Acta Crystallographica Section B
Structural Science
ISSN 0108-7681

Structural characterization of [1,4]diazepino[6,5-*b*]indoles by powder diffraction

Svetlana Yu. Ryabova,[a] Nina A. Rastorgueva,[a] Eduard J. Sonneveld,[b] Rene Peschar,[b] Henk Schenk,[b] Viktor A. Tafeenko,[c] Leonid A. Aslanov[c] and Vladimir V. Chernyshev[c]*

[a]Department of Medicinal Chemistry, State Scientific Center of Antibiotics, Nagatinskaya str. 3a, 113105 Moscow, Russia, [b]Laboratory for Crystallography, Institute of Molecular Chemistry, University of Amsterdam, Nieuwe Achtergracht 166, Amsterdam 1018 WV, The Netherlands, and [c]Department of Chemistry, Moscow State University, 119992 Moscow, Russia

Correspondence e-mail: vladimir@struct.chem.msu.ru

Received 23 July 2004
Accepted 24 February 2005

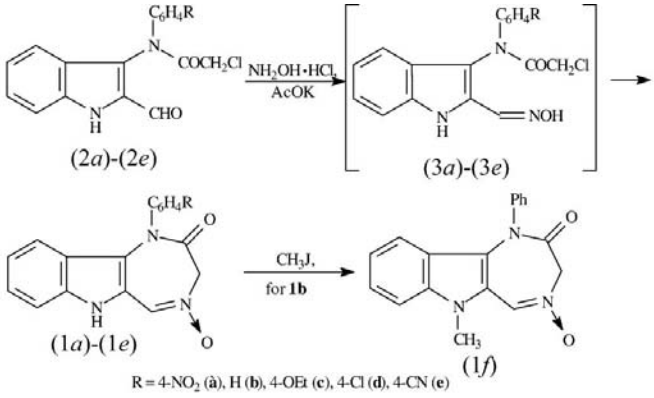
As part of a systematic structural study of potentially pharmacologically active [1,4]diazepino[6,5-*b*]indoles, the crystal structures of nine compounds have been determined from laboratory powder diffraction data. The investigated compounds are: 2-oxo-1-(4-nitrophenyl)-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{17}H_{12}N_4O_4$ (1*a*); 2-oxo-1-phenyl-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{17}H_{13}N_3O_2$ (1*b*); 2-oxo-1-(4-ethoxyphenyl)-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{19}H_{17}N_3O_3$ (1*c*); 2-oxo-1-(4-chlorophenyl)-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{17}H_{12}N_3O_2Cl$ (1*d*); 2-oxo-1-(4-cyanophenyl)-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{18}H_{12}N_4O_2$ (1*e*); 6-methyl-2-oxo-1-phenyl-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{18}H_{15}N_3O_2$ (1*f*); 2-formyl-3-[*N*′-(ω-chloracetyl)-*N*′-(4-nitrophenyl)]aminoindole, $C_{17}H_{12}N_3O_4Cl$ (2*a*); 2-formyl-3-[*N*′-(ω-chloracetyl)-*N*′-(4-nitrophenyl)]aminoindole solvate with toluene (2:1), $C_{17}H_{12}N_3O_4Cl{\cdot}0.5C_7H_8$ (2*as*); 2-formyl-3-[*N*′-(ω-chloracetyl)-*N*′-(4-cyanophenyl)]aminoindole, $C_{18}H_{12}N_3O_2Cl$ (2*e*). Compounds (1*a*)–(1*f*) crystallize in non-centrosymmetric triclinic, monoclinic and orthorhombic space groups. The three-dimensional structures of (1*a*)–(1*e*) demonstrate identical intermolecular NH(indole)···O←N hydrogen bonds, which form linear chains of connected molecules. A comparison of the crystal structures (2*a*), (2*e*) and (2*as*) shows that the solvent used in the re-crystallization of (2*a*) and (2*e*), which are intermediates in the synthesis of (1*a*) and (1*e*), affects the intermolecular hydrogen-bond formation and, as a result, leads to essentially different yields of the goal products.

1. Introduction

Benzodiazepines were introduced as psychotherapeutic agents more than 40 years ago and are still widely used for this purpose. Some of them are also known as anticonvulsants (clonazepam, diazepam, chlordiazepoxide, nitrazepam and oxazepam), while others are used as tranquilizers (chlozepid, sibazon, phenazepam and hydazepam). Indole-containing polycyclic compounds are also known as efficient pharmaceuticals (Mashkovskii, 1998, 2000; Granik, 2001), *e.g.* the antidepressants pyrazidole, tetrindole and incazan, the neuroleptic agent carbidine, and the antihystamine drugs dimebon and diazolin. Recently, a new series of synthetic 3-amino-4-arylpyridazino[4,3-*b*] indoles (pyridazinoindoles) were identified as inhibitors of *Mycobacterium tuberculosis* (Velezheva *et al.*, 2004). Hence, fused systems involving the indole and [1,4]diazepine rings are of interest from the viewpoint of a search for new biologically active compounds. In this respect, it is noted that some [1,4]diazepino[1,2-*a*]indole

derivatives were found to exhibit pronounced psychotropic activity (Freed & Freed, 1968; Reynolds & Carson, 1968; Freed & Hertz, 1968; Gatta *et al.*, 1975).

In spite of their potential usefulness, [1,4]diazepino[1,2-*a*]indoles have not been studied extensively (Garcia *et al.*, 1973), apparently due to the fact that they are difficult to synthesize, although different methods of obtaining their derivatives have been published (Garcia *et al.*, 1973; Hiremath *et al.*, 1990; Boschelli *et al.*, 1994). Garcia and co-workers (Garcia *et al.*, 1973) demonstrated that an indole derivative with the phenacyl and bromacetylamino groups in positions 2 and 3, respectively, can be cyclized to the corresponding [1,4]diazepino[6,5-*b*]indole using ammonia. The preparative method to synthesize benzo[1,4]diazepines is the reaction based on the interaction of chloracetylamino-2-carbonyl derivatives of benzene series with hydroxylamine (Granik, 2001). Recently, a new preparative method for the synthesis of [1,4]diazepino[6,5-*b*]indoles (1*a*)–(1*f*) from 2-formyl-3-(*N*′-ω-chloracetyl-*N*′-aryl)aminoindoles (2*a*)–(2*e*) (see scheme below) has been developed (Ryabova *et al.*, 1996, 2003; Lantsetti *et al.*, 2002; Lantsetti & Ryabova, 2001).



Using this method, the polycrystalline samples of the following compounds have been obtained:

(1*a*) 2-oxo-1-(4-nitrophenyl)-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{17}H_{12}N_4O_4$;

(1*b*) 2-oxo-1-phenyl-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{17}H_{13}N_3O_2$;

(1*c*) 2-oxo-1-(4-ethoxyphenyl)-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{19}H_{17}N_3O_3$;

(1*d*) 2-oxo-1-(4-chlorophenyl)-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{17}H_{12}N_3O_2Cl$;

(1*e*) 2-oxo-1-(4-cyanophenyl)-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{18}H_{12}N_4O_2$;

(1*f*) 6-methyl-2-oxo-1-phenyl-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole-4-oxide, $C_{18}H_{15}N_3O_2$;

(2*a*) - 2-formyl-3-[*N*′-(ω-chloracetyl)-*N*′-(4-nitrophenyl)]-aminoindole, $C_{17}H_{12}N_3O_4Cl$;

(2*as*) 2-formyl-3-[*N*′-(ω-chloracetyl)-*N*′-(4-nitrophenyl)]-aminoindole solvate with toluene (2:1), $C_{17}H_{12}N_3O_4Cl{\cdot}0.5C_7H_8$;

(2*e*) 2-formyl-3-[*N*′-(ω-chloracetyl)-*N*′-(4-cyanophenyl)]-aminoindole, $C_{18}H_{12}N_3O_2Cl$.

As part of a systematic structural study of potentially pharmacologically active [1,4]diazepino[6,5-*b*]indoles the crystal structures of these nine compounds have been determined from powder diffraction data using methods, based on the direct space approach and global optimization (David *et al.*, 2002; Harris *et al.*, 2001; Chernyshev, 2001).

2. Experimental

2.1. Synthesis

All compounds have been synthesized as polycrystalline powders in the Department of Medicinal Chemistry, State Scientific Centre of Antibiotics, Moscow, Russia, in accordance with the literature (Ryabova *et al.*, 1996, 2003; Lantsetti & Ryabova, 2001; Lantsetti *et al.*, 2002). The molecular structures were validated by the results of IR, NMR and PMR spectroscopy, and mass spectrometry.

2.2. Data collection and indexing

Powder diffraction data were collected at room temperature in the transmission mode of the Guinier camera. The unit-cell dimensions of all the compounds were determined using *ITO* (Visser, 1969). The monoclinic and orthorhombic space groups were determined on the basis of systematic extinction rules. The unit-cell parameters and space groups were further tested with Pawley fits (Pawley, 1981) and confirmed by crystal structure solutions.[1] Crystallographic data for (1*a*)–(1*f*), (2*a*), (2*as*) and (2*e*) are summarized in Table 1, where the unit-cell parameters are the values after the final Rietveld refinement.

2.3. Structure solution from powder data

The structures were solved with the systematic grid-search procedure (Chernyshev & Schenk, 1998), using 100 X_{obs} low-angle values. Approximate models of the molecules were built up with the program *PCMODEL* (Serena Software, 1999). In the models obtained for (1*a*)–(1*f*), the dihedral angle between the indole bicycle and the aryl group was around 90°. This angle changed further at the stage of structural refinement. For the triclinic compounds (1*a*) and (1*e*) attempts to find a solution in the space group $P\bar{1}$ failed. The correct solutions were found in the non-centrosymmetric space group *P*1 with 9 degrees of freedom – no translations were allowed for one of the two independent molecules so that the origin would be fixed.

2.4. Rietveld refinement

In the final bond-restrained Rietveld refinement all patterns were fitted using the program *MRIA* (Zlokazov & Chernyshev, 1992) using a split-type pseudo-Voigt peak profile function (Toraya, 1986). March–Dollase (Dollase, 1986) and symmetrized harmonics expansion (Ahtee *et al.*, 1989; Järvinen, 1993) texture formalisms were used when processing

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: WS5016). Services for accessing these data are described at the back of the journal.

Table 1
Experimental details.

	(1*a*)	(1*b*)	(1*c*)	(1*d*)	(1*e*)
Formula	$C_{17}H_{12}N_4O_4$†	$C_{17}H_{13}N_3O_2$	$C_{19}H_{17}N_3O_3$	$C_{17}H_{12}N_3O_2Cl$	$C_{18}H_{12}N_4O_2$
System	Triclinic	Orthorhombic	Monoclinic	Orthorhombic	Triclinic
Space group	*P*1	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	*P*1
a (Å)	10.888 (7)	23.97 (2)	13.671 (9)	24.71 (2)	10.756 (8)
b (Å)	12.881 (9)	10.608 (8)	10.379 (8)	10.883 (7)	13.101 (9)
c (Å)	5.495 (3)	5.457 (3)	5.688 (3)	5.454 (3)	5.535 (3)
α (°)	91.42 (2)	90	90	90	97.02 (2)
β (°)	91.51 (2)	90	99.04 (2)	90	89.07 (2)
γ (°)	76.84 (2)	90	90	90	101.33 (3)
V (Å^3)	750.0 (8)	1387 (2)	797.1 (9)	1467 (2)	759.0 (9)
Z	2	4	2	4	2
D_x (Mg m^{-3})	1.489	1.395	1.397	1.475	1.384
Diffractometer	Guinier	Guinier	XPert	Guinier	Guinier
Radiation	Cu $K\alpha_1$	Cu $K\alpha_1$	Cu $K\alpha_1$	Cu $K\alpha_1$	Cu $K\alpha_1$
2θ (°)	5.5–70	6–75	5.004–59.980	6–70	5.5–65
2θ step (°)	0.01	0.01	0.008	0.01	0.01
R_p‡	0.0487	0.0876	0.0447	0.0686	0.0603
	0.0462	0.0710	0.0403	0.0617	0.0512
R_{wp}	0.0632	0.1180	0.0585	0.0875	0.0786
	0.0583	0.0859	0.0515	0.0764	0.0657
R_{exp}	0.0279	0.0401	0.0467	0.0337	0.0296

	(1*f*)	(2*a*)	(2*as*)	(2*e*)
Formula	$C_{18}H_{15}N_3O_2$	$C_{17}H_{12}N_3O_4Cl$	$C_{17}H_{12}N_3O_4Cl{\cdot}0.5C_7H_8$	$C_{18}H_{12}N_3O_2Cl$
System	Orthorhombic	Monoclinic	Triclinic	Monoclinic
Space group	$Pna2_1$	$P2_1/c$	$P\overline{1}$	$P2_1/n$
a (Å)	14.925 (9)	13.080 (11)	12.118 (12)	14.698 (14)
b (Å)	18.18 (1)	15.177 (15)	12.746 (13)	14.120 (14)
c (Å)	5.435 (3)	8.505 (7)	7.023 (6)	7.687 (7)
α (°)	90	90	86.71 (2)	90
β (°)	90	92.45 (2)	96.83 (3)	93.07 (2)
γ (°)	90	90	117.68 (3)	90
V (Å^3)	1475 (2)	1687 (3)	954 (2)	1593 (3)
Z	4	4	2	4
D_x (Mg m^{-3})	1.375	1.409	1.404	1.408
Diffractometer	Guinier	Guinier	Guinier	Guinier
Radiation	Cu $K\alpha_1$	Cu $K\alpha_1$	Cu $K\alpha_1$	Cu $K\alpha_1$
2θ (°)	6–65	6–80	6.5–75	7–79
2θ step (°)	0.01	0.01	0.01	0.01
R_p‡	0.0504	0.0577	0.0630	0.0535
	0.0438	0.0543	0.0550	0.0481
R_{wp}	0.0660	0.0735	0.0812	0.0684
	0.0535	0.0666	0.0712	0.0595
R_{exp}	0.0275	0.0317	0.0331	0.0311

† The sample of (1*a*) contained a small amount of NaCl. ‡ R_p, R_{wp} and R_{exp} are defined according to Young & Wiles (1982). The results of the final bond-restrained Rietveld refinement are given in the first row of each pair of rows and the results of the Pawley fit are given in the second row of each pair.

textured patterns. The anisotropy of diffraction-line broadening, observed in the pattern of (1*b*), was approximated by a quartic form in *hkl* (Popa, 1998). The preliminary Rietveld refinement of the Guinier pattern of (1*c*) showed strong texture effects. Therefore, a new powder pattern was measured in a capillary mode on an XPert PRO X-ray powder diffraction system equipped with an Xcelerator as the detector and this data set was used in the refinement. The sample (1*a*) contained a small amount of NaCl, which gave six additional peaks to the pattern. These peaks were taken into account during the two-phase Rietveld refinement. A common isotropic displacement parameter was refined for each moiety in all the compounds. One more isotropic displacement parameter was refined for the Cl atom in (1*d*), (2*a*), (2*as*) and (2*e*). H atoms were not refined but positioned geometrically with C—H 0.93–0.98 Å and N—H 0.86 Å.

Restraints were applied to intramolecular bond lengths and contacts in all moieties. The strength of the restraints was a function of the interatomic distance and, for intramolecular bond lengths, corresponded to an r.m.s. deviation of 0.03 Å. Additional restraints were applied to ensure the planarity of some of the fragments. The conformations of all nine molecules are shown in Figs. 1 and 2, prepared with *PLATON* (Spek, 2003). The diffraction profiles and the differences between the measured and calculated profiles after the final bond-restrained Rietveld refinement are shown in Fig. 3.

3. Result and discussion

3.1. Compounds (1*a*)–(1*f*)

All bond lengths in (1*a*)–(1*f*) are typical (Allen *et al.*, 1987) for bonds of their types within the standard uncertainties of 0.01–0.04 Å obtained in this powder study. The dihedral angle between the least-squares planes of the indole bicycle and the aryl group ranges from 65.6 (5)° in (1*a*) and 66.0 (4)° in (1*f*) to 82.8 (6)° in (1*e*); these differences are probably due to the crystal packing forces. The diazepine ring adopts the boat conformation in all the compounds (1*a*)–(1*f*). The three-dimensional structures of (1*a*)–(1*e*) demonstrate identical intermolecular N6—H6···O15 hydrogen bonds (Table 2), which form linear chains of connected molecules. In the triclinic compounds (1*a*) and (1*e*) these linear chains are formed by alternating independent molecules *A* and *B* (Fig. 4).

An interesting feature of (1*a*)–(1*f*) is that they all crystallize in non-centrosymmetric space groups. Owing to the boat conformation of the diazepine ring, the molecules (1*a*)–(1*f*) display conformational chirality. However, the crystals of these compounds contain only one of the two possible enantiomers, in contrast to the crystal structures of many 1,4-benzodiazepine derivatives, like diazepam (Camerman & Camerman, 1972), nitrazepam (Gilli *et al.*, 1977) and chlordiazepoxide (Bertolasi *et al.*, 1982), which crystallize in centrosymmetric space groups with two enantiomers in the unit cell. To find an answer to the question why (1*a*)–(1*f*) prefer the crystallization in non-centrosymmetric space groups, a special search for the organic compounds containing the non-substituted diazepine moiety has been carried out in the Cambridge Structural Database (Allen, 2002). The total number of selected crystal structures containing the full set of atomic coordinates was 66, and among those 47 and 19 crystallize in centrosymmetric and non-centrosymmetric space groups, respectively. Taking into account the compounds (1*a*)–(1*f*) characterized in this work, the total number of non-centrosymmetric compounds is equal to 25. Interestingly, almost 50% (12 compounds) of non-centrosymmetric compounds crystallize in the orthorhombic space group $P2_12_12_1$. The less preferred space groups are $P1$ (three compounds), $P2_1$ (3), $P6_1$ (2), $C2$ (1), $C222_1$ (1), $Pnc2$ (1), $Pna2_1$ (1) and $P4_32_12$ (1). Detailed analysis of the molecules of these 25 compounds shows an interesting feature, namely that only two crystal structures (refcodes FILYAA and BORXEL) contain the diazepine moiety with the amide nitrogen N1 (see Fig. 1 for notation) bonded to an H atom, while in the other 23 compounds N1 is 'blocked', *i.e.* bonded to a non-H atom (C or O). This observation allows us to quantitatively estimate the probability $p1$ of a bond of N1 to a non-H atom when diazepine derivatives crystallize in non-centrosymmetric space groups. This probabilty $p1$ (= 23/25) is greater than 0.9.

In the 27 centrosymmetric crystal structures (from a total number of 47) the amide nitrogen N1 is bonded to an H atom. However, there are two aforementioned non-centrosymmetric compounds (FILYAA and BORXEL) with the same N—H bonding. Therefore, we may estimate the probabilty $p2$ for

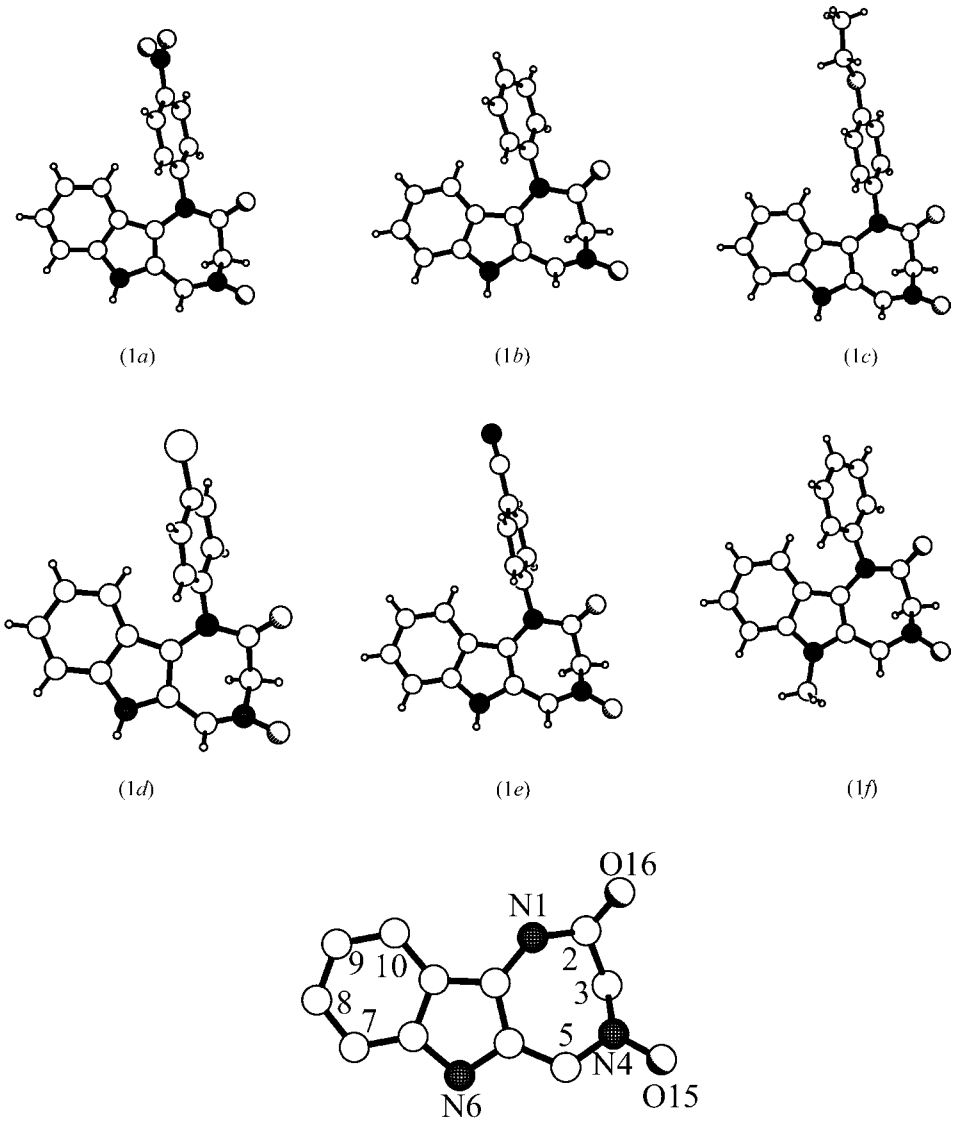


Figure 1
View of the molecules (1*a*)–(1*f*) and atom numbering scheme in the tricycle.

diazepine derivatives having N1 bonded to an H atom to crystallize in a centrosymmetric space group as 27/29, *i.e.* $p2$ is greater than 0.9. The mandatory condition for the formation of the centrosymmetric molecular crystal is the ability of the molecule to form centrosymmetric molecular blocks. The diazepine-containing molecules with the amide moiety —N(H)—(C═O)— may easily form such centrosymmetric blocks, or dimers, *via* intermolecular N—H···O hydrogen bonding. Strictly speaking, the intermolecular N—H···O interactions between such molecules may form three different configurations of hydrogen bonds: a linear chain (Fig. 5*a*), a twofold dimer (Fig. 5*b*) and a centrosymmetric dimer (Fig. 5*c*). Surprisingly, the configurations (5*a*) and (5*b*) (Fig. 5) are both present in the crystal structure (BORXEL), which is non-centrosymmetric. In the non-centrosymmetric structure FILYAA the ability to form centrosymmetric hydrogen-bonded dimers is blocked by the solvate molecule (acetone) involved in hydrogen bonding (Fig. 5*f*). The centrosymmetric dimers (Fig. 5*c*) are present in more than 70% of the centrosymmetric structures of diazepine derivatives containing the —N(H)—(C═O)— moiety. In the remaining 30% of such structures, the centrosymmetric clusters are formed by other functional groups. For example, in CAGWOW the amide hydrogen and lone pair of pyridine nitrogen form the centrosymmetric dimer (Fig. 5*d*), while in SEYRIX1 such a dimer is formed by the keto and oxo groups (Fig. 5*e*). It is worth noting that the presence of functional groups able to form dimers is responsible for the formation of centrosymmetric crystals of diazepine derivatives with a 'blocked' N1 atom. These dimers can be formed by oxo and keto groups (RAMSIH; Fig. 5*g*), the lone pair of N4 (see Fig. 1 for notation) and the oxo group (LOFXAF; Fig. 5*h*), and the acid group —COOH (Fig. 5i). In addition, there are non-obvious intermolecular interactions, such as the halogen···π system of the benzene ring (DIZPAM) (Fig. 5j), which may lead to the centrosymmetric dimers.

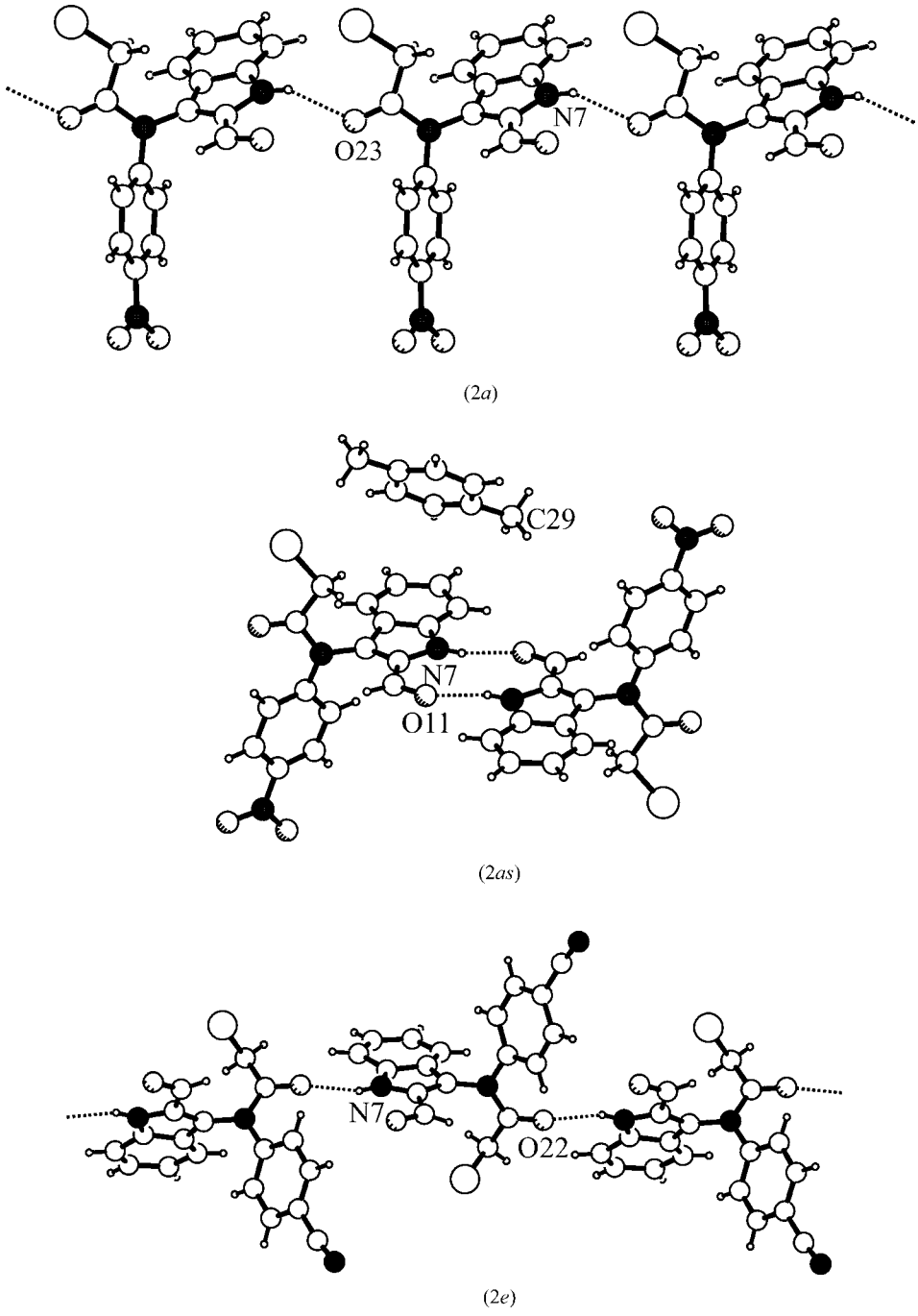


Figure 2
Molecular structures and hydrogen bonding in (2*a*), (2*as*) and (2*e*). The toluene molecule in (2*as*) lies on an inversion centre, so methyl (C29) is disordered between two sites with equal occupancies.

For the centrosymmetric crystals, we may define the crystal building blocks of different orders: first order – centrosymmetric molecules, second order – centrosymmetric dimers, highest order – centrosymmetric (hydrogen-bonded) clusters, formed by more than two molecules. The statistical analysis shows a clear hierarchy in the subsequent use of building blocks, *i.e.* the blocks of highest orders are used in centrosymmetric crystals when there are no building blocks of the first and second orders. Now we again

Table 2
N—H···O hydrogen-bonding geometry (Å, °) for (1*a*)–(1*e*).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
(1*a*)				
N6*A*—H6*A*···O15*B*	0.86	2.16	2.86 (2)	139
N6*B*—H6*B*···O15*A*^{i}	0.86	2.22	2.93 (2)	139
(1*b*)				
N6—H6···O15^{ii}	0.86	2.02	2.78 (2)	146
(1*c*)				
N6—H6···O15^{iii}	0.86	1.87	2.54 (2)	134
(1*d*)				
N6—H6···O15^{iv}	0.86	2.15	2.87 (2)	141
(1*e*)				
N6*A*—H6*A*···O15*B*	0.86	2.25	2.94 (2)	137
N6*B*—H6*B*···O15*A*^{i}	0.86	2.43	3.19 (2)	148

Symmetry codes: (i) $x-1, y, z$; (ii) $-x+2, y+\frac{1}{2}, -z+\frac{1}{2}$; (iii) $-x, y+\frac{1}{2}, -z+1$; (iv) $-x+2, y-\frac{1}{2}, -z+\frac{5}{2}$.

consider the diazepine derivatives with the 'blocked' N1 atom to estimate the probability $p3$ of the formation of centrosymmetric crystals with the use of crystal building blocks of the highest orders. The total number of structures under consideration is 45, including 25 non-centrosymmetric and 20 centrosymmetric crystal structures. Excluding seven centrosymmetric structures containing the easily recognized centrosymmetric dimers, like those shown in Fig. 5(*g*), (*h*) and (*i*), we obtain the 13 centrosymmetric structures formed by the centrosymmetric building blocks of the highest orders. The probability $p3$ (= 13/45) is less than 0.3. This means that the probabilty of formation of non-centrosymmetric crystals in the aforementioned case is greater than 0.7. Therefore, the crystallization of (1*a*)–(1*f*) in non-centrosymmetric space groups could be predicted with a high probability.

The molecular structures of (1*b*) and (1*f*), confirmed by their crystal structures, demonstrate the possibility of (1*a*)–(1*e*) reacting with methyl iodide under conditions of interphase catalysis to produce 6-methylderivatives (at the indole NH group).

A preliminary investigation of the biological activity of (1*a*)–(1*e*) shows moderate antihypoxic and hypotensive effects for some compounds. A detailed study of their pharmacological activity is in progress. However, the intriguing question, which we hope to find an answer to, concerns the possible affinity of diazepinoindoles with the benzodiazepine binding

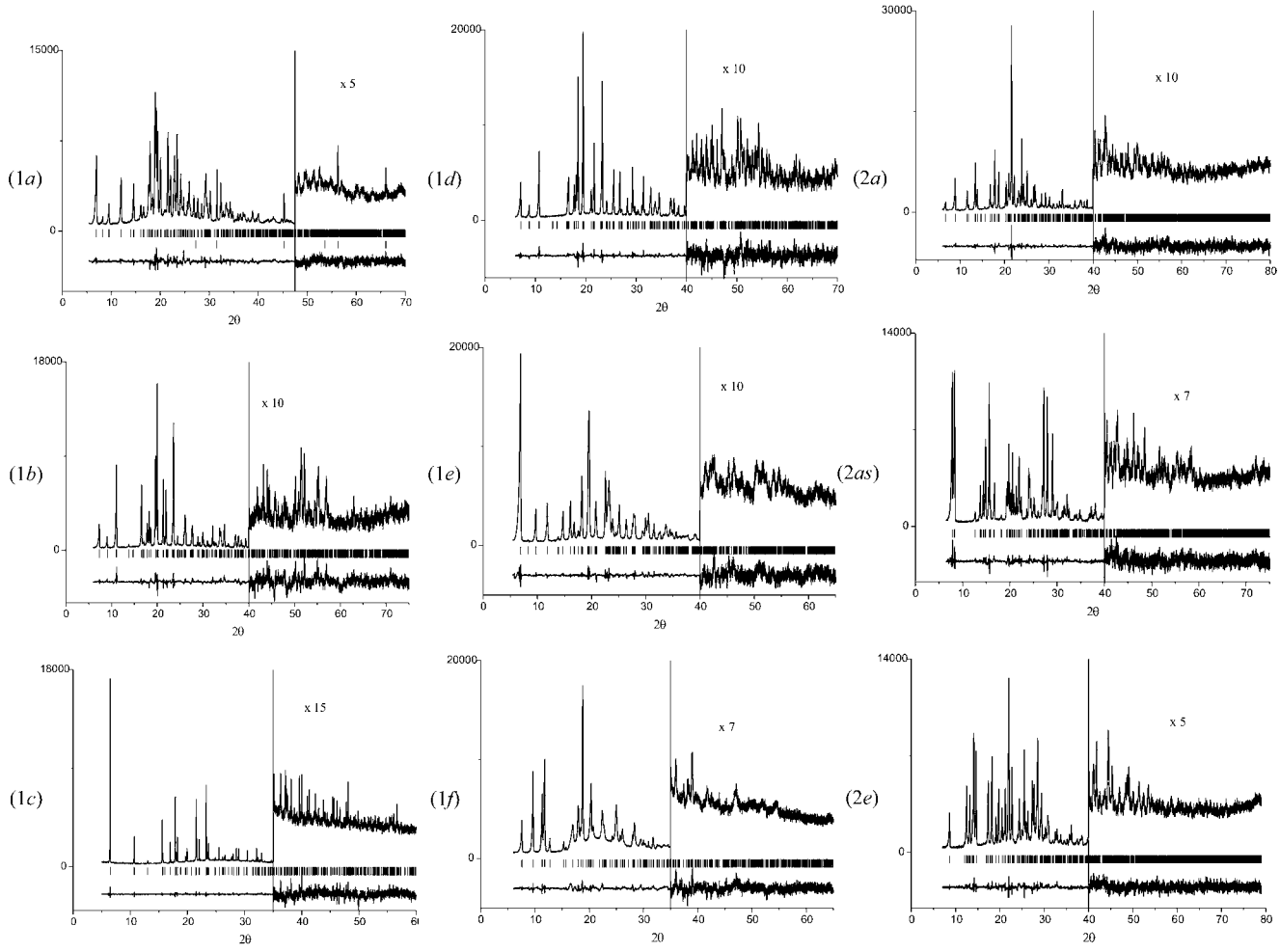


Figure 3
Rietveld plots of (1*a*)–(1*f*), (2*a*), (2*as*) and (2*e*).

Table 3
Hydrogen-bonding geometry (Å, °) for (2*a*), (2*as*) and (2*e*).

D—H···A	D—H	H···A	D···A	D—H···A
(2*a*)				
N7—H7···O23^{i}	0.86	2.19	2.930 (9)	143
(2*as*)				
N7—H7···O11^{ii}	0.86	2.00	2.84 (1)	164
(2*e*)				
N7—H7···O22^{iii}	0.86	2.06	2.86 (1)	156

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

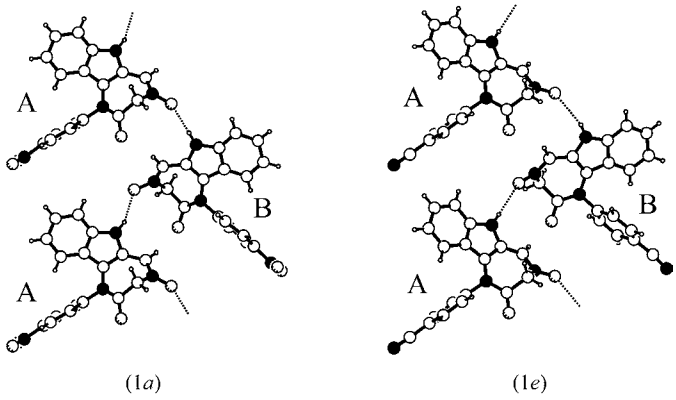


Figure 4
Hydrogen bonding in (1*a*) and (1*e*) viewed down the *c* axis. The independent molecules are labelled as *A* and *B*.

site of the $GABA_A$ receptor. γ-Aminobutyric acid (GABA) has been recognized as a neurotransmitter for several decades. It is now evident that GABA mediates most inhibitory transmission events in the vertebrate brain (Barnard *et al.*, 1998). The interaction with benzodiazepines has been a major influence in studies on GABA receptors because of the long history of the therapeutic application of benzodiazepines. Owing to the steric similarities of the diazepinoindoles investigated (1*a*)–(1*f*) with the benzodiazepines and β-carbolines (which belong to a class of drug which is chemically unrelated to benzodiazepines, although they can interact with a high affinity with the $GABA_A$ receptor; Ferretti *et al.*, 2004), we hope to obtain pharmacologically efficient diazepinoindoles by varying the substituents tropic to GABA. Such work is in progress.

3.2. Compounds (2*a*), (2*as*) and (2e)

It is known that 3-[*N*-aryl-*N*-(chloracetyl)amino]-2-formylindoles (2) (the key starting compounds in the synthesis of indolodiazepine) with strong electronegative substituents (NO_2 and CN groups) in the *N*-aryl cycle are able to form solvates with benzene, toluene, ethyl acetate and chloroform, but not with alcohols. These solvates can be decomposed further by heating to 5–10 K above the boiling point of the corresponding solvent. We found that for the synthesis of (1*a*) and (1*e*) it is necessary to use the aldehydes (2*a*) and (2*e*) as recrystallized from propan-2-ol to obtain the highest yield (65%) of the desired products (Ryabova *et al.*, 1996, 2003;

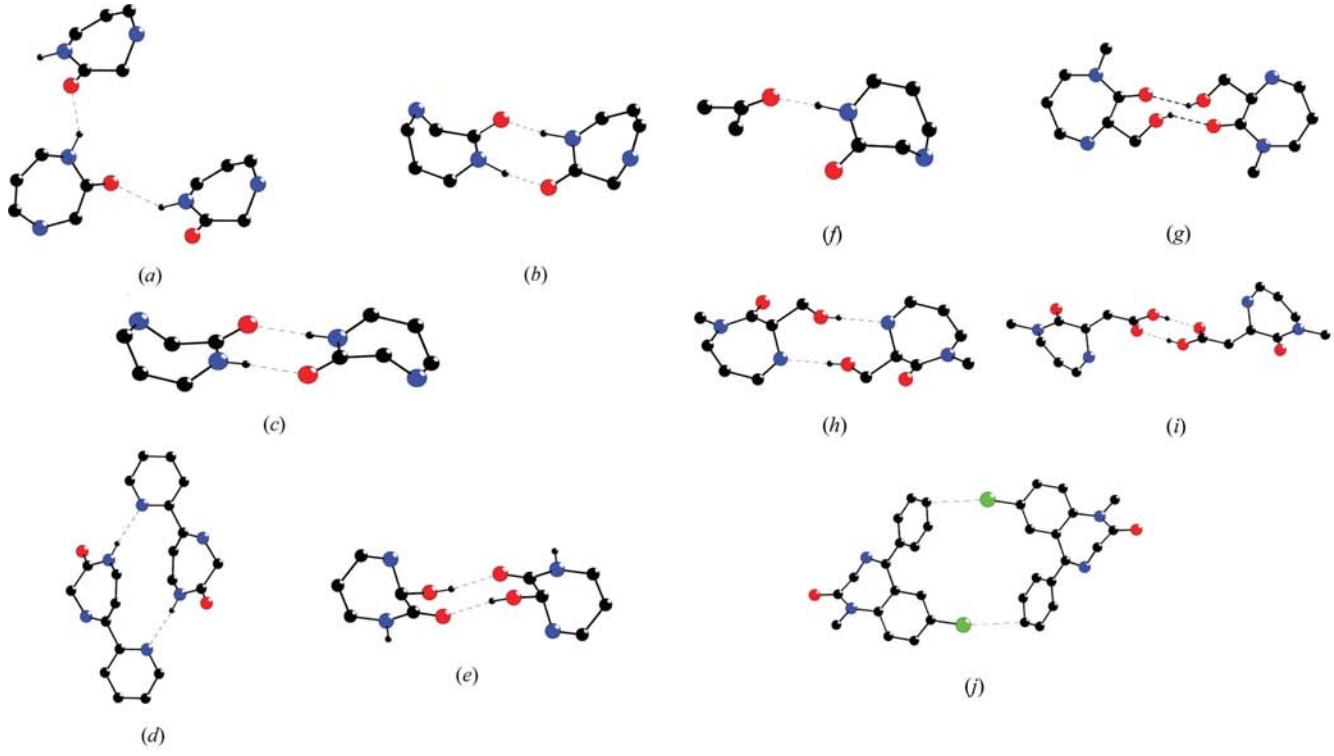


Figure 5
DIAMOND (Brandenburg, 2001) view of the possible molecular aggregations for the derivatives of diazepine.

Lantsetti & Ryabova, 2001; Lantsetti *et al.*, 2002). However, the use of aldehydes (2*a*) and (2*e*) when re-crystallized from one of the above solvents (benzene, toluene, ethyl acetate and chloroform) resulted in a sharp decrease in the yield of the desired products (1*a*) and (1*e*) down to 15%.

A comparison of the crystal structures of (2*a*), (2*e*) and (2*as*) shows that the solvent used in the re-crystallization of (2*a*) and (2*e*) affects the intermolecular hydrogen-bond formation. In the crystals of (2*a*) and (2*e*) obtained from propan-2-ol the molecules form chains *via* NH(indole)$\cdots$O=C hydrogen bonds (Fig. 2, Table 3). At the same time, in the crystal of (2*as*), obtained from toluene, the participation of the formyl group in hydrogen bonding leads to the formation of centrosymmetric dimers [Fig. 2, (2*as*), Table 3]. The existence of similar dimers in the solution is able to hinder the condensation of hydroxylamine with the aldehyde group and to decrease the rate of oxime intermediate formation. As a result, the yields of the end products drop because of the competing reactions.

4. Summary

The present study allowed the full structural characterization of several representatives of a new family of organic compounds based on the laboratory powder diffraction data. In spite of the limited accuracy, which is lower than that obtained in a single-crystal or high-resolution synchrotron powder diffraction study, the structural results obtained are useful for the further investigations of [1,4]diazepino[6,5-*b*]indoles. These future investigations may cover computer-aided drug discovery, design-model calculation and crystal engineering. The aggregation of organic molecules in the solid state depends on the many weak intermolecular forces such as hydrogen bonds, π–π stacking, dipole–dipole and van der Waals interactions *etc.* Nowadays, it is hardly possible to predict all the details of crystal packing based only on molecular geometry. Therefore, any systematic experimental study of the crystal structures formed by molecules from one family of compounds may reveal the most important intermolecular forces, which play a decisive role in the aggregation of the molecules.

This work has been supported by The Netherlands Organization for Scientific Research, NWO (VAT, LAA and VVC) and by the ICDD Grant-in-Aid 00-16 (EJS, SYuR and VVC).

References

Ahtee, M., Nurmela, M., Suortti, P. & Järvinen, M. (1989). *J. Appl. Cryst.* **22**, 261–268.

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.

Allen, F. H., Kennard, O., Watson, D. C., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans. 2*, pp. S1–19.

Barnard, E. A., Skolnik, P., Olsen, R. W., Mohler, H., Sieghart, W., Biggio, G., Braestrup, C., Bateson, A. N. & Langer, S. Z. (1998). *Pharmacol. Rev.* **50**, 291–313.

Bertolasi, V., Sacerdoti, M., Gilli, G. & Borea, P. A. (1982). *Acta Cryst.* B**38**, 1768–1772.

Boschelli, D. H., Connor, D. T., Kramer, J. B. & Unangst, P. C. (1994). US Patent 5489586.

Brandenburg, K. (2001). *Diamond*2.1e. Crystal Impact GbR, Germany.

Camerman, A. & Camerman, N. (1972). *J. Am. Chem. Soc.* **94**, 268–272.

Chernyshev, V. V. (2001). *Russ. Chem. Bull. Int. Ed.* **50**, 2273–2292.

Chernyshev, V. V. & Schenk, H. (1998). *Z. Kristallogr.* **213**, 1–3.

David, W. I. F., Shankland, K., McCusker, L. B. & Baerlocher, Ch. (2002). Editors. *Structure Determination from Powder Diffraction Data.* New York: Oxford University Press.

Dollase, W. A. (1986). *J. Appl. Cryst.* **19**, 267–272.

Ferretti, V., Gilli, P. & Borea, P. A. (2004). *Acta Cryst.* B**60**, 481–489.

Freed, M. E. & Freed, E. H. (1968). US Patent 3736324.

Freed, M. E. & Hertz, E. (1968). US Patent 3641030.

Garcia, T. T., Berjamin, L. E. & Ian Fryer, R. (1973). *J. Heterocycl. Chem.* **10**, 51–53.

Gatta, F., Zaccari, V., Huidolbro-Toro, J. P. & Chiavarelli, S. (1975). *Farmaco Ed. Sci.* **30**, 58–69.

Gilli, G., Bertolasi, V., Sacerdoti, M. & Borea, P. A. (1977). *Acta Cryst.* B**33**, 2664–2667.

Granik, V. G. (2001). *Lekarstva [Drugs]*, p. 144, 146, 191. Moscow: Vuzovskaya Kniga (in Russian).

Harris, K. D. M., Tremayne, M. & Kariuki, B. M. (2001). *Angew. Chem. Int. Ed. Engl.* **40**, 1626–1651.

Hiremath, S. P., Sonar, V. N., Sekhar, K. R. & Pourohit, M. G. (1990). *Proc. Natl. Acad. Sci. India Sect. A*, **60**, 367–376.

Järvinen, M. (1993). *J. Appl. Cryst.* **26**, 525–531.

Lantsetti, N. A. & Ryabova, S. Yu. (2001). *Nitrogen Containing Heterocycles and Alkaloids*, edited by V. G. Kartsev & G. A. Tolstikova, Vol. 2, p. 422. Moscow: Iridium Press.

Lantsetti, N. A., Ryabova, S. Yu., Alekseeva, L. M., Shashkov, A. S. & Granik, V. G. (2002). *Russ. Chem. Bull.* **51**, 506–512.

Mashkovskii, M. D. (1998). *Lekarstva XX Veka [Drugs of the XX Century]*. Moscow: Novaya Volna (in Russian).

Mashkovskii, M. D. (2000). *Lekarstvennye Sredstva [Drugs]*, Vol. 1, pp. 72, 76, 95, 278. Moscow: Novaya Volna (in Russian).

Pawley, G. S. (1981). *J. Appl. Cryst.* **14**, 357–361.

Popa, N. C. (1998). *J. Appl. Cryst.* **31**, 176–180.

Reynolds, B. E. & Carson, J. R. (1968). US Patent 3689503.

Ryabova, S. Yu., Rastorgueva, N. A., Lisitsa, E. A., Alekseeva, L. M. & Granik, V. G. (2003). *Russ. Chem. Bull.* **52**, 1386–1398.

Ryabova, S. Yu., Tugusheva, N. Z., Alekseeva, L. M. & Granik, V. G. (1996). *Pharm. Chem. J.* **30**, 472–477.

Serena Software (1999). *PCMODEL for Windows*, Version 7.0. Serena Software, Bloomington, USA.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

Toraya, H. (1986). *J. Appl. Cryst.* **19**, 440–447.

Velezheva, V. S., Brennan, P. J., Marshakov, V. Yu., Gusev, D. V., Lisichkina, I. N., Peregudov, A. S., Tchernousova, L. N., Smirnova, T. G., Andreevskaya, S. N. & Medvedev, A. E. (2004). *J. Med. Chem.* **47**, 3455–3461.

Visser, J. W. (1969). *J. Appl. Cryst.* **2**, 89–95.

Young, R. A. & Wiles, D. B. (1982). *J. Appl. Cryst.* **15**, 430–438.

Zlokazov, V. B. & Chernyshev, V. V. (1992). *J. Appl. Cryst.* **25**, 447–451.