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N^{η}-Nitro-L-arginine Methyl Ester Hydrochloride

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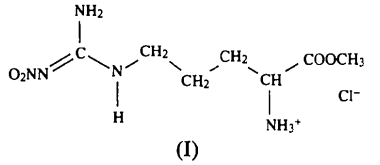
Abstract

The α-amino group of the title compound, $C_7H_{16}N_5O_4^+.Cl^-$, is positively charged; the nitroguanidinium moiety remains neutral. All atoms in the nitroguanidinium group are nearly coplanar. The side chain of the molecule consists of two planar groups which intersect almost perpendicularly at C^{δ}.

Comment

Endothelium-derived relaxing factor, recently identified as nitric oxide (NO), is the endogeneous stimulator of the soluble guanylate cyclase and is synthesized from L-arginine by nitric oxide synthase (NOS). N^{η}-Nitro-L-arginine methyl ester and other L-arginine analogues such as N^{η}-amino-L-arginine, N^{η}-methyl-L-arginine or N^{η}-nitro-L-arginine, act as inhibitors of NOS and induce an increase in blood pressure in animal models of sepsis or in patients in septic shock (Mülsch & Busse, 1990; Moncada, Palmer & Higgs, 1991; Rand, 1992; Moncada, 1992; Cobb *et al.*, 1992). Therefore, it is important to decide the precise molecular structure of these inhibitors in order to investigate more closely the relationship between the function and structure of these inhibitors. In this study, the crystal structure of N^{η}-nitro-L-arginine methyl ester was determined as the hydrochloride form, (I).



(I)

The molecular structure is illustrated in Fig. 1. All atoms forming the nitroguanidinium group are nearly coplanar. The hydrocarbon side chain is not fully extended, but folded at C^{δ} [C(5)]. The N(1)—C(2)—C(3)—C(4)—C(5) chain is *trans*-zigzag planar, as is C(5)—N(2)—C(6)—N(4)—N(5)—O(4); they intersect perpendicularly at C(5). The α-amino group is protonated and three amino atoms are involved in the hydrogen-bonding network. The three C—N distances in the nitroguanidinium group are nearly equal, as observed in L-arginine dihydrate (Lehmann, Verbist, Hamilton & Koetzle, 1973).

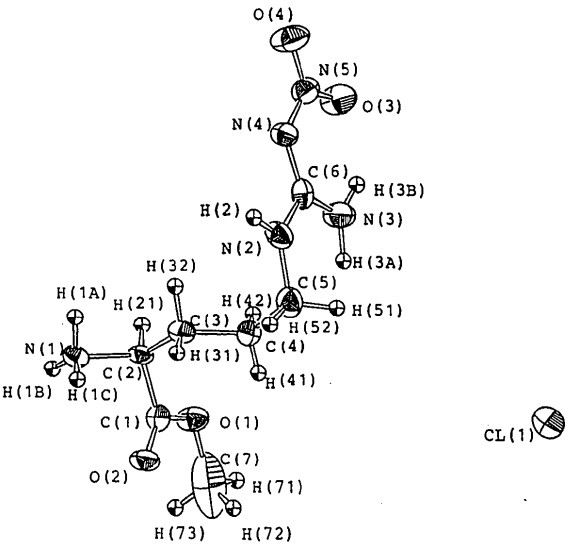


Fig. 1. Perspective view of the title compound with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

Experimental

Crystal data

$C_7H_{16}N_5O_4^+.Cl^-$
M_r = 269.69
Monoclinic
$P2_1$
a = 5.440 (1) Å
b = 10.108 (1) Å
c = 11.484 (2) Å
β = 103.03 (2)°
V = 615.2 (3) Å^3
Z = 2
D_x = 1.456 Mg m^{-3}
D_m = 1.448 (3) Mg m^{-3}
D_m measured by flotation
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 15.15–16.45°
μ = 0.320 mm^{-1}
T = 296 K
Plate
0.20 × 0.20 × 0.10 mm
Colourless
Crystal source: evaporation from 0.05*N* HCl/50% ethanol

Data collection

Riguku AFC-5*R* diffractometer
ω–2θ scans
Absorption correction: empirical (*DIFABS*; Walker & Stuart, 1983)
T_{min} = 0.78, T_{max} = 1.23
1634 measured reflections
1485 independent reflections
903 observed reflections [$I > 3\sigma(I)$]
R_{int} = 0.028
θ_{max} = 27.5°
$h = 0 \rightarrow 7$
$k = 0 \rightarrow 12$
$l = -14 \rightarrow 13$
3 standard reflections monitored every 150 reflections
intensity variation: −0.13%

Refinement

Refinement on F
R = 0.048
wR = 0.052
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.36 e Å^{-3}

$S = 1.58$
903 reflections
153 parameters
H-atom parameters not refined
$w = 4F_o^2/\sigma^2(F_o^2)$

Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	B_{eq}
Cl(1)	−0.0126 (3)	0.0127	0.1317 (2)	3.54 (7)
O(1)	0.0097 (8)	0.0212 (6)	0.8255 (4)	3.3 (2)
O(2)	0.367 (1)	−0.0701 (5)	0.9251 (5)	3.0 (2)
O(3)	0.041 (1)	0.7121 (6)	0.5370 (5)	4.6 (3)
O(4)	0.319 (1)	0.8451 (6)	0.6356 (6)	4.8 (3)
N(1)	0.462 (1)	0.1588 (6)	1.0588 (5)	2.4 (2)
N(2)	0.538 (1)	0.4254 (7)	0.6626 (6)	3.0 (3)
N(3)	0.150 (1)	0.4673 (6)	0.5386 (6)	3.7 (3)
N(4)	0.417 (1)	0.6366 (6)	0.6493 (5)	2.7 (2)
N(5)	0.252 (1)	0.7310 (7)	0.6052 (5)	3.1 (3)
C(1)	0.235 (1)	0.0236 (9)	0.8959 (5)	2.4 (3)
C(2)	0.320 (1)	0.1631 (7)	0.9301 (6)	2.1 (2)
C(3)	0.492 (1)	0.2164 (7)	0.8527 (6)	2.7 (3)
C(4)	0.369 (1)	0.2132 (8)	0.7206 (6)	2.9 (3)
C(5)	0.525 (1)	0.2816 (9)	0.6427 (7)	3.3 (3)
C(6)	0.356 (1)	0.511 (1)	0.6138 (5)	2.7 (3)
C(7)	0.110 (2)	0.121 (2)	0.793 (1)	9.2 (8)

Table 2. *Selected geometric parameters* (Å, °)

O(1)—C(1)	1.310 (7)	N(3)—C(6)	1.327 (8)
O(1)—C(7)	1.59 (2)	N(4)—N(5)	1.328 (8)
O(2)—C(1)	1.190 (9)	N(4)—C(6)	1.35 (1)
O(3)—N(5)	1.251 (7)	C(1)—C(2)	1.51 (1)
O(4)—N(5)	1.236 (8)	C(2)—C(3)	1.52 (1)
N(1)—C(2)	1.505 (8)	C(3)—C(4)	1.513 (9)
N(2)—C(5)	1.47 (1)	C(4)—C(5)	1.53 (1)
N(2)—C(6)	1.335 (9)		
C(1)—O(1)—C(7)	116.1 (7)	N(1)—C(2)—C(1)	106.7 (5)
C(5)—N(2)—C(6)	124.6 (7)	N(1)—C(2)—C(3)	109.8 (5)
N(5)—N(4)—C(6)	117.6 (5)	C(1)—C(2)—C(3)	111.7 (5)
O(3)—N(5)—O(4)	119.3 (7)	C(2)—C(3)—C(4)	112.8 (5)
O(3)—N(5)—N(4)	125.0 (6)	C(3)—C(4)—C(5)	113.6 (6)
O(4)—N(5)—N(4)	115.6 (6)	N(2)—C(5)—C(4)	111.7 (7)
O(1)—C(1)—O(2)	125.6 (8)	N(2)—C(6)—N(3)	119.8 (8)
O(1)—C(1)—C(2)	111.5 (7)	N(2)—C(6)—N(4)	111.9 (6)
O(2)—C(1)—C(2)	122.8 (5)	N(3)—C(6)—N(4)	128.3 (7)

D—H···*A*	H···*A*	*D*···*A*
N(1)—H(1*A*)···O(2^{i})	1.94	2.886 (7)
N(1)—H(1*B*)···Cl(1^{ii})	2.40	3.244 (6)
N(1)—H(1*C*)···Cl(1^{iii})	2.25	3.158 (6)
N(2)—H(2)···Cl(1^{iv})	2.25	3.205 (6)
N(3)—H(3*A*)···O(3^{v})	1.93	2.843 (8)

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

The positions of H atoms on N(2) and C(7) could not be located from difference Fourier synthesis and so were calculated geometrically. Other H atoms were subsequently located from difference Fourier synthesis and not refined.

Programs used for data collection and cell refinement: *MSC/AFC Data Collection and Refinement Software* (Rigaku Corporation, 1988). Programs used to solve structure: *SHELXS*86 (Sheldrick, 1985); *DIRDIF* (Beurskens, 1984). All calculations including data reduction: *TEXSAN* (Molecular Structure Corporation, 1985).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: AS1106). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Structural Studies of Intermediates in the Synthesis of Mifepristone (RU 486). I. An 11β-Substituted Steroid

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Abstract

The title compound, 11β-[4-(dimethylamino)phenyl]-3,3-(ethylenedioxy)-17α-(1-propynyl)estra-9-en-5α,17β-diol ($C_{31}H_{41}NO_4$), is the key intermediate in the synthesis of RU 486 and its overall conformation is similar to that of RU 486. The orientation of the (dimethylamino)phenyl ring, which seems to be con-