Data collection

CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: refined from ΔF (*DIFABS*; Walker & Stuart, 1983)
T_{min} = 0.60, T_{max} = 1.19
1477 measured reflections
1456 independent reflections
676 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.024
θ_{max} = 24.0°
$h = 0 \rightarrow 13$
$k = 0 \rightarrow 14$
$l = 0 \rightarrow 12$
3 standard reflections monitored every 150 reflections
intensity variation: none

Refinement

Refinement on F
Final R = 0.0520
wR = 0.0562
S = 1.278
676 reflections
100 parameters
H atoms in calculated positions except for H attached to P which was located in a difference map and refined isotropically
$w = 1/\sigma^2(F_o)$
$(\Delta/\sigma)_{max}$ = 0.0109
$\Delta\rho_{max}$ = 0.48 e Å^{-3}
$\Delta\rho_{min}$ = −0.38 e Å^{-3}
Extinction correction: Zachariasen type 2 Gaussian isotropic
Extinction coefficient: 1.88209×10^{-7}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Data collection: Enraf–Nonius CAD-4AJ. Cell refinement: Enraf–Nonius CAD-4AJ. Data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1985). Program(s) used to solve structure: *MITHRIL* (Gilmore, 1984). Program(s) used to refine structure: *TEXSAN LS* (Molecular Structure Corporation, 1985). Software used to prepare material for publication: *TEXSAN FINISH* (Molecular Structure Corporation, 1985).

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

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

	x	y	z	U_{eq}
Br1	0.5091 (1)	0.2500	−0.04161 (10)	0.0655
P1	0.3820 (3)	0.2500	0.2597 (3)	0.0640
C1	0.4723 (9)	0.2500	0.3880 (11)	0.0550
C2	0.5106 (9)	0.1552 (8)	0.4334 (9)	0.0957
C3	0.5831 (11)	0.1551 (9)	0.5297 (11)	0.1107
C4	0.6163 (13)	0.2500	0.5764 (11)	0.0984
C5	0.2946 (7)	0.1274 (7)	0.2525 (8)	0.0568
C6	0.2107 (8)	0.1033 (8)	0.3387 (9)	0.0634
C7	0.1508 (8)	0.0044 (9)	0.3330 (8)	0.0674
C8	0.1696 (10)	−0.0691 (8)	0.2484 (10)	0.0866
C9	0.2551 (11)	−0.0446 (11)	0.1651 (11)	0.0989
C10	0.3167 (9)	0.0541 (11)	0.1669 (9)	0.0825

Table 2. *Geometric parameters* (Å, °)

P1—C1	1.80 (1)	C5—C10	1.37 (1)
P1—C5	1.785 (8)	C6—C7	1.38 (1)
C1—C2	1.35 (1)	C7—C8	1.36 (1)
C2—C3	1.38 (1)	C8—C9	1.39 (2)
C3—C4	1.34 (1)	C9—C10	1.39 (2)
C5—C6	1.40 (1)		
C1—P1—C5	109.5 (4)	P1—C5—C6	119.8 (7)
C5—P1—C5^i	114.8 (5)	P1—C5—C10	119.5 (7)
P1—C1—C2	120.1 (6)		

Symmetry code: (i) $x, \frac{1}{2} - y, z$.

Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55968 (16 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: HA1023]

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Acta Cryst. (1993). C**49**, 1018–1022

Structures of Two Ribonucleotide Reductase Inhibitors: 1-Hydroxy-1-methylurea and 1-Hydroxy-3-methylurea

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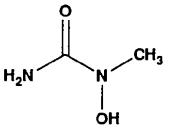
Abstract

The conformation of O—N—C=O in both 1-hydroxy-1-methylurea and 1-hydroxy-3-methylurea is antiperiplanar and is stabilized by intramolecular NH···O hydrogen bonding. Pyramidalization of the N atom carrying the hydroxy group is observed in both compounds and the N—O bonds are twisted by about 17° out of the N—(C=O)—N urea planes. The methyl C atom of 1-hydroxy-1-methylurea is not situated in the urea plane but the corresponding atom in 1-hydroxy-3-methylurea is included in the plane. 1-Hydroxy-3-methylurea is consequently the more planar of the two compounds.

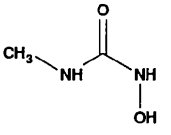
0108-2701/93/051018-05$06.00

Comment

1-Hydroxy-1-methylurea (1-MeHU) and 1-hydroxy-3-methylurea (3-MeHU) reduce the white-blood-cell count in L1210 leukemic mice (Lerner, Bianchi, Yiacas & Borman, 1966). In a structure-activity study of hydroxyurea analogues, 1-MeHU was shown to inhibit DNA synthesis in HeLa cells without affecting RNA and protein synthesis (Young, Schochetman, Hodas & Balis, 1967). It was found that substitution of the proton of the hydroxy group led to inactive compounds. In the structure-activity study of hydroxyurea analogues by Yu & Van Scott (1974), the antimitotic activity of the compounds was tested on vaginal epithelium from ICR mice. 1-MeHU was found to be as active as hydroxyurea, but the activity of 3-MeHU was lower. The results indicated that the electronic and steric effects of the substituents at the 1 and 3 positions of hydroxyurea affected antimitotic activity.



1-MeHu



3-MeHU

The anticancer drug hydroxyurea has been shown to impair DNA synthesis by inhibiting the enzyme ribonucleotide reductase (RNR) (Krakoff, Brown & Reichard, 1968). The drug destroys (reduces) the tyrosyl free radical of RNR, thereby leaving the enzyme inactive (Atkin, Thelander, Reichard & Lang, 1973; Gräslund, Ehrenberg & Thelander, 1982; Thelander, Gräslund & Thelander, 1985; Howell *et al.*, 1992). The hydroxyurea analogues 1- and 3-MeHU inhibit RNR by the same mechanism, but with lower (by about half) effect than hydroxyurea (Kjøller Larsen, Sjöberg & Thelander, 1982). On the other hand, all three compounds were found to be equally effective as radical scavengers. The study of Kjøller Larsen *et al.* (1982) of the effect of a series of hydroxyurea analogues directly on the *E. coli* RNR indicated that, in addition to one-electron oxidizability, the planarity of the compounds seems to be of importance. This is in good agreement with the early structure-activity studies of Young *et al.* (1967) and Yu *et al.* (1974).

Structure determinations of 1- and 3-MeHU were performed in order to compare the structures with that of hydroxyurea (Larsen & Jerslev, 1966; Berman & Kim, 1967; Thiessen, Levy & Flaig, 1978) and of other hydroxamic acids (Larsen, 1988). The molecular structures including the atomic labelling of 1- and 3-MeHU are presented in Fig. 1. Bond lengths and angles of the two structures are very similar. The lengths of the carbonyl bonds C2=O2 [1.2548 (5) and 1.256 (1) Å, respectively, in 1- and 3-MeHU] are longer than the mean value of 1.230 Å (range 1.19–1.27 Å) found for a series of hydroxamic acids (Larsen, 1988), probably as a result of hydrogen bonding. Hydroxyurea, formohydroxamic acid, salicylohydroxamic acid and pivalohydroxamic acid (Berman & Kim, 1967; Larsen, 1978, 1988; Due, Rasmussen & Larsen, 1987) have similar C=O bond lengths (>1.25 Å).

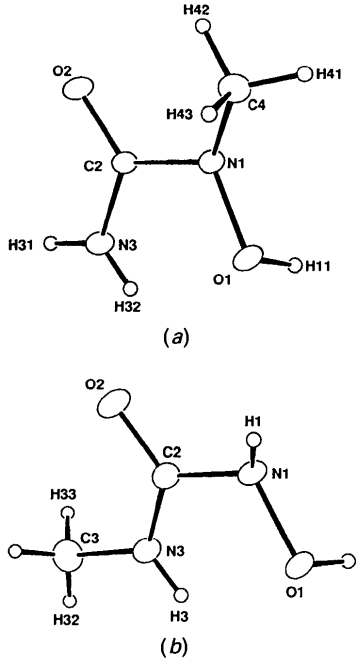


Fig. 1. Molecular structures of (*a*) 1-MeHU and (*b*) 3-MeHU (Johnson, 1976). Atomic displacement ellipsoids are drawn at the 50% probability level for non-H atoms.

1- and 3-MeHU each have a roughly planar part consisting of the urea moiety N1, C2, O2 and N3. The maximum deviations from the least-squares planes are −0.023 (1) and −0.015 (1) Å, respectively. In 1-MeHU, the methyl C atom is situated −0.571 (1) Å from the plane of the urea moiety, while in 3-MeHU it is included in the plane [deviation 0.011 (1) Å]. In both compounds, the N1 atom has pyramidal character in contrast to the N3 atom. This is reflected in the distances of N1 and N3 from the planes defined by the three atoms to which they are attached [0.310 (1) and 0.045 (1) Å, respectively, in 1-MeHU, −0.309 (1) and −0.049 (1) Å in 3-MeHU]. The sums of the valence angles at N1 and N3 are 345.85 and 360°, respectively, in 1-MeHU, and 340 and 359° in 3-MeHU. A slight pyramidal character of the hydroxylated N atom was also found in hydroxyurea (Thiessen *et al.*, 1978); this is in agreement with results retrieved for a series of hydroxamic acids [general formula *R*(C=O)NHOH] from the Cambridge Structural Database (Larsen, 1988) in which the N atom carrying the hydroxy group was found to be more or less pyramidal. The distances of the N atoms from the plane defined by the three bonded atoms were found to be in the range 0–0.303 Å.

The N—O bond is twisted by approximately 17° out of the plane of the urea moiety in both 1- and 3-MeHU (*cf.* torsion angles given in Table 2). The distances of the O1 atoms from the planes are −0.317 (1) and −0.339 (1) Å, respectively, for 1- and 3-MeHU. The geometry of O1—N1—C2=O2 is antiperiplanar with torsion angles of 167.37 (4) and 165.62 (8)° for 1- and 3-MeHU, respectively. This conformation is stabilized by intramolecular hydrogen bonding between O1 and an H atom of N3 in both compounds (*cf.* Table 2). The antiperiplanar conformation is also seen in, *e.g.*, hydroxyurea and 1-hydroxybiuret (Larsen & Jerslev, 1966; Larsen, 1977) but the conformation in hydroxamic acids in general can be synperiplanar as well as antiperiplanar, depending on the possibilities for hydrogen bonding (Larsen, 1988).

Fig. 2 shows stereoviews of the crystal packing. All possible hydrogen-bond donors and acceptors are involved in hydrogen bonding in both structures (see Table 2 and Fig. 2). In 1-MeHU, the hydrogen bond N3—H31···O2 connects the molecules in pairs parallel to the *b* axis with the pairs connected to each other along the *c* axis by the hydrogen bonds O1—H11···O2. The three-dimensional hydrogen-bonding network is completed by the weak N3—H32···O2 bonds along the *a* axis. In 3-MeHU, the molecules are connected in pairs around centers of symmetry through the hydrogen bonds N1—H1···O2 and N3—H3···O1. The result is a continuous connection between molecules forming zigzag rows along the *a* axis. These rows of molecules are connected along the *b* axis by the hydrogen bond O1—H11···O2.

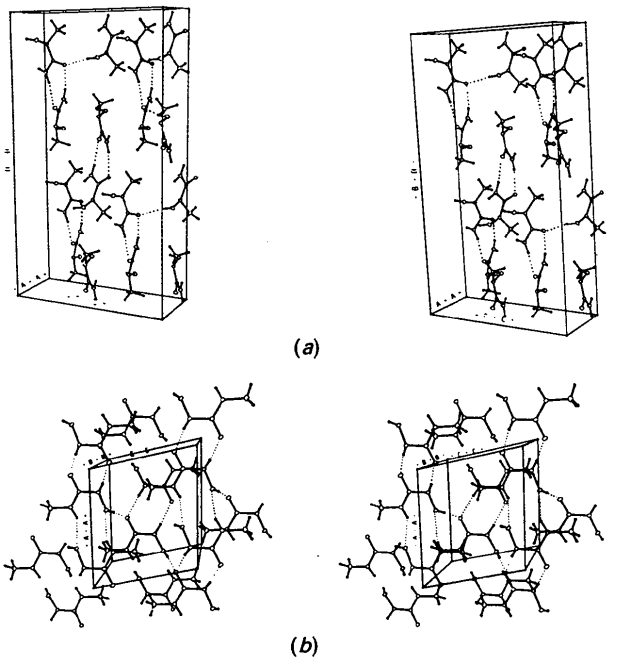


Fig. 2. Crystal packing of molecules in (*a*) 1-MeHU (*c* horizontal, *b* vertical) and (*b*) 3-MeHU (*c* horizontal, *a* vertical).

3-MeHU is the more planar of the two hydroxyurea analogues, but both structures are less planar than hydroxyurea. It was found earlier that, among hydroxyurea analogues, the most potent inhibitors of RNR of *E. coli* are almost planar molecules (Kjøller Larsen *et al.*, 1982). The lower degree of planarity of 1- and 3-MeHU might be the reason for the lower inhibitory effect of these analogues. The X-ray structure of the small tyrosyl-radical-carrying subunit of *E. coli* RNR has been determined (Nordlund, Sjöberg & Eklund, 1990), but no obvious cleft or pocket leads to the tyrosyl radical, which is buried within the protein. It is not yet known whether small and/or planar molecules are able to penetrate the protein and react directly with the free radical group.

Experimental

1-MeHU

Crystal data

$C_2H_6N_2O_2$
M_r = 90.08
Orthorhombic
*Fdd*2
a = 5.2049 (9) Å
b = 23.375 (4) Å
c = 13.155 (3) Å
V = 1600.4 (2) Å^3
Z = 16
D_x = 1.495 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 22 reflections
θ = 21.40–21.87°
μ = 0.1228 mm^{-1}
T = 122 K
Thin rectangular plates
0.60 × 0.35 × 0.10 mm
Colourless
Crystal source: synthesized as described by Ohlin Mathieson Chemical Co. (1963, 1964); single crystals from slow cooling of hot ethyl acetate solution

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
8928 measured reflections
5288 independent reflections
3271 observed reflections [$I > 3\sigma(I)$]
R_{int} = 0.018
θ_{max} = 55.00°
h = −10 → 11
k = −52 → 56
l = −32 → 32
2 standard reflections monitored every 300 reflections
frequency: 166 min
intensity variation: −1.5%

Refinement

Refinement on F
Final R = 0.029
wR = 0.037
S = 0.840
3271 reflections
78 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F) + 0.0009F^2]$
$(\Delta/\sigma)_{max}$ = 0.00
$\Delta\rho_{max}$ = 0.546 e Å^{-3}
$\Delta\rho_{min}$ = −0.449 e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.3.1)

3-MeHU

Crystal data

$C_2H_6N_2O_2$
M_r = 90.08
Monoclinic
$P2_1/N$
a = 8.202 (1) Å
b = 7.081 (1) Å
c = 7.316 (1) Å
β = 101.378 (9)°
V = 416.5 (2) Å^3
Z = 4
D_x = 1.437 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.5418 Å

Cell parameters from 18 reflections
θ = 35.07–46.14°
μ = 1.0474 mm^{-1}
T = 110 K
Rectangular
0.35 × 0.25 × 0.20 mm
Colourless
Crystal source: synthesized as described by Francesconi & Parrozzani (1901); single crystals from slow cooling of hot ethanol solution

Data collection

Enraf-Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
3685 measured reflections
864 independent reflections
797 observed reflections [$I > 3\sigma(I)$]
R_{int} = 0.018

θ_{max} = 75.00°
$h = -10 \rightarrow 10$
$k = -8 \rightarrow 8$
$l = -9 \rightarrow 9$
2 standard reflections monitored every 300 reflections
frequency: 166 min
intensity variation: −0.9%

Refinement

Refinement on F
Final R = 0.046
wR = 0.066
S = 1.498
797 reflections
79 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F) + 0.0016F^2]$

$(\Delta/\sigma)_{max}$ = 0.01
$\Delta\rho_{max}$ = 0.284 e Å^{-3}
$\Delta\rho_{min}$ = −0.482 e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.3.1)

All H atoms were located in a difference Fourier map after refinement of positional and anisotropic displacement parameters for the non-H atoms. Data reduction: *BEGIN*, *SDP* (B. A. Frenz & Associates, Inc., 1982). Program(s) used to solve structure: *MULTAN* (Main *et al.*, 1980) for 1-MeHU and *SHELXS86* (Sheldrick, 1986) for 3-MeHU. Program(s) used to refine structure: *LSFM*, *SDP* (B. A. Frenz & Associates, Inc., 1982). Molecular grapics: *ORTEP*II (Johnson, 1976).

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

$B_{eq} = (4/3)\Sigma_i\Sigma_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
1-MeHU				
O2	0.65430 (7)	0.42873 (2)	0.531	1.169 (4)
O1	0.12592 (7)	0.34428 (2)	0.46611 (4)	1.385 (5)
N3	0.23689 (8)	0.45003 (2)	0.49608 (4)	1.189 (5)
N1	0.38937 (7)	0.35798 (2)	0.47351 (4)	1.039 (4)
C2	0.43374 (8)	0.41336 (2)	0.50393 (4)	0.883 (4)
C4	0.5359 (1)	0.31064 (2)	0.51569 (4)	1.231 (5)
3-MeHU				
O1	0.37919 (8)	0.0727 (1)	1.1356 (1)	1.33 (1)
O2	0.02073 (9)	0.1113 (1)	0.7881 (1)	1.43 (1)
N1	0.2110 (1)	0.1166 (1)	1.0570 (1)	1.18 (1)
N3	0.2955 (1)	0.1188 (1)	0.7724 (1)	1.29 (1)
C2	0.1717 (1)	0.1126 (1)	0.8656 (2)	1.09 (2)
C3	0.2659 (1)	0.1186 (2)	0.5699 (2)	1.70 (2)

Table 2. *Selected bond lengths* (Å), *bond angles* (°), *torsion angles* (°) *and hydrogen-bond geometry* (Å, °)

1-MeHU		3-MeHU	
O1—N1	1.4115 (5)	O1—N1	1.420 (1)
N1—C2	1.3744 (6)	N1—C2	1.374 (1)
O2—C2	1.2548 (5)	O2—C2	1.256 (1)
N3—C2	1.3399 (6)	N3—C2	1.331 (1)
N1—C4	1.4541 (7)	N3—C3	1.453 (1)
O1—N1—C2	113.39 (4)	O1—N1—C2	114.95 (8)
O2—C2—N1	120.41 (4)	O2—C2—N1	118.2 (1)
O2—C2—N3	122.57 (4)	O2—C2—N3	123.6 (1)
N3—C2—N1	116.85 (4)	N1—C2—N3	118.16 (8)
C2—N1—C4	121.17 (4)	C2—N3—C3	122.08 (8)
O1—N1—C4	111.29 (4)		
O1—N1—C2—O2	167.37 (4)	O1—N1—C2—O2	165.62 (8)
O1—N1—C2—N3	−17.19 (7)	O1—N1—C2—N3	−17.3 (1)
C4—N1—C2—O2	30.98 (7)	C3—N3—C2—O2	−2.0 (2)
C4—N1—C2—N3	−153.58 (5)	C3—N3—C2—N1	−178.86 (9)

A—H···B	A···B	H···B	A—H···B
1-MeHU			
O1—H11···O2^{i}	2.7465 (5)	1.95 (1)	159 (1)
N3—H31···O2^{ii}	2.9264 (5)	2.07 (1)	170 (1)
N3—H32···O2^{iii}	3.1073 (5)	2.40 (1)	146 (1)
N3—H32···O1	2.5690 (6)	2.16 (1)	111 (1)
3-MeHU			
O1—H11···O2^{iv}	2.662 (1)	1.83 (2)	176 (2)
N1—H1···O2^{v}	2.891 (1)	2.03 (2)	174 (2)
N1—H3···O1^{vi}	2.949 (1)	2.24 (1)	142 (1)
N3—H3···O1	2.630 (1)	2.23 (2)	108 (1)

Symmetry code: (i) $x-\frac{3}{4}, \frac{3}{4}-y, z-\frac{1}{4}$; (ii) $1-x, 1-y, z$; (iii) $x-1, y, z$; (iv) $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$; (v) $-x, -y, 2-z$; (vi) $1-x, -y, 2-z$.

The authors thank Mr Flemming Hansen for collecting the X-ray data. The diffractometer and an X-ray generator were acquired by means of grants from the Danish National Science Research Council. PharmaBiotec is acknowledged for financial support.

Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55924 (31 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AB1049]

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Acta Cryst. (1993). C**49**, 1022–1024

N,N'-Dibenzylethylenediamineterphthalate Dimer

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Abstract

The titled macrocyclic dimer, 3,6,13,16-tetrabenzyl-3,6,13,16-tetraazatricyclo[16.2.2.2^{8,11}]tetracosa-1(21),-8,10,11,18(22),19-hexaene-2,7,12,17-tetraone, lies upon an inversion center; the N—C—C—N torsion angles of the ethylenediamine segment are ±145.7 (3)° and the *para*-phenylene subcyclic moieties are distorted from planarity toward the interior of the molecule.

Comment

The related 20-membered macrocyclic trimer of the title compound has been shown (Vögtle, Puff, Friedrichs & Müller, 1982) to form a stable 'neutral component complex' (Newkome, Taylor, Fronczek, Delord, Kohli & Vögtle, 1981), in which its crystal structure confirmed the presence of a single guest chloroform molecule within the macrocyclic cavity. During our repetition of the procedure for this trimer, the corresponding dimer and tetramer were isolated and spectrally characterized (Newkome & Rogers, 1988). Since this unusually stable host–guest relationship offers a novel entrance to microdetection using surface acoustic wave (SAW) devices (Overton, Yan, Zhang, Klinkhahorn & Newkome, 1990), the crystal structure of the dimer was undertaken to ascertain the conformational relationship(s) to that of the trimer and to provide coordinates for use in docking computations aimed at ascertaining if a neutral component complex may form between the title dimer and small solvent molecules, such as methylene chloride.

The title dimer, illustrated in Fig. 1, lies on an inversion center. The macrocyclic nature of this dimer imposes distortions upon it such that the phenylene moieties are nonplanar, with the two substituted (*para*) C atoms lying 0.011 (3) and 0.019 (3) Å to the same side of the best plane of the other four, toward the exterior of the molecule. The diminished bond angles for C5—C4—C9 and C6—C7—C8 further denote a slight elongation of the rings. The N—C—C—N torsion angles are ±145.7 (3)°. The lactam C atoms C3 and C10 bonded at the *para* positions lie 0.183 (3) and 0.247 (3) Å out of the plane, in the same direction as C4 and C7. The C(ring)—C(lactam) bonds form unequal angles with ring C—C bonds, averaging 116.4 (2) and 125.3 (2)°. The N atoms are slightly pyramidal, lying 0.099 (3) and 0.096 (3) Å out of the plane defined by the C atoms bonded to them. The

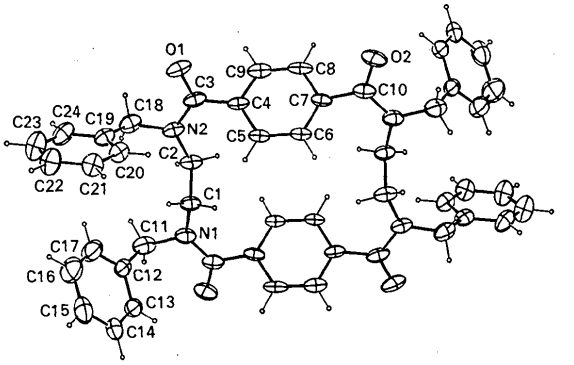

Fig. 1. The title molecule with thermal ellipsoids drawn at the 20% probability level and H atoms drawn as circles of arbitrary radii.

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