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4-Amino-*N*-isopropylbenzamidinium chloride ethanol solvate

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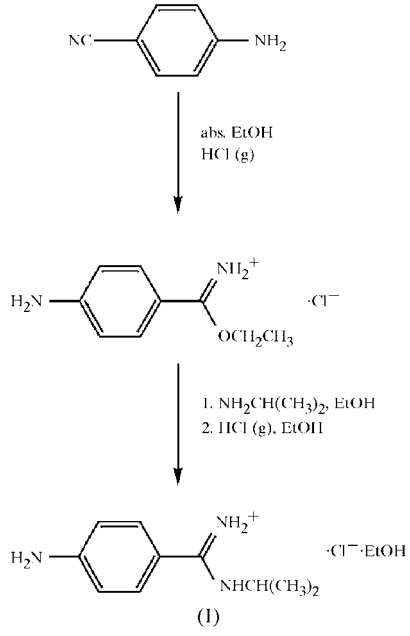
The title compound, $C_{10}H_{16}N_3^+\cdot Cl^-\cdot C_2H_6O$, is an important intermediate in the convergent synthesis of amidine-substituted polycyclic heterocycles, a class of compounds that shows significant anticancer activity. The molecule of (I) is not planar, having a dihedral angle of 25.00 (7)° between the aniline and amidine (–C—NH═C═NH_2) groups. The protonation of the amidine molecular fragment is accompanied by delocalized C—N bond distances of 1.320 (2) and 1.317 (2) Å. The cations and chloride anions are involved in a network of hydrogen bonds, resulting in the formation of infinite chains propagating along the *b* direction. The chains are further grouped within the *ab* plane, in such a way that the structure is segregated into layers dominated by hydrophobic interactions involving *N*-isopropyl residues and layers dominated by N—H···Cl [N···Cl = 3.275 (2)–3.596 (2) Å], O—H···Cl [O···Cl = 3.229 (3) Å] and N—H···O [N···O = 2.965 (3) Å] hydrogen bonds.

Comment

Amidine compounds have been widely investigated because of their biological activities. One of the first groups of amidine-substituted organic compounds included pentamidine and its analogs, which were prepared for screening against a rat model of *Pneumocystis carinii* pneumonia (PCP) (Tidwell *et al.*, 1990; Patric *et al.*, 1997). In addition to their activity against PCP, these compounds were also evaluated for DNA affinity and showed modest anti-HIV-1 activity and selectivity in primary lymphocytes (Kumar *et al.*, 1996). Amidine compounds show antiparasitic activity (Danan *et al.*, 1997) and antifungal activity (Del Poeta, Schell, Dykstra, Jones, Tidwell, Czarny *et al.*, 1998), as well as activity against a wide range of eucaryotic pathogens for *Candida albicans* and *Cryptococus neoformans*. Selected compounds were also found to be active against *Aspergillus fumigantus*, *Fusarium solani* and *Candida* species other than *C. albicans* (Del Poeta, Schell, Dykstra, Jones, Tidwell, Kumar *et al.*, 1998).

We have synthesized and characterized a number of heterocyclic amidines and bis-amidines of benzodithiophene, benzothienofuran, naphtho[2,1-*b*]furan and benzothiazole, which have potential as anticancer agents (Boyd, 1991; Starčević *et al.*, 2002, 2003; Hranjec *et al.*, 2003; Ćaleta *et al.*, 2003; Matković-Čalogović *et al.*, 2003).



(I)

The molecule of the title compound, (I) (Fig. 1), is not planar. The carboxamidinium moiety has a synperiplanar disposition with respect to the aniline group [C1—C6—C7—N2 = 25.8 (2)°]. This twist may serve to accommodate the formation of intermolecular hydrogen bonds. Deviation from coplanarity is observed, however, in other *N*-isopropylamidine derivatives, such as 6-(*N*-isopropylamidino)-2-methylbenzothiazole and 2-amino-6-(*N*-isopropylamidino)benzothiazole, synthesized in the form of their hydrocloride salts (Ćaleta *et al.*, 2003), in 2-amino-6-(2-morpholinoethyl)-1,3-benzothia-

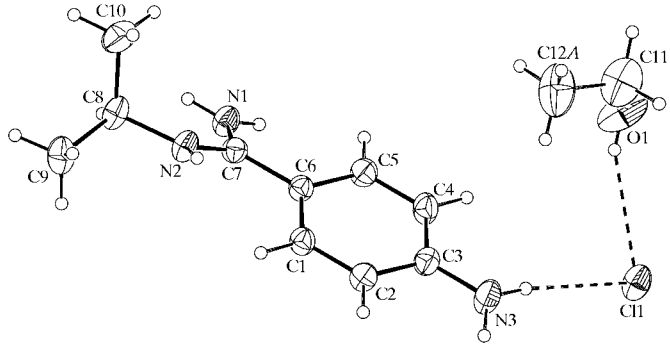


Figure 1
The structure of (I), shown with 50% probability displacement ellipsoids. Dashed lines indicate intermolecular hydrogen bonds. Only the major component of the disordered ethanol methyl group is shown.

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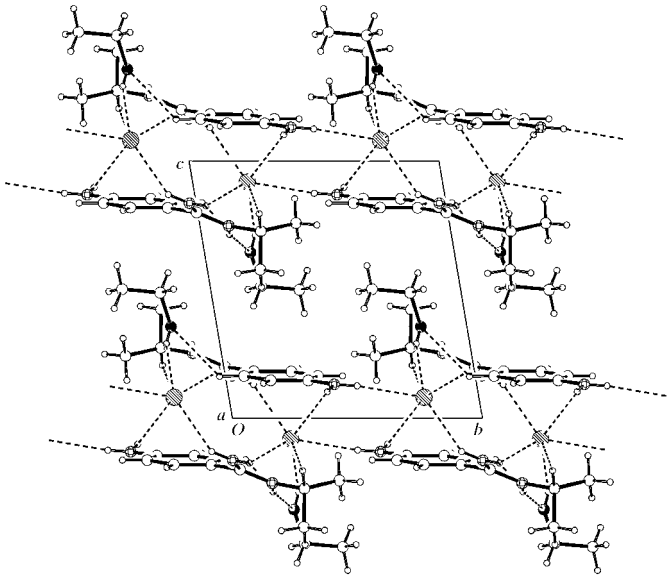

Figure 2
The crystal structure of (I). The non-H atoms are indicated as follows: C empty spheres, O black, N net and Cl striped. Hydrogen bonds are indicated by dashed lines. Only the major component, C12*A*, of the disordered EtOH methyl group is shown.

zolecarboxamidinium chloride (Ćaleta *et al.*, 2004) and 1,3-benzothiazole-6-carboxamidinium chloride dihydrate (Matković-Čalogović *et al.*, 2003).

The isopropyl substituent at atom N2 has an anticlinal disposition relative to atom N1 [C7—N2—C8—C9 = 143.84 (19)° and C7—N2—C8—C10 = −92.5 (2)°]. The C7—N1 and C7—N2 bond distances are equal to within 3σ (Table 1), reflecting the protonation of the amidine group, while the N2—C8 bond [1.470 (2) Å] is σ in character. The N3—C3 and C6—C7 bond distances are shortened [1.365 (2) and 1.473 (2) Å, respectively] and exhibit partial π character, indicating some degree of π-electron delocalization through both the phenyl amidine moieties. Other bond distances are within expected values (Allen *et al.*, 1987).

The cations and chloride ions are involved in a network of intermolecular hydrogen bonds, resulting in the formation of infinite chains propagating in the *b* direction (Fig. 2). The different moieties present are grouped into an *AB* pattern of layers, parallel to the crystallographic *ab* plane, and composed alternately of amidinium cations and chloride ions. The layer formed principally by the *N*-isopropyl group of the cation and the ethyl residues of EtOH solvent molecules is characterized by hydrophobic interactions, while the layer containing the chloride ions is dominated by intermolecular hydrogen bonds. The chloride ion participates in N—H···Cl hydrogen-bond formation as a multiple proton acceptor, interacting with both the amine and amidine NH groups [N···Cl = 3.275 (2)–3.596 (2) Å; Table 2]. The chloride ion is also involved in an O—H···Cl hydrogen bond with the ethanol O atom [O···Cl = 3.229 (3) Å]. The amidine NH group acts as a donor to the ethanol O atom, with an N···O distance of 2.965 (3) Å.

Experimental

Compound (I) was prepared from 4-aminobenzonitrile by a modified Pinner reaction (Ferroni *et al.*, 1995) (see scheme). A suspension of 4-aminobenzonitrile (9 g, 0.076 mmol) in absolute ethanol (130 ml) was cooled to 273 K and saturated with dry HCl gas. The suspension was stirred until IR spectra indicated the absence of the cyano peak (8 d). The imine ester hydrochloride intermediate was precipitated from the solution by the addition of dry diethyl ether, filtered off, washed with dry ether and dried over KOH. Isopropylamine (19.5 ml, 0.23 mmol) was added to a suspension of the crude imine ester hydrochloride in absolute ethanol (130 ml). The mixture was stirred at room temperature for 5 d. The crude product (9.35 g, yield 69%, m.p. 517–521 K) was filtered off, washed with acetone and recrystallized from ethanol. IR (KBr, cm^{-1}): 3480, 3300, 3080, 2950, 1650, 1590; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.98–9.03 (*m*, 2H, amidine H), 8.65 (*s*, 1H, amidine H), 7.48 (*d*, 2H, aromatic H, J = 8.72 Hz), 6.64 (*d*, 2H, aromatic H, J = 8.71 Hz), 6.17 (*s*, 2H, amine H), 4.02–4.04 (*m*, 1H, HCH), 1.24 (*d*, 6H, HCH_3, J = 6.46 Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 161.1 (*s*), 153.9 (*s*), 129.9 (*s*, 2C), 113.9 (*s*), 112.7.

Crystal data

$C_{10}H_{16}N_3^+\cdot Cl^-\cdot C_2H_6O$	Z = 2
M_r = 259.78	D_x = 1.168 Mg m^{-3}
Triclinic, $P\overline{1}$	Mo $K\alpha$ radiation
a = 8.7458 (15) Å	Cell parameters from 2250 reflections
b = 9.2177 (14) Å	θ = 6–20°
c = 9.7938 (15) Å	μ = 0.25 mm^{-1}
α = 96.339 (12)°	T = 296 (2) K
β = 105.022 (14)°	Prism, colourless
γ = 100.649 (13)°	0.48 × 0.19 × 0.18 mm
V = 738.9 (2) Å^3	

Data collection

Oxford Diffraction Xcalibur2 diffractometer fitted with a Sapphire 3 CCD detector	2461 reflections with $I > 2\sigma(I)$
	R_{int} = 0.022
	θ_{max} = 27.0°
φ and ω scans	$h = -11 \rightarrow 11$
9188 measured reflections	$k = -11 \rightarrow 11$
3183 independent reflections	$l = -12 \rightarrow 12$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0883P)^2 + 0.0256P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.047	
$wR(F^2)$ = 0.145	
S = 1.11	$(\Delta/\sigma)_{max} < 0.001$
3183 reflections	$\Delta\rho_{max}$ = 0.30 e Å^{-3}
184 parameters	$\Delta\rho_{min}$ = −0.27 e Å^{-3}
H atoms treated by a mixture of constrained and independent refinement	

Table 1
Selected geometric parameters (Å, °).

N1—C7	1.320 (2)	N3—C3	1.365 (2)
N2—C7	1.317 (2)	C6—C7	1.473 (2)
N2—C8	1.470 (2)		
C7—N2—C8	126.21 (15)	N2—C7—C6	119.07 (15)
N2—C7—N1	121.42 (15)	N1—C7—C6	119.51 (14)

The methyl C atom of the ethanol solvent molecule is disordered; the relative occupancies of the two positions, C12*A* (major component) and C12*B*, were refined to a final ratio of 0.73 (1):0.27 (1). The C12*A*—C11 [1.419 (5) Å] and C12*B*—C11 [1.472 (9) Å] bond distances were loosely restrained to a Csp^3—Csp^3 value (using the DFIX command in *SHELXL97*; Sheldrick, 1997). H atoms bonded to

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···Cl1^{i}	0.86	2.56	3.344 (2)	153
N1—H1B···Cl1^{ii}	0.86	2.51	3.275 (2)	148
O1—H1O···Cl1	0.73 (3)	2.54 (3)	3.229 (3)	158 (3)
N2—H2N···O1^{iii}	0.78 (3)	2.22 (3)	2.965 (3)	162 (3)
N3—H13N···Cl1	0.88 (3)	2.49 (3)	3.356 (2)	172 (2)
N3—H23N···Cl1^{iv}	0.87 (3)	2.79 (2)	3.596 (2)	155 (2)
C1—H1···O1^{iii}	0.93	2.56	3.277 (3)	135
C8—H8···Cl1^{i}	0.98	2.76	3.708 (2)	164

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

C atoms were introduced at calculated positions and refined as riding [U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(C), and C—H = 0.93 (C_{ar}—H), 0.96 (C_{methyl}—H), 0.97 ($C_{methylene}$—H) and 0.98 Å ($C_{tertiary}$—H)]. The H atoms of the $N1H_2$ group were also refined as riding [N—H = 0.86 Å and U_{iso}(H) = 1.2U_{eq}(N)]. The H atoms bonded to atoms N2, N3 and O1 were found in difference Fourier maps and refined freely.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2004); cell refinement: *CrysAlis CCD*; data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON98* (Spek, 1998); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA1107). Services for accessing these data are described at the back of the journal.

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