KARLBERG, B. E., LARSSON, R., OHMAN, K. P., NORLANDER, B., WIRSEN, A., HED, J., LUNDH, B. L. & FLOCK, A. (1983). *Eur. J. Clin. Pharmacol.* **25**, 179–186.

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

TAYLOR, E. M., CAMERON, D., EDEN, R. J., FIELDEN, R. & OWEN, D. A. A. (1981). *J. Cardiovasc. Pharmacol.* **3**, 337–354.

TAYLOR, E. M., ROE, A. M. & SLATER, R. A. (1979). *Clin. Sci.* **57**, 433S-436S

WATKIN, D. J., CARRUTHERS, J. R. & BETTERIDGE, P. W. (1985). *CRYSTALS User Guide.* Chemical Crystallography Laboratory, Univ. of Oxford, England.

Acta Cryst. (1994). **B50**, 71–85

Crystal and Molecular Structures of Pyridazinone Cardiovascular Agents

BY KEITH PROUT,* COLIN BANNISTER, KEITH BURNS AND MINGQIN CHEN

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

AND BRIAN H. WARRINGTON AND J. G. VINTER†

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

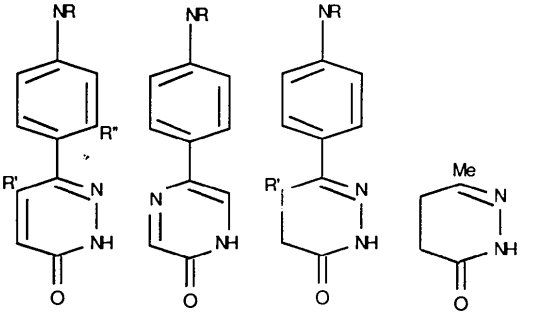
(*Received* 6 *April* 1993; *accepted* 7 *June* 1993)

Abstract

The crystal and molecular structures of 11 6-substituted pyridazinone derivatives: 6-phenyl-3(2*H*)-pyridazinone–acetic acid (1/1) (1), 6-(4-aminophenyl)-3(2*H*)-pyridazinone (2), 6-(4-aminophenyl)-5-methyl-3(2*H*)-pyridazinone (3), 6-(4-acetamidophenyl)-3(2*H*)-pyridazinone (4), 6-(4-acetamido-2-methoxyphenyl)-3(2*H*)-pyridazinone (5), 6-(2-aminophenyl)-3(2*H*)-pyridazinone (6), 6-phenyl-3(2*H*)-pyrazinone (7), 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (8), (*R*)-(−)-6-[4-(3-bromopropionamido)phenyl]-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (9), (*R*)-(−)-6-(4-ammoniophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (−)-tartrate–dichloromethane–methanol (1/1/1) (10), 4,5-dihydro-6-methyl-3(2*H*)-pyridazinone (11) have been determined as part of a study to determine the relationship between their cardiovascular properties and molecular structure and dimensions. For the two optically resolved chiral derivatives (9) and (10) the absolute configuration has been determined.

Introduction

The crystal and molecular structures of compounds (1)–(11) were determined as part of an investigation into quantitative structure–activity relationships in pyridazinone derivatives as antiaggregatory, antihypertensive and inotropic agents.



Peripheral vasodilator agents are in clinical use to lower blood pressure; however, the reduction of blood pressure initiates the activation of β-adrenoceptors in the heart with a consequent undesirable increase in heart rate. These undesirable effects of vasodilators are inhibited by β-adrenoceptor antagonists with the result that the combined use of vasodilators and β-blockers has been widely adopted for the treatment of hypertension. An effort by SmithKline Beecham Research to combine the vasodilator and β-blocker function in the one molecule

* Author for correspondence.

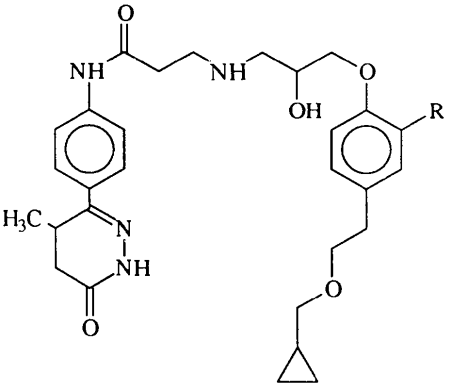
† Present address: Baylays Glen, Weston, Hitchin, Herts SG4 7AS, England.

led to the development of the hydrazinopyridazine, prizidilol (Taylor, Cameron, Eden, Fielden & Owen, 1981; Taylor, Roe & Slater, 1979; Prout, Burns & Roe, 1993). Although long-term toxicological effects prevented the completion of the development of prizidilol, substantially favourable clinical data established the therapeutic significance of the combination of vasodilator and β-blocker functions in the same molecule. In the search for alternative antihypertensive agents with a similar therapeutic profile, attention focused on non-hydrazino derivatives (Slater, Howsen, Swayne, Taylor & Reavil, 1988). These authors noted that a large series of 6-arylpyridazinones had been earlier identified as having antihypertensive properties in animals. They also have some formal resemblance to the vasodilator function of prizidilol but lack the hydrazine moiety.

Subsequently, a large selection of pyridazinones were shown to be effective phosphodiesterase (III) inhibitors (Bakewell, Coates, Corner, Reeves & Warrington, 1990; Coates, Prain, Reeves & Warrington, 1990) and the hypothesis that these compounds were electronically mimicking c-AMP was successfully used to construct a predictive model for these and other known cardiovascular drugs (Davis, Warrington & Vinter, 1987; Vinter, Davis & Saunders, 1987).

In the course of modelling the pyridazinones, X-ray investigations were important in collecting data concerning the environment of the pyridazinone oxygen which was thought to mimic one of the phosphate oxygens of c-AMP. Furthermore, the extent of planarity of the phenyl ring with the hetero ring needed investigation. Other properties such as bond lengths (bond order), and particularly the disposition of the chiral 5-methyl group on the highly active 5-methyl-6-phenyl-4,5-dihydropyridazinones (9) and (10) could be elucidated by crystallography.

Molecules (1)–(6) are diaryl systems where one ring is a pyridazinone and the other ring is phenyl. In three of these molecules the phenyl ring is substituted at the 4-position [4-amino (2) and (3), 4-acetamido (4) and (5)] and in two molecules in the 2-position [2-methoxy (5) and 2-amino (6)]. In (3) the pyridazinone ring has a 5-methyl group. Substitution at the 5-pyridazinone position leads to a reduction in biological activity whereas the presence of the 2-aryl substituent does not. Compound (7) is an aryl pyrazinone, the structure of which was included for purposes of comparison. In compounds (8) to (11) the 4,5-ene double bond has been reduced and in (9) and (10) an asymmetric centre has been introduced at the 5-position. (9) and (10) are optically resolved and the crystals examined were of the most active enantiomer. (9) is the synthetic intermediate in the synthesis of a new series of compounds based on (12) (Bakewell, Coates, Corner, Reeves & Warrington, 1990; Coates, Prain, Reeves & Warrington, 1990).



(12)

Experimental

All samples were prepared by SmithKline & French Research Ltd (W. J. Coates, S. J. Bakewell, B. H. Warrington, H. D. Prain, R. A. Slater, W. Howson, D. R. Reavil & R. Novelli) and were characterized by elemental analysis, proton NMR and infra-red and mass spectrometry. The crystals were grown in Oxford and, after preliminary X-ray precession and Weissenberg photography, the X-ray data were collected with an Enraf–Nonius CAD-4 diffractometer, following the procedures recommended in the manufacturer's manual. 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 absorption when Cu $K\alpha$ radiation was used. All calculations were carried out on a VAX 11/750 computer using *MULTAN*78 or *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) for direct methods and *CRYSTALS* (Watkin, Carruthers & Betteridge, 1985) for all other calculations. Atomic scattering factors and anomalous-dispersion corrections were taken from Cromer & Waber (1974).

Although the molecules are fairly simple and very similar, the crystal structures proved quite difficult to solve. For compounds (8) and (9) with two molecules in the asymmetric unit there were particular difficulties that are described later. For the rest, the molecular skeletons are to a good approximation centrosymmetric and planar. Direct methods tend to give a 'chicken-wire' pattern in the E map typically associated with multi-ring aromatics. The orientation of the molecule could, with more or less difficulty, be recognized from this pattern, and the data renormalized. Rephasing then gave a fairly clean E map. The trial structure was then refined by full-matrix least

Table 1. *Crystal data, data-collection parameters and information on the refinement*

	(1) $C_{10}H_8N_2O.CH_3CO_2H$	(2) $C_{10}H_9N_3O$	(3) $C_{11}H_{11}N_3O$	(4) $C_{12}H_{11}N_3O_2$	(5) $C_{13}H_{13}N_3O_3$	(6) $C_{10}H_9N_3O$
M_r	232.24	187.2	201.23	229.24	259.27	187.2
Crystal class	Monclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
a (Å)	10.128 (3)	9.000 (4)	8.017 (2)	4.434 (1)	17.048 (2)	7.360 (2)
b (Å)	11.035 (4)	9.398 (1)	7.199 (5)	15.267 (2)	9.50 (1)	7.469 (3)
c (Å)	11.198 (4)	11.355 (8)	8.944 (2)	17.045 (2)	7.540 (2)	33.061 (7)
α ( )	90	90	90	90	90	90
β ( )	113.71	110.97 (4)	98.29	69.42 (2)	90.57 (2)	90
γ ( )	90	90	90	90	90	90
V (Å^3)	1145.87	896.84	510.81	1080.23	1221.1	1817.5
Space group	$P2_1/c$	$P2_1/a$	$P2_1$	$P2_1/c$	$P2_1/c$	$Pbca$
Z	4	4	2	4	4	8
D_x (Mg m^{-3})	1.35	1.38	1.31	1.41	1.41	1.36
$F(000)$	488	392	212	480	544	784
Crystal size (mm)	0.9 × 0.9 × 0.5	1.0 × 0.85 × 0.43	0.5 × 0.3 × 0.4	0.17 × 0.2 × 0.45	0.2 × 0.12 × 0.9	0.4 × 0.15 × 0.8
Radiation	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$
μ (cm^{-1})	1.06	1.02	0.95	5.9	6.14	5.67
$\sin(\theta/\lambda)_{max}$	0.62	0.64	0.704	0.63	-	0.63
h_{min}–h_{max}	−11–11	−11–10	−11–11	−5–5	−21–21	−1–9
k_{min}–k_{max}	−1–13	−1–11	−1–10	−1–19	−1–11	−1–9
l_{min}–l_{max}	−1–13	−1–14	−1–12	−1–21	−1–9	−1–40
No. of reflections measured	3787	3297	2637	4148	4268	4452
No. of independent reflections	2253	1703	1598	-		-
R_{int} (%)	5.37	2.77	2.58	-	-	-
No. of observed [$I > 3\sigma(I)$] reflections	1201	668	1158	1725	2096	1485
R (%)	6.09	3.91	4.53	3.88	4.78	6.25
wR (%)	7.97	4.32	5.78	5.2	6.66	8.95
No. of parameters	204	137	148	166	186	137
R.m.s. (shift/e.s.d.)	0.12	0.25	0.36	0.62	0.81	0.58
ρ_{max} (e Å^{-3})	0.4	0.16	0.1	0.16	0.33	0.30
ρ_{min} (e Å^{-3})	-	−0.16	−0.29	−0.17	−0.32	−0.32
Weights	66.9 66.0	9.2 12.4 4.0	63.3 79.5 17.7	66. 60.9	383 479 103	2245 3187 1150 197

	(7) $C_{10}H_8N_2O$	(8) $C_{10}H_{11}N_3O$	(9) $C_{14}H_{15}BrN_2O_2$	(10) $C_{11}H_{14}N_3O.C_4H_3O_6.CH_2Cl_2.CH_3OH$	(11) $C_5H_6N_2O.H_2O$
M_r	172.19	189.22	337.2	470.31	130.15
Crystal class	Monoclinic	Triclinic	Monoclinic	Orthorhombic	Orthorhombic
a (Å)	7.612 (4)	7.470 (2)	10.960 (2)	7.162 (3)	6.417 (1)
b (Å)	5.765 (4)	11.520 (2)	9.697 (6)	8.026 (3)	6.892 (2)
c (Å)	19.249 (4)	11.898 (4)	13.5885 (8)	39.96 (2)	15.629 (5)
α ( )	90	112.85 (2)	90	90	90
β ( )	101.30 (4)	102.06 (2)	98.644 (9)	90	90
γ ( )	90	96.57 (2)	90	90	90
V (Å^3)	828.27	900.7	1428.3	2297.1	691.19
Space group	$P2_1/c$	$P\bar{1}$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
Z	4	4	4	4	4
D_x (Mg m^{-3})	1.38	1.4	1.57	1.36	1.25
$F(000)$	360	400	684	984	280
Crystal size (mm)	0.4 × 0.6 × 0.8	0.4 × 0.5 × 0.65	0.75 × 0.5 × 0.3	0.7 × 0.5 × 0.25	1 × 1 × 0.5
Radiation	Mo $K\alpha$	Mo $K\alpha$	Cu $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (cm^{-1})	1.01	1.02	39.91	3.25	0.9117
$\sin(\theta/\lambda)_{max}$	0.725	0.6	0.63	0.63	0.68
h_{min}–h_{max}	−11–10	−8–8	−13–13	−6–8	−1–8
k_{min}–k_{max}	−1–8	−13–12	−12–12	−9–9	−1–8
l_{min}–l_{max}	−1–27	−1–13	−1–17	−1–44	−1–21
No. of reflections measured	2625	4207	6838	5653	1585
No. of independent reflections	2582	3164	5758	3828*	1090
R_{int} (%)	3.99	3.38	1.28	4.52	3.82
No. of observed [$I > 3\sigma(I)$] reflections	1430	1847	5625	1662	845
R (%)	4.64	4.17	2.97	9.84	6.04
wR (%)	6.26	5.18	4.03	10.01	7.57
No. of parameters	127	321	394	290	93
R.m.s. (shift/e.s.d.)	0.44	0.10	0.18	0.18	1.04
ρ_{max} (e Å^{-3})	0.33	0.21	0.86	1.31	0.48
ρ_{min} (e Å^{-3})	−0.27	-	−0.98	−1.02	−0.18
Weights	148 194 48	55.3 72.1 17.4	236 399 69	9.5 −0.95 5.76	13.7 6.38 9.62

* Including Friedel pairs.

squares and heteroatoms identified. The H atoms were located by calculating the difference electron density in the ring planes and the planes defined by the expected methyl hydrogen positions. In the final refinement the positions or thermal parameters or all parameters of the H atoms were included according to a individual circumstances and extinction parameters were refined. The least-squares refinement minimized $\sum w||F_o| - |F_c||^2$ and used a truncated Chebyshev polynomial weighting scheme with 2, 3 or 4 coefficients (Carruthers & Watkin, 1979).

(1) 6-Phenyl-3(2*H*)-pyridazinone–acetic acid (1/1). Large transparent tablets of a solvate were obtained from acetic acid solution. Over 24 h these crystals lost solvent and became chalk-like and opaque. For the data collection a crystal was sealed in a capillary held in the meniscus of its mother liquor. During the last 8 h of data collection, the crystal became opaque and the control reflections rapidly declined to 77% of their initial value at which point the data collection was stopped. Although a correction for crystal decomposition was applied the accuracy of many

high-order reflections was undoubtedly reduced. No reflections were eliminated from the data and a larger final R resulted. The structure was determined by direct methods (*MULTAN*80) and refined with a two-block approximation (space and temperature parameters) to the normal matrix. For the H atoms positional and isotropic temperature parameters were refined.

(2) 6-(4-Aminophenyl)-3(2*H*)-pyridazinone. Long needle-like yellow crystals were obtained from the slow evaporation of a saturated solution in ethanol. The structure was determined using *MULTAN*78, and refined by full-matrix least squares. The H-atom isotropic temperature factors, U, were fixed at 0.05 Å^2.

(3) 6-(4-Aminophenyl)-5-methyl-3(2*H*)-pyridazinone. Light-brown brick-shaped crystals were prepared by the slow cooling of a saturated solution in ethanol. The structure was solved with *MULTAN*78, with ease, perhaps because the molecular skeleton is noncoplanar, and was refined by full-matrix least squares. The y parameter of C(8) was used to fix the origin. The H-atom positional and temperature factors were refined.

(4) 6-(4-Acetamidophenyl)-3(2*H*)-pyridazinone. Long colourless needle-like crystals were obtained from a slowly cooled saturated solution in dimethylformamide. The structure was determined by direct methods using *MULTAN*80 and refined by full-matrix least squares. The H-atom temperature factors were refined, but not the positional parameters.

(5) 6-(4-Acetamido-2-methoxyphenyl)-3(2*H*)-pyridazinone. Needle-like colourless crystals were obtained from a slowly cooled saturated solution in dimethylformamide. The structure was determined by direct methods *MULTAN*80 and refined by full-matrix least squares. The H-atom temperature factors were refined, but not the positional parameters.

(6) 6-(2-Aminophenyl)-3(2*H*)-pyridazinone. Flat yellow crystals were obtained from the slow cooling of a saturated solution in ethanol. The structure was solved by direct methods using *MULTAN*80 and refined by full-matrix least squares. The H atoms were located but not refined.

(7) 6-Phenyl-3(2*H*)-pyrazinone. Orange tablet-like crystals obtained from a slowly cooled saturated solution in ethanol. The structure was solved by direct methods using *MULTAN*78 and refined by least squares with a two-block approximation, one for positions and one for temperature parameters. The H-atom temperature factors (U) were set to 0.05 Å^2 and not refined.

(8) 6-(4-Aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone. The crystals were obtained as small cubes by the slow cooling of saturated solution in ethanol. The asymmetric unit contains two molecules. All attempts to solve the structure by direct methods gave 'chicken-wire' patterns that could not be successfully interpreted. Each molecule as seen by X-rays approximates to a pseudocentrosymmetric 4,4′-disubstituted diphenyl skeleton and, if the two molecules in the asymmetric unit have parallel molecular planes, then they are related by a noncrystallographic symmetry centre. In the Patterson in addition to the typically hexagonal patterns associated with phenyl groups that define the molecular plane, there will be a set of large peaks resembling those from a linear grouping of three heavy atoms, one located at the centre of gravity of the diphenyl skeleton and one at the centre of each phenyl ring. These large peaks and the associated hexagonal patterns were identified, enabling the orientation and position of the molecules to be established. Still assuming a 4,4′-disubstituted diphenyl model an electron density distribution was calculated that revealed the true structure. The heteroatoms were identified and the structure refined using a two-block (space and temperature parameters) approximation to the normal matrix. The H-atom temperature factors were not refined.

(9) (−)-6-[4-(3-Bromopropionamido)phenyl]-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone. Tabular crystals were grown by slow evaporation of a solution in methanol. The sample was optically resolved and thus contained only one enantiomer with the asymmetric centre in the pyridazinone group. This together with the observed absences required the space group to be $P2_1$. Two data sets were collected; the first data set contained $-h$ to h, -1 to k and -1 to l (4166 reflections), the second $-h$ to h, 0 to k and 0 to l together with the Friedel equivalent of each observed reflection (subject to the limitations of the diffractometer geometry). The first data set was used for the structure solution and the second for the final refinement.

A Patterson synthesis indicated four Br atoms related by the symmetry elements of $P2_1/a$. Use of the program package *DIRDIF* with the Br-atom position and space group $P2_1$ as input suggested a model for two 4-(3-bromopropionamido)phenyl fragments but again with overall symmetry $P2_1/a$. These fragments were refined by Fourier and least-squares methods until the pyridazinone moiety was discernible in the electron density synthesis as an apparently disordered group of atoms. From this group two pyridazinone fragments of the same chirality were selected to create a model of the crystal structure with space-group symmetry $P2_1$. The model was refined with isotropic temperature factors and harsh restraints from $R=0.228$ to $R=0.140$, then H atoms were included in calculated positions and the restrained structure refined anisotropically to $R=0.075$. A refinement of an extinction parameter, a polarity parameter (a multiplier for the imaginary

part of the anomalous-scattering factor) and the scale factor, followed by refinement of all parameters together without restraints, converged at $R = 0.032$ but the polarity parameter (-0.71) indicated that the model was the wrong enantiomer. At this stage the structure was inverted to give the correct enantiomer and the refinement (full-matrix, anisotropic for non-H atoms, riding hydrogen with isotropic temperature factors) repeated on the second more complete data set. The polarity parameter (Rogers, 1981) was unity at convergence confirming that the model was now based on the true enantiomorph.

(10) (−)-6-(4-Ammoniophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (−)-tartrate–dichloromethane–methanol (1/1/1). Crystals were grown by slow evaporation of a solution of equal molar quantities of the free amine base and (−)-tartaric acid in a mixed methanol/dichloromethane solvent. Systematic absences indicate space group $P2_12_12_1$ with four asymmetric units in the unit cell. For the simple salt this gives a calculated density of 1.01 Mg m^{-3}, in contrast to the measured density of 1.39 Mg m^{-3}. If the unit cell contains in addition four molecules of methanol and four molecules of dichloromethane then the calculated density is increased to 1.36 Mg m^{-3}, rather worse agreement with the calculated density than might be expected.

The structure was eventually solved when *SHELXS*86 (Sheldrick, 1985) became available in the laboratory. The *E* map based on phases from *SHELXS*86 showed recognizable fragments of the anion and cation which were developed by Fourier and least-squares refinement to give a model containing the complete anion and cation and the methanol and dichloromethane solvent. All H atoms were located in difference syntheses except that attached to either O(110) or O(103). The model was chosen to have the known correct chirality for the (−)-tartrate and hence for the (−)-pyridazinone cation. The model was refined with anisotropic temperature factors and riding H atoms. The solvent molecules are rather poorly resolved and the final *R* value (0.0926) larger than is truly satisfactory.

(11) 4,5-Dihydro-6-methyl-3(2*H*)-pyridazinone. Tabular crystals were grown from slow cooling of a solution in water. *MULTAN*80, using default options, gave most of the non-H atoms. Some care was required to choose the correct six-membered ring from the chicken-wire pattern in the *E* map. Once the correct atoms were chosen, an electron density synthesis revealed the other non-H atoms, including the oxygen of a water of crystallization. All H atoms were located from a series of electron density syntheses calculated in the later stages of the analysis and their positions were refined using a riding model and for temperature factors restraints were applied to make the component of thermal vibration along each bond equal for both atoms making the bond.

Results and discussion

General

Fig. 1 defines the numbering scheme used in the text and tables. Table 2* gives atomic coordinates, Tables 3, 4 and 5, a summary of the significant molecular dimensions of the 6-arylpyridazinone skeletons and Table 6, hydrogen-bonding details. The analysis of compound (10) is notably less accurate than the others and significance should not be attached to some of the eye-catching discrepencies in bond lengths and angles although the contrast [with (8*a*), (8*b*), (9*a*) and (9*b*)] in torsion angles about the bond 6—8 is significant. For the dihydropyridazinones the torsion angles are all referred to the same absolute configuration for the purpose of ease of comparison. For brevity the dimensions of the counter ions (for salts) and of the solvent molecules are not tabulated but they conform to expected values. The H-atom coordinates are not quoted in Table 2 because the observed positions do not differ significantly from the computer-predicted positions. For each of Figs. 2–12 the numbered asymmetric unit is presented as 50% thermal ellipsoids and the location in the crystal packing of this unit, whose coordinates appear in Table 2, is shown by the arrow. In general the asymmetric unit has the same orientation in both sections of the diagram but in some the view of the molecule is rotated from the view in the crystallographic projection to show all atoms without overlap.

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71264 (240 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: HA0118]

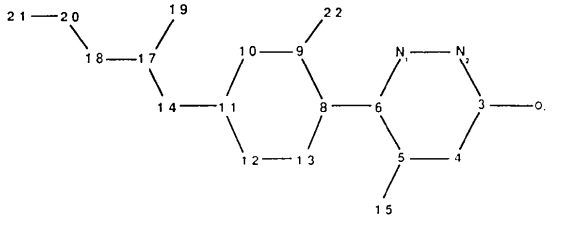


Fig. 1. Atom numbering used in the text and tables for molecules (or ions) (1) through (11). Not all atoms are present in every molecule and in (7) the N atoms are at positions 5 and 2 not 1 and 2.

Table 2. *Atomic parameters with standard deviations calculated from the least-squares normal matrix in parentheses*

	x	y	z	U_{eq}*
(1) 6-Phenyl-3(2*H*)-pyridazinone acetic acid (1/1)				
N(1)	0.2225 (3)	0.0278 (2)	0.5773 (3)	0.0510
N(2)	0.1470 (3)	-0.0198 (3)	0.4573 (3)	0.0523
C(3)	0.0663 (4)	0.0414 (3)	0.3468 (3)	0.0508
C(4)	0.0617 (4)	0.1700 (3)	0.3622 (3)	0.0511
C(5)	0.1337 (4)	0.2194 (3)	0.4806 (3)	0.0495
C(6)	0.2169 (4)	0.1450 (3)	0.5894 (3)	0.0464
O(7)	0.0046 (3)	-0.0181 (2)	0.2439 (2)	0.0581
C(8)	0.3024 (4)	0.1955 (3)	0.7202 (3)	0.0499
C(9)	0.3520 (4)	0.1195 (3)	0.8300 (4)	0.0566
C(10)	0.4368 (4)	0.1652 (4)	0.9508 (4)	0.0614
C(11)	0.4751 (5)	0.2858 (4)	0.9670 (4)	0.0628
C(12)	0.4269 (5)	0.3616 (4)	0.8620 (4)	0.0655
C(13)	0.3398 (4)	0.3177 (3)	0.7377 (4)	0.0569
C(1*s*)	0.2715 (5)	-0.3276 (4)	0.6661 (4)	0.0630
C(2*s*)	0.1903 (4)	-0.3491 (3)	0.5229 (3)	0.0527
O(3*s*)	0.1544 (4)	-0.2709 (2)	0.4412 (3)	0.0641
O(4*s*)	0.1600 (3)	-0.4633 (2)	0.4922 (3)	0.0612
(2) 6-(4-Aminophenyl)-3(2*H*)-pyridazinone				
N(1)	0.6353 (4)	0.4532 (4)	0.2924 (3)	0.0407
N(2)	0.5434 (4)	0.4573 (4)	0.1669 (3)	0.0428
C(3)	0.3955 (5)	0.4029 (5)	0.1121 (4)	0.0460
C(4)	0.3331 (5)	0.3350 (6)	0.1959 (4)	0.0459
C(5)	0.4196 (5)	0.3299 (6)	0.3205 (4)	0.0430
C(6)	0.5741 (4)	0.3932 (5)	0.3678 (4)	0.0345
O(7)	0.3251 (3)	0.4133 (4)	-0.0051 (2)	0.0527
C(8)	0.6742 (4)	0.3905 (5)	0.5041 (3)	0.0343
C(9)	0.8194 (5)	0.4617 (5)	0.5489 (4)	0.0418
C(10)	0.9159 (5)	0.4561 (5)	0.6754 (4)	0.0422
C(11)	0.8687 (5)	0.3783 (5)	0.7599 (4)	0.0411
C(12)	0.7225 (5)	0.3101 (5)	0.7166 (4)	0.0463
C(13)	0.6271 (5)	0.3171 (5)	0.5903 (4)	0.0406
N(14)	0.9621 (5)	0.3715 (6)	0.8870 (3)	0.0575
(3) 6-(4-Aminophenyl)-5-methyl-3(2*H*)-pyridazinone				
N(1)	0.6674 (3)	0.3477 (5)	0.8010 (3)	0.0386
N(2)	0.8100 (3)	0.3143 (5)	0.8978 (3)	0.0371
C(3)	0.8585 (4)	0.1492 (5)	0.9636 (3)	0.0353
C(4)	0.7393 (4)	0.0009 (6)	0.9279 (3)	0.0347
C(5)	0.5935 (3)	0.0280 (5)	0.8346 (3)	0.0324
C(6)	0.5625 (3)	0.2095	0.7683 (3)	0.0309
O(7)	0.9953 (3)	0.1380 (5)	1.0494 (3)	0.0466
C(8)	0.4099 (3)	0.2557 (5)	0.6595 (3)	0.0311
C(9)	0.3132 (4)	0.4102 (6)	0.6835 (3)	0.0380
C(10)	0.1787 (4)	0.4645 (6)	0.5773 (4)	0.0431
C(11)	0.1368 (3)	0.3659 (6)	0.4433 (3)	0.0384
C(12)	0.2333 (4)	0.2120 (6)	0.4190 (3)	0.0409
C(13)	0.3672 (4)	0.1563 (6)	0.5250 (3)	0.0373
N(14)	0.0031 (4)	0.4194 (7)	0.3369 (4)	0.0557
C(15)	0.4643 (5)	-0.1237 (6)	0.8088 (5)	0.0475
(4) 6-(4-Acetamidophenyl)-3(2*H*)-pyridazinone				
N(1)	0.5716 (5)	0.3337 (1)	0.5650 (1)	0.0407
N(2)	0.7965 (5)	0.3912 (1)	0.5186 (1)	0.0419
C(3)	1.0465 (6)	0.3754 (2)	0.4464 (1)	0.0402
C(4)	1.0610 (6)	0.2872 (2)	0.4171 (2)	0.0431
C(5)	0.8400 (6)	0.2283 (2)	0.4609 (2)	0.0413
C(6)	0.5937 (5)	0.2535 (1)	0.5371 (1)	0.0351
O(7)	1.2385 (5)	0.4351 (1)	0.4113 (1)	0.0499
C(8)	0.3492 (5)	0.1903 (1)	0.5882 (1)	0.0343
C(9)	0.1789 (6)	0.2058 (1)	0.6728 (1)	0.0371
C(10)	-0.0633 (5)	0.1497 (2)	0.7188 (1)	0.0369
C(11)	-0.1416 (5)	0.0758 (1)	0.6821 (1)	0.0334
C(12)	0.0362 (6)	0.0580 (2)	0.5986 (2)	0.0411
C(13)	0.2765 (6)	0.1147 (2)	0.5528 (1)	0.0418
C(14)	-0.4030 (4)	0.0247 (1)	0.7312 (1)	0.0359
C(17)	-0.5016 (6)	-0.0539 (1)	0.7119 (2)	0.0388
C(18)	-0.8061 (7)	-0.0893 (2)	0.7748 (2)	0.0478
O(19)	-0.3568 (5)	-0.0949 (1)	0.6485 (1)	0.0557
(5) 6-(4-Acetamido-2-methoxyphenyl)-3(2*H*)-pyridazinone				
N(1)	0.1522 (1)	0.3201 (2)	0.9884 (3)	0.0367
N(2)	0.0806 (1)	0.3712 (2)	1.0286 (3)	0.0378
C(3)	0.0170 (1)	0.2976 (2)	1.0858 (3)	0.0366
C(4)	0.0319 (1)	0.1504 (3)	1.1145 (3)	0.0394
C(5)	0.1027 (1)	0.0960 (2)	1.0780 (3)	0.0384
C(6)	0.1634 (1)	0.1850 (2)	1.0118 (3)	0.0326
O(7)	-0.0468 (1)	0.3582 (2)	1.1082 (3)	0.0471
C(8)	0.2435 (1)	0.1349 (2)	0.9693 (3)	0.0319
C(9)	0.3072 (1)	0.2184 (2)	1.0168 (3)	0.0354
C(10)	0.3832 (1)	0.1871 (2)	0.9665 (3)	0.0346
C(11)	0.3962 (1)	0.0685 (2)	0.8627 (3)	0.0300
C(12)	0.3337 (1)	0.0212 (2)	0.8198 (3)	0.0313
C(13)	0.2581 (1)	0.0113 (2)	0.8722 (3)	0.0319
N(14)	0.4705 (1)	0.0327 (2)	0.7950 (2)	0.0321
C(17)	0.5337 (1)	0.1191 (2)	0.7778 (3)	0.0327
C(18)	0.6027 (1)	0.0561 (3)	0.6849 (3)	0.0424
O(19)	0.5350 (1)	0.2413 (2)	0.8315 (2)	0.0442
O(22)	0.1940 (1)	-0.0688 (2)	0.8303 (2)	0.0422
C(23)	0.2024 (2)	-0.1776 (3)	0.7031 (4)	0.0519
(6) 6-(2-Aminophenyl)-3(2*H*)-pyridazinone				
N(1)	0.9877 (3)	0.05078 (3)	0.07414 (6)	0.0426
N(2)	0.9345 (3)	0.1201 (3)	0.03882 (6)	0.0426
C(3)	0.7597 (3)	0.1395 (4)	0.02491 (8)	0.0431
C(4)	0.6249 (3)	0.0690 (4)	0.05235 (9)	0.0457
C(5)	0.6735 (3)	0.0007 (4)	0.08791 (8)	0.0446
C(6)	0.8627 (3)	-0.0102 (3)	0.09905 (8)	0.0398
O(7)	0.7341 (3)	0.2100 (3)	-0.00837 (6)	0.0553
C(8)	0.9234 (4)	0.0876 (3)	0.13750 (8)	0.0446
C(9)	1.0882 (4)	-0.1866 (4)	0.14132 (9)	0.0505
C(10)	1.1272 (5)	-0.2652 (5)	0.1787 (1)	0.0654
C(11)	1.0168 (6)	-0.2427 (6)	0.2118 (1)	0.0704
C(12)	0.8603 (6)	-0.1366 (6)	0.20882 (9)	0.0696
C(13)	0.8157 (5)	-0.0647 (4)	0.17201 (9)	0.0578
N(22)	1.2098 (3)	-0.2061 (4)	0.11000 (8)	0.0598
(7) 6-Phenyl-3(2*H*)-pyrazinone				
C(1)	0.8013 (2)	0.0622 (3)	0.3404 (1)	0.0362
N(2)	0.8980 (2)	0.0775 (3)	0.4080 (1)	0.0367
C(3)	1.0069 (2)	0.2600 (3)	0.4316 (1)	0.0355
C(4)	1.0028 (3)	0.4410 (3)	0.3792 (1)	0.0391
N(5)	0.9097 (2)	0.4318 (3)	0.3152 (1)	0.0374
C(6)	0.8078 (2)	0.2374 (3)	0.2937 (1)	0.0309
O(7)	1.1019 (2)	0.2649 (2)	0.4921 (1)	0.0444
C(8)	0.7085 (2)	0.2340 (3)	0.2193 (1)	0.0311
C(9)	0.5982 (3)	0.0490 (3)	0.1920 (1)	0.0411
C(10)	0.5078 (3)	0.0495 (4)	0.1222 (1)	0.0472
C(11)	0.5261 (3)	0.2329 (4)	0.0781 (1)	0.0453
C(12)	0.6346 (3)	0.4163 (4)	0.1044 (1)	0.0456
C(13)	0.7250 (3)	0.4190 (3)	0.1745 (1)	0.0395
(8) 6-(4-Aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone				
Molecule (8*a*)				
N(1*a*)	0.3417 (3)	-0.1274 (2)	0.1268 (2)	0.0342
N(2*a*)	0.3794 (3)	-0.2348 (2)	0.1483 (2)	0.0348
C(3*a*)	0.3138 (4)	0.3593 (2)	0.0700 (2)	0.0350
C(4*a*)	0.1774 (5)	-0.3849 (3)	-0.0528 (3)	0.0432
C(5*a*)	0.2192 (5)	-0.2809 (3)	-0.0958 (3)	0.0411
C(6*a*)	0.2665 (3)	-0.1481 (2)	0.0113 (2)	0.0308
O(7*a*)	0.3561 (3)	-0.4454 (2)	0.1009 (2)	0.0424
C(8*a*)	0.2387 (3)	-0.0362 (2)	-0.0159 (2)	0.0304
C(9*a*)	0.2701 (4)	0.0876 (2)	0.0807 (2)	0.0354
C(10*a*)	0.2563 (4)	0.1392 (3)	0.0547 (2)	0.0385
C(11*a*)	0.2091 (3)	0.1794 (2)	-0.0708 (2)	0.0343
C(12*a*)	0.1750 (4)	0.0563 (3)	-0.1676 (3)	0.0389
C(13*a*)	0.1890 (4)	-0.0481 (2)	-0.1407 (2)	0.0355
N(14*a*)	0.1929 (4)	0.2852 (2)	-0.0989 (2)	0.0440
Molecule (8*b*)				
N(1*b*)	0.6367 (3)	-0.5089 (2)	0.3603 (2)	0.0349
N(2*b*)	0.6190 (3)	-0.4017 (2)	0.3341 (2)	0.0358
C(3*b*)	0.6993 (3)	-0.2783 (2)	0.4093 (2)	0.0330
C(4*b*)	0.8254 (4)	-0.2495 (3)	0.5371 (2)	0.0375
C(5*b*)	0.7968 (4)	-0.3550 (2)	0.5802 (2)	0.0371
C(6*b*)	0.7226 (3)	-0.4878 (2)	0.4747 (2)	0.0303
O(7*b*)	0.6736 (3)	-0.1932 (2)	0.3724 (2)	0.0401
C(8*b*)	0.7354 (3)	-0.6013 (2)	0.5023 (2)	0.0308
C(9*b*)	0.6565 (3)	-0.7269 (2)	0.4083 (2)	0.0328
C(10*b*)	0.6591 (4)	-0.8331 (2)	0.4334 (2)	0.0356
C(11*b*)	0.7460 (4)	-0.8195 (2)	0.5568 (2)	0.0355
C(12*b*)	0.8270 (4)	-0.6954 (2)	0.6505 (2)	0.0355
C(13*b*)	0.8209 (4)	-0.5890 (2)	0.6239 (2)	0.0340
N(14*b*)	0.7486 (4)	-0.9250 (2)	0.5832 (3)	0.0471
(9) (*R*)-(−)-6-[4-(3-Bromopropionamido)phenyl]-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone				
Molecule (9*a*)				
N(1*a*)	0.5707 (2)	-0.1187 (3)	0.8144 (2)	0.0373
N(2*a*)	0.6612 (2)	-0.1019 (3)	0.8979 (2)	0.0392
C(3*a*)	0.7177 (2)	-0.2014 (3)	0.9558 (2)	0.0397
C(4*a*)	0.6899 (3)	-0.3458 (3)	0.9196 (3)	0.0443
C(5*a*)	0.5553 (3)	-0.3592 (3)	0.8680 (2)	0.0379
C(6*a*)	0.5221 (2)	-0.2384 (3)	0.8001 (1)	0.0323

Table 2 (*cont.*)

	x	y	z	U_{eq}*
O(7*a*)	0.7920 (2)	−0.1735 (3)	1.0306 (2)	0.0524
C(8*a*)	0.4161 (2)	−0.2506 (3)	0.7177 (2)	0.0318
C(9*a*)	0.3691 (3)	−0.1346 (3)	0.6643 (2)	0.0343
C(10*a*)	0.2620 (3)	−0.1421 (3)	0.5949 (2)	0.0345
C(11*a*)	0.2007 (2)	−0.2668 (3)	0.5780 (2)	0.0328
C(12*a*)	0.2499 (3)	−0.3835 (3)	0.6272 (2)	0.0398
C(13*a*)	0.3566 (3)	−0.3752 (3)	0.6964 (3)	0.0413
N(14*a*)	0.0900 (2)	−0.2858 (2)	0.5108 (2)	0.0342
C(15*a*)	0.4673 (3)	−0.3683 (5)	0.9435 (3)	0.0616
C(17*a*)	0.0129 (2)	−0.1877 (3)	0.4660 (2)	0.0341
C(18*a*)	−0.0921 (2)	−0.2437 (4)	0.3906 (2)	0.0382
O(19*a*)	0.0259 (2)	−0.0648 (2)	0.4808 (2)	0.0460
C(20*a*)	−0.0848 (3)	−0.1841 (3)	0.2880 (2)	0.0402
Br(21*a*)	0.06607 (3)	−0.23860 (5)	0.23936 (2)	0.0457
Molecule (9*b*)				
N(1*b*)	1.0237 (2)	−0.3755 (3)	0.8389 (2)	0.0387
N(2*b*)	1.1180 (2)	−0.3940 (3)	0.9195 (2)	0.0390
C(3*b*)	1.1507 (2)	−0.3021 (3)	0.9933 (2)	0.0350
C(4*b*)	1.0818 (3)	−0.1690 (3)	0.9837 (2)	0.0381
C(5*b*)	1.0427 (2)	−0.1272 (3)	0.8756 (2)	0.0339
C(6*b*)	0.9875 (2)	−0.2518 (3)	0.8178 (2)	0.0327
O(7*b*)	1.2290 (2)	−0.3324 (3)	1.0651 (1)	0.0438
C(8*b*)	0.8868 (2)	−0.2344 (3)	0.7328 (2)	0.0318
C(9*b*)	0.8456 (3)	−0.1043 (3)	0.6995 (2)	0.0346
C(10*b*)	0.7489 (3)	−0.0880 (3)	0.6233 (2)	0.0353
C(11*b*)	0.6887 (2)	−0.2020 (3)	05780 (2)	0.0295
C(12*b*)	0.7306 (3)	−0.3339 (3)	0.6075 (2)	0.0353
C(13*b*)	0.8290 (3)	−0.3478 (3)	0.6835 (2)	0.0372
N(14*b*)	0.5891 (2)	−0.1762 (2)	0.5018 (2)	0.0323
C(15*b*)	1.1504 (3)	−0.0730 (4)	0.8271 (3)	0.0548
C(17*b*)	0.5092 (2)	−0.2689 (3)	0.4528 (2)	0.0325
C(18*b*)	0.4138 (3)	−0.2063 (3)	0.3722 (2)	0.0389
O(19*b*)	0.5108 (2)	−0.3916 (2)	0.4694 (2)	0.0444
C(20*b*)	0.4136 (2)	−0.2794 (3)	0.2740 (2)	0.0412
Br(21*b*)	0.56899 (3)	−0.25220 (5)	0.22204 (2)	0.0554

(10) (*R*)-(−)-6-(4-Ammoniophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (−)-tartrate–dichloromethane–methanol (1/1/1)

Dihydropyridazinone cation				
N(1)	−0.977 (1)	−0.930 (1)	−0.4355 (4)	0.0563
N(2)	−0.964 (1)	−0.818 (1)	−0.4625 (2)	0.0569
C(3)	−0.811 (2)	−0.737 (1)	−0.4715 (3)	0.0608
C(4)	−0.652 (1)	−0.751 (1)	−0.4490 (2)	0.0530
C(5)	−0.712 (1)	−0.784 (1)	−0.4122 (2)	0.0533
C(6)	−0.856 (1)	−0.915 (1)	−0.4128 (2)	0.0481
O(7)	−0.805 (1)	−0.654 (1)	−0.4976 (2)	0.0567
C(8)	−0.8733 (8)	−1.0307 (6)	−0.3837 (1)	0.0473
C(9)	−1.0504 (7)	−1.0821 (6)	−0.3725 (1)	0.0508
C(10)	−1.0679 (7)	−1.1798 (6)	−0.3449 (1)	0.0531
C(11)	−0.9139 (8)	−1.2296 (5)	−0.3280 (1)	0.0346
C(12)	−0.7404 (7)	−1.1839 (6)	−0.3378 (1)	0.0419
C(13)	−0.7178 (7)	−1.0857 (6)	−0.3652 (1)	−0.0459
N(14)	−0.935 (1)	−1.3263 (7)	−0.2972 (2)	0.0385
C(15)	−0.797 (2)	−0.626 (2)	−0.3971 (3)	0.0854
Tartrate anion				
O(1*t*)	−1.0368 (8)	−0.6602 (8)	−0.3054 (2)	0.0514
C(2*t*)	−0.949 (1)	−0.7764 (9)	−0.2949 (2)	0.0362
O(3*t*)	−1.0220 (7)	−0.9105 (7)	−0.2832 (2)	0.0446
C(4*t*)	−0.738 (1)	−0.773 (1)	−0.2938 (2)	0.0415
O(5*t*)	−0.6779 (8)	−0.6093 (7)	−0.3003 (2)	0.0503
C(6*t*)	−0.662 (1)	−0.842 (1)	−0.2612 (2)	0.0358
O(7*t*)	−0.7304 (8)	−0.7529 (8)	−0.2337 (1)	0.0456
C(8*t*)	−0.446 (1)	−0.8349 (9)	−0.2613 (2)	0.0327
O(9*t*)	−0.3676 (8)	−0.7464 (7)	−0.2413 (2)	0.0447
O(10*t*)	−0.3695 (7)	−0.9244 (6)	−0.2839 (1)	0.0343
Dichloromethane solvent				
Cl(1*sa*)	−0.484 (1)	−0.2268 (7)	−0.4404 (2)	0.1651
Cl(2*sa*)	−0.191 (1)	−0.4155 (7)	−0.4676 (2)	0.1840
C(3*sa*)	−0.302 (2)	−0.221 (2)	−0.4667 (4)	0.1200
Methanol solvent				
C(1*sb*)	−0.308 (3)	−0.572 (3)	−0.3683 (5)	0.1611
O(2*sb*)	−0.371 (1)	−0.622 (2)	−0.3392 (3)	0.1075

(11) 4,5-Dihydro-6-methyl-3(2*H*)-pyridazinone

N(1)	0.5751 (3)	0.7777 (4)	0.2657 (1)	0.0464
N(2)	0.4588 (3)	0.7709 (4)	0.1900 (1)	0.0438
C(3)	0.2538 (3)	0.7964 (4)	0.1829 (2)	0.0479
C(4)	0.1415 (4)	0.8430 (5)	0.2644 (2)	0.0553
C(5)	0.2415 (4)	0.7473 (6)	0.3387 (2)	0.0591
C(6)	0.4744 (4)	0.7700 (4)	0.3358 (1)	0.0491
O(7)	0.1690 (3)	0.7960 (5)	0.1119 (1)	0.0664
C(8)	0.5946 (6)	0.7718 (7)	0.4177 (2)	0.0720
O(1*w*)	−0.2399 (3)	0.7334 (7)	0.0611 (1)	0.0748

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

Molecular conformation and dimensions

The expected conformation of a 6-arylpyridazinone, by analogy with the known structures of diphenyls and related compounds, is that of a generally flat molecule. Intuitively this general flatness would be expected to be perturbed by the presence of a 5-substituent in the pyridazinone ring or a 2-substituent in the aryl ring. Molecules (1), (2), (3), (5) and (6) illustrate this trend with the largest dihedral angle, 51°, between the planes of the rings, for the 5-methylpyridazinone (3). However, this dihedral angle, 21°, for compound (4) with no 2-aryl substituent is unexpectedly large suggesting that the potential-energy well with respect to rotation about the bond 6—8 is flat bottomed. The tendency for flat molecules is retained on reduction of the pyridazinone as in (8*a*) and (8*b*). The angles between the aryl plane and the mean plane of the reduced pyridazinone are 11.0 and 4.8°, respectively. In the 5-methyldihydropyridazinones (9) and (10), the 5-methyl substituent is axial and the C—CH_3 bond is approximately perpendicular to the mean dihydropyridazinone plane; thus, when the phenyl ring and the mean plane of the pyridazinone are coplanar the 5-methyl group is far removed from the phenyl *ortho*-C H atoms. Although the presence of the 5-methyl substituent in the reduced pyridazinone does not necessarily perturb the general tendency towards flatness for the whole molecule, a dihedral angle of 22.6° between the phenyl plane and the mean pyridazinone plane is observed in (10) compared with 14.8 and 15.9° for (9*a*) and (9*b*), respectively. On comparing the 1—6—8—9 torsion angles the difference is more dramatic; −32.2° in (10) and −3.5 and 4.5° in (9*a*) and (9*b*), respectively. These observations again support the suggestion of a flat-bottomed potential well.

For molecules (1) to (10) the dimensions of the aryl groups show only those variations predicted from substituent effects (Domenicano & Murray-Rust, 1979). There are no obvious correlations between the aryl-group dimensions and the overall planarity of the molecule or state of reduction of the pyridazinone ring or the nature of the heterocycle (pyridazinone or pyrazinone). The pyridazinone and

Table 3. *Bonded distances* (Å) *with standard deviations in parentheses for the pyridazinones in crystals* (1)–(11)

The corresponding measurements for the counter ions and/or solvent molecules (1) and (10) do not differ significantly from those found in the CSD.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8*a*)	(8*b*)	(9*a*)	(9*b*)	(10)	(11)
14—11	–	1.388 (5)	1.382 (4)	1.404 (2)	1.412 (2)	–	–	1.393 (3)	1.370 (3)	1.418 (3)	1.410 (3)	1.461 (8)	–
11—10	1.377 (7)	1.388 (6)	1.391 (4)	1.392 (2)	1.391 (3)	1.371 (5)	1.380 (2)	1.388 (4)	1.412 (3)	1.386 (4)	1.398 (4)	1.355 (4)	-
10—9	1.374 (5)	1.388 (5)	1.386 (4)	1.382 (2)	1.386 (2)	1.399 (4)	1.384 (2)	1.386 (4)	1.382 (4)	1.394 (4)	1.384 (4)	1.358 (4)	–
9—8	1.403 (5)	1.392 (5)	1.390 (4)	1.393 (3)	1.389 (3)	1.426 (4)	1.395 (2)	1.399 (3)	1.396 (3)	1.395 (4)	1.390 (4)	1.408 (4)	–
8—13	1.393 (5)	1.382 (5)	1.399 (4)	1.391 (3)	1.408 (3)	1.399 (4)	1.393 (2)	1.395 (3)	1.401 (3)	1.384 (4)	1.392 (4)	1.407 (4)	–
13—12	1.401 (5)	1.384 (6)	1.385 (4)	1.382 (3)	1.387 (3)	1.370 (5)	1.389 (2)	1.377 (4)	1.368 (3)	1.398 (4)	1.376 (4)	1.360 (4)	–
12—11	1.364 (6)	1.386 (6)	1.387 (4)	1.389 (2)	1.399 (3)	1.402 (6)	1.376 (2)	1.399 (4)	1.391 (3)	1.382 (4)	1.384 (4)	1.354 (4)	–
6—8	1.479 (5)	1.487 (5)	1.487 (3)	1.483 (2)	1.484 (2)	1.466 (3)	1.483 (2)	1.471 (3)	1.474 (3)	1.493 (3)	1.485 (3)	1.49 (1)	1.487 (4)
6—1	1.304 (4)	1.301 (5)	1.309 (3)	1.305 (2)	1.310 (2)	1.316 (3)	1.359 (2)	1.284 (3)	1.289 (3)	1.280 (4)	1.283 (4)	1.26 (1)	1.270 (3)
1—2	1.356 (4)	1.386 (4)	1.353 (3)	1.354 (2)	1.351 (2)	1.336 (3)	1.367 (2)	1.404 (3)	1.400 (3)	1.401 (3)	1.402 (3)	1.41 (1)	1.400 (3)
2—3	1.358 (4)	1.352 (5)	1.353 (3)	1.357 (2)	1.364 (3)	1.374 (3)	1.361 (2)	1.332 (3)	1.331 (3)	1.338 (4)	1.350 (3)	1.33 (1)	1.330 (3)
3—7	1.253 (4)	1.256 (5)	1.247 (3)	1.248 (2)	1.243 (2)	1.234 (3)	1.245 (2)	1.234 (3)	1.238 (3)	1.234 (3)	1.235 (3)	1.23 (1)	1.237 (3)
3—4	1.432 (5)	1.418 (6)	1.438 (4)	1.431 (3)	1.437 (3)	1.444 (4)	1.447 (2)	1.493 (4)	1.497 (3)	1.501 (4)	1.492 (4)	1.46 (1)	1.497 (4)
4—5	1.345 (5)	1.350 (6)	1.349 (4)	1.345 (3)	1.343 (3)	1.331 (4)	1.296 (2)	1.500 (4)	1.502 (3)	1.541 (4)	1.522 (3)	1.55 (1)	1.483 (4)
5—6	1.429 (4)	1.428 (5)	1.500 (4)	1.425 (2)	1.443 (3)	1.379 (2)	1.503 (3)	1.498 (3)	1.503 (4)	1.517 (4)	1.47 (1)	1.503 (4)	
14—17	–	–	–	1.357 (2)	1.362 (2)	–	–	–	–	1.355 (3)	1.459 (3)	–	–
17—18	–	–	–	1.498 (3)	1.499 (3)	–	–	–	–	1.522 (4)	1.523 (3)	–	–
17—19	–	–	–	1.219 (2)	1.230 (2)	–	–	–	–	1.213 (3)	1.211 (3)	–	–
18—20	–	–	–	–	–	–	–	–	–	1.522 (4)	1.510 (4)	–	–
20—21	–	–	–	–	–	–	–	–	–	1.943 (3)	1.956 (3)	–	–

Table 4. *Interbond angles* (°) *with standard deviations in parentheses for the pyridazinones in crystals* (1)–(11)

The corresponding measurements for the counter ions and/or solvent molecules (1) and (10) do not differ significantly from those found in the CSD.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8*a*)	(8*b*)	(9*a*)	(9*b*)	(10)	(11)
12—11—10	119.7 (4)	119.0 (4)	118.1 (3)	118.5 (2)	119.8 (2)	120.1 (3)	119.2 (1)	118.0 (2)	117.7 (2)	119.3 (2)	119.3 (2)	121.5 (3)	–
11—10—9	121.0 (4)	120.2 (4)	120.9 (2)	120.9 (2)	118.9 (2)	122.1 (3)	120.5 (2)	120.7 (2)	120.4 (2)	119.8 (2)	119.3 (2)	120.6 (2)	–
10—9—8	120.3 (4)	121.1 (4)	121.0 (3)	120.9 (2)	122.5 (3)	118.1 (3)	120.8 (1)	121.7 (2)	122.3 (2)	121.2 (2)	122.1 (3)	120.8 (2)	–
9—8—13	118.3 (3)	117.8 (4)	118.0 (3)	117.7 (2)	117.9 (2)	118.2 (3)	118.2 (1)	116.6 (2)	116.7 (2)	118.0 (2)	117.2 (2)	117.0 (2)	–
8—13—12	120.1 (4)	121.6 (4)	120.7 (3)	121.7 (2)	120.2 (2)	122.7 (3)	120.3 (1)	122.1 (3)	121.7 (2)	121.0 (3)	121.8 (2)	120.7 (2)	–
13—12—11	120.6 (4)	120.2 (4)	121.2 (3)	120.2 (2)	120.4 (2)	118.7 (3)	120.9 (1)	120.9 (2)	121.1 (2)	120.6 (3)	120.4 (2)	120.0 (2)	–
1—6—5	121.1 (3)	121.2 (3)	122.0 (2)	121.3 (2)	121.5 (2)	119.7 (2)	119.8 (1)	121.8 (2)	122.0 (2)	123.8 (2)	123.0 (2)	124.0 (8)	–
6—1—2	117.2 (3)	117.2 (4)	117.7 (2)	116.7 (2)	116.9 (2)	118.4 (2)	119.9 (1)	116.7 (2)	117.7 (2)	117.2 (2)	117.4 (2)	116.5 (8)	117.0 (2)
1—2—3	127.1 (3)	126.7 (4)	126.6 (2)	127.9 (2)	127.6 (2)	127.5 (2)	123.2 (1)	128.1 (2)	127.8 (2)	127.0 (2)	125.5 (2)	125.1 (8)	126.5 (2)
2—3—4	114.8 (3)	115.0 (4)	114.5 (2)	113.9 (2)	114.0 (2)	113.2 (2)	113.3 (1)	114.6 (2)	116.8 (2)	115.2 (2)	115.5 (2)	116.2 (8)	115.5 (2)
3—4—5	119.3 (3)	121.1 (4)	121.3 (2)	120.0 (2)	120.1 (2)	120.7 (2)	124.5 (1)	111.8 (2)	114.4 (2)	111.2 (2)	112.4 (2)	112.3 (8)	111.4 (3)
4—5—6	120.5 (2)	119.9 (4)	117.9 (2)	120.1 (2)	119.9 (2)	120.4 (2)	119.3 (1)	112.3 (2)	114.6 (2)	110.0 (2)	108.7 (2)	107.5 (8)	110.9 (3)
2—3—7	118.2 (3)	120.0 (4)	119.6 (3)	120.5 (2)	120.3 (2)	119.1 (2)	122.3 (1)	121.9 (2)	120.8 (2)	121.2 (3)	120.4 (3)	121 (1)	120.7 (2)
4—3—7	127.0 (3)	125.1 (4)	125.9 (3)	125.6 (2)	125.7 (2)	127.7 (2)	124.4 (1)	123.4 (2)	122.4 (2)	123.5 (3)	124.0 (2)	123 (1)	123.5 (2)
1—6—8	116.4 (3)	116.8 (4)	114.7 (2)	116.9 (2)	114.7 (2)	117.8 (2)	123.4 (1)	118.0 (2)	117.2 (2)	116.5 (3)	116.7 (2)	116.3 (8)	118.3 (3)
5—6—8	122.5 (3)	122.0 (4)	122.3 (2)	121.8 (2)	123.8 (2)	122.5 (2)	116.8 (1)	120.0 (2)	119.6 (2)	119.3 (3)	120.4 (2)	119.5 (7)	119.0 (3)
6—8—9	120.2 (3)	120.8 (4)	120.2 (2)	121.0 (2)	118.7 (2)	122.7 (2)	122.0 (1)	122.0 (2)	121.4 (2)	120.8 (3)	121.2 (3)	120.5 (5)	–
6—8—13	121.4 (3)	121.4 (4)	121.6 (3)	121.2 (2)	123.2 (3)	119.1 (2)	119.8 (1)	121.2 (2)	121.8 (2)	121.1 (3)	121.6 (2)	122.4 (5)	–
10—11—14	–	121.5 (4)	121.2 (3)	117.8 (2)	123.2 (2)	–	–	121.4 (3)	121.3 (2)	124.5 (2)	123.9 (2)	119.4 (5)	–
12—11—14	–	119.5 (4)	120.7 (3)	123.6 (2)	117.0 (2)	–	–	120.6 (2)	121.0 (2)	116.1 (2)	116.8 (2)	119.0 (5)	–
11—14—17	–	–	–	128.3 (2)	127.1 (2)	–	–	–	–	128.0 (2)	127.9 (2)	–	–
14—17—18	–	–	–	115.5 (2)	115.4 (3)	–	–	–	–	114.2 (2)	114.4 (2)	–	–
14—17—19	–	–	–	123.7 (2)	123.3 (2)	–	–	–	–	124.4 (2)	124.6 (2)	–	–
18—17—19	–	–	–	120.8 (2)	121.3 (3)	–	–	–	–	121.4 (3)	121.0 (2)	–	–
17—18—20	–	–	–	–	–	–	–	–	–	110.1 (2)	111.1 (2)	–	–
18—20—21	–	–	–	–	–	–	–	–	–	111.8 (2)	111.6 (2)	–	–

Table 5. *Torsion angles* (°) *with standard deviations in parentheses for the pyridazinones in crystals* (1)–(11)

The corresponding measurements for the counter ions and/or solvent molecules (1) and (10) do not differ significantly from those found in the CSD.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8*a*)	(8*b*)	(9*a*)	(9*b*)	(10)	(11)
1—6—8—9	−17.0 (4)	6.3 (6)	−50.7 (4)	−21.2 (3)	39.7 (3)	−34.8 (4)	0.8 (2)	−7.9 (3)	0.4 (3)	−3.9 (4)	4.5 (4)	−32 (1)	–
8—6—1—2	−175.8 (4)	−179.5 (6)	−179.1 (4)	179.5 (3)	−178.8 (3)	179.4 (4)	179.5 (2)	175.3 (3)	178.2 (3)	173.2 (4)	−179.5 (4)	178 (1)	178.8 (4)
6—1—2—3	0.7 (5)	−1.2 (6)	−2.5 (5)	−0.7 (3)	−2.4 (3)	1.2 (4)	−1.7 (2)	15.1 (3)	8.6 (3)	12 (4)	19.8 (4)	21 (1)	14.2 (4)
1—2—3—7	179.4 (4)	−179.4 (5)	178.9 (4)	−178.7 (3)	176.9 (3)	178.6 (4)	−175.8 (2)	−175.8 (2)	179.1 (3)	178.4 (4)	174.5 (4)	173 (1)	176.8 (4)
1—2—3—4	−0.6 (4)	−0.3 (5)	−2.5 (4)	1.5 (3)	3.9 (3)	−2.2 (4)	3.0 (2)	2.8 (3)	0.6 (3)	7.2 (4)	−2.5 (5)	−9 (1)	2.0 (4)
2—3—4—5	−0.6 (4)	0.8 (6)	0.9 (4)	−0.6 (3)	−2.7 (3)	−2.7 (4)	−1.8 (2)	−32.1 (3)	−19.0 (3)	−35.2 (4)	−31.5 (4)	−25 (1)	−32.3 (4)
3—4—5—6	1.6 (5)	0.1 (6)	1.6 (4)	−0.8 (3)	0.5 (3)	−2.3 (4)	−0.8 (2)	43.5 (3)	27.6 (3)	43.9 (4)	46.0 (4)	44 (1)	45.2 (4)
3—4—5—15	–	–	174.9 (4)	–	–	–	–	–	–	−78.1 (4)	−74.8 (4)	−74 (1)	–
15—5—6—1	–	–	173.6 (4)	–	–	–	–	–	–	94.0 (4)	90.7 (4)	83 (1)	–
15—5—6—8	–	–	−5.8 (4)	–	–	–	–	–	–	−78.2 (4)	−89.5 (5)	−90 (1)	–
4—5—6—8	177.6	−180.0 (6)	177.7 (5)	−178.8 (3)	179.4 (3)	−178.7 (4)	−178.3 (2)	155.7 (3)	163.8 (3)	159.1 (4)	147.5 (4)	151 (1)	151.4 (4)
4—5—6—1	−1.5 (4)	−1.7 (5)	−2.8 (4)	1.6 (3)	1.2 (3)	1.2 (4)	2.3 (2)	−28.4 (3)	−20.4 (3)	−28.7 (4)	−32.3 (4)	−36 (1)	−32.6 (4)
5—6—8—9	163.9 (4)	−175.4 (5)	128.8 (4)	159.2 (3)	−138.7 (3)	145.2 (4)	−178.6 (2)	176.2 (3)	175.6 (3)	168.9 (4)	175.3 (4)	142 (1)	–
5—6—1—2	0.4 (4)	2.2 (5)	1.4 (4)	−0.9 (3)	−0.5 (3)	−0.4 (4)	−1.1 (2)	0.6 (3)	2.4 (3)	0.8 (4)	0.3 (4)	5 (1)	−2.0 (4)

Table 6. *Hydrogen contacts* (Å)

Superscripts denote the equivalent positions of the marked atoms relative to the reference molecule at x, y, z.

(1) 6-Phenyl-3(2*H*)-pyridazinone–acetic acid (1/1)

O(7)···O(4s^{i})	2.567 (5)	O(3s)···N(2)	2.781 (5)

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

(2) 6-(4-Aminophenyl)-3(2*H*)-pyridazinone

O(7)···N(14^{i})	3.076 (5)	O(7)···N(2^{ii})	2.795 (5)

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

(3) 6-(4-Aminophenyl)-5-methyl-3(2*H*)-pyridazinone

O(7)···N(2^{i})	2.806 (4)		

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

(4) 6-(4-Acetamidophenyl)-3(2*H*)-pyridazinone

N(2)···O(7^{i})	2.890 (3)	N(14)···O(7^{ii})	2.983 (3)

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

(5) 6-(4-Acetamido-2-methoxyphenyl)-3(2*H*)-pyridazinone

N(2)···O(7^{i})	2.835 (3)	N(14)···O(19^{ii})	2.929 (3)

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

(6) 6-(2-Aminophenyl)-3(2*H*)-pyridazinone

N(2)···O(7^{i})	2.736 (4)		

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

(7) 6-Phenyl-3(2*H*)-pyrazinone

O(7)···N(2^{i})	2.756 (2)		

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

(8) 6-(4-Aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone

O(7a)···N(14a^{i})	2.993 (4)	O(7a)···N(2b^{ii})	2.867 (4)
O(7b)···N(2a^{ii})	2.913 (4)	O(7b)···N(14b^{iii})	3.025 (4)

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

(9) (−)-6-[4-(3-Bromopropionamido)phenyl]-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone

N(14a)···O(19a^{i})	2.999 (3)	N(14b)···O(19b^{i})	3.016 (3)
N(2a)···O(7b^{ii})	2.889 (4)	O(7a)···N(2b^{ii})	2.929 (4)

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

(10) (−)-6-(4-Ammoniophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (−)-tartrate–dichloromethane–methanol (1/1/1)

O(5t)···O(2sb)	2.70 (1)	N(14)···O(1t^{i})	2.80 (1)
N(14)···O(5t^{i})	2.93 (1)	N(14)···O(7t^{ii})	2.76 (1)
N(14)···O(9t^{iii})	2.74 (1)	N(2)···O(7t^{iv})	2.93 (1)
O(3t)···O(10t^{v})	2.49 (1)	O(1t)···O(2sb^{v})	2.76 (1)
O(7t)···O(10t^{vi})	2.82 (1)		

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

(11) 4,5-Dihydro-6-methyl-3(2*H*)-pyridazinone

O(7)···O(1w)	2.775 (3)	N(2)···O(1w^{i})	2.805 (3)
O(7)···O(1w^{ii})	2.773 (3)		

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

pyrazinone rings which are situated *para* to the amino substituents also affect the phenyl-ring bond angles. However, any possible conjugation between the two rings must depend upon the overlap of orbitals which, resonance energy studies suggest, becomes unimportant when orbitals are rotated by more than about 30–40°. This implies that adding a bulky *ortho* substituent to either ring, and (possibly) preventing the molecule from being planar, will restrict π-electron interaction. (3), which contains a pyridazinone ring with a methyl substituent, has a dihedral angle of 53°. This twist in (3) might substantially reduce the inter-ring conjugation which would be observed as a longer inter-ring bond length 6—8 and a change in endocyclic phenyl angle 9—8—13 when compared with the planar unmethylated molecules (1) and (2). However, the bond lengths and angles in the two structures differ by only 0.008 Å and the C—CH_3 bond length in (11), 1.487 (4) Å, is not significantly different from the average of the 6—8 bond lengths in the 6-aryl compounds (1) to (10). In all molecules the 6—8 bond is significantly shorter than a typical single C—C bond length, but there appears to be no systematic variation between this length and the dihedral angle between the two rings. Indeed no trend can be observed between the

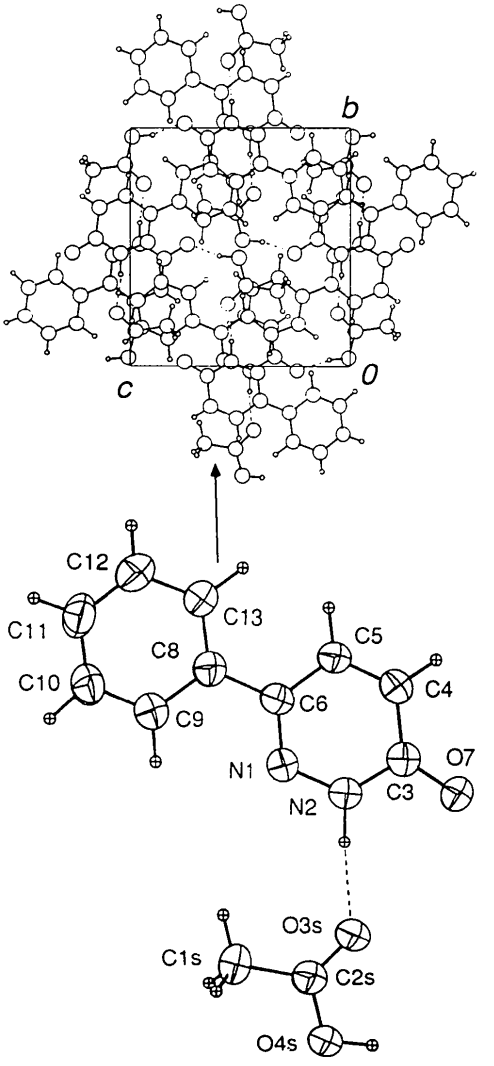


Fig. 2. 6-Phenyl-3(2*H*)-pyridazinone–acetic acid (1/1) (1), seen in projection down *a*. The molecules form zigzag chains along twofold screw axes parallel to *b* by hydrogen bonding from N(2) through the acetic acid solvate to O(7) of the next molecule in the chain.

dihedral angle and any bond length or angle in these systems.

X-ray diffraction and theoretical studies on a number of systems containing the amide moiety have concluded that the π-electrons are readily delocalized. The bond lengths and angles in the pyridazinone rings of (1) and (2) (which do not differ significantly) suggest that in each, the electron delocalization extends throughout the unsubstituted pyridazinone rings. For (3), in which a methyl group is substituted at the 5-position, there is an apparently significant increase in the length of the 5—6 bond. It is plausible to attribute the lengthening of the 5—6 bond in (3) to a loss in electron delocalization due to the 53° rotation of the phenyl group in (3) but it is more likely to be a vagary in small sample statistics.

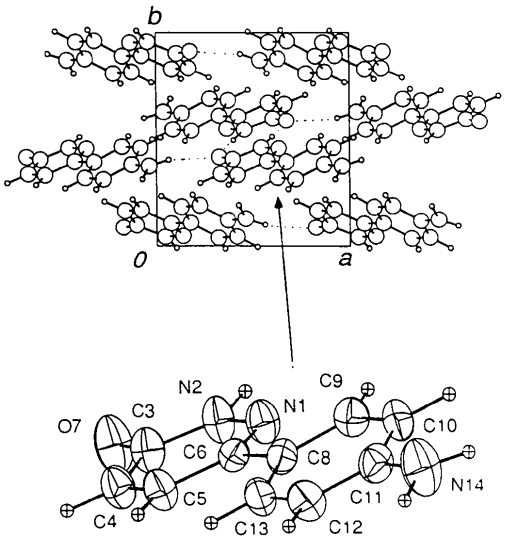


Fig. 3. 6-(4-Aminophenyl)-3(2*H*)-pyridazinone (2), seen in projection down *c*. The molecules form centrosymmetric hydrogen bonded dimers *via* N(2)···O(7′) links. The dimers are linked by N(14)···O(7) hydrogen bonds to form cyclic tetramers.

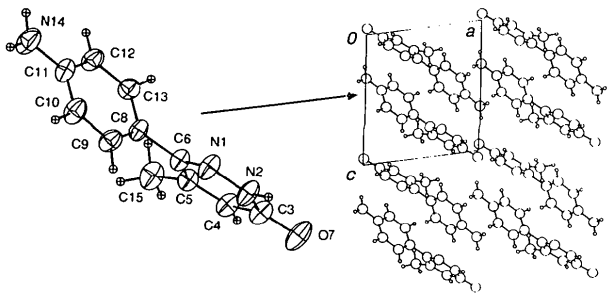


Fig. 4. 6-(4-Aminophenyl)-5-methyl-3(2*H*)-pyridazinone (3), seen in projection down *b*. The molecules form hydrogen-bonded chains *via* N(2)···O(7′) links, along the twofold screw axes parallel to *b*. The amino group N(14) does not form hydrogen bonds.

The lengthening in the 5—6 bond in (3) is not accompanied by the shortening of the 1—6 bond that occurs on hydrogenation of the 4—5 bond in (8), (9), (10) and (11). The reduction of the 4—5 bond leads to a breakdown of electron delocalization over the 6, 1, 2, 3, 4 section of the ring with the lengths of the bonds 1—6, 1—2, 2—3 and 3—4 approaching the values expected for a C—N bond (1.279 Å), an N—N single bond (1.454 Å), the C=N of a δ-lactam (1.334 Å) and the C=O of a δ-lactam (1.240 Å), respectively (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987).

It has previously been observed in cytosine rings that endocyclic ring angles (Taylor & Kennard, 1982;

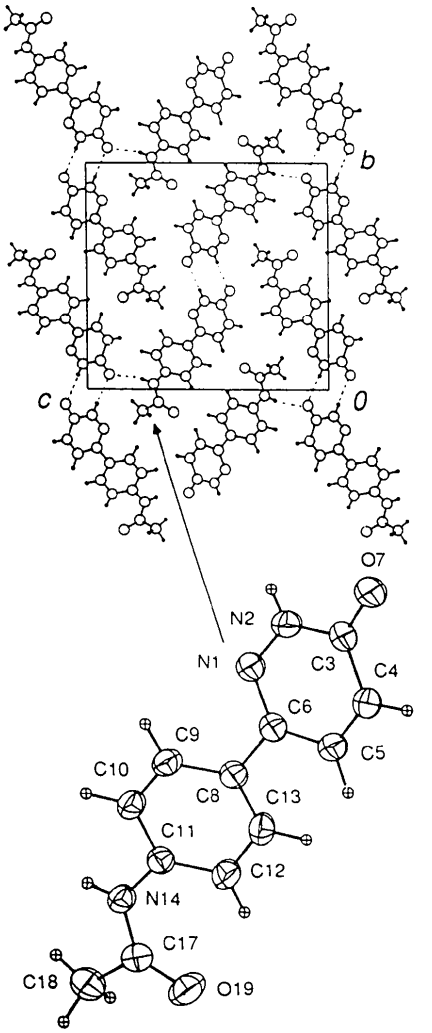


Fig. 5. 6-(4-Acetamidophenyl)-3(2*H*)-pyridazinone (4), seen in projection down *a*. The molecules form centrosymmetric hydrogen-bonded dimers *via* N(2)···O(7′) links. A second hydrogen bond, from O(7) to an amide nitrogen N(14) of a molecule related by a twofold screw axis parallel to *b*, links the dimers to form hydrogen-bonded ribbons parallel to [011].

Bannister, Burns, Prout, Watkin, Cooper, Durant, Ganellin & Sach, 1993), where the ring nitrogen is substituted by a hydrogen, are always larger than those where the nitrogen is not substituted (Singh, 1965). In cytosine rings these differences are usually about 5° whereas in the pyridazinone system differences between C—N—C and C—NH—C angles are larger, usually 8–10°. The very large endocyclic angle (1—2—3 average value 127.0°) at the amide nitrogen atoms N(2) and the related small endocyclic angles at N(1) (6—1—2 average value 117.2°) and at the carbonyl carbon C(3) (2—3—4 average value 114.7°) are the most obvious dimensional features of the pyridazinone heterocycle. The value of the 1—2—3 angle in the pyrazinone (7), 124.5°, is rather lower. The magnitudes of the angles 1—2—3 and 2—3—4 are in no way anomalous in amide chemistry. For (4), (5), (8*a*) and (8*b*) very similar values are observed for the corresponding angles 11—14—17 and 14—17—18 in the acyclic amide groups. Examination of the Cambridge Structural Database (CSD) shows that the observed values are typical of those found in cyclic systems, δ-lactams and related compounds. A search of the CSD suggested mean endocyclic angles of 115.8 (2.7)° at the carbonyl group and 124.7 (3.1)° at the nitrogen. Nevertheless, the magnitudes of the angles in the cyclic pyridazinones are surprising. For the acyclic amide groups it is conventional to attribute the large value(s) of the angles(s) 11—14—17 (and 14—17—19) to steric repulsions between the atoms of the 10—11 bond and the 17—18 bond. However, if the amide is part of a planar six-membered ring the expected values of the endocyclic ring angles are 120° and the 127° angle at N(2) represents a substantial distortion from the norm that requires other endocylic angles to be < 120° in compensation. The larger part of this compensation is provided by the accompanying carbonyl group where the N—C—C angle at the carbonyl C atom (2—3—4) is generally significantly less than 120° (generally about 115°) independent of its steric environment. As indicated by the cyclic and acyclic amide groups observed in this work, steric considerations appear to influence the direction of the C=O bond which does not lie on the bisector of the N—C—C angle but is displaced either towards or

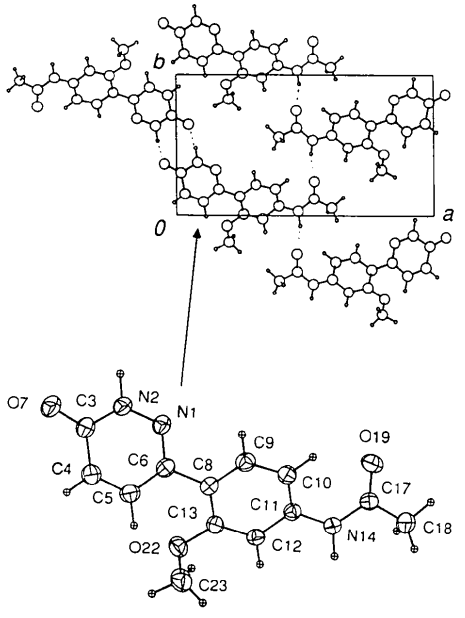


Fig. 6. 6-(4-Acetamido-2-methoxyphenyl)-3(2*H*)-pyridazinone (5), seen in projection down *c* but with only sufficient of the crystal packing shown to illustrate the salient features of the hydrogen bonding. The diagram shows molecules linked *via* O(19)···N(14) to form a hydrogen-bonded chain along a twofold screw axis parallel to *b* and one molecule is seen forming a hydrogen-bonded dimer. The effect of dimer formation is to link the chains into sheets in the *ab* plane. Each sheet is related to its neighbouring sheets (not shown) by the *c* glide (see Table 6).

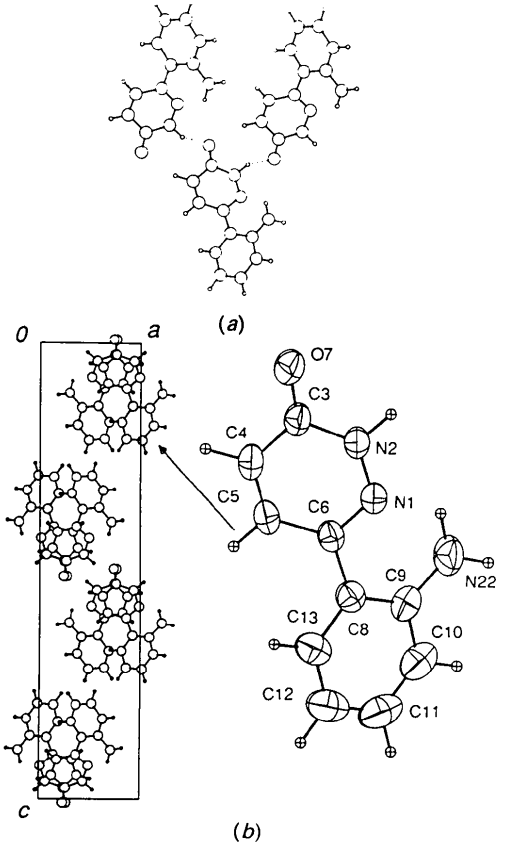


Fig. 7. 6-(2-Aminophenyl)-3(2*H*)-pyridazinone (6), seen (*a*) in projection down *a* showing the hydrogen bonded [N(2)···O(7)] chain generated by a twofold screw axis parallel to *b* and (*b*) down *b*. The amino group N(22) is not engaged in hydrogen bonding.

away from the amide nitrogen according to the steric constraints on the molecule.

If the apparent distortions of the amide group cannot be attributed in all cases to steric effects it becomes prudent to argue that the 127° angle at the amide nitrogen and the 115° N—C—C angle at the carbonyl are intrinsic values that are a consequence of the electronic structure rather than values resulting from steric strain.

In the dihydropyridazinones (8), (9), (10) and (11), atoms 3 and 6 are trigonal planar sp^2 carbon centres and bonding requirements determine that the torsion angles 5—6—1—2 and 1—2—3—4 should be 0°. If the torsion angles are averaged over the six independently observed molecules then the values 1.0 and 0.2° are obtained and the whole of the twist in the molecule required to accommodate the sp^3 centres at atoms 4 and 5 takes place at the N—N bond 1—2 with an average value of the torsion angles 6—1—2—3 of 15.2°. The individual picture is more complex (see Fig. 13) so that the spread in the values of 6—1—2—3 is from 8.6 to 21.4° and although the average value of 1—2—3—4 is closer to zero than for 5—6—1—2 the spread of 1—2—3—4, −8.8 to 7.2°, is much larger than for 5—6—1—2, −2.0 to 4.6°, suggesting a greater flexibility in the amide than in the C=N bond. The conformation of the 6-methydihydropyridazinone (11) is very similar to that of the 6-aryl compound (8*a*) suggesting that the aryl substituent does not play a significant part in determining the dihydropyridazinone conformation. The small overall differences in the dihydropyridazinone conformations are best attributed to crystal-packing forces. Studies using molecular mechanics (Davis, Warrington & Vinter, 1987) suggest that there are a range of closely similar conformations with very similar energies. The torsion angles 3—4—5—15, 15—5—6—1 and 15—5—6—8 show that in the observed conformation of the 5-methyl derivatives (9) and (10) the C—CH_3 bond is equatorial and approximately perpendicular to the mean ring plane.

Absolute configuration of (9) *and* (10)

In formal terms the chiral centre is *R*, informally if the molecule is viewed from nitrogen (1) and carbon

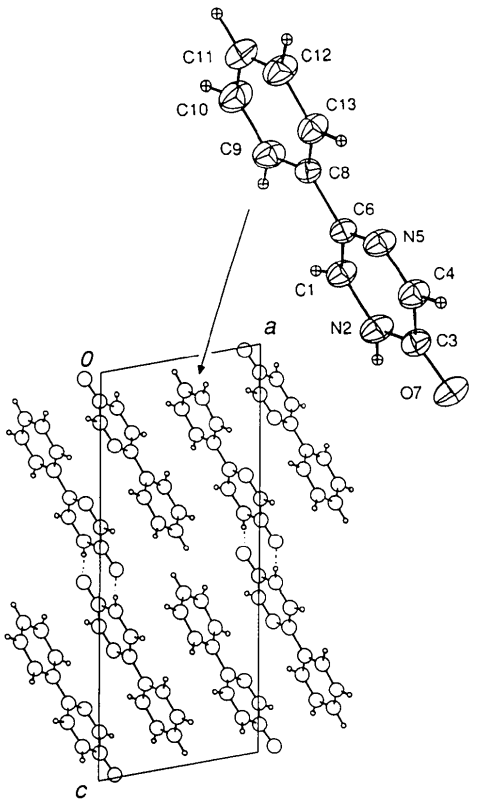


Fig. 8. 6-Phenyl-3(2*H*)-pyrazinone (7), seen in projection down *b*. The molecules form hydrogen-bonded dimers [N(2)···O(7)] about crystallographic symmetry centres.

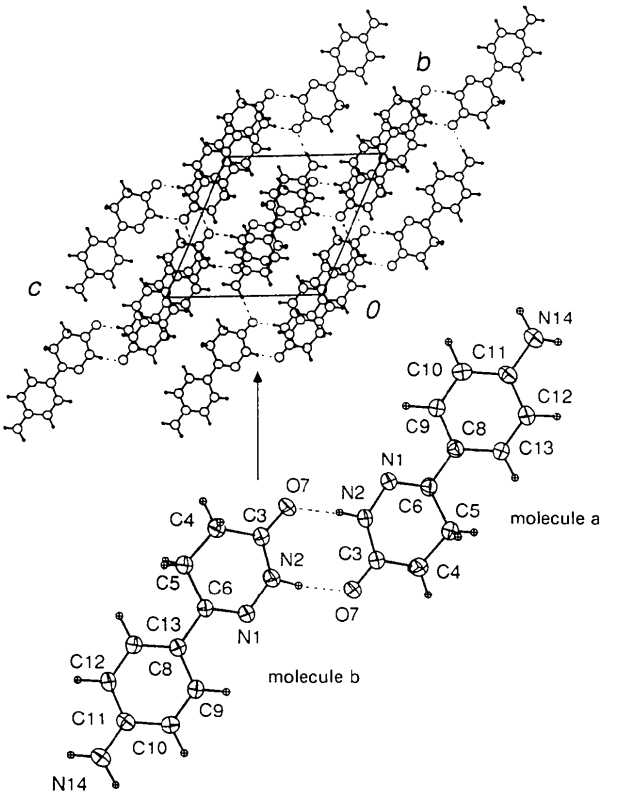


Fig. 9. 6-(4-Aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (8), seen in projection down *a*. The molecules *a* and *b* of the chosen asymmetric unit form pseudocentrosymmetric hydrogen-bonded [N(2*a*)···O(7*b*)] dimers. These dimeric units are linked into sheets by N(14*a*)···O(7*a*) and N(14*b*)···O(7*b*) hydrogen bonds to form ribbons parallel *b* (see Table 6).

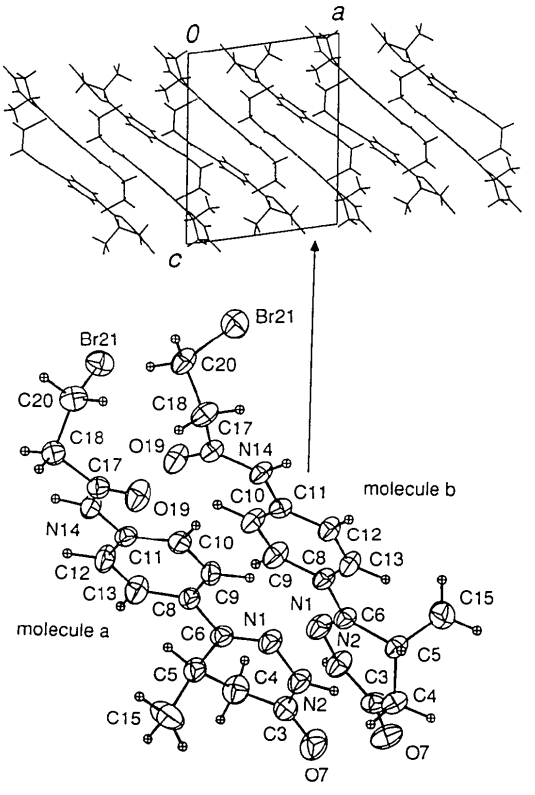


Fig. 10. (*R*)-(−)-6-[4-(3-Bromopropionamido)phenyl]-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (9), seen in projection down *b*. Molecule *a* of the chosen asymmetric unit forms a pseudocentrosymmetric hydrogen-bonded [N(2*a*)···O(7*b*)] dimer with molecule *b* of the asymmetric unit at $2-x, \frac{1}{2}+y, 2-z$ and these dimers are linked into chains by [N(14*a*)···O(19*a*)] hydrogen bonds from *a* and *b* molecules of one asymmetric unit to the *a* and *b* molecules of the asymmetric unit at $-x, \frac{1}{2}+y, 1-z$ (see Table 6).

(5) with the 6-aryl group at the top and carbonyl at the bottom then the methyl group is on the observer's left hand. This confirms a prediction from modelling studies based on the idea that an advantageous hydrophobic interaction with the phosphodiesterase receptor could exist only for the *R* enantiomer (Davis, Warrington & Vinter, 1987).

Hydrogen bonding and the arrangement of the molecules

Details of the hydrogen bonding are given in Table 6 and illustrated in Figs. 2–12. The —NH—C=O moieties of all the pyridazinone molecules encountered in this work and in the literature form a hydrogen-donor bond at the NH group and at least one, occasionally two, hydrogen acceptor bonds at the carbonyl O atom. These hydrogen bonds may link the pyridazinone groups to form dimers, Fig. 3, or to form chains, Fig. 4. In the dimers the molecules are related by a symmetry centre (or psuedosymmetry centre) and in the chains by a twofold screw axis. There are indications that dimers are favoured by the majority of structures, but when bulky substituents are present chains may be found as an alternative. The pyridazinone nitrogen atom N(1) does not form intermolecular hydrogen bonds.

Dimers are found in the crystals of (2), (4), (5), (7), (8) and (9) (Figs. 3, 5, 6, 8, 9 and 10). For (2) the dimers are linked about a second symmetry centre by a second hydrogen bond from the carbonyl oxygen to the amine nitrogen O(7)···N(14) to form tetramers; for (4) and (5) the dimers are linked into chains, by an O(7)···N(14) hydrogen bond in (4) and an O(19)···N(14) hydrogen bond in (5); for (8) two

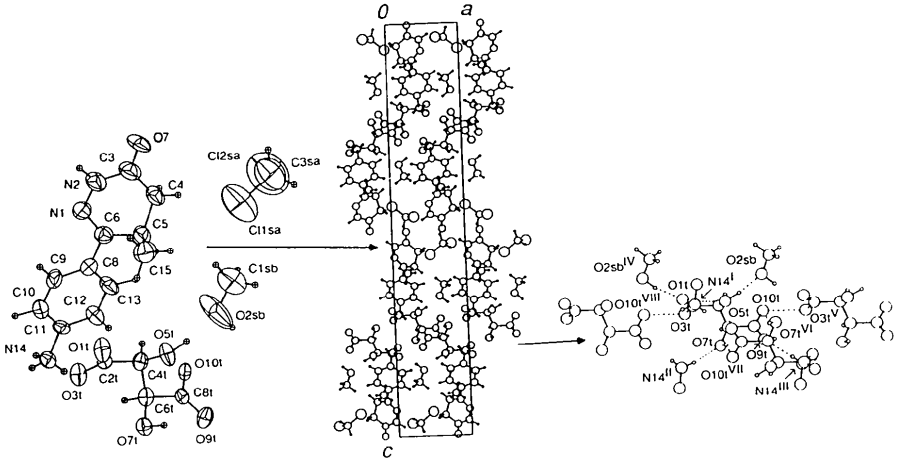


Fig. 11. (*R*)-(−)-6-(4-Ammoniophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (−)-tartrate–dichloromethane–methanol (1/1/1) (10), seen in projection down *b*. The asymmetric unit contains a pyridazinone cation, a tartrate anion and a methanol and dichloromethane of solvation. The anions form hydrogen-bonded layers in the *ab* plane to which the cations are attached by hydrogen bonding to N(14) and the methanol solvent by hydrogen bonding to O(2*sb*). N(2)···O(7) hydrogen bonds along a twofold screw axis link the layers into a three-dimensional network. The hydrogen-bonding environment of the tartrate anion is detailed on the right of the diagram (also see Table 6).

crystallographically nonequivalent molecules form a dimer about a pseudocentre of symmetry and the dimers are linked by O(7)···N(14) hydrogen bonds between equivalent molecules related by unit-cell translations to form ribbons parallel to *b*; in (9) again two crystallographically nonequivalent molecules form a dimer about a pseudocentre of symmetry and are linked to form sheets by O(19)···N(14) hydrogen bonds between equivalent molecules related by the twofold screw axis; and in (7), the pyrazinone, there is no additional hydrogen bonding.

In (3), (6) and (10) (Figs. 4, 7 and 11) the N(2)···O(7) hydrogen bond links the molecules into chains. For (3) and (6) there is no additional intermolecular hydrogen bonding but in (6) there is what may be an N(1)···N(22) intramolecular hydrogen bond. The N(1)···N(22) contact distance is 2.785 (4) Å but the molecular geometry requires an N(1)···H—N(22) angle of 130°. For (10) an N(2)···O(7) hydrogen bond links cations related by a twofold axis parallel to *a*, into chains. The tartrate anions and methanol solvent form hydrogen-bonded sheets parallel to the *ab* plane. These sheets are hydrogen bonded to the ammonium nitrogen atom N(14) of the cation so that the anion sheets together with the cation chains form a three-dimensional network with channels parallel to *a* (see Fig. 11). The dichloromethane solvent is found in these channels.

(1) and (11) also contain chains but the chains are built up from pyridazinone molecules and solvent molecules (Figs. 2 and 12). For (1) N(2) of one pyridazinone hydrogen bonds to the acetic acid C=O and the acetic acid C—OH then hydrogen bonds to the oxygen atom O(7) of a second chain propagated by a twofold screw axis. For (11) the role of the solvent water is similar to that of the acetic acid solvent except that within the chain the water hydrogen bonds three pyridazinone molecules.

The persistence of the hydrogen-bonding pattern of N2 and O7 in every pyridazinone structure despite the presence of additional donor and acceptor atoms in many of the structures examined suggests that this arrangement may be important for some highly directional interaction with a biological macromolecule or receptor.

Factors affecting hydrogen bonding

It has been found that the readily delocalized π-system in the N—C=O moiety, which can counteract perturbations in the system, is one of the major factors in the ability of this fragment to form hydrogen bonds. Previous structure determinations suggest that the formation of a hydrogen bond increases the conjugation in the N—C=O fragment, which may be observed as a shortening of the C—NH bond, typically by about 0.025 Å, and a

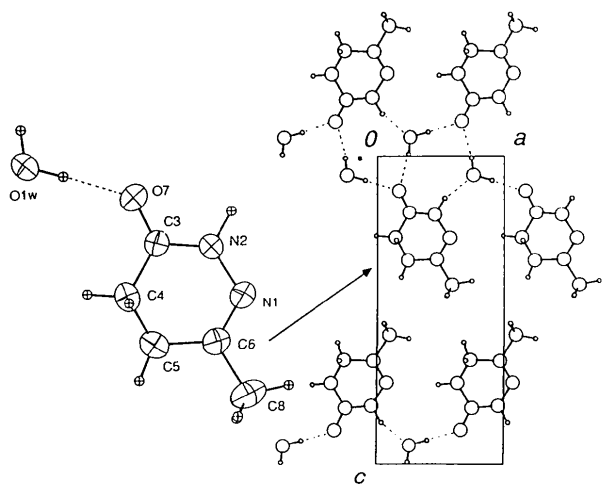


Fig. 12. 4,5-Dihydro-6-methyl-3(2*H*)-pyridazinone (11), seen in projection down *b*, but with only sufficient of the crystal packing shown to illustrate the salient features of the hydrogen bonding. The dihydropyridazinone molecule and the solvent together form flat hydrogen-bonded ribbons in the *ac* plane extended along *a*.

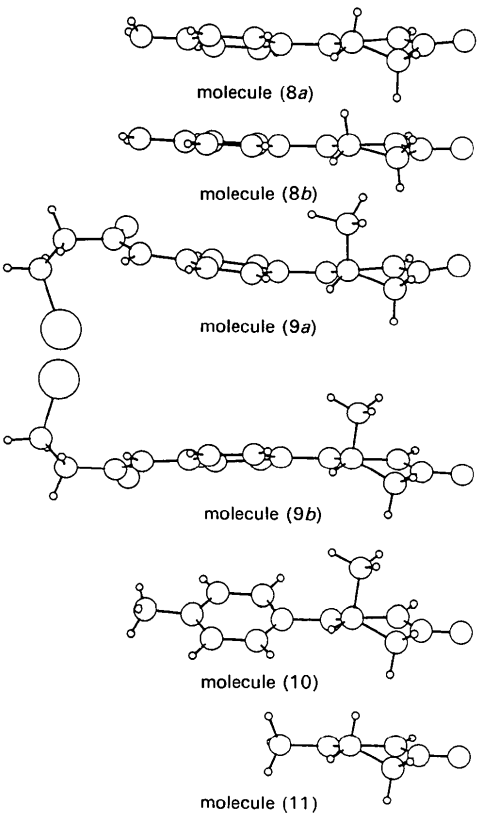


Fig. 13. The six crystallographically independent dihydro-3(2*H*)-pyridazinone systems each viewed along the C(5)···N(1) vector, showing the variations in molecular conformation.

shortening of the C=O bond by about 0.014 Å (Ottersen, 1976). Furthermore, it has been observed that increased conjugation of the N—C=O fragment leads to an increase in the conjugation over the entire molecular system. It would therefore seem reasonable to postulate that any ring substituent which could affect the π-electron delocalization may affect the strength of the hydrogen bond.

When the bond lengths and angles, for the pyridazinone rings in molecules (1) to (11) and other structures, were corrected using the statistical package *MINITAB* (1982) reasonable correlations were observed for bonds 1—6, 1—2 and 2—3 and angles 5—6—1 and 6—1—2 against N···O hydrogen-bond lengths. No correlation was observed between the carbonyl bond 3—7 or the endocyclic carbonyl angle 2—3—4 and hydrogen-bond length. It has been suggested that the N···O distance is not always a reliable guide to hydrogen-bond strength and that a much truer representation may be the H···O distance. Using the normalization procedure described by Taylor & Kennard (1983), the systematic errors in the H-atom positions were corrected for and the H···O distances and N—H···O angles measured. It was found that whilst the ring bond lengths correlate well with H···O distances, the correlation of H···O distance with angles 5—6—1 and 6—1—2 is very poor. As observed for the N···O distance, no correlation exists between bond 3—7 or angle 2—3—4 and H···O, but there does appear to be a good correlation between carbonyl bond length and N—H···O angle.

The results obtained illustrate that a correlation exists between the π-electron distribution in the ring, as reflected in its dimensions, and the hydrogen-bond strength, as reflected by the N···O and H···O distances. It appears that the hydrogen-bond length increases, and therefore the strength decreases, when a strong electron-withdrawing group such as chlorine is added to the ring, whereas the opposite is true in the presence of an electron donor such as methyl. It is therefore likely that by adding substituents to the pyridazinone ring at the 5-position will affect the π-electrons in the N—C=O moiety and hence modify the strength of the N—H···O hydrogen bond formed.

We thank the SERC (UK) and Smith Kline & French Research Ltd (now SmithKline Beecham) for CASE studentships for CB and KB.

References

ALLEN, F. H., KENNARD, O., WATSON, D. G., BRAMMER, L., ORPEN, A. G. & TAYLOR, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, S1–S19.

BAKEWELL, S. J., COATES, W. J., CORNER, M. B., REEVES, M. L. & WARRINGTON, B. H. (1990). *Eur. J. Med. Chem.* **25**, 765–774.

BANNISTER, C., BURNS, K., PROUT, C. K., WATKIN, D. J., COOPER, D. G., DURANT, G. J., GANELLIN, C. R. & SACH, G. S. (1993). *Acta Cryst.* B**49**, 547–560.

CARRUTHERS, J. R. & WATKIN, D. J. (1979). *Acta Cryst.* A**35**, 698–699.

COATES, W. J., PRAIN, H. D., REEVES, M. L. & WARRINGTON, B. H. (1990). *J. Med. Chem.* **331**, 1735–1741.

CROMER, D. T. & WABER, J. T. (1974). *International Tables for X-ray Crystallography*, edited by J. A. IBERS & W. C. HAMILTON, Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

DAVIS, A., WARRINGTON, B. H. & VINTER, J. G. (1987). *J. Comput. Aided Mol. Des.* **1**, 97–120.

DOMENICANO, A. & MURRAY-RUST, P. (1979). *Tetrahedron Lett.* **24**, 2818–2819.

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN*80. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

MINITAB (1982). Release 82.1. Statistics Department, Penn. State, USA.

OTTERSEN, T. (1976). *Adv. Mol. Relax. Proc.* **9**, 105–128.

PROUT, K., BURNS, K. & ROE, A. M. (1993). *Acta Cryst.* B**49**, 68–71.

ROGERS, D. (1981). *Acta Cryst.* A**37**, 734–741.

SHELDRICK, G. (1985). *Crystallographic Computing* 3, edited by G. M. SHELDRICK, C. KRÜGER & R. GODDARD, pp. 175–189. Oxford Univ. Press.

SINGH, C. (1965). *Acta Cryst.* **19**, 861–864.

SLATER, R. A., HOWSEN, W., SWAYNE, G. T. G., TAYLOR, E. M. & REAVIL, D. R. (1988). *J. Med. Chem.* **31**, 345–351.

TAYLOR, E. M., CAMERON, D., EDEN, R. J., FIELDEN, R. & OWEN, D. A. A. (1981). *J. Cardiovasc. Pharmacol.* **3**, 337–354.

TAYLOR, E. M., ROE, A. M. & SLATER, R. A. (1979). *Clin. Sci.* **57**, 433S–436S.

TAYLOR, R. & KENNARD, O. (1982). *J. Mol. Struct.* **78**, 1–28.

TAYLOR, R. & KENNARD, O. (1983). *Acta Cryst.* B**39**, 517–525.

VINTER, J. G., DAVIS, A. & SAUNDERS, M. R. (1987). *J. Comput. Aided Mol. Des.* **1**, 31–53.

WATKIN, D. J., CARRUTHERS, J. R. & BETTERIDGE, P. W. (1985). *CRYSTALS User Guide.* Chemical Crystallography Laboratory, Univ. of Oxford, England.