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Hydrogen-bonded ribbons in ethyl (*E*)-3-[2-amino-4,6-bis(dimethylamino)pyrimidin-5-yl]-2-cyanoacrylate and 2-[(2-amino-4,6-di-1-piperidylpyrimidin-5-yl)methylene]malononitrile

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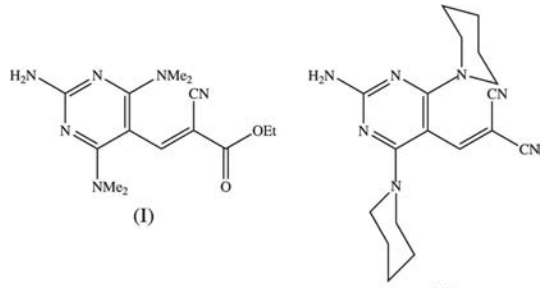
The pyrimidine rings in ethyl (*E*)-3-[2-amino-4,6-bis(dimethylamino)pyrimidin-5-yl]-2-cyanoacrylate, $C_{14}H_{20}N_6O_2$, (I), and 2-[(2-amino-4,6-di-1-piperidylpyrimidin-5-yl)methylene]malononitrile, $C_{18}H_{23}N_7$, (II), which crystallizes with $Z' = 2$ in the $P\overline{1}$ space group, are both nonplanar with boat conformations. The molecules of (I) are linked by a combination of N—H···N and N—H···O hydrogen bonds into chains of edge-fused $R_2^2(8)$ and $R_4^4(20)$ rings, while the two independent molecules in (II) are linked by four N—H···N hydrogen bonds into chains of edge-fused $R_2^2(8)$ and $R_2^2(20)$ rings. This study illustrates both the readiness with which highly-substituted pyrimidine rings can be distorted from planarity and the significant differences between the supramolecular aggregation in two rather similar compounds.

Comment

As part of a programme involving the synthesis of new heterocyclic compounds with potential biological activity, we have investigated the functionalization at position C-5 in pyrimidines *via* modification of 4,6-dichloro-5-formylpyrimidines, using base-catalyzed condensation of the formyl group with an activated methylene reagent, followed by substitution at positions 4 and 6 using strongly nucleophilic amines. We report here the molecular and supramolecular structures of two examples, both prepared starting from 2-amino-4,6-dichloropyrimidine-5-carbaldehyde. Ethyl (*E*)-3-[2-amino-4,6-bis(dimethylamino)pyrimidin-5-yl]-2-cyanoacrylate, (I), was prepared from the starting pyrimidine by successive reaction with ethyl cyanoacetate to give the intermediate (III) (see *Experimental*), followed by excess dimethylamine to give the product (I), while 2-[(2-amino-4,6-di-1-piperidylpyrimidin-5-yl)methylene]malononitrile, (II), was prepared by reaction of the same pyrimidine with malononitrile to form the intermediate (IV) followed by excess piperidine giving the product (II).



In each of compounds (I) (Fig. 1) and (II), which crystallizes with $Z' = 2$ in the $P\overline{1}$ space group (Fig. 2), the pyrimidine component is markedly nonplanar. The ring-puckering parameters (Cremer & Pople, 1975) (Table 1) are defined for the atom sequence N1—C2—N3—C4—C5—C6 in compound (I) and for N*x*1—C*x*2—N*x*3—C*x*4—C*x*5—C*x*6 (where $x = 1$ or 2 for the type 1 and 2 molecules) in compound (II); these parameters show that the conformations of these rings are best described as boat conformations, for which the idealized values of the ring-puckering parameters are $\theta = 90^\circ$ and $\varphi = (60k)^\circ$, where k represents zero or an integer. We have previously observed such nonplanarity in a number of extensively substituted pyrimidine derivatives exhibiting boat (Quesada *et al.*, 2004) or twist-boat (Melguizo *et al.*, 2003; Quesada *et al.*, 2002, 2003) conformations, and by comparison with less extensively substituted analogues, the distortions from planarity were ascribed to steric factors (Melguizo *et al.*, 2003). The occurrence of nonplanar pyrimidine rings here in the presence of four substituents on each pyrimidine ring is certainly consistent with the earlier interpretation. The conformations of the three independent pyrimidine rings in compounds (I) and (II) are thus very similar and the molecules are all chiral; the ring-puckering parameters show that the two independent molecules selected as the asymmetric unit in

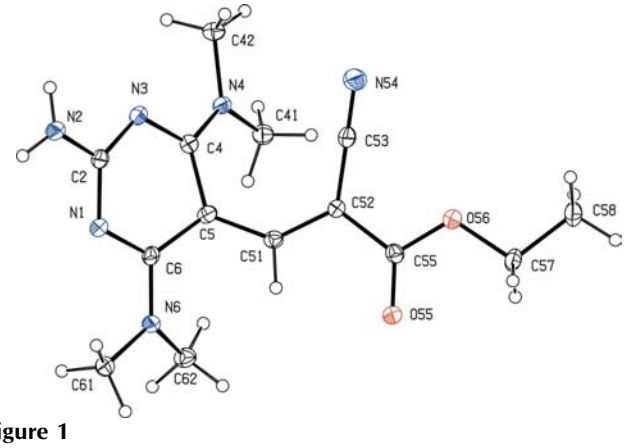


Figure 1
A molecule of compound (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

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compound (II) are of the same hand. The piperidine rings in compound (II) all adopt chair conformations. The bond distances are all within the normal ranges and there is no geometric evidence for any significant polarization of the molecular–electronic structures.

The molecules of compound (I) are linked into chains of edge-fused rings by two independent hydrogen bonds (Table 2). Amino atom N2 in the molecule at (x, y, z) acts as hydrogen-bond donor, *via* H2*A* and H2*B*, respectively, to ring atom N1 in the molecule at ($2-x$, $1-y$, $1-z$) and carbonyl atom O55 in the molecule at (x, y, $1+z$). Propagation of these two hydrogen bonds by inversion and translation then generates a chain of edge-fused rings running parallel to the [001] direction, with $R_2^2(8)$ (Bernstein *et al.*, 1995) rings centred at $(1, \frac{1}{2}, n+\frac{1}{2})$ (where n represents zero or an integer), and $R_4^4(20)$ rings centred at $(1, \frac{1}{2}, n)$ (where n represents zero or an integer) (Fig. 3). There are no direction-specific interactions between adjacent chains.

The supramolecular aggregation of compound (II) is dominated by four independent N—H···N hydrogen bonds (Table 3) which link the molecules into a chain of rings somewhat different from that in compound (I), while weaker C—H···N hydrogen bonds link these chains into sheets. The two independent molecules within the selected asymmetric unit are linked by the N—H···N hydrogen bonds involving H12*A* and H22*A* to form a dimeric unit which has approximate twofold rotational symmetry around ($\sim\frac{1}{4}$, y, $\sim\frac{1}{2}$). These dimeric units are linked by two further N—H···N hydrogen

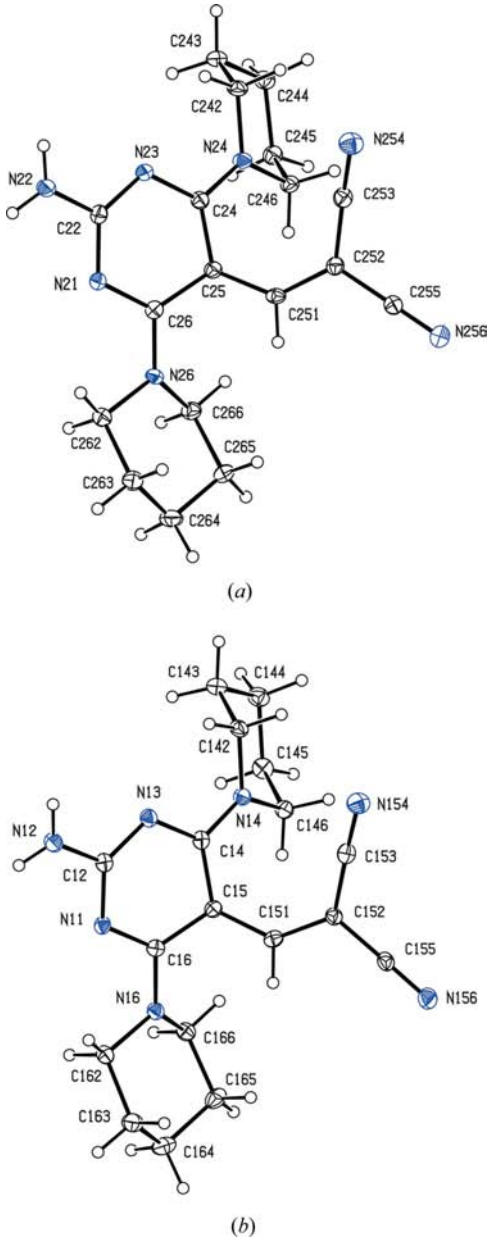

Figure 2
The two independent molecules of compound (II), showing the atom-labelling scheme for (*a*) a type 1 molecule and (*b*) a type 2 molecule. Displacement ellipsoids are drawn at the 30% probability level.

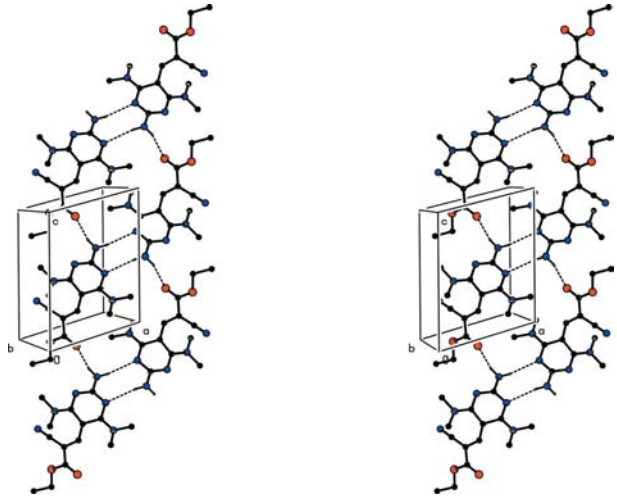

Figure 3
A stereoview of part of the crystal structure of compound (I), showing the formation of a hydrogen-bonded chain of edge-fused $R_2^2(8)$ and $R_4^4(20)$ rings along [001]. For the sake of clarity, H atoms bonded to C atoms have all been omitted.

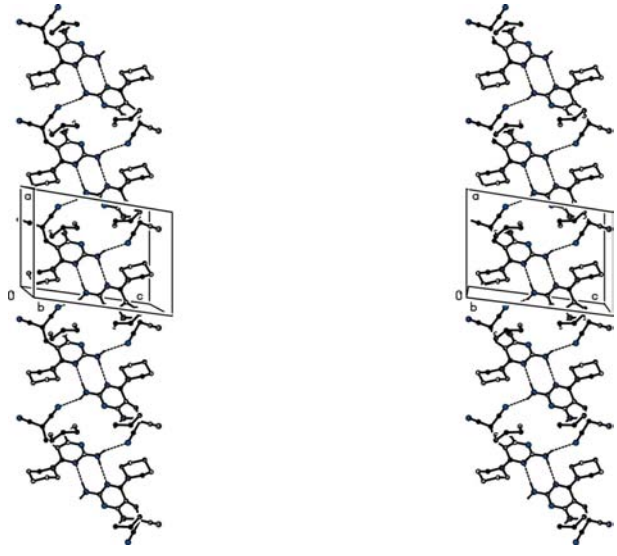

Figure 4
A stereoview of part of the crystal structure of compound (II), showing the formation of a hydrogen-bonded chain of edge-fused $R_2^2(8)$ and $R_2^2(20)$ rings along [100]. For the sake of clarity, H atoms bonded to C atoms have all been omitted.

bonds, involving H12*B* and H22*B*, into a chain of edge-fused rings running parallel to the [100] direction and containing alternating $R_2^2(8)$ and $R_2^2(20)$ rings (Fig. 4). Fairly weak C—H···N hydrogen bonds, all involving C atoms within the piperidine rings as the donors and nitrile N atoms as the acceptors, link the [100] chains into sheets parallel to (010); the C—H bonds involved are likely to be of low acidity so that the structural significance of these interactions may be marginal.

Experimental

For the synthesis of compound (I), a catalytic quantity of triethylamine (3 drops) together with calcium chloride (15 mg) were added to a solution of 2-amino-4,6-dichloropyrimidine-5-carbaldehyde (1.0 mmol) and ethyl 2-cyanoacetate (1.0 mmol) in ethanol (10 ml), and this mixture was stirred at ambient temperature for 2 h. The resulting precipitate was collected by filtration, washed with ethanol, dried and finally recrystallized from ethanol to give ethyl (*E*)-3-(2-amino-4,6-dichloropyrimidin-5-yl)-2-cyanoacrylate, (III), in 85% yield. For the synthesis of compound (II), a catalytic quantity of triethylamine (3 drops) together with calcium chloride (15 mg) were added to a solution of 2-amino-4,6-dichloropyrimidine-5-carbaldehyde (1.0 mmol) and malononitrile (1.0 mmol) in ethanol (10 ml), and this mixture was stirred at ambient temperature for 2 h. The resulting solid was collected by filtration, washed with ethanol, dried and finally recrystallized from ethanol to give 2-[(2-amino-4,6-dichloropyrimidin-5-yl)methylene]malononitrile, (IV), in 70% yield. For the conversion of (III) and (IV) to (I) and (II), respectively, the intermediate (III) or (IV) (0.4 mmol) was then added to a large excess of the appropriate amine (0.5 ml) in ethanol (10 ml) and heated under reflux for 1 h. On cooling to ambient temperature, the products (I) and (II) were precipitated as yellow crystalline solids, which were collected by filtration, washed with ethanol and dried at atmospheric pressure to give crystals suitable for single-crystal X-ray diffraction. For (I): yield 50% and m.p. 503–505 K; for (II): yield 70% and m.p. 467–468 K (HR–MS: found 337.2016; $C_{18}H_{23}N_7$ requires 337.2015).

Compound (I)

Crystal data

$C_{14}H_{20}N_6O_2$
M_r = 304.36
Triclinic, $P\overline{1}$
a = 8.5570 (15) Å
b = 9.893 (2) Å
c = 9.9739 (18) Å
α = 87.534 (13)°
β = 77.251 (15)°
γ = 67.431 (14)°
V = 759.6 (3) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 120 (2) K
0.37 × 0.34 × 0.15 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.971, T_{max} = 0.986
18938 measured reflections
3468 independent reflections
1715 reflections with $I > 2\sigma(I)$
R_{int} = 0.085

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.069
$wR(F^2)$ = 0.236
S = 1.03
3468 reflections
204 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.43 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}

Table 1
Ring-puckering parameters (Å, °) for the pyrimidine rings in compounds (I) and (II).

Parameter	(I)	(II), molecule 1	(II) molecule 2
Q	0.248 (3)	0.218 (3)	0.221 (3)
θ	74.4 (7)	73.0 (8)	75.0 (8)
φ	234.6 (8)	230.9 (8)	229.7 (8)

Table 2
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2*A*···N1^{i}	0.86	2.55	3.398 (4)	170
N2—H2*B*···O55^{ii}	0.86	2.17	2.966 (3)	153

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

Table 3
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N12—H12*A*···N21	0.86	2.19	3.021 (3)	162
N12—H12*B*···N254^{i}	0.86	2.36	3.126 (3)	148
N22—H22*A*···N11	0.86	2.24	3.049 (3)	156
N22—H22*B*···N154^{ii}	0.86	2.51	3.235 (3)	143
C162—H62*A*···N154^{ii}	0.99	2.54	3.472 (4)	156
C164—H64*B*···N256^{iii}	0.99	2.58	3.412 (4)	142
C246—H46*C*···N256^{iv}	0.99	2.58	3.515 (4)	158
C266—H66*C*···N256^{iv}	0.99	2.42	3.345 (4)	156

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

Compound (II)

Crystal data

$C_{18}H_{23}N_7$
M_r = 337.43
Triclinic, $P\overline{1}$
a = 9.6960 (8) Å
b = 14.752 (3) Å
c = 15.418 (3) Å
α = 116.332 (13)°
β = 96.794 (10)°
γ = 93.587 (9)°
V = 1946.1 (6) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.07 mm^{-1}
T = 120 (2) K
0.62 × 0.38 × 0.32 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.962, T_{max} = 0.977
38120 measured reflections
8590 independent reflections
4805 reflections with $I > 2\sigma(I)$
R_{int} = 0.049

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.065
$wR(F^2)$ = 0.206
S = 1.10
8590 reflections
451 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

Crystals of compounds (I) and (II) are triclinic; for each compound the space group $P\overline{1}$ was selected and confirmed by the subsequent structure analysis. All H atoms were located in difference maps and then treated as riding atoms with distances C—H = 0.95 (alkene), 0.98 (CH_3) or 0.99 Å (CH_2) and N—H = 0.86 Å, and with U_{iso}(H) = kU_{eq}(carrier), where k = 1.5 for the methyl groups and 1.2 for all other H atoms. For compound (I), the proportion of the reflections

labelled 'observed' was quite low, *ca* 49%, even at 120 K. Analysis of the refined structure of (II) using *PLATON* (Spek, 2003) showed that there were voids within the structure, centred at approximately $(0, 0, \frac{1}{2})$ and accounting for some 13.6% of the total unit-cell volume. Several significant peaks corresponding to electron densities up to 2.02 e $Å^{-3}$ were located within the void space. However, these peaks could not be reconciled with any plausible molecular species, possibly because of disorder and/or mobility. Accordingly, the SQUEEZE option in *PLATON* was utilized; while this reduced *R* from 0.104 to 0.065, the quality of the data set did not permit a meaningful evaluation of the electron population in the void.

For both compounds, data collection: *COLLECT* (Hooft, 1999); cell refinement: *DIRAX/LSQ* (Duisenberg *et al.*, 2000); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *OSCAIL* (McArdle, 2003) and *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PRPKAPPA* (Ferguson, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3200). Services for accessing these data are described at the back of the journal.

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