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2-Methyl-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-3-ium chloride, a product of the thermal decomposition of nimustine hydrochloride (ACNU)

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Key indicators

Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.010 Å
R factor = 0.038
wR factor = 0.086
Data-to-parameter ratio = 6.8

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The title compound, $C_7H_9N_4O^+\cdot Cl^-$, was obtained as a product of the thermal decomposition of nimustine hydrochloride (ACNU). In the crystal structure, intermolecular N—H···O hydrogen bonds link the cations into centrosymmetric dimers, which are further connected by N—H···Cl and C—H···Cl hydrogen bonding to form two-dimensional networks.

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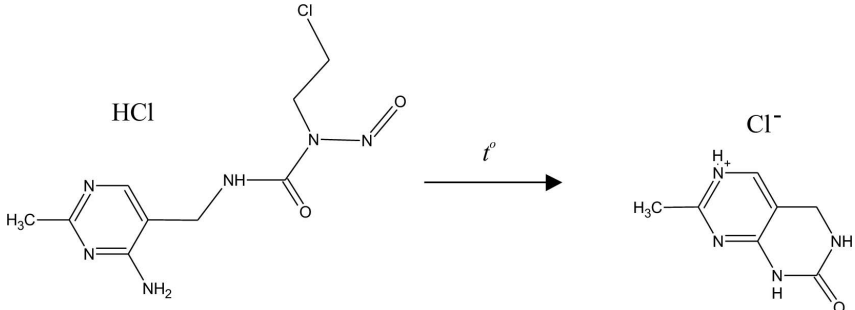
Comment

Nimustine hydrochloride, 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU), (I), is a widely used antitumour drug for malignant gliomas (Yoshida *et al.*, 1994). ACNU is often used in combination with radiotherapy (Beppu *et al.*, 2003) and chemotherapy (Beppu *et al.*, 2000) to treat supratentorial malignant gliomas. All of the above result in a continuing interest in the metabolites of ACNU (Nishigaku, Nakamura, Kinoshita *et al.*, 1985; Nishigaku, Nakamura & Tanaka, 1985).



(I) (II)

In our study of the thermal behaviour of nimustine hydrochloride, dissolved in a mixture of methanol and water, we unexpectedly discovered the formation of colourless single crystals. An X-ray crystal structure determination allowed us to establish their chemical identity as 2-methyl-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-3-ium chloride, (II) (Fig. 1). The cation of (II), obtained from the cation of (I) at high temperature, corresponds to the protonated form of 7-methyl-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one, (III), identified by Nishigaku, Nakamura & Tanaka (1985) as a metabolite of the *in vitro* decomposition of ACNU. Compound (III), an intramolecular cyclized product, was formed spontaneously in phosphate buffer (pH 7.4) with simultaneous liberation of the alkylating moiety (Nishigaku, Nakamura & Tanaka, 1985).

All bond lengths and angles in (II) (Table 1) are in normal ranges (Allen *et al.*, 1987). The pyrimidin-2-one ring is in an envelope conformation. The deviation of atom C4 from the mean plane defined by atoms N1, N3, C2, C4, C9 and C10 is

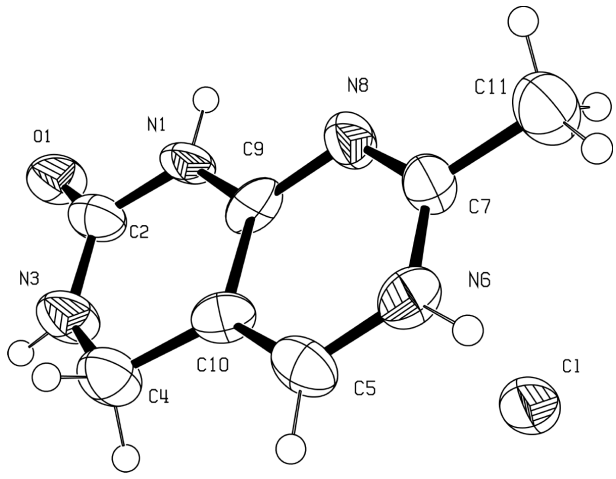


Figure 1
View of (II), with the atomic labelling scheme and 50% probability displacement ellipsoids.

0.185 (9) Å. In the crystal structure, intermolecular N—H···O hydrogen bonds (Table 2) link the cations into centrosymmetric dimers, which are further connected by N—H···Cl and C—H···Cl hydrogen bonding (Table 2) to form two-dimensional networks (Fig. 2).

Experimental

A powdered sample of (I) (2 mg), obtained by a known procedure (Mori, 1990), was dissolved in a mixture of methanol (5 ml) and water (5 ml). A small bottle of this solution was placed in water heated to 323 (5) K. After gradual cooling to room temperature, a few small colourless single crystals were formed.

Crystal data

$C_7H_9N_4O^+\cdot Cl^-$
M_r = 200.63
Triclinic, $P\overline{1}$
a = 4.877 (3) Å
b = 8.104 (6) Å
c = 11.832 (7) Å
α = 105.60 (7)°
β = 91.87 (7)°
γ = 102.17 (7)°
V = 438.3 (5) Å^3
Z = 2
D_x = 1.520 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 5.3–8.6°
μ = 0.40 mm^{-1}
T = 298 (2) K
Prism, colourless
0.15 × 0.06 × 0.05 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω scans
Absorption correction: none
1639 measured reflections
821 independent reflections
421 reflections with $I > 2\sigma(I)$
R_{int} = 0.098
θ_{max} = 20.0°
$h = -4 \rightarrow 4$
$k = -7 \rightarrow 7$
$l = -11 \rightarrow 11$
1 standard reflection
frequency: 120 min
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.086
S = 0.97
821 reflections
120 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0243P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.004 (1)

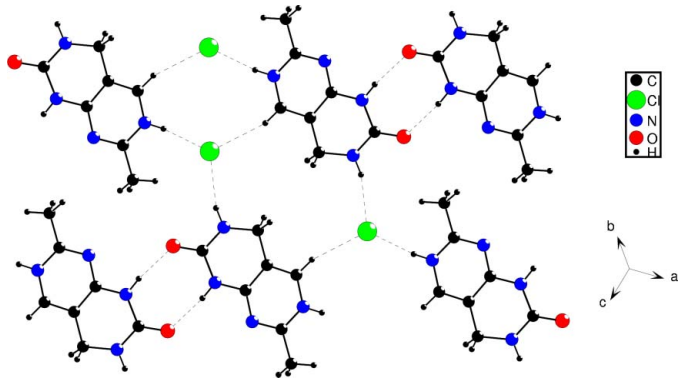


Figure 2
View of the two-dimensional hydrogen-bonding network in (II). The hydrogen bonds are shown as dashed lines.

Table 1
Selected geometric parameters (Å, °).

O1—C2	1.244 (7)	N8—C7	1.329 (7)
N1—C9	1.367 (7)	N8—C9	1.341 (8)
N1—C2	1.406 (7)	C4—C10	1.510 (8)
N3—C2	1.336 (7)	C5—C10	1.359 (8)
N3—C4	1.448 (7)	C7—C11	1.487 (7)
N6—C7	1.343 (7)	C9—C10	1.400 (8)
N6—C5	1.356 (7)		
C9—N1—C2	124.8 (6)	N3—C4—C10	110.6 (5)
C2—N3—C4	128.1 (6)	N8—C9—N1	116.0 (6)
C7—N6—C5	122.0 (5)	N8—C9—C10	125.2 (6)
C7—N8—C9	116.7 (5)	C5—C10—C9	115.1 (6)
O1—C2—N3	124.2 (7)	C5—C10—C4	124.1 (7)
N3—C2—N1	115.2 (6)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O1^{i}	0.86	2.01	2.859 (6)	170
N3—H3···Cl^{ii}	0.86	2.40	3.221 (6)	161
N6—H6···Cl^{iii}	0.86	2.24	3.092 (6)	172
C5—H5···Cl^{iv}	0.93	2.61	3.501 (7)	161

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

After location in a difference Fourier map, all H atoms were placed in calculated positions (N—H = 0.86 Å and C—H = 0.93–0.97 Å) and included in the refinement in the riding-model approximation, with U_{iso}(H) values set at 1.2 or 1.5 (for methyl) times U_{eq}(carrier atom). Owing to the poor crystal quality and small crystal size, the diffraction was observed only up to θ_{max} = 20°.

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *XCAD4* (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *DIAMOND* (Brandenburg, 2001) and *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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References

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

Beppu, T., Kamada, K., Nakamura, R., Oikawa, H., Takeda, M., Fukuda, T., Arai, H., Ogasawara, K. & Ogawa, A. (2003). *J. Neuro-Oncol.* **61**, 161–170.

Beppu, T., Yoshida, Y., Arai, H., Wada, H., Suzuki, M., Ogawa, A., Hakozaki, S. & Kubo, N. (2000). *J. Neuro-Oncol.* **49**, 213–218.

Brandenburg, K. (2001). *DIAMOND*. Version 2.1e. Crystal Impact GbR, Bonn, Germany.

Enraf–Nonius (1994). *CAD-4 EXPRESS*. Enraf–Nonius, Delft, The Netherlands.

Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.

Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.

Harms, K. & Wocadlo, S. (1995). *XCAD4*. University of Marburg, Germany.

Mori, H. (1990). *Chem. Pharm. Bull.* **38**, 1400–1402.

Nishigaku, T., Nakamura, K., Kinoshita, T., Kuwano, H. & Tanaka, M. (1985). *J. Pharmacobiodyn*. **8**, 401–408.

Nishigaku, T., Nakamura, K. & Tanaka, M. (1985). *J. Pharmacobiodyn*. **8**, 409–416.

Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.

Yoshida, J., Kajita, Y., Wakabayashi, T. & Sugita, K. (1994). *Acta Neurochir. (Wien)*, **127**, 55–59.