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Anticancer and Antifertility Agents. II. *N,N'*-Hexamethylenebis(3-pyridinecarboxamide)

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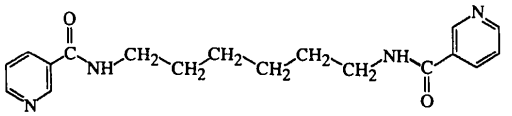
Abstract

The centrosymmetric molecule *N,N'*-hexamethylenebis(3-pyridinecarboxamide), $C_{18}H_{22}N_4O_2$, contains a crystallographic centre of inversion, with only half of the molecule constituting the asymmetric unit. There are intermolecular N—H···O=C hydrogen bonds [N···O 2.996 (2) Å] present in the structure.

Comment

Hexamethylenebisacetamide (HMBA) is an agent currently undergoing clinical trials that induces differentiation of certain types of cancer cells to non-malignant phenotypes (Andreeff *et al.*, 1992). In order to discover more effective anticancer agents, identify structure–activity relationships, understand molecular mechanisms and provide structural data for drug design, a series of compounds structurally related to HMBA have been synthesized and their crystal structures determined (Zhang, Liu, Wei & Shao, 1996). The title compound, (I), is one of these compounds.



(I)

The title compound (Fig. 1) can inhibit proliferation of lung cancer cells (Ao, Tanaka, Nakao, Yamagami & Fujii, 1991) and it has been proven from pharmacological experiments (Zhang & Wang, 1980; Zhang, Xing & Wang, 1982) to possess antifertility activity in male rats. It can inhibit spermatogenesis over a long period and does not produce any toxic effects with effective dosage (Li, Qin, Zhang & Li, 1979). Because of this, it may turn out to be an improved male sterilization drug.

Because intermolecular N—H···O=C hydrogen bonds occur in HMBA (Bailey, 1955), this kind of intermolecular interaction could be assumed to occur in the title compound and is realised along the approximate direction of the *b* axis, where there are intermolecular N—H···O=C hydrogen bonds of length 2.996 (2) Å [O=C at $x, y-1, z$].

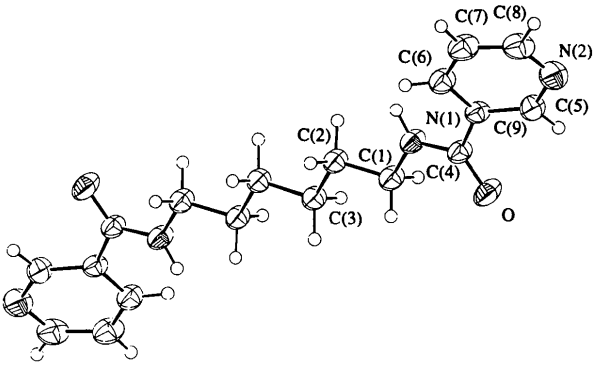


Fig. 1. View of $C_{18}H_{22}N_4O_2$ showing the labelling of the non-H atoms. Displacement ellipsoids are shown at 50% probability levels and H atoms are drawn as small circles of arbitrary radii.

Experimental

The title compound was prepared by condensation of nicotinic acid and 1,6-hexanediamine in a 2:1 molar ratio using Schlenk techniques. Recrystallization was from ethanol solution. The density D_m was measured by flotation in $CHCl_3/Cl(CH_2)_3Cl$ solution.

Crystal data

$C_{18}H_{22}N_4O_2$
M_r = 326.4
Monoclinic
$P2_1/n$
a = 5.2240 (10) Å
b = 5.0960 (10) Å
c = 31.006 (6) Å
β = 94.53 (3)°
V = 822.8 (3) Å^3
Z = 2
D_x = 1.317 Mg m^{-3}
D_m = 1.3167 (10) Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 6–10°
μ = 0.083 mm^{-1}
T = 296.0 (1) K
Rod
0.40 × 0.20 × 0.20 mm
Colourless

Data collection

Rigaku AFC-6*S* diffractometer
2θ scans
Absorption correction: ψ scans (Coppens, Leiserowitz & Rabinovich, 1965)
T_{min} = 0.995, T_{max} = 1.000
2293 measured reflections
1892 independent reflections
1537 observed reflections [$F \geq 4.0\sigma(F)$]
R_{int} = 0.032
θ_{max} = 27.5°
$h = 0 \rightarrow 6$
$k = 0 \rightarrow 6$
$l = -39 \rightarrow 40$
3 standard reflections monitored every 150 reflections
intensity decay: 3%

Refinement

Refinement on F
R = 0.0411
wR = 0.0639
S = 1.62
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: none

1537 reflections
153 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F) + 0.001F^2]$

Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.3.1)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
O	0.3725 (2)	0.6828 (2)	0.1022 (1)	0.051 (1)
N(1)	0.4777 (2)	0.2584 (2)	0.0950 (1)	0.039 (1)
N(2)	−0.1524 (2)	0.5030 (3)	0.1916 (1)	0.053 (1)
C(1)	0.6379 (3)	0.3119 (2)	0.0595 (1)	0.040 (1)
C(2)	0.7755 (3)	0.0686 (3)	0.0460 (1)	0.039 (1)
C(3)	0.9338 (3)	0.1218 (3)	0.0077 (1)	0.038 (1)
C(4)	0.3571 (2)	0.4528 (2)	0.1139 (1)	0.036 (1)
C(5)	0.2004 (2)	0.3792 (2)	0.1505 (1)	0.036 (1)
C(6)	0.2505 (3)	0.1635 (3)	0.1768 (1)	0.043 (1)
C(7)	0.0975 (3)	0.1217 (3)	0.2108 (1)	0.050 (1)
C(8)	−0.0978 (3)	0.2956 (3)	0.2168 (1)	0.052 (1)
C(9)	−0.0035 (3)	0.5418 (3)	0.1592 (1)	0.043 (1)

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

O—C(4)	1.232 (2)	C(3)—C(3^i)	1.517 (3)
N(1)—C(1)	1.460 (2)	C(4)—C(5)	1.498 (2)
N(1)—C(4)	1.334 (2)	C(5)—C(6)	1.381 (2)
N(2)—C(8)	1.331 (2)	C(5)—C(9)	1.392 (2)
N(2)—C(9)	1.334 (2)	C(6)—C(7)	1.386 (2)
C(1)—C(2)	1.509 (2)	C(7)—C(8)	1.375 (2)
C(2)—C(3)	1.523 (2)		
C(1)—N(1)—C(4)	120.7 (1)	C(4)—C(5)—C(6)	123.9 (1)
C(8)—N(2)—C(9)	116.6 (1)	C(4)—C(5)—C(9)	118.0 (1)
N(1)—C(1)—C(2)	111.7 (1)	C(6)—C(5)—C(9)	118.1 (1)
C(1)—C(2)—C(3)	111.7 (1)	C(5)—C(6)—C(7)	118.5 (1)
C(2)—C(3)—C(3^i)	112.9 (1)	C(6)—C(7)—C(8)	118.9 (1)
O—C(4)—N(1)	122.2 (1)	N(2)—C(8)—C(7)	124.0 (1)
O—C(4)—C(5)	120.9 (1)	N(2)—C(9)—C(5)	123.9 (1)
N(1)—C(4)—C(5)	116.9 (1)		

Symmetry code: (i) $2-x, -y, -z$.

The structure was solved and refined using *SHELXTL-Plus* (Sheldrick, 1990). All calculations were carried out using *SHELXTL-Plus* and the figure was produced with *PLATON* (Spek, 1990).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: TA1081). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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17α-Ethynyl-19-nor-3-oxo-4-androsten-17β-yl Acetate (Norethindrone Acetate)

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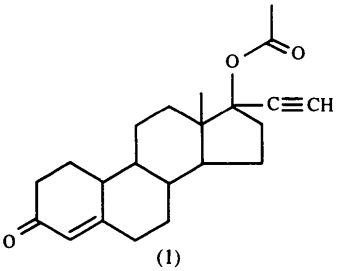
Abstract

The steroid skeleton of the title compound, $C_{22}H_{28}O_3$, is almost identical to the parent molecule norethindrone. The ethynyl residue donates a C≡C—H···O=C hydrogen-bond interaction, with an H···O separation of 2.18 Å.

Comment

17α-Ethynyl steroids are widely used as constituents of contraceptive agents and numerous crystal structures have been determined (*e.g.* van Geerestein, 1988). The structure of the parent molecule of the title compound, norethindrone, was reported by Mornon, Lepicard & Delettre (1976). Recently, Lutz, van der Maas & Kanters (1994) pointed out that ethynyl steroids may serve as a model to study C—H···O interactions donated by the ethynyl residue C≡C—H. The latter is known to be one of the most acidic C—H groups and therefore one of the strongest C—H hydrogen-bond donors (see Desiraju, 1991; Steiner, 1994*a*). In this context, the crystal structure of the title compound (1) was determined.



(1)

The molecular conformation of the steroid skeleton (Fig. 1) is almost identical with that of norethindrone (Mornon, Lepicard & Delettre, 1976), and therefore