803 (2)	0.2604 (1)	0.03661 (7)	0.0741
O(23)	0.9024 (5)	0.2913 (3)	−0.0138 (2)	0.0896
N(24)	0.6087 (5)	0.1899 (3)	−0.0015 (2)	0.0630
C(25)	0.4325 (6)	0.2280 (3)	−0.0018 (2)	0.0473
N(26)	0.2622 (5)	0.1891 (3)	−0.0247 (2)	0.0548
C(27)	0.2540 (9)	0.0992 (4)	−0.0545 (3)	0.0784
C(28)	0.053 (1)	0.0763 (7)	−0.0853 (5)	0.1262
Compound (7)				
N(1)	0.5529 (2)	0.4029 (2)	0.7602 (3)	0.0561
C(2)	0.4883 (3)	0.4115 (2)	0.6432 (4)	0.0689
C(3)	0.3988 (3)	0.4030 (3)	0.6515 (5)	0.0768
C(4)	0.3741 (2)	0.3841 (2)	0.7846 (6)	0.0750
C(5)	0.4395 (2)	0.3730 (2)	0.9074 (4)	0.0629
C(6)	0.5295 (2)	0.3836 (2)	0.8917 (3)	0.0526
C(7)	0.4129 (2)	0.3532 (3)	1.0546 (5)	0.0857
C(9)	0.5770 (2)	0.3689 (4)	1.1678 (3)	0.1036
C(108)	0.4788 (3)	0.3822 (5)	1.1803 (4)	0.074 (4)
C(208)	0.4878 (3)	0.3270 (4)	1.1700 (5)	0.0804
C(10)	0.6074 (2)	0.3781 (2)	1.0186 (3)	0.0633
C(11)	0.6755 (2)	0.3139 (2)	0.9896 (3)	0.0574
C(12)	0.7611 (2)	0.3110 (2)	1.1040 (3)	0.0507
C(13)	0.8372 (2)	0.2616 (2)	1.0522 (4)	0.0521
N(14)	0.8117 (2)	0.1745 (1)	1.0324 (3)	0.0484
C(15)	0.8580 (2)	0.1209 (2)	0.9602 (3)	0.0398
N(16)	0.8283 (1)	0.0404 (1)	0.9564 (2)	0.0420
C(17)	0.8667 (2)	−0.0231 (2)	0.8847 (3)	0.0405
O(18)	0.8369 (1)	−0.0942 (1)	0.8872 (2)	0.0544
C(19)	0.9404 (2)	0.0034 (2)	0.8122 (3)	0.0415
C(20)	0.9643 (2)	0.0848 (2)	0.8232 (3)	0.0452
N(21)	0.9254 (1)	0.1456 (1)	0.8957 (2)	0.0446
C(22)	0.9868 (2)	−0.0612 (2)	0.7329 (3)	0.0489
C(23)	0.9301 (2)	−0.0953 (2)	0.5944 (3)	0.0428
C(24)	0.8692 (2)	−0.0464 (2)	0.5023 (3)	0.0485
N(25)	0.8179 (2)	−0.0735 (2)	0.3785 (3)	0.0527
C(26)	0.8253 (2)	−0.1539 (2)	0.3404 (3)	0.0488
C(27)	0.7667 (3)	−0.1824 (2)	0.2007 (4)	0.0703
C(28)	0.8850 (2)	−0.2065 (2)	0.4249 (3)	0.0550
C(29)	0.9373 (2)	−0.1774 (2)	0.5518 (3)	0.0527
O(30)	0.7190 (2)	0.0425 (2)	0.1837 (2)	0.0663
Compound (8)				
C(1)	0.7729 (4)	−0.2738 (2)	0.2821 (3)	0.0564
C(2)	0.8007 (4)	−0.3374 (2)	0.2673 (3)	0.0624
C(3)	0.8807 (4)	−0.3713 (2)	0.3534 (3)	0.0575
C(4)	0.9316 (4)	−0.3424 (2)	0.4561 (3)	0.0576
C(5)	0.9050 (4)	−0.2790 (2)	0.4716 (3)	0.0545
C(6)	0.8246 (4)	−0.2436 (1)	0.3841 (3)	0.0452
C(7)	0.7977 (4)	−0.1743 (2)	0.4003 (4)	0.0625
C(8)	0.9537 (4)	−0.1357 (1)	0.3751 (3)	0.0510
C(9)	0.9407 (4)	−0.0670 (2)	0.4088 (3)	0.0538
C(10)	0.8132 (4)	−0.0283 (1)	0.3393 (3)	0.0489
N(11)	0.8587 (3)	−0.0221 (1)	0.2171 (2)	0.0430
C(12)	0.7724 (3)	0.0117 (1)	0.1387 (3)	0.0383
N(13)	0.8336 (3)	0.0191 (1)	0.0312 (2)	0.0374
C(14)	0.7522 (3)	0.0540 (1)	−0.0543 (3)	0.0387
O(15)	0.8125 (2)	0.0587 (1)	−0.1530 (2)	0.0489
C(16)	0.5989 (3)	0.0845 (1)	−0.0232 (3)	0.0391
C(17)	0.5462 (4)	0.0737 (1)	0.0850 (3)	0.0456
N(18)	0.6273 (3)	0.0378 (1)	0.1677 (2)	0.0427
C(19)	0.5072 (3)	0.1252 (1)	−0.1119 (3)	0.0460
C(20)	0.5898 (3)	0.1880 (1)	−0.1316 (3)	0.0404
C(21)	0.6795 (4)	0.2005 (2)	−0.2296 (3)	0.0528
C(22)	0.7486 (4)	0.2589 (2)	−0.2444 (3)	0.0629
C(23)	0.7263 (5)	0.3035 (2)	−0.1610 (3)	0.0648
N(24)	0.6399 (4)	0.2934 (1)	−0.0645 (3)	0.0638
C(25)	0.5757 (4)	0.2366 (2)	−0.0525 (3)	0.0530
O(26)	0.3803 (4)	0.0150 (2)	0.3328 (3)	0.0970
O(27)	0.5619 (4)	0.0852 (1)	0.5196 (3)	0.0974
Compound (9)				
C(1)	0.330 (1)	−0.955 (1)	0.1215 (9)	0.0959
C(2)	0.428 (1)	−1.069 (1)	0.1865 (9)	0.0979
C(3)	0.400 (1)	−1.056 (1)	0.3019 (80)	0.0883
N(4)	0.281 (1)	−0.940 (1)	0.357 (7)	0.0898
C(5)	0.190 (1)	−0.830 (1)	0.2902 (7)	0.0795
C(6)	0.210 (1)	−0.828 (1)	0.1736 (7)	0.0728
C(7)	0.100 (1)	−0.694 (1)	0.106 (1)	0.0973
S(8)	0.2214 (5)	−0.5985 (4)	0.0092 (3)	0.0903
S(81)	0.070 (3)	−0.518 (3)	0.175 (2)	0.079 (3)
C(9)	0.335 (1)	−0.538 (1)	0.0896 (8)	0.0930
C(10)	0.253 (2)	−0.418 (2)	0.1739 (8)	0.0835
N(11)	0.156 (1)	−0.2693 (8)	0.1212 (6)	0.0712
C(12)	0.031 (1)	−0.1594 (8)	0.1797 (6)	0.0614
N(13)	−0.0551 (9)	−0.0365 (7)	0.1186 (5)	0.0586
C(14)	−0.186 (1)	0.0779 (8)	0.1746 (6)	0.0588
O(15)	−0.2661 (8)	0.1918 (7)	0.1194 (5)	0.0706
C(16)	−0.227 (1)	0.0654 (8)	0.2959 (6)	0.0592
C(17)	−0.134 (1)	−0.0604 (9)	0.3509 (7)	0.0675
N(18)	−0.0032 (9)	−0.1741 (8)	0.2926 (5)	0.0632
C(19)	−0.367 (1)	0.1953 (9)	0.3576 (8)	0.0683
C(20)	−0.3161 (9)	0.3257 (8)	0.3899 (6)	0.0552
C(21)	−0.339 (1)	0.4565 (9)	0.3222 (7)	0.0717
C(22)	−0.294 (1)	0.5753 (9)	0.3464 (7)	0.0766
C(23)	−0.232 (1)	0.5683 (9)	0.4436 (8)	0.0831
N(24)	−0.197 (1)	0.4394 (9)	0.5141 (6)	0.0868
C(25)	−0.243 (1)	0.3207 (9)	0.4874 (6)	0.0667
C(1′)	0.655 (1)	0.961 (1)	0.8739 (9)	0.0959
C(2′)	0.563 (1)	1.071 (1)	0.803 (1)	0.0979
C(3′)	0.604 (1)	1.055 (1)	0.6891 (8)	0.0883
N(4′)	0.729 (1)	0.938 (1)	0.6416 (7)	0.0898
C(5′)	0.817 (1)	0.836 (1)	0.7120 (7)	0.0795
C(6′)	0.785 (1)	0.840 (1)	0.8276 (7)	0.0728
C(7′)	0.883 (1)	0.714 (1)	0.903 (1)	0.0899
S(8′)	0.7619 (5)	0.5940 (4)	0.9694 (4)	0.0899
S(81′)	0.942 (2)	0.516 (2)	0.829 (1)	0.079 (3)
C(9′)	0.747 (2)	0.514 (1)	0.841 (1)	0.1083
C(10′)	0.718 (2)	0.384 (1)	0.8373 (9)	0.0881
N(11′)	0.835 (1)	0.2483 (8)	0.8906 (6)	0.0712
C(12′)	0.965 (1)	0.1492 (8)	0.8287 (6)	0.0614
N(13′)	1.0551 (9)	0.0204 (7)	0.8841 (5)	0.0586
C(14′)	1.187 (1)	−0.0976 (8)	0.8318 (6)	0.0588

Table 2 (*cont.*)

	x	y	z	U_{iso}/U_{eq}
O(15′)	1.2597 (8)	−0.2130 (7)	0.8868 (5)	0.0706
C(16′)	1.233 (1)	−0.0707 (9)	0.7124 (6	0.0592
C(17′)	1.140 (1)	0.0626 (9)	0.6650 (7)	0.0675
N(18′)	1.007 (1)	0.1762 (8)	0.7194 (5)	0.0632
C(19′)	1.374 (1)	−0.1925 (9)	0.6437 (7)	0.0683
C(20′)	1.3128 (9)	−0.3147 (8)	0.6054 (6)	0.0552
C(21′)	1.318 (1)	−0.4515 (9)	0.6623 (7)	0.0717
C(22′)	1.262 (1)	−0.5531 (9)	0.6193 (7)	0.0766
C(23′)	1.192 (1)	−0.517 (1)	0.5228 (8)	0.0831
N(24′)	1.177 (1)	−0.3816 (9)	0.4620 (6)	0.0868
C(25′)	1.237 (1)	−0.2857 (9)	0.5081 (6)	0.0667
Compound (10)				
C(1)	1.1558 (8)	0.4214 (3)	0.5276 (4)	0.0767
C(2)	1.1569 (6)	0.3816 (3)	0.4264 (3)	0.0587
O(3)	1.0416 (3)	0.4132 (1)	0.3324 (2)	0.0572
C(4)	1.0362 (4)	0.3883 (2)	0.2295 (3)	0.0453
C(5)	1.1279 (5)	0.3342 (2)	0.2111 (3)	0.0510
C(6)	1.1140 (5)	0.3152 (2)	0.1027 (3)	0.0565
C(7)	1.0108 (5)	0.3515 (2)	0.0181 (3)	0.0540
N(8)	0.9197 (4)	0.4047 (2)	0.0347 (2)	0.0507
C(9)	0.9301 (4)	0.4235 (2)	0.1387 (3)	0.0448
C(10)	0.8197 (5)	0.4798 (2)	0.1546 (3)	0.0483
C(11)	0.6556 (5)	0.4521 (2)	0.1651 (3)	0.0484
C(12)	0.5372 (5)	0.5073 (2)	0.1746 (3)	0.0457
C(13)	0.3735 (5)	0.4805 (2)	0.1825 (3)	0.0426
N(14)	0.2570 (4)	0.5343 (2)	0.1862 (2)	0.0457
C(15)	0.2556 (4)	0.5722 (2)	0.2742 (3)	0.0407
N(16)	0.3533 (3)	0.5528 (2)	0.3776 (2)	0.0394
C(17)	0.3577 (4)	0.5888 (2)	0.4734 (3)	0.0412
O(18)	0.4484 (3)	0.5678 (1)	0.5644 (2)	0.0487
C(19)	0.2554 (4)	0.6475 (2)	0.4581 (3)	0.0423
C(20)	0.1614 (5)	0.6614 (2)	0.3527 (3)	0.0492
N(21)	0.1566 (4)	0.6253 (2)	0.2609 (2)	0.0476
C(22)	0.2523 (5)	0.6900 (2)	0.5573 (3)	0.0505
C(23)	0.3992 (5)	0.7350 (2)	0.6026 (3)	0.0432
C(24)	0.4461 (6)	0.7537 (2)	0.7148 (3)	0.0638
N(25)	0.5721 (5)	0.7950 (2)	0.7616 (3)	0.0777
C(26)	0.6580 (6)	0.8201 (2)	0.6978 (4)	0.0697
C(27)	0.6221 (6)	0.8051 (2)	0.5870 (4)	0.0748
C(28)	0.4921 (6)	0.7620 (2)	0.5414 (4)	0.0674

isocytosine ring [one with N(13) protonated, the other with N(18) protonated]. The remaining two atoms of (8) capable of forming hydrogen bonds, N(14) and N(18), hydrogen bond to the water solvent but this hydrogen-bonding pattern does not differentiate the possible states of protonation of N(18).

The structure of the crystal of (9) as presently interpreted has two independent molecules, *A* and *B*, in the asymmetric unit in space group *P*1 that form a hydrogen-bonded dimer by hydrogen bonding between the isocytosine groups. To a reasonable approximation but not on detailed examination, these two molecules might be related by an inversion centre with a hydrogen-bonding pattern closely similar to that found in (2) and (8). However, these pseudo-symmetric dimers are in turn bonded together to form chains parallel to *c* by a further hydrogen bond, 2.94 Å, between the one remaining potential hydrogen donor N(18) of molecule *A* and the N(24′) atom of molecule *B* at $x+1$, y, z in an adjacent dimer. In contrast, the N(24)···N(18′) distance is too long (3.52 Å) to be considered a hydrogen bond. From chemistry, N(24′) [and N(24)] is not protonated, so to form a hydrogen bond N(18) must be protonated and molecule *A* must be in the tautomeric form (12). To form the dimer, molecule *B* then must have the tautomeric form (11) with N(18′) unprotonated and be unable to form a hydrogen bond to the neighbouring N(24). Thus, the two molecules of (9) in the asymmetric unit are differentiated in the tautomeric form of the isocytosine ring and hydrogen-bonding environment.

In the crystal structure of (10) each molecule is hydrogen bonded to each of two adjacent molecules by a pair of centrosymmetrically related hydrogen bonds. The pyridine N(8) hydrogen bonds to the acyclic N(14) atom of a molecule related about the symmetry centre at $0,0,\frac{1}{2}$ and O(18) hydrogen bonds the cyclic amide N(16) atom of a molecule related about the symmetry centre at 0,0,0, so that the molecules are linked to form a ribbon-like arrangement parallel to the *c* axis containing only isocytosine groups in the tautomeric form (11). Adjacent ribbons are related by a 2_1 screw axis along *b* and held together by van der Waals interactions. Although there is a close contact between O(3) and C(10) (2.788 Å), the O(3)···H(10) distance of 2.45 Å and the O(3)···H(10)—C(10) and H(10)—C(10)···O(3) angles of 99.6 and 60.2°, respectively, strongly suggest that intramolecular hydrogen bonding does not occur.

In the thiadiazole-1-oxides (3), (4) and (6), the most significant feature of the crystal structure, shown for (4) in Fig. 4, is the hydrogen-bonded chain in which the 3- and 4-amino groups 'chelate' the sulphoxide O atom. In (3) there are two molecules in the asymmetric unit, (3*a*) and (3*b*) in different conformations and both with disordered thiadiazole-1-oxide groups. The hydrogen-bonded chain feature persists and there is additional hydrogen bonding between the amino N(20) atom and the thiadiazole N(18) atom [and N(120) and N(118)], linking the chains into sheets.

Apart from those situations where observed variations can be attributed to clearly identified disorder phenomena, the bonded distances and interbond angles show little or no significant deviation from predictable values from an examination of known structures.

In all compounds containing the isocytosine group, the group is planar. In the cation form in (1) the isocytosine protonated so that the problem of tautomeric forms does not arise. For the molecules in (2), (5) and (8) the interpretation of the crystallography and the intermolecular hydrogen bonding

Table 3. *Molecular and intermolecular dimensions* (Å, °) *with standard deviations in parentheses*

Compound (1)

N(1)—C(2)	1.344 (6)	C(14)—N(15)	1.347 (6)
N(1)—C(8)	1.344 (6)	N(15)—C(16)	1.394 (6)
C(2)—C(3)	1.372 (7)	C(16)—O(17)	1.224 (5)
C(3)—C(5)	1.361 (7)	C(16)—C(18)	1.451 (6)
Br(4)—C(3)	1.891 (4)	C(18)—C(19)	1.349 (6)
C(5)—C(6)	1.393 (6)	C(18)—C(21)	1.508 (7)
C(6)—C(8)	1.394 (6)	C(19)—N(20)	1.378 (6)
C(6)—C(7)	1.496 (7)	C(21)—C(22)	1.505 (7)
C(8)—C(9)	1.496 (6)	C(22)—C(23)	1.383 (6)
C(9)—C(10)	1.527 (6)	C(22)—C(28)	1.384 (6)
C(10)—C(11)	1.521 (6)	C(23)—N(24)	1.329 (6)
C(11)—C(12)	1.508 (6)	N(24)—C(25)	1.348 (7)
C(12)—N(13)	1.472 (6)	C(25)—C(27)	1.383 (7)
N(13)—C(14)	1.320 (6)	C(25)—C(26)	1.484 (8)
C(14)—N(20)	1.334 (6)	C(27)—C(28)	1.377 (7)

C(10)—C(9)—C(8)	111.2 (3)	C(18)—C(16)—O(17)	125.8 (5)
C(9)—C(10)—C(11)	111.6 (4)	C(18)—C(16)—N(15)	115.4 (4)
C(10)—C(11)—C(12)	114.9 (4)	C(16)—C(18)—C(19)	118.3 (4)
C(12)—N(13)—C(14)	125.0 (4)	C(21)—C(18)—C(19)	122.4 (4)
N(20)—C(14)—N(13)	123.5 (4)	C(21)—C(18)—C(16)	119.2 (4)
N(15)—C(14)—N(13)	118.3 (4)	N(20)—C(19)—C(18)	122.0 (4)
N(15)—C(14)—N(20)	118.2 (4)	C(19)—N(20)—C(14)	121.4 (4)
C(16)—N(15)—C(14)	124.6 (4)	C(18)—C(21)—C(22)	113.2 (3)
N(15)—C(16)—O(17)	118.8 (4)		

N(1)—C(8)—C(9)—C(10)	−87.9 (7)	C(11)—C(12)—N(13)—C(14)	162.2 (7)
C(8)—C(9)—C(10)—C(11)	−178.6 (7)	C(12)—N(13)—C(14)—N(20)	2.7 (7)
C(9)—C(10)—C(11)—C(12)	−178.0 (7)	C(16)—C(18)—C(21)—C(22)	−63.2 (7)
C(10)—C(11)—C(12)—N(13)	−58.9 (7)	C(18)—C(21)—C(22)—C(23)	91.7 (7)

Compound (2)

C(3)—C(2)	1.365 (7)	C(11)—C(12)	1.518 (6)
C(3)—C(5)	1.375 (7)	C(12)—N(13)	1.460 (5)
Br(4)—C(3)	1.894 (4)	N(13)—C(14)	1.324 (5)
C(5)—C(6)	1.387 (6)	C(14)—N(20)	1.345 (5)
C(6)—C(8)	1.399 (6)	C(14)—N(15)	1.347 (5)
C(6)—C(7)	1.512 (7)	N(15)—C(16)	1.371 (5)
C(8)—N(1)	1.333 (6)	C(16)—O(17)	1.248 (5)
C(8)—C(9)	1.509 (5)	C(16)—C(18)	1.427 (6)
N(1)—C(2)	1.339 (6)	C(18)—C(19)	1.344 (7)
C(9)—C(10)	1.511 (6)	C(19)—N(20)	1.360 (6)
C(10)—C(11)	1.521 (5)		

C(10)—C(9)—C(8)	116.0 (4)	C(16)—N(15)—C(14)	121.5 (3)
C(11)—C(10)—C(9)	111.6 (4)	N(15)—C(16)—O(17)	119.4 (4)
C(10)—C(11)—C(12)	113.7 (4)	C(18)—C(16)—O(17)	123.7 (4)
C(11)—C(12)—N(13)	113.8 (4)	C(18)—C(16)—N(15)	116.9 (4)
C(12)—N(13)—C(14)	123.5 (4)	C(16)—C(18)—C(19)	118.5 (4)
N(20)—C(14)—N(13)	120.1 (4)	N(20)—C(19)—C(18)	123.5 (4)
N(15)—C(14)—N(13)	117.9 (4)	C(19)—N(20)—C(14)	117.5 (4)
N(15)—C(14)—N(20)	122.1 (4)		

N(1)—C(8)—C(9)—C(10)	3.9 (6)	C(10)—C(11)—C(12)—N(13)	80.8 (6)
C(8)—C(9)—C(10)—C(11)	−169.4 (6)	C(11)—C(12)—N(13)—C(14)	83.3 (6)
C(9)—C(10)—C(11)—C(12)	−173.0 (6)	C(12)—N(13)—C(14)—N(15)	175.2 (6)

Compound (3)

Molecule (*a*)		Molecule (*b*)	
Br(4)—C(3)	1.891 (3)	Br(104)—C(103)	1.891 (3)
N(1)—C(8)	1.335 (5)	N(101)—C(108)	1.333 (4)
N(1)—C(2)	1.339 (5)	N(101)—C(102)	1.345 (4)
C(2)—C(3)	1.368 (5)	C(102)—C(103)	1.375 (5)
C(3)—C(5)	1.382 (5)	C(103)—C(105)	1.372 (5)
C(5)—C(6)	1.383 (5)	C(105)—C(106)	1.383 (4)
C(6)—C(8)	1.403 (5)	C(106)—C(108)	1.405 (4)
C(6)—C(7)	1.506 (5)	C(106)—C(107)	1.492 (5)
C(8)—C(9)	1.511 (5)	C(108)—C(109)	1.512 (4)
C(9)—C(10)	1.519 (5)	C(109)—C(110)	1.517 (4)
C(10)—C(11)	1.516 (5)	C(110)—C(111)	1.520 (4)
C(11)—C(12)	1.527 (4)	C(111)—C(112)	1.518 (4)
C(12)—N(13)	1.458 (3)	C(112)—N(113)	1.457 (3)
N(13)—C(14)	1.305 (4)	N(113)—C(114)	1.305 (4)
C(14)—N(15)	1.334 (3)	C(114)—N(115)	1.328 (2)
C(14)—N(25)	1.334 (3)	C(114)—N(125)	1.334 (3)
C(14)—C(19)	1.501 (4)	C(114)—C(119)	1.506 (4)
S(16)···O(27)	1.036 (7)	S(116)···O(127)	1.228 (6)
S(16)···S(26)	1.235 (3)	S(116)···S(126)	1.291 (4)
S(16)—O(17)	1.486 (3)	S(116)—O(117)	1.492 (2)
S(16)—N(15)	1.658 (3)	S(116)—N(115)	1.661 (2)
S(16)—N(18)	1.688 (3)	S(116)—N(118)	1.680 (2)
S(16)—N(25)	1.863 (8)	S(116)—N(125)	1.865 (7)
S(16)—N(28)	1.927 (7)	S(116)—N(128)	1.845 (7)
S(26)···O(17)	1.093 (5)	S(126)···O(117)	1.045 (4)
S(26)—O(27)	1.488 (3)	S(126)—O(127)	1.481 (3)
S(26)—N(25)	1.658 (3)	S(126)—N(125)	1.666 (3)
S(26)—N(28)	1.688 (3)	S(126)—N(128)	1.691 (3)
S(26)—N(15)	1.840 (6)	S(126)—N(115)	1.895 (4)
S(26)—N(18)	1.868 (6)	S(126)—N(118)	1.941 (4)
N(15)···N(25)	0.55 (1)	N(115)···N(125)	0.595 (7)
O(27)···O(17)	0.874 (6)	O(127)···O(117)	0.722 (5)
N(18)···N(28)	0.61 (1)	N(118)···N(128)	0.578 (7)
N(18)—C(19)	1.338 (3)	N(118)—C(119)	1.324 (2)
N(28)—C(19)	1.339 (3)	N(128)—C(119)	1.332 (3)
C(19)—N(20)	1.319 (4)	C(119)—N(120)	1.316 (4)

C(10)—C(9)—C(8)	112.6 (3)	C(110)—C(109)—C(108)	115.1 (3)
C(9)—C(10)—C(11)	112.7 (3)	C(111)—C(110)—C(109)	111.1 (3)
C(12)—C(11)—C(10)	113.6 (3)	C(110)—C(111)—C(112)	112.4 (2)
C(11)—C(12)—N(13)	111.2 (2)	C(111)—C(112)—N(113)	110.2 (2)
C(12)—N(13)—C(14)	120.6 (2)	C(112)—N(113)—C(114)	123.1 (2)
N(15)—C(14)—N(13)	123.0 (3)	N(115)—C(114)—N(113)	124.7 (3)
N(25)—C(14)—N(13)	122.0 (3)	N(125)—C(114)—N(113)	121.3 (3)
C(19)—C(14)—N(13)	123.6 (2)	C(119)—C(114)—N(113)	122.2 (2)
C(19)—C(14)—N(15)	112.7 (2)	C(119)—C(114)—N(115)	112.7 (2)
C(19)—C(14)—N(25)	112.4 (3)	C(119)—C(114)—N(125)	112.6 (3)
S(16)—N(15)—C(14)	108.7 (2)	S(116)—N(115)—C(114)	107.5 (2)
S(26)—N(25)—C(14)	108.8 (3)	S(126)—N(125)—C(114)	109.6 (3)
N(15)—S(16)—O(17)	108.3 (3)	N(115)—S(116)—O(117)	108.1 (2)
N(25)—S(26)—O(27)	108.9 (5)	N(125)—S(126)—O(127)	110.5 (4)
N(18)—S(16)—O(17)	106.6 (3)	N(118)—S(116)—O(117)	106.2 (2)
N(28)—S(26)—O(27)	106.4 (5)	N(128)—S(126)—O(127)	109.6 (4)
N(18)—S(16)—N(15)	97.9 (2)	N(118)—S(116)—N(115)	99.3 (1)
N(28)—S(26)—N(25)	98.4 (2)	N(128)—S(126)—N(125)	96.4 (2)
S(16)—N(18)—C(19)	107.9 (2)	S(116)—N(118)—C(119)	106.7 (2)
S(26)—N(28)—C(19)	107.3 (3)	S(126)—N(128)—C(119)	109.8 (3)
N(18)—C(19)—N(20)	123.8 (3)	N(118)—C(119)—N(120)	123.5 (2)
N(28)—C(19)—N(20)	121.0 (3)	N(128)—C(119)—N(120)	122.4 (3)
C(14)—C(19)—N(20)	123.1 (2)	C(114)—C(119)—N(120)	122.7 (2)
C(14)—C(19)—N(18)	112.3 (2)	C(114)—C(119)—N(118)	113.5 (2)
C(14)—C(19)—N(28)	113.1 (3)	C(114)—C(119)—N(128)	111.3 (3)

N(1)—C(8)—C(9)—C(10)	58.2 (4)
C(8)—C(9)—C(10)—C(11)	62.2 (4)
C(9)—C(10)—C(11)—C(12)	−173.0 (4)
C(10)—C(11)—C(12)—N(13)	−76.2 (4)
C(11)—C(12)—N(13)—C(14)	175.1 (4)
C(12)—N(13)—C(14)—N(15)	−13.8 (4)
C(12)—N(13)—C(14)—N(25)	−14.4 (4)
C(12)—N(13)—C(14)—C(19)	176.7 (4)
N(101)—C(108)—C(109)—C(110)	9.3 (4)
C(108)—C(109)—C(110)—C(111)	175.1 (4)
C(109)—C(110)—C(111)—C(112)	175.7 (4)
C(110)—C(111)—C(112)—N(113)	178.2 (4)
C(111)—C(112)—N(113)—C(114)	−176.2 (4)
C(112)—N(113)—C(114)—N(115)	9.4 (4)
C(112)—N(113)—C(114)—N(125)	−21.2 (4)
C(112)—N(113)—C(114)—C(119)	−177.5 (4)

Compound (4)

Br(4)—C(3)	1.89 (1)	C(14)—C(19)	1.52 (1)
N(1)—C(2)	1.338 (5)	N(15)—S(16)	1.66 (1)
N(1)—C(8)	1.339 (5)	S(16)—O(17)	1.478 (7)
C(2)—C(3)	1.379 (5)	S(16)—N(18)	1.719 (9)
C(3)—C(5)	1.382 (5)	N(18)—C(19)	1.31 (1)
C(5)—C(6)	1.382 (5)	C(19)—N(20)	1.32 (1)
C(6)—C(8)	1.381 (5)	N(20)—C(21)	1.50 (1)
C(6)—C(7)	1.50 (2)	C(21)—C(22)	1.47 (1)
C(8)—C(9)	1.52 (1)	C(22)—C(23)	1.390 (4)
C(9)—C(10)	1.52 (2)	C(22)—C(27)	1.393 (4)
C(10)—C(11)	1.50 (1)	C(23)—C(24)	1.389 (4)
C(11)—C(12)	1.50 (1)	C(24)—C(25)	1.392 (5)
C(12)—N(13)	1.47 (1)	C(25)—C(26)	1.388 (5)

Table 3 (*cont.*)

N(13)—C(14)	1.30 (1)	C(26)—C(27)	1.389 (4)
C(14)—N(15)	1.29 (1)		

C(8)—C(9)—C(10)	113.9 (8)	N(15)—S(16)—O(17)	108.4 (5)
C(9)—C(10)—C(11)	112.3 (10)	N(18)—S(16)—O(17)	106.0 (4)
C(10)—C(11)—C(12)	113.5 (10)	N(18)—S(16)—N(15)	98.0 (4)
C(11)—C(12)—N(13)	109.9 (10)	S(16)—N(18)—C(19)	104.9 (7)
C(12)—N(13)—C(14)	122.0 (9)	N(20)—C(19)—N(18)	122.7 (10)
N(13)—C(14)—N(15)	126.4 (11)	C(14)—C(19)—N(18)	115.9 (9)
C(19)—C(14)—N(15)	111.1 (9)	C(14)—C(19)—N(20)	121.4 (9)
C(19)—C(14)—N(13)	122.4 (9)	C(21)—N(20)—C(19)	121.8 (9)
S(16)—N(15)—C(14)	110.0 (8)	N(20)—C(21)—C(22)	112.7 (7)

N(1)—C(8)—C(9)—C(10)	−100 (1)	C(12)—N(13)—C(14)—C(19)	168 (1)
C(8)—C(9)—C(10)—C(11)	−176 (1)	N(13)—C(14)—C(19)—N(20)	4 (1)
C(9)—C(10)—C(11)—C(12)	180 (1)	C(21)—N(20)—C(19)—C(14)	−177 (1)
C(10)—C(11)—C(12)—N(13)	178 (1)	C(19)—N(20)—C(21)—C(22)	74 (1)
C(11)—C(12)—N(13)—C(14)	−175 (1)	N(20)—C(21)—C(22)—C(23)	56 (1)
C(12)—N(13)—C(14)—N(15)	−8 (1)		

Compound (5)

N(1)—C(6)	1.343 (2)	C(12)—C(13)	1.374 (3)
N(1)—C(2)	1.344 (3)	C(13)—C(14)	1.382 (3)
C(2)—C(3)	1.362 (3)	C(15)—C(16)	1.511 (3)
C(3)—C(4)	1.384 (4)	C(16)—C(17)	1.536 (3)
C(4)—C(5)	1.370 (3)	C(17)—N(18)	1.451 (2)
C(5)—C(6)	1.408 (3)	N(18)—C(19)	1.329 (2)
C(6)—N(7)	1.373 (2)	C(19)—N(25)	1.343 (2)
N(7)—C(8)	1.457 (2)	C(19)—N(20)	1.348 (2)
N(7)—C(15)	1.466 (2)	N(20)—C(21)	1.368 (2)
C(8)—C(9)	1.515 (3)	C(21)—O(22)	1.239 (2)
C(9)—C(14)	1.383 (3)	C(21)—C(23)	1.436 (2)
C(9)—C(10)	1.391 (3)	C(23)—C(24)	1.338 (3)
C(10)—C(11)	1.383 (3)	C(24)—N(25)	1.366 (2)
C(11)—C(12)	1.373 (4)		

C(8)—N(7)—C(6)	119.6 (2)	N(20)—C(19)—N(18)	117.5 (1)
C(15)—N(7)—C(6)	120.2 (1)	N(20)—C(19)—N(25)	121.9 (2)
C(15)—N(7)—C(8)	118.4 (2)	C(21)—N(20)—C(19)	122.0 (1)
C(9)—C(8)—N(7)	116.4 (2)	N(20)—C(21)—O(22)	119.2 (2)
C(16)—C(15)—N(7)	113.4 (2)	C(23)—C(21)—O(22)	124.5 (2)
C(17)—C(16)—C(15)	111.5 (2)	C(23)—C(21)—N(20)	116.3 (2)
C(16)—C(17)—N(18)	109.6 (2)	C(21)—C(23)—C(24)	118.8 (2)
C(17)—N(18)—C(19)	124.7 (1)	N(25)—C(24)—C(23)	123.4 (2)
N(25)—C(19)—N(18)	120.6 (1)	C(24)—N(25)—C(19)	117.5 (1)

N(1)—C(6)—N(7)—C(8)	168.3 (3)	C(8)—N(7)—C(15)—C(16)	119.4 (3)
N(1)—C(6)—N(7)—C(15)	3.8 (3)	N(7)—C(15)—C(16)—C(17)	−168.9 (3)
C(6)—N(7)—C(8)—C(9)	81.3 (3)	C(15)—C(16)—C(17)—N(18)	73.4 (3)
C(15)—N(7)—C(8)—C(9)	−114.0 (3)	C(16)—C(17)—N(18)—C(19)	178.0 (3)
N(7)—C(8)—C(9)—C(10)	−163.9 (3)	C(17)—N(18)—C(19)—N(20)	−175.9 (3)
N(7)—C(8)—C(9)—C(14)	20.0 (3)	C(17)—N(18)—C(19)—N(25)	4.4 (3)
C(6)—N(7)—C(15)—C(16)	−75.9 (3)		

Compound (6)

N(1)—C(2)	1.345 (4)	C(12)—C(14)	1.382 (4)
N(1)—C(6)	1.346 (4)	C(14)—C(15)	1.386 (4)
C(2)—C(3)	1.381 (4)	C(16)—C(17)	1.509 (6)
C(3)—C(4)	1.375 (4)	C(17)—C(18)	1.529 (5)
C(4)—C(5)	1.377 (4)	C(18)—N(19)	1.458 (6)
C(5)—C(6)	1.385 (4)	N(19)—C(20)	1.330 (5)
C(6)—N(7)	1.367 (6)	C(20)—N(21)	1.301 (5)
N(7)—C(8)	1.434 (7)	C(20)—C(25)	1.500 (6)
N(7)—C(16)	1.472 (6)	S(22)—O(23)	1.487 (4)
C(8)—C(9)	1.528 (6)	S(22)—N(24)	1.666 (4)
C(9)—C(10)	1.384 (4)	S(22)—N(21)	1.674 (4)
C(9)—C(15)	1.385 (4)	N(24)—C(25)	1.304 (5)
C(10)—C(11)	1.388 (4)	C(25)—N(26)	1.306 (5)
C(11)—C(12)	1.381 (4)	N(26)—C(27)	1.459 (6)
C(12)—F(13)	1.381 (4)	C(27)—C(28)	1.449 (9)

C(8)—N(7)—C(6)	121.7 (4)	S(22)—N(21)—C(20)	106.5 (3)
C(16)—N(7)—C(6)	120.2 (4)	N(21)—S(22)—O(23)	105.3 (2)
C(16)—N(7)—C(8)	118.1 (4)	N(21)—S(22)—N(24)	98.9 (2)
C(9)—C(8)—N(7)	114.2 (4)	N(24)—S(22)—O(23)	105.2 (2)
C(17)—C(16)—N(7)	112.8 (4)	S(22)—N(24)—C(25)	107.3 (3)
C(18)—C(17)—C(16)	111.9 (4)	N(26)—C(25)—N(24)	123.8 (4)
C(17)—C(18)—N(19)	111.3 (4)	C(20)—C(25)—N(24)	112.9 (4)
C(18)—N(19)—C(20)	122.4 (3)	C(20)—C(25)—N(26)	123.3 (4)
N(19)—C(20)—N(21)	122.9 (4)	C(27)—N(26)—C(25)	122.2 (4)
C(25)—C(20)—N(21)	114.0 (4)	N(26)—C(27)—C(28)	112.2 (6)
C(25)—C(20)—N(19)	123.0 (3)		

N(1)—C(6)—N(7)—C(8)	−175.8 (4)	C(8)—N(7)—C(16)—C(17)	88.1 (4)
N(1)—C(6)—N(7)—C(16)	4.7 (4)	N(7)—C(16)—C(17)—C(18)	171.2 (4)
C(6)—N(7)—C(8)—C(9)	−80.8 (4)	C(16)—C(17)—C(18)—N(19)	64.5 (4)
N(7)—C(8)—C(9)—C(10)	−0.3 (4)	C(17)—C(18)—N(19)—C(20)	−138.6 (4)
C(6)—N(7)—C(16)—C(17)	−92.4 (4)	C(18)—N(19)—C(20)—N(21)	4.9 (4)
C(9)—C(8)—N(7)—C(16)	98.7 (4)	C(18)—N(19)—C(20)—C(25)	−175.5 (4)

Compound (7)

N(1)—C(2)	1.332 (4)	C(15)—N(21)	1.311 (3)
N(1)—C(6)	1.344 (4)	C(15)—N(16)	1.367 (3)
C(2)—C(3)	1.361 (6)	N(16)—C(17)	1.387 (3)
C(3)—C(4)	1.364 (6)	C(17)—O(18)	1.228 (3)
C(4)—C(5)	1.381 (5)	C(17)—C(19)	1.438 (4)
C(5)—C(6)	1.387 (4)	C(19)—C(20)	1.357 (4)
C(5)—C(7)	1.500 (5)	C(19)—C(22)	1.500 (4)
C(6)—C(10)	1.512 (4)	C(20)—N(21)	1.363 (3)
C(7)—C(108)	1.467 (2)	C(22)—C(23)	1.512 (4)
C(7)—C(208)	1.474 (2)	C(23)—C(24)	1.383 (4)
C(9)—C(208)	1.498 (2)	C(23)—C(29)	1.385 (4)
C(9)—C(108)	1.508 (2)	C(24)—N(25)	1.338 (4)
C(9)—C(10)	1.514 (2)	N(25)—C(26)	1.348 (4)
C(10)—C(11)	1.505 (4)	C(26)—C(28)	1.376 (4)
C(11)—C(12)	1.521 (4)	C(26)—C(27)	1.503 (4)
C(12)—C(13)	1.524 (4)	C(28)—C(29)	1.376 (4)
C(13)—N(14)	1.455 (3)	C(108)···C(208)	0.904 (8)
N(14)—C(15)	1.345 (3)		

C(5)—C(7)—C(108)	113.3 (2)	N(14)—C(15)—N(21)	121.4 (2)
C(5)—C(7)—C(208)	115.1 (2)	N(16)—C(15)—N(21)	123.1 (2)
C(9)—C(108)—C(7)	115.9 (2)	N(16)—C(15)—N(14)	115.4 (2)
C(9)—C(208)—C(7)	116.1 (2)	C(17)—N(16)—C(15)	123.5 (2)
C(10)—C(9)—C(208)	116.9 (2)	N(16)—C(17)—O(18)	119.8 (2)
C(10)—C(9)—C(108)	119.4 (2)	C(19)—C(17)—O(18)	126.2 (2)
C(6)—C(10)—C(11)	111.5 (3)	C(19)—C(17)—N(16)	114.0 (2)
C(9)—C(10)—C(11)	113.7 (3)	C(17)—C(19)—C(20)	117.6 (2)
C(9)—C(10)—C(6)	113.2 (1)	C(22)—C(19)—C(20)	124.5 (2)
C(12)—C(11)—C(10)	114.8 (3)	C(22)—C(19)—C(17)	117.8 (2)
C(13)—C(12)—C(11)	113.0 (2)	N(21)—C(20)—C(19)	126.9 (2)
C(12)—C(13)—N(14)	110.2 (2)	C(20)—N(21)—C(15)	114.9 (2)
C(13)—N(14)—C(15)	122.2 (2)		

C(9)—C(10)—C(6)—N(1)	171.5 (5)	C(9)—C(10)—C(11)—C(12)	−57.1 (5)
N(1)—C(6)—C(10)—C(11)	−58.8 (5)	C(10)—C(11)—C(12)—C(13)	−165.6 (5)
C(6)—C(10)—C(11)—C(12)	173.5 (5)	C(11)—C(12)—C(13)—N(14)	−64.9 (5)
C(9)—C(10)—C(6)—C(5)	−6.1 (5)	C(12)—C(13)—N(14)—C(15)	166.5 (5)

Compound (8)

C(1)—C(2)	1.384 (5)	C(21)—C(22)	1.375 (5)
C(2)—C(3)	1.361 (5)	C(22)—C(23)	1.360 (5)
C(3)—C(4)	1.372 (5)	C(23)—N(24)	1.340 (4)
C(4)—C(5)	1.379 (5)	N(24)—C(25)	1.325 (4)
C(5)—C(6)	1.390 (4)	C(6)—C(7)	1.503 (5)
C(6)—C(1)	1.380 (5)	C(7)—C(8)	1.535 (5)
C(10)—N(11)	1.460 (4)	C(8)—C(9)	1.517 (4)
N(11)—C(12)	1.324 (4)	C(9)—C(10)	1.515 (4)
C(12)—N(13)	1.347 (3)	C(16)—C(17)	1.339 (4)
N(13)—C(14)	1.372 (4)	C(17)—N(18)	1.361 (4)
C(14)—O(15)	1.246 (3)	N(18)—C(12)	1.345 (3)
C(14)—C(16)	1.448 (4)	C(16)—C(19)	1.504 (4)
C(19)—C(20)	1.513 (4)	C(25)—C(20)	1.379 (4)
C(20)—C(21)	1.378 (4)		

C(6)—C(7)—C(8)	112.3 (3)	C(12)—N(13)—C(14)	122.0 (2)
C(7)—C(8)—C(9)	113.9 (3)	N(13)—C(14)—O(15)	119.6 (2)
C(8)—C(9)—C(10)	116.3 (3)	N(13)—C(14)—C(16)	117.2 (2)
C(9)—C(10)—N(11)	111.1 (2)	O(15)—C(14)—C(16)	123.2 (3)
C(10)—N(11)—C(12)	123.4 (2)	C(14)—C(16)—C(17)	116.7 (3)
N(11)—C(12)—N(13)	118.6 (2)	C(16)—C(17)—N(18)	125.1 (3)
N(11)—C(12)—N(18)	119.8 (3)	C(12)—N(18)—C(17)	117.4 (3)
N(13)—C(12)—N(18)	121.6 (3)		

C(1)—C(6)—C(7)—C(8)	−98.6 (5)	C(10)—N(11)—C(12)—N(13)	173.9 (5)
C(5)—C(6)—C(7)—C(8)	80.5 (5)	C(10)—N(11)—C(12)—N(18)	−5.8 (5)
C(6)—C(7)—C(8)—C(9)	−170.8 (5)	C(14)—C(16)—C(19)—C(20)	−73.9 (5)

Table 3 (*cont.*)

C(7)—C(8)—C(9)—C(10)	−66.0 (5)	C(16)—C(19)—C(20)—C(21)	103.7 (5)
C(8)—C(9)—C(10)—N(11)	−66.4 (5)	C(16)—C(19)—C(20)—C(25)	−77.8 (5)
C(9)—C(10)—N(11)—C(12)	−176.9 (5)	C(17)—C(16)—C(19)—C(20)	106.9 (5)

Compound (9)

	Molecule *A*		Molecule *B*
C(1)—C(2)	1.370 (11)	C(1′)—C(2′)	1.373 (12)
C(2)—C(3)	1.357 (11)	C(2′)—C(3′)	1.352 (12)
C(3)—N(4)	1.323 (8)	C(3′)—N(4′)	1.314 (8)
N(4)—C(5)	1.340 (7)	N(4′)—C(5′)	1.319 (7)
C(5)—C(6)	1.366 (10)	C(5′)—C(6′)	1.357 (10)
C(6)—C(1)	1.368 (8)	C(6′)—C(1′)	1.351 (8)
C(6)—C(7)	1.530 (11)	C(6′)—C(7′)	1.503 (10)
C(7)—S(8)	1.823 (12)	C(7′)—S(8′)	1.834 (10)
C(7)—S(81)	1.783 (24)	C(7′)—S(81′)	1.942 (18)
S(8)—C(9)	1.692 (11)	S(8′)—C(9′)	1.766 (13)
S(81)—C(9)	2.299 (24)	S(81′)—C(9′)	1.667 (19)
C(9)—C(10)	1.449 (13)	C(9′)—C(10′)	1.303 (15)
C(10)—N(11)	1.487 (13)	C(10′)—N(11′)	1.478 (11)
N(11)—C(12)	1.331 (9)	N(11′)—C(12′)	1.328 (10)
C(12)—N(13)	1.350 (8)	C(12′)—N(13′)	1.359 (8)
N(13)—C(14)	1.366 (9)	N(13′)—C(14′)	1.370 (9)
C(14)—O(15)	1.242 (8)	C(14′)—O(15′)	1.231 (8)
C(14)—C(16)	1.436 (9)	C(14′)—C(16′)	1.442 (9)
C(16)—C(17)	1.349 (9)	C(16′)—C(17′)	1.353 (9)
C(17)—N(18)	1.371 (9)	C(17′)—N(18′)	1.360 (9)
N(18)—C(12)	1.336 (9)	N(18′)—C(12′)	1.324 (9)
C(16)—C(19)	1.510 (10)	C(16′)—C(19′)	1.508 (10)
C(19)—C(20)	1.498 (7)	C(19′)—C(20′)	1.510 (7)
C(20)—C(21)	1.377 (9)	C(20′)—C(21′)	1.380 (9)
C(21)—C(22)	1.336 (10)	C(21′)—C(22′)	1.342 (10)
C(22)—C(23)	1.321 (8)	C(22′)—C(23′)	1.336 (8)
C(23)—N(24)	1.378 (10)	C(23′)—N(24′)	1.375 (10)
N(24)—C(25)	1.350 (7)	N(24′)—C(25′)	1.340 (7)
C(25)—C(20)	1.380 (9)	C(25′)—C(20′)	1.366 (9)

C(6)—C(7)—S(8)	113.1 (8)	C(6′)—C(7′)—S(8′)	112.4 (6)
C(6)—C(7)—S(81)	108.2 (10)	C(6′)—C(7′)—S(81′)	109.0 (8)
C(7)—S(8)—C(9)	107.0 (5)	C(7′)—S(8′)—C(9′)	96.0 (6)
C(7)—S(81)—C(9)	86.7 (10)	C(7′)—S(81′)—C(9′)	95.4 (8)
S(8)—C(9)—C(10)	120.7 (9)	S(8′)—C(9′)—C(10′)	123.0 (12)
S(81)—C(9)—C(10)	62.1 (11)	S(81′)—C(9′)—C(10′)	120.6 (6)
C(9)—C(10)—N(11)	112.0 (7)	C(9′)—C(10′)—N(11′)	115.7 (8)
C(10)—N(11)—C(12)	123.1 (7)	C(10′)—N(11′)—C(12′)	121.2 (8)
N(11)—C(12)—N(13)	116.4 (7)	N(11′)—C(12′)—N(13′)	116.4 (7)
N(11)—C(12)—N(18)	120.2 (7)	N(11′)—C(12′)—N(18′)	121.7 (7)
N(13)—C(12)—N(18)	123.4 (7)	N(13′)—C(12′)—N(18′)	122.0 (7)
C(12)—N(13)—C(14)	118.5 (7)	C(12′)—N(13′)—C(14′)	123.9 (6)
N(13)—C(14)—O(15)	119.1 (7)	N(13′)—C(14′)—O(15′)	120.4 (7)
N(13)—C(14)—C(16)	119.4 (7)	N(13′)—C(14′)—C(16′)	114.6 (6)
C(14)—C(16)—C(17)	118.5 (7)	C(14′)—C(16′)—C(17′)	117.3 (8)
C(16)—C(17)—N(18)	121.0 (8)	C(16′)—C(17′)—N(18′)	126.3 (8)
C(12)—N(18)—C(17)	119.2 (7)	C(12′)—N(18′)—C(17′)	115.7 (7)

C(1)—C(6)—C(7)—S(8)	−60 (1)	C(1′)—C(6′)—C(7′)—S(8′)	70 (1)
C(1)—C(6)—C(7)—S(81)	−142 (1)	C(1′)—C(6′)—C(7′)—S(81′)	142 (1)
C(5)—C(6)—C(7)—S(8)	121 (1)	C(5′)—C(6′)—C(7′)—S(8′)	−107 (1)
C(5)—C(6)—C(7)—S(81)	39 (1)	C(5′)—C(6′)—C(7′)—S(81′)	−36 (1)
C(6)—C(7)—S(8)—C(9)	−57 (1)	C(6′)—C(7′)—S(8′)—C(9′)	65 (1)
C(6)—C(7)—S(81)—C(9)	79 (1)	C(6′)—C(7′)—S(81′)—C(9′)	−68 (1)
C(7)—S(8)—C(9)—C(10)	−66 (1)	C(7′)—S(8′)—C(9′)—C(10′)	158 (1)
C(7)—S(81)—C(9)—C(10)	−172 (1)	C(7′)—S(81′)—C(9′)—C(10′)	−158 (1)
S(8)—C(9)—C(10)—N(11)	−61 (1)	S(8′)—C(9′)—C(10′)—N(11′)	−55 (1)
S(81)—C(9)—C(10)—N(11)	−91 (1)	S(81′)—C(9′)—C(10′)—N(11′)	36 (1)
C(9)—C(10)—N(11)—C(12)	159 (1)	C(9′)—C(10′)—N(11′)—C(12′)	−96 (1)
C(10)—N(11)—C(12)—N(13)	−174 (1)	C(10′)—N(11′)—C(12′)—N(13′)	−174 (1)
C(10)—N(11)—C(12)—N(18)	5 (1)	C(10′)—N(11′)—C(12′)—N(18′)	8 (1)
C(17)—C(16)—C(19)—C(20)	93 (1)	C(17′)—C(16′)—C(19′)—C(20′)	−95 (1)
C(14)—C(16)—C(19)—C(20)	−85 (1)	C(14′)—C(16′)—C(19′)—C(20′)	81 (1)
C(16)—C(19)—C(20)—C(21)	97 (1)	C(16′)—C(19′)—C(20′)—C(21′)	−93 (1)
C(16)—C(19)—C(20)—C(25)	−83 (1)	C(16′)—C(19′)—C(20′)—C(25′)	84 (1)

Compound (10)

C(1)—C(2)	1.495 (7)	C(15)—N(16)	1.380 (4)
C(2)—O(3)	1.439 (5)	N(16)—C(17)	1.387 (4)
O(3)—C(4)	1.373 (4)	C(17)—O(18)	1.251 (4)
C(4)—C(5)	1.372 (5)	C(17)—C(19)	1.418 (5)
C(5)—C(6)	1.386 (6)	C(19)—C(20)	1.363 (5)
C(6)—C(7)	1.366 (5)	C(20)—N(21)	1.345 (5)
C(7)—N(8)	1.348 (5)	N(21)—C(15)	1.314 (4)
N(8)—C(9)	1.338 (5)	C(19)—C(22)	1.507 (5)
C(9)—C(4)	1.413 (5)	C(22)—C(23)	1.496 (6)
C(9)—C(10)	1.495 (5)	C(23)—C(24)	1.402 (5)
C(10)—C(11)	1.532 (6)	C(24)—N(25)	1.333 (6)
C(11)—C(12)	1.501 (6)	N(25)—C(26)	1.324 (6)
C(12)—C(13)	1.512 (5)	C(26)—C(27)	1.371 (6)
C(13)—N(14)	1.452 (5)	C(27)—C(28)	1.373 (6)
N(14)—C(15)	1.337 (4)	C(28)—C(23)	1.357 (6)

C(1)—C(2)—O(3)	107.9 (4)	C(10)—C(11)—C(12)	113.3 (4)
C(2)—O(3)—C(4)	117.0 (3)	C(11)—C(12)—C(13)	113.8 (3)
O(3)—C(4)—C(5)	124.6 (3)	C(12)—C(13)—N(14)	113.3 (3)
N(16)—C(15)—N(21)	121.7 (3)	C(13)—N(14)—C(15)	126.7 (3)
C(15)—N(16)—C(17)	122.6 (3)	N(14)—C(15)—N(16)	118.9 (3)
N(16)—C(17)—O(18)	119.0 (3)	N(14)—C(15)—N(21)	119.4 (3)
O(3)—C(4)—C(9)	115.4 (3)	N(16)—C(17)—C(19)	115.6 (3)
C(7)—N(8)—C(9)	119.1 (3)	C(17)—C(19)—C(20)	117.0 (3)
N(8)—C(9)—C(10)	117.9 (3)	O(18)—C(17)—C(19)	125.4 (3)
C(4)—C(9)—C(10)	121.8 (3)	C(19)—C(20)—N(21)	126.7 (4)
C(9)—C(10)—C(11)	111.6 (3)	C(20)—N(21)—C(15)	116.4 (3)

C(1)—C(2)—O(3)—C(4)	173.7 (5)	C(12)—C(13)—N(14)—C(15)	−78.5 (4)
C(2)—O(3)—C(4)—C(5)	2.6 (5)	C(13)—N(14)—C(15)—N(16)	−12.3 (4)
O(3)—C(4)—C(9)—C(10)	−5.6 (5)	C(13)—N(14)—C(15)—N(21)	170.5 (4)
C(4)—C(9)—C(10)—C(11)	85.9 (4)	C(17)—C(19)—C(22)—C(23)	75.8 (5)
C(9)—C(10)—C(11)—C(12)	−176.7 (4)	C(19)—C(22)—C(23)—C(24)	−153.1 (5)
C(10)—C(11)—C(12)—C(13)	178.8 (4)	C(20)—C(19)—C(22)—C(23)	−105.7
C(11)—C(12)—C(13)—N(14)	−177.1 (4)	C(19)—C(22)—C(23)—C(28)	28.9

Table 4. *Interatomic distances* (Å) *and angles* (°) *associated with hydrogen bonding or contacts to counter-ions*

The superscript denotes the following equivalent position relative to the reference molecule at x, y, z.

Compound (1)

Br(1)···N(13)	3.366 (4)	B(1)···H(15)	2.502
Br(1)···N(15)	3.258 (4)	Br(1)···H(16)	2.318
Br(2)···N(20)^{i}	3.198 (4)	Br(2)···H(18)^{i}	2.336
Br(3)···N(1)	3.265 (4)	Br(3)···H(1)	2.240
Br(3)···N(24)^{ii}	3.212 (4)	Br(3)···H(22)^{ii}	2.289

Symmetry codes: (i) $4-x, -y, 2-z$; (ii) $1+x, -1+y, z$.

Compound (2)

N(20)···O(21)^{i}	2.771 (5)	O(21)···H(18)	1.898
N(20)—H(18)···O(21)^{i}	144.1		
N(13)···O(17)^{ii}	2.848 (5)	O(17)^{ii}···H(14)	1.910
N(13)—H(14)···O(17)^{ii}	162.1		
N(15)···N(15)^{ii}	2.877 (7)	N(15)^{ii}···H(15)^{ii}	1.885
N(15)···H(15)^{ii}—N(15)^{ii}	171.1		
O(21)···O(17)^{ii}	2.849 (5)	O(17)^{iii}···H(19)	2.034
O(21)—H(19)···O(17)^{iii}	172.3		
O(21)···O(21)^{iv}	2.850 (9)	O(21)···H(20)^{iv}	2.314
O(21)—H(20)···O(21)^{iv}	111.4		

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

Compound (3)

N(13)···O(117)^{i}	2.907 (4)	O(117)^{i}···H(14)	2.018
N(13)—H(14)···O(117)^{i}	169.0		
N(20)···O(117)^{i}	2.874 (4)	O(117)^{i}···H(16)	2.301
N(20)—H(16)···O(117)^{i}	168.0		
N(13)···O(127)^{i}	2.919 (6)	O(127)^{i}···H(14)	2.038
N(13)—H(14)···O(127)^{i}	165.7		
N(20)···O(127)^{i}	2.889 (6)	O(127)^{i}···H(16)	2.120
N(20)—H(16)···O(127)^{i}	149.3		
N(113)···O(17)^{ii}	2.954 (5)	O(17)^{ii}···H(114)	2.057

Table 4 (*cont.*)

N(113)—H(114)···O(17)^{ii}	173.9		
N(120)···O(17)^{iii}	2.911 (5)	O(17)^{iii}···H(116)	1.925
N(120)—H(116)···O(17)^{ii}	168.1		
N(113)···O(27)^{iii}	2.882 (7)	O(27)^{iii}···H(114)	2.018
N(113)—H(114)···O(27)^{ii}	160.4		
N(120)···O(27)^{ii}	2.867 (7)	O(27)^{ii}···H(116)	2.007
N(120)—H(116)···O(27)^{ii}	142.7		
N(20)···N(18)^{iii}	2.977 (4)	N(18)^{iii}···H(15)	2.047
N(20)—H(15)···N(18)^{iii}	172.6		
N(20)···N(28)^{iii}	2.962 (5)	N(28)^{iii}···H(15)	2.085
N(20)—H(15)···N(28)^{ii}	155.7		
N(120)···N(118)^{iv}	2.956 (4)	N(118)^{iv}···H(115)	2.103
N(120)—H(115)···N(118)^{iv}	154.2		
N(120)···N(128)^{iv}	2.990 (5)	N(128)^{iv}···H(115)	2.086
N(120)—H(115)···N(128)^{iv}	168.1		

Symmetry codes: (i) $-x, -y, 1-z$; (ii) $-1-x, -y, -z$; (iii) $-x, 1-y, -2-z$; (iv) $-1-x, -1-y, 3-z$.

Compound (4)

O(17)···N(13)^{i}	2.957 (12)	O(17)···H(14)^{i}	2.000
O(17)···H(14)—N(13)^{i}	174.1		
O(17)···N(20)^{i}	2.815 (12)	O(17)···H(15)^{i}	1.856
O(17)···H(15)—N(20)^{i}	178.5		

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

Compound (5)

N(5)···O(22)^{i}	2.799 (2)	O(22)^{i}···H(18)	1.899
N(18)—H(18)···O(22)^{i}	179.2		
N(20)···N(20)^{i}	2.863 (3)	N(20)^{i}···H(19)	1.970
N(20)—H(19)···N(20)^{i}	171.4		
N(25)···N(25)^{ii}	2.780 (3)	N(25)^{ii}···H(22)	2.013
N(25)—H(22)···N(25)^{ii}	142.3		

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

Compound (6)

O(23)···N(19)^{i}	2.860 (5)	O(23)^{i}···H(17)	1.849
O(23)···H(17)—N(19)	167.0		
O(23)···N(26)^{i}	2.873 (5)	O(23)^{i}···H(18)	2.006
O(23)···H(18)—N(26)^{i}	151.2		

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

Compound (7)

N(25)···O(30)	2.830 (3)	N(25)···H(29)	1.856
N(25)···H(29)—O(30)	176.4		
N(1)···O(30)^{i}	2.827 (3)	N(1)···H(28)^{i}	1.868
N(1)···H(28)^{i}—O(30)^{i}	174.9		
N(14)···O(30)^{ii}	2.993 (3)	O(30)^{ii}···H(17)	2.212
N(14)—H(17)···O(30)^{ii}	150.4		
N(16)···O(30)^{ii}	2.846 (3)	O(39)^{ii}···H(18)	2.014
N(16)—H(18)···O(30)^{ii}	140.7		

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

Compound (8)

N(13)···N(13)^{i}	2.909	N(13)···H(15)^{i}	2.01
N(13)···H(15)^{i}—N(13)^{i}	162.3	H(15)···H(15)^{i}	1.16
O(15)···N(11)^{i}	2.875	O(15)···H(14)^{i}	2.02
O(15)···H(14)^{i}—N(11)^{i}	173.0		
O(15)···O(26)^{ii}	2.973*		
N(24)···O(27)^{iii}	2.832	N(24)···H(27)^{iii}	1.68
N(24)···H(27)^{iii}—O(27)^{iii}	169.6		
O(26)···N(18)	2.82	O(26)···H(17)	1.97
O(26)···H(17)—N(18)	150.9		
O(26)···O(27)	2.945	O(26)···H(26)	1.94
O(26)···H(26)—O(27)	159.2		

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

Compound (9)

N(13)···N(13′)^{i}	2.879	N(13)···H(12′)^{i}	1.94
N(13)···H(12′)^{i}—N(13′)^{i}	168.8		
O(15)···N(11′)^{i}	2.798	O(15)···H(11′)^{i}	1.87
O(15)···H(11′)^{i}—N(11′)^{i}	166.3		
O(15′)···N(11)^{i}	2.864	O(15′)···H(11)^{i}	1.92
O(15′)···H(11′)^{i}—N(11′)^{i}	174.3		
N(24′)···N(18)^{ii}	2.904	N(24′)···H(13)^{ii}	2.01
N(24′)···H(13)^{ii}—N(18)^{ii}	156.9		

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

Compound (10)

N(8)···N(14)^{i}	3.000	N(8)···H(17)^{i}	2.09
N(8)···H(17)^{i}—N(14)^{i}	172.8		
O(18)···N(16)^{ii}	2.865	O(18)···H(18)^{ii}	1.89
O(18)···H(18)^{ii}—N(16)^{ii}	168.8		

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

* No H atom was found along the O(15)···O(26)^{ii} vector.

requires that both tautomeric forms are present in the crystal in a disordered array. In (9) both tautomeric forms are present without disorder and in (7) and (10) there is a single tautomeric form present in the crystal unambiguously defined by the crystallography and it is required to have the cyclic amide form (11). The four possibilities, the dication, the two tautomeric forms and the disordered mixture of tautomeric forms are best distinguished by their endocyclic ring angles at the N atoms.

Examination of the Cambridge Structural Database [see also Chatar Singh (1965)] indicates that, in six-membered rings, protonated N atoms have endocyclic angles $>120°$ and unprotonated N atoms endocyclic angles $<120°$. Further, N atoms in peptide-like linkages form —CO—NH—C— angles of about 124°, very significantly $>120°$. Thus, the expectation is that the dication should have both endocyclic angles at $N > 120°$. This is observed in oxmetidine dihydrochloride (Prout, Burns, Watkin, Durant & Brown, 1993). For (11), the expectation is that the angle at the cyclic-amide N atom should be about 124° and at the other N atom the endocyclic angle should be about 116°. For the alternative tautomeric form (12), the angle at the N adjacent to the carbonyl group would be less than in (11) and the other endocyclic N atom angle would be greater, thus both angles might be expected to be about 120°. For the disordered structures the angles should be an average of the values for forms (11) and (12). The crystal structure of the parent isocytosine has been described and contains both tautomeric forms (Sharma & McConnell, 1965). The observed endocyclic angles at N follow the predicted pattern and the observed bond lengths are consistent with the CNDO-predicted bond orders.

In (7) and (10), for which independent evidence from the hydrogen bonding indicates form (11), it is found that, for (7), the endocyclic angle at the cyclic amide N(16) atom is 123.5° and at the cyclic imine

Table 5. *A schematic overview of chain conformations defined by IUPAC conventions*

pyridyl—1st atom—[a]2nd atom—[b]3rd atom—[c]4th atom—[d]N

Compound	*a*	*b*	*c*	*d*
(1)	−*ap**	−*ap*	−*sc*	+*ap*
(2)	−*ap*	−*ap*	+*sc*	+*sc*
(3*a*)	+*sc*	−*ap*	−*sc*	+*ap*
(3*b*)	+*ap*	+*ap*	+*ap*	−*ap*
(4)	−*ap*	+*ap*	+*ap*	+*ap*
(5)	−*sc*†	−*ap*	+*sc*	+*ap*
(6)	−*ac*‡	+*ap*	+*sc*	+*ac*
(7)	+*ap*	−*ap*	−*sc*	+*ap*
(8)	−*ap*	−*sc*	−*sc*	+*ap*
(9)	Disordered			
(10)	−*ap*	*ap*	−*ap*	+*sc*

* Antiperiplanar.
† Synclinal.
‡ Anticlinal.

N(21) atom it is 114.9°. For (10), the angle at the cyclic amide N(21) is 122.6° and the angle at the cyclic imine N atom 116.4°. Thus, the endocyclic angles are consistent with the attribution. For (9) the molecules *B*, attributed form (11) from the hydrogen-bonding pattern, has endocyclic angles at N(13′) of 123.9° and N(18′) of 115.7°. These values are very similar to those observed in (10) and contrast sharply with the corresponding values for molecule *A* [N(13), 118.5°, and N(18), 119.2°], which in turn are generally consistent with protonation at N(18) and no protonation at N(13). For (9), the average of the values of the endocyclic angles at N(13) and N(13′) is 121.1°, and at N(18), N(18′) is 117.5°. These average values are remarkably close to the values of the endocyclic N atom angles observed for the distorted systems in (2), 121.5 and 117.5°, (5), 122.0 and 117.5° and (8), 122.0 and 117.4°, for which it is predicted that the disorder will average the interbond angles.

For (3) each thiadiazole group is found to be disordered over two locations. In the structure refinement chemically equivalent dimensions were constrained to be the same for each group at each location. The resulting dimensions do not differ significantly from those observed for (4) and (6). The dimensions indicate little π-electron delocalization over the whole cyclic system with long S—N bonds and C—C at the expected length for an sp^2—sp^2 single bond. However, the N—C bonds with an average length of about 1.31 Å show that there is considerable π character within the individual N—C—N groups. The whole —$CH_2NH(C_2N_2S)$-$NHCH_2$— is planar (Table 3) but the S atom is pyramidal.

For the substituted pyridine heterocycles any observed deviation from regular geometries follows the rules of Domenicano & Murray-Rust (1979). In (10) the 3-ethoxy group is coplanar with the aromatic ring and has a *trans* conformation with the CH_2 group away from the 2-butyl chain.

The four-atom chain is very flexible except in (7). The observed torsion angles in the four-atom connecting chain are given for each molecule in Table 3 and are summarized in accordance with IUPAC conventions in Table 5. For all examples, the first atom of the chain is necessarily coplanar with the pyridyl and the fourth is necessarily coplanar with the isocytosine or thiadiazole group. The tertiary-amino group in (5) and (6) is planar indicating a strong π-bonding interaction with the pyridyl π-aromatic system. Consequently, the second atom of the chain is coplanar with the pyridyl group. For

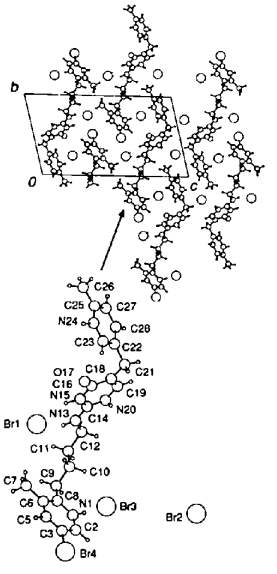


Fig. 1. 2-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone trihydrobromide, (1). The crystal structure seen in projection down *a* showing the hydrogen-bonded environments of the bromide ions.

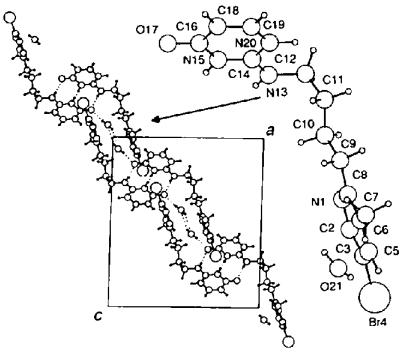


Fig. 2. 2-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-4-pyrimidone, (2). The partial crystal structure seen in projection down *b*. The molecules are hydrogen bonded to form dimers at the isocytosine residues about what must be pseudo-inversion centres at $\frac{3}{4},\frac{3}{4},\frac{3}{4}$, *etc.* in *I*2/*a*. In fact, only one molecule in any pair is protonated at N(15) and the other at N(20) to give one molecule in each of the two tautomeric forms (11) and (12). The water molecules lie in channels parallel to the *b* axis at 0,*y*,0, *etc.*

those compounds with butyl chains the bond *a* (Table 5) is coplanar with the pyridyl, in (2), or makes an angle of about 60° with the heterocycle plane in (3*a*) and (7), or an angle of about 90° with the pyridyl plane in (1), (3*b*) and (4). The conformation about the bond *a* is antiperiplanar (*ap*) in all except (3*b*) where it is synclinal (*sc*) and for the aminopropyl compounds it is (−)synclinal in (5) and (−)anticlinal in (6), but the observed torsion angles differ by only 16.5°. In all the molecules bond *b* is antiperiplanar. Bond *c* is (±)synclinal except in (3*b*) and (4), for which all the bonds in the chain are antiperiplanar. The conformation about bond *d* is antiperiplanar except for (2) [(+)synclinal] and (6) [(−)anticlinal]. (5) and (6) have a benzyl substituent on the first (N) atom of the chain. For each molecule the plane of the benzyl group is approximately perpendicular to the 2-aminopyridyl plane and includes

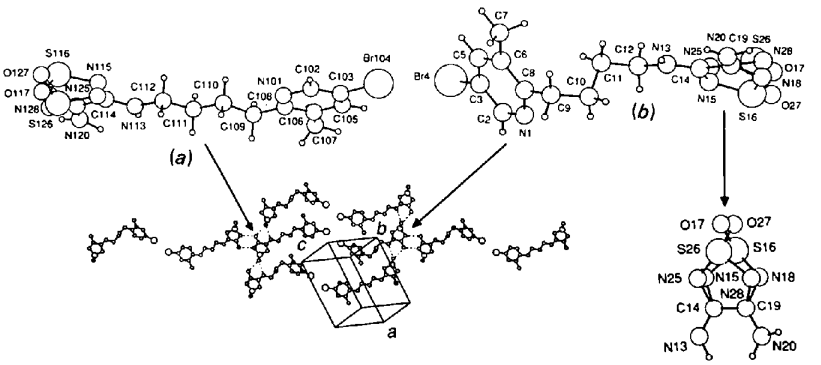


Fig. 3. 3-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-4-amino-1,2,5-thiadiazole-1-oxide, (3). The crystal structure seen in generalized projection perpendicular to the hydrogen-bonded molecular ribbons. The two molecules (*a*) and (*b*) of the asymmetric unit have been rotated from the view in the crystal structure to show the disorder of the thiadiazole which is highlighted in the inset. The amino H atoms on N(13) [N(113)] and N(20) [N(12)] chelate the sulfoxide O(17) atoms [O(27), O(117), O(127)] to form hydrogen-bonded chains of alternating (*a*) and (*b*) molecules. Pairs of (*a*) molecules and pairs of (*b*) molecules then hydrogen bond across inversion centres *via* N(18) and N(20), *etc.* to give the ribbons.

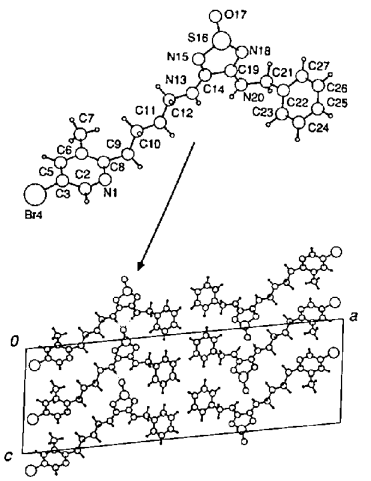


Fig. 4. 3-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-4-benzylamino-1,2,5-thiadiazole-1-oxide, (4). The crystal structure seen in projection down *b*. Hydrogen bonding from N(13) and N(20) of one molecule to O(17) of the molecule related by the operator $x, \frac{1}{2}-y, \frac{1}{2}+z$ links the molecules into corrugated ribbons parallel to the *a* axis.

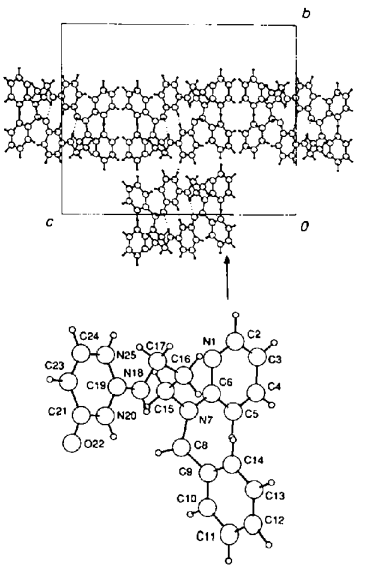


Fig. 5. 2-[3-(*N*-Benzyl-*N*-2-pyridylamino)propylamino]-4-pyrimidone, (5). The partial crystal structure seen in projection down *a*. The molecules are hydrogen bonded to form dimers at the isocytosine residues about what must be pseudo-inversion centres at 0,0,0, *etc.* in *Pbna* because, as in (2), only one molecule in any pair is protonated at N(15) and the other at N(20), to give one molecule in each of the two tautomeric forms (11) and (12). The dimers related by a pseudo-twofold axis at *x*, $\frac{1}{4}$,0, *etc.* are linked to form chains parallel to *b* by an N(20)—H···N(20) hydrogen bond between molecules, one in each of the two tautomeric forms (11) and (12).

the N—CH_2(benzyl) vector. Apart from the conformation at *d* the chains in (5) and (6) are virtually identical. (8) and (10) have *n*-buytl connecting chains. In (10) the butyl chain has the expected antiperiplanar conformation and is closely similar to that observed in burimamide (Kamenar, Prout & Ganellin, 1973). (8) has an unusual conformation for a butyl chain with (−)synclinal linkages at C(8)—C(9) and C(9)—C(10).

In (7) the butyl chain is conformationally restricted by the bridging propyl group from the pyridine to the side chain so that the first C atom is in a cyclohexene ring. The cyclohexene ring is however disordered over two conformations. The C(8) loca-

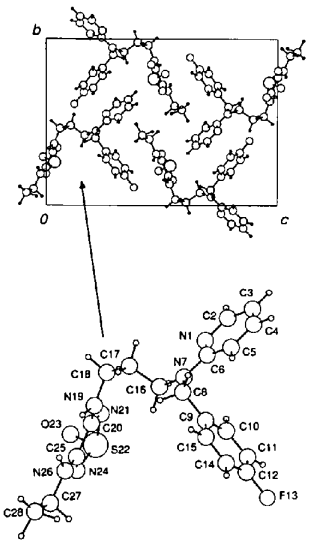


Fig. 6. 3-[3-(*N*-4-Fluorobenzyl-*N*-2-pyridylamino)propylamino]-4-ethylamino-1,2,5-thiadiazole-1-oxide, (6). The crystal structure seen in projection down *a*. Hydrogen bonding from N(19) and N(26) of one molecule to O(23) of the molecule related by a unit-cell translation in *a* links the molecules into chains parallel to the *a* axis.

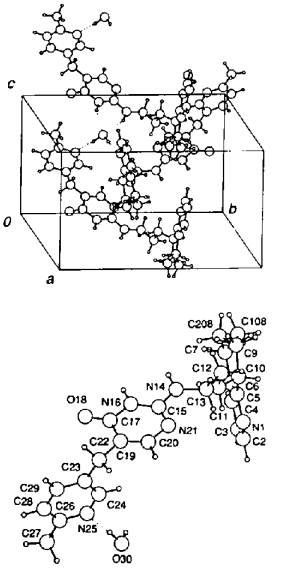


Fig. 7. 5-(6-Methyl-3-pyridylmethyl)-2-[3-(5,6,7,8-tetrahydro-8-quinolyl)propylamino]-4-pyrimidone, (7). The partial crystal structure seen in a generalized projection to illustrate the water environment which represents the only hydrogen bonding in the crystal. The molecule is present only as the tautomer (11) as shown.

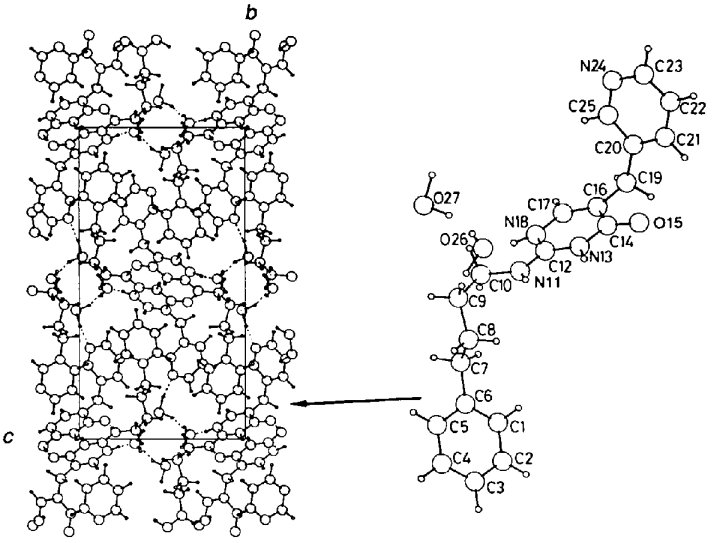


Fig. 8. 2-(4-Phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone, (8). The crystal structure seen in projection down *a*. The molecules are hydrogen bonded to form dimers at the isocytosine residues about what must be pseudo-inversion centres at 0,0,0, *etc* in $P2_1/c$. As in the previous examples the two molecules are one in each of the two tautomeric forms (11) and (12). The water molecules are in channels parallel to *a* at $x,\frac{1}{2},0$, *etc*. and are linked in hydrogen-bonded pairs.

tion is resolved into two, C(108) and C(208) (see *Experimental*). C(9) has an abnormally large temperature factor and C(10) is too flat for an sp^3 C atom so that further unresolved disorder must be assumed. The true torsional angles about the bonds C(6)—C(10), C(10)—C(9) and C(10)—C(11) will differ from the observed values by amounts greater than those suggested by the standard deviation in the atomic parameters. Nevertheless, modelling studies suggest that these deviations will only be of the order of a few degrees. In (9) the methylthioethyl chains are disordered in each of the two molecules in the asymmetric unit. For each molecule there are two resolved S atoms and presumably two chain conformations. Further, the first, C(7), and fourth, C(10), C atoms are well defined in each molecule and their locations must be common to each of the two conformations. For molecule *A* [C(1)—C(25)], the distance C(7)···C(10) is 3.44 Å and in molecule *B* [C(1′)—C(25′)], the analogous distance C(7′)···C(10′) is 3.92 (1) Å. The shorter distance is spanned either by two synclinal linkages C(7)—C(8) [(−)*sc*], S(8)—C(9) [(−)*sc*] or by a synclinal and an antiperiplanar linkage C(7)—S(81) [(+)*sc*], S(81)—C(9) [(−)*ap*]. However, the S(81)—C(9) distance, 2.299 (24) Å, is too long for an S—C bond and it is presumed that there is some unresolved disorder at the C(9) site. The longer distance is spanned by a synclinal and an antiperiplanar linkage in both cases; C(7′)—S(8′), S(8′)—C(9′) (+)*sc* and (+)*ap*, respectively, and C(7′)—S(81′), S(81′)—C(9′) (−)*sc* and (+)*ap*, respectively, with reasonable bond lengths and angles. Thus, there appears to be a difference in chain conformation in the two tautomeric forms.

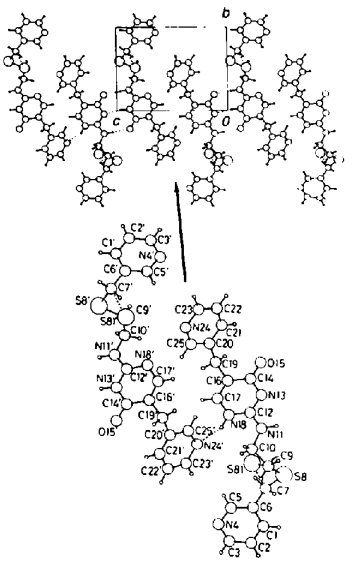


Fig. 9. 2-[2-(3-Pyridylmethylthio)ethylamino]-5-(3-pyridylmethyl)-4-pyrimidone, (9). The crystal structure, space group $P\bar{1}$, seen in projection down *a*. Two molecules, one in each of the tautomeric forms (11) and (12), link to form a near centrosymmetric hydrogen-bonded dimer and these dimers are linked into chains parallel to *c* by a hydrogen bond from N(18) of one molecule to N(24)′ of another [note the absence of the hydrogen bond N(24)···B(18)′].

For these histamine H_1 antagonists the torsion angles about the bonds between the first and second atoms and between the second and third atoms of the connecting chain have, for 16 out of a total of 20 observations, values near enough to 180° to be described as antiperiplanar, but in all reported X-ray structure analyses of molecules with the methylthio-

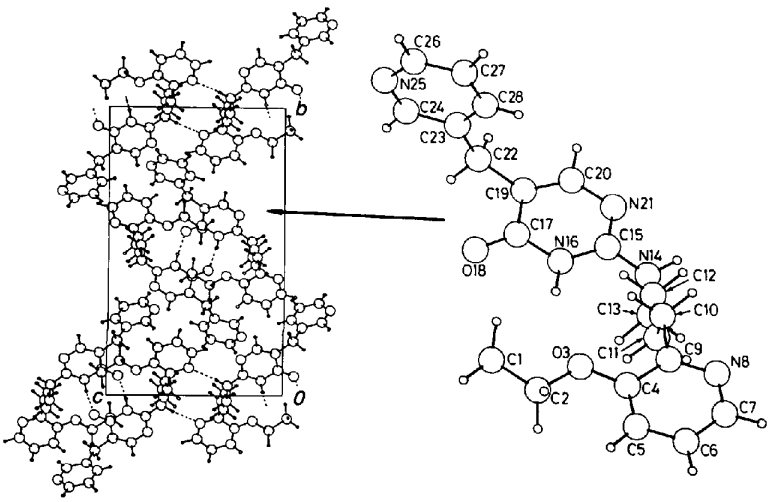


Fig. 10. 2-[4-(3-Ethoxy-2-pyridyl)butylamino]-5-(3-pyridylmethyl)4-pyrimidone, (10). The crystal structure seen in projection down *a*. The crystal contains only tautomer (11). These molecules are linked at the isocytosine residues by only two hydrogen bonds [contrast (2), (5) and (9)] to form hydrogen-bonded centrosymmetric dimers about the inversion centres at 0,0,0, *etc*, then they are further linked in pairs about the inversion centres at 0,0,$\frac{1}{2}$, *etc*. into ribbons by hydrogen bonds from the pyridine N(8) atom to the acyclic N(14) atom.

ethyl chains, there are no antiperiplanar linkages between the first atom and S, and S and the third atom. Although the butyl and methylthioethyl chains each have a variety of conformations in reported solid-state structures, the two groups of conformations have no conformations in common. To generalize, for this series of compounds the chains in the active H_1 antagonists tend to be more extended than in the H_2 antagonists.

Similar conformations of the connecting chain lead to the possibility of superposition of the significant hydrogen-bonding entities in similar isocytosine and thiadiazole-1-oxide entities. Thus, the conformations of (5) and (6) found in the crystal may be superposed with a good fit, Fig. 11. The benzyl substituents point in opposite directions, but a molecular-mechanics simulation predicts that the rotation of either benzyl group about the C—NH, to achieve a more complete superposition results in conformations little different in energy from those in the crystal. Further, if it is assumed that the isocytosine ring in (5) is protonated at N(20), *i.e.* tautomer (11), then this H atom superposes on the H atom of N(26) in (6), Fig. 12, but if (5) is protonated at N(25) *i.e.* tautomer (12), then no match is possible for the conformation of (5) and (6) in the crystal or any other low-energy conformation that also gives a match at the pyridyl group. Similar superpositions can be achieved for other isocytosine thiadiazole-1-oxide pairs if conformations close in energy to the global-minimum energy are used instead of the conformation found in the crystal. The conformation found in the crystal is itself close in energy to that of the global-minimum energy conformation.

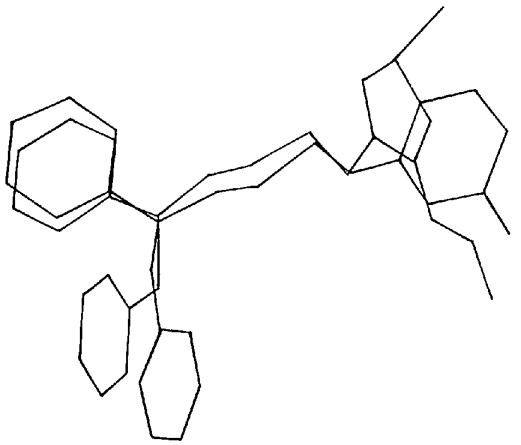


Fig. 11. The conformation of (5) found in the crystal superimposed on that of (6) also found in the crystal, matching the N atoms in the molecules. For clarity the H atoms are omitted.

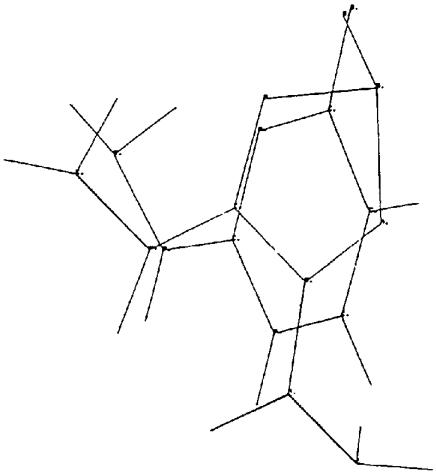
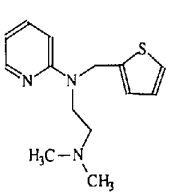


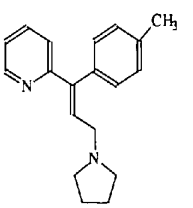
Fig. 12. Detail of the isocytosine, thiadiazole-1-oxide superposition for (5) and (6) showing the H atom positions.

Molecular-modelling studies on H_1 histamine antagonists

The compounds studied by crystallography were chosen subject to the constraint of the availability of suitable crystalline samples, but this picture of the conformational space and hence of structure activity relationships can be extended using molecular-modelling techniques. This extended study included the compounds of which the crystal structures are reported here: seven of the older types of H_1 antagonist: methapyrilene (13) (Clark & Palenik, 1972), *Z* isomer of triprolidine (Pepinsky, Rathlev & Turley, 1959) and triprolidine (14) (James & Williams, 1974*a*) and (15), (*R*)- and (*S*)-chloropheniramine (16) and (17) (James & Williams, 1974*b*), diphenylpyraline (18) (Precigoux, Barrans, Busetta & Marsau, 1975), clemastine (19) (Ebnother & Weber, 1976), and cyproheptadine (20) (Birknes, 1977); five thiadiazole-1-oxide derivatives compounds, (21)–(25), that had been synthesized and screened for H_1 antagonist activity; the isocytosines (26), (27) and (28).



(13)



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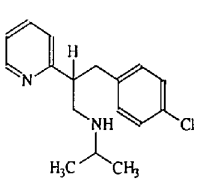

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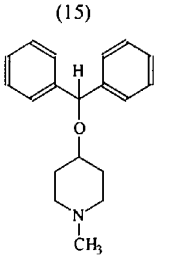

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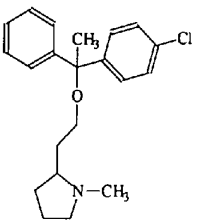

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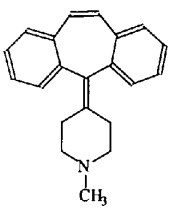

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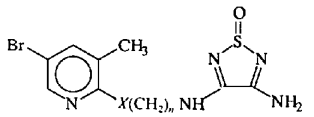
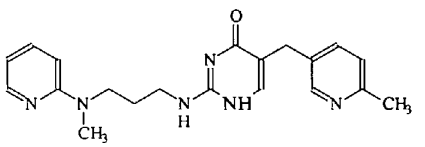


(3) $X = CH_2$ $n = 3$ (21) $X = NH$ $n = 3$
(22) $X = O$ $n = 3$ (23) $X = CH_2$ $n = 2$
(24) $X = NH$ $n = 2$ (25) $X = O$ $n = 2$



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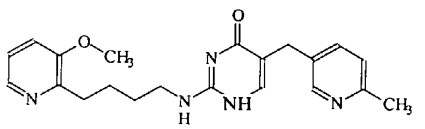

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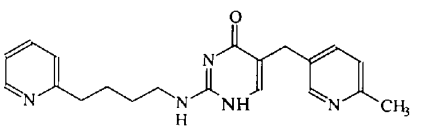
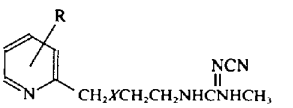


(28)

These molecules all have the chemical characteristics that might reasonably be associated with histamine H_1 antagonism but exhibit a wide range of activities and common to all molecules are an aromatic ring and a basic N atom separated by a more or less flexible chain. Those with common functional groups might be assumed to bind *via* the same specific interactions to the same receptor and, in the conformations of the antagonists associated with biological activity, must be able to adopt similar relative positions. It is postulated that the availability of a low-energy conformation(s) that satisfies this criterion will be strongly correlated with biological activity but it is also recognised that, in such a group of compounds, there will be many factors influencing activity and the conformational properties will only be a part of these.

The significance of the aromatic ring to the basic N group in the crystal structures of long established and specific H_1-histamine antagonists has been studied previously, and it has been shown that high activity is associated with a pyridyl N atom (or corresponding aromatic C atom) to quaternary N-atom separation distance of between 5.2 and 6.0 Å. In a separate study Prout, Burns, Watkin, Cooper, Durant, Ganellin & Sach (1993) have shown that for a series of specific H_2 antagonists of general formula (29), the most active molecules have a predominance of conformations in which the separation distance $N^{i}\cdots N^{ii}$ is less than 5 Å, where N^{i} is the pyridine N atom and N^{ii} the N atom of the guanidine to which the four-atom chain is attached.



(29)

Conformational analysis

The conformational space of the molecules was explored using the *COSMIC* program system (Vinter *et al.*, 1987) which generated the 100 lowest energy conformations or all those conformations within 5 kcal mol^{-1} of the overall minimum, whichever was the smaller. These low-energy conformations were then searched for those conformations in which an N···N separation, analogous to the pyridyl N to quaternary N distance in the established H_1 antagonists, was in the region 5.2–6.0 Å. If the molecule did not contain an aromatic N atom, the corresponding aromatic C atom was chosen and if there were two aromatic groups, then both were considered. Other measures of chain extension were considered, for example, aromatic ring centroid to amine N, but the results are not reported because they did not significantly enhance the conclusions.

The results are recorded in Table 6. For the three compounds, (14), (24) and (25), that have maximum N···N separations of < 5.4 Å the biological activity is low. Another molecule, diphenylpyraline, (18), with low activity has a large maximum interatomic separation (7.8 Å) and its minimum separation is also rather large at 5.2 Å, and it is possible this molecule tends to adopt conformations that are too extended for high activity. Correlations were sought between the percentage of these conformations with particular N—N distances and biological activity, Table 6. For a representative group of established histamine H_1 antagonists (13)–(19), Fig. 13 shows pA_2 (Schild, 1947) *versus* the percentage of the lowest energy conformations with the N···N distance in the region 5.2–6.0 Å. The plot shows that, as might be expected, there is a general trend suggesting that activity is associated with large percentages of conformations meeting the distance requirement.

The 1,2,5-thiadiazole-1-oxide compound (3) has a molecular structure that is not obviously related to

Table 6. *Separations* (Å) *between pyridyl* N *atoms* (*or equivalent* C *atoms*) *and amine* N *atoms for the* H_1*-histamine antagonists*

		Ring 1* (pyridyl)			Ring 2*				
		Max.	Min.	%N···N†	Max.	Min.	%N···N†	$pA_2(H_1)$ ileum‡	$pA_2(H_2)$ atrium§
(1)	Temalastine	6.9	2.8	22	-	-		9.55	~5.7¶
(2)		6.2	3.2	36	-	-	-	8.8	< 4.27
(3)		7.2	2.6	32		-		8.9	< 4.27
(4)		6.2	2.9	38	-	-		7.8	< 4.27
(5)		6.6	3.0	42	7.8	3.4	35	8.36	< 4.74
(6)		6.8	2.6	25	7.4	3.0	35	8.07	< 4.27
(7)		6.0	3.4	34	-	-	-	8.92	< 4.27
(8)		-	-	-	-	-	-	7.36	6.32
(9)		7.8	3.4	24	-	-	-	6.18	5.90
(10)		6.2	2.9	32	-	-	-	7.65	6.71
(13)	Methapyrilene	6.0	2.4	29	7.4	2.6	37	8.63	Not tested**
(14)	(*Z*)-Triprolidine††	5.4	2.2	4	6.4	5.0	40	6.9	Not tested
(15)	Triprolidine††	6.2	2.6	56	6.0	2.4	16	9.9	Not tested
(16)	Chlorpheniramine (*R*)	6.2	2.6	36	6.2	2.8	29	7.5	Not tested
(17)	Chlorpheniramine (*S*)	5.6	3.0	21	6.2	2.8	21	9.3	Not tested
(18)	Diphenylpyraline	7.8	5.2	18	>8	5.4	21	6.8	Not tested
(19)	Clemastine	>8	3.0	31	>8	2.8	48	9.4	Not tested
(21)		6-6	2.4	11	-	-	-	8.69	Not tested
(22)		6.6	2.6	13	-	-	-	8.12	Not tested
(23)		6.0	2.4	16	-	-	-	8.54	Not tested
(24)		5.2	2.4	0	-	-	-	7.13	Not tested
(25)		5.2	2.2	0	-	-	-	5.93	Not tested
(26)		6.2	2.8	10	-	-	-	8.35	4.36
(27)		6.6	2.6	21	-	-	-	7.77	7.49
(28)		7.0	3.2	24	-	-	-	7.28	7.49

* Refers to the two aromatic rings as defined in the text.

† Refers to the percentage of the low-energy conformations (within 5 kcal of the global minimum) with N···N separation distances from the aromatic N atom to the first N atom in the side chain in the 5.2–6.0 Å region.

‡ H_1-receptor histamine antagonism.

§ H_2-receptor histamine antagonism.

¶ Slope < 0.5 non-competitive.

** Not tested but of a class of compound known to be H_2 inactive.

†† Triprolidine has an *E* configuration about the double bond.

the established antihistamines but it is highly active as an H_1 antagonist and has, in the crystal, appropriate N···N separations of 5.754 (4) and 6.562 (3) Å in the two molecules of the asymmetric unit. The conformational space of this and the related 1,2,5-thiadiazole-1-oxides (21)–(25) was explored and pA_2 was plotted *versus* the percentage of conformations with N···N in the 5.2–6.0 Å range in Fig. 13. As with the established antihistamines there is general

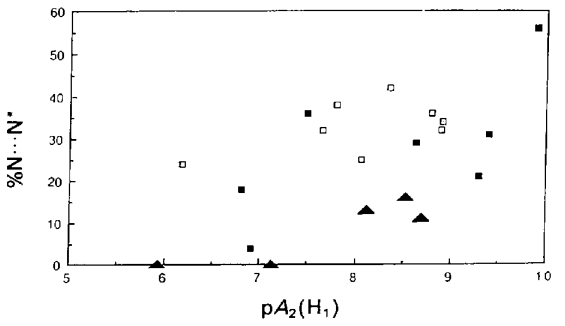


Fig. 13. Scatter plot of activity *versus* number of conformations of low energy with N···N* distances in the region of 5.2–6.9 Å for (■) established H2 antihistamines, (▲) thiadiazole-1-oxide derivatives and (▪) isocytosine derivatives.

increase in H_1 activity as the percentage of extended conformations increases. For the isocytosine series no correlation is seen, Fig. 13.

Thus, it may be that there is a general relationship between N···N separation and activity, but there must be the expectation that there is an associated specific stereochemistry for interaction with the receptor. To investigate this, the conformationally flexible antagonists were compared with the rigid H_1 antagonist cyproheptadine (20), which has only two conformations, both with the piperidine ring in the chair form, one as in Fig. 14 and the other related to this by an apparent rotation of 180° about the exocyclic double bond; the N···N separations are 5.70 and 5.14 Å, respectively. The relative positions of the aromatic ring and amine group may be defined by the vector between the pyridyl N atom (or equivalent) and the amine N atom referred to the axes defined relative to the aromatic ring, as seen in Fig. 14. One axis lies along the C_a—C_b bond, the second is perpendicular to the first and in the plane of the aromatic ring, and the third is mutually perpendicular to these two. The corresponding vector for the second conformation is similarly defined. To attempt to quantify the results the conformations were compared with those of cyproheptadine by

calculating two 'measures of fit' (m.o.f.): (1) a vector length criterion in terms of the distance of the amine N atom from pyridyl (or equivalent) and (2) a vector-direction criterion in terms of the three vector components (ignoring chirality). The measure of fit for a conformation was defined as: m.o.f. = exp[−(value in cyproheptadine − value in their particular conformation)]^2.

The Gaussian form was chosen because it has a maximum value of 1.0 when the conformation matches exactly and its gradient is gentle where the difference in values is small. The latter property is an advantage because it is not certain that the cyproheptadine separation is the optimal value for binding at the receptor, so some leeway is desirable. Conformations were considered to match if they gave m.o.f.s better than 0.9 for distance and 0.5 for each vector component. These limits were chosen after tighter criteria for the vector components had been tried and found to give very few matches. The matches for the two conformations are summarized in Table 7.

The poorly active compounds discussed previously, including diphenylpyraline, failed to match either cyproheptadine conformation. However, four much more active antagonists also failed to match, these being methapyrilene and triprolidine, (23) and (26). It was suspected that a representative picture of conformational space was not obtained in all cases, such as in the case of triprolidine. This is because of the difficulty the molecular-mechanics method has with conjugated π-systems. For the other molecules, it may simply be the limited number of conformations *COSMIC* retains.

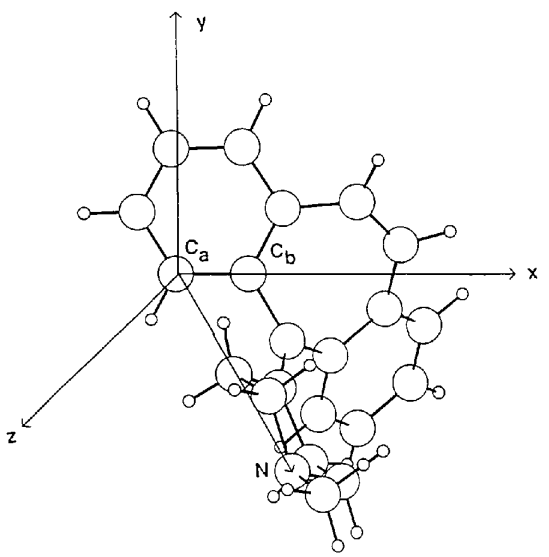


Fig. 14. A molecule of cyproheptadine in the conformation found in the crystal (Birknes, 1977) showing the coordinate system used to define the N···N vector and indicating its direction.

Table 7. *Numbers of conformations with vectors matching those of cyproheptadine and satisfying the m.o.f. defined in the text*

Cyproheptadine conformation (1) *is as defined by* Fig. 12 *and conformation* (2) *is the related conformation defined in the text.*

		Cyproheptadine conformation (1)	(2)
(2)		8	5
(3)		11	1
(5)		0	13
(6)		1	2
(7)		22	21
(13)	Methapyrilene	0	0
(14)	*Z*-Triprolidine	0	0
(15)	Triprolidine	0	0
(16)	Chlorpheniramine (*R*)	0	4
(17)	Chlorpheniramine (*S*)	3	0
(18)	Diphenylpyraline	0	0
(19)	Clemastine	2	4
(21)		2	2
(22)		0	3
(23)		0	0
(24)		0	0
(25)		0	0
(26)		0	0

Some of the molecules have more than one aromatic ring and as has been indicated, it was the pyridyl which was used to produce the results above. However, the calculations were also performed for the other ring and the results are given in Table 6. Generally, in low-energy conformations the significant atom of the second ring is further away from the basic N atom and the measured distance correlates less well with biological activity. This is particularly true for *cis*-triprolidine, but since this is a poorly active antagonist the correlation is not so good using this ring. This result is not surprising since, although the presence of the second ring may enhance activity, it is in no way essential to activity.

Concluding remarks

The results may indicate that for good H_1-histamine activity, a molecule should be able to attain a particular separation between the aromatic ring and amine N atom. The values observed for cyproheptadine (5.3–5.6 Å between the C adjacent to the chain and amine N) seem optimal. The optimal orientation of the ring is more difficult to define. The above approach has assumed the cyproheptadine conformations to be ideal. This is probably not the case at least in part because of the significant role played by entropy effects in determining the activity of rigid molecules. Comparing distances and vectors between all the molecules, not just with cyproheptadine, would give a less biased indication of an ideal conformation. In any case, better methods for searching conformational space are required.

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Structure of the Stacked Cyclic Oligoamides: 1,6-Diaza-2,7-cyclodecadione and 1,5,9-Triaza-2,6,10-cyclododecatrione. A Ring Model of the α-Helix

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Abstract

The structure of two cyclic amides, comprised of methylene and peptide groups, is described. The cyclic amides form parallel columns of stacked hydrogen-bonded rings. The cyclic dimer of butyramide (1,6-diaza-2,7-cyclodecadione) (I), $C_8H_{14}N_2O_2$, forms monoclinic crystals, space group $P2_1/n$, $a = 4.874$ (2), $b = 11.714$ (4), $c = 8.088$ (2) Å,

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