Table 6. *Hydrogen-bonding geometry (Å, °) for cyclo(Gly-L-Ser)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3···O4^{i}	0.86 (2)	2.01 (3)	2.837 (2)	163 (3)
N6—H6···O7^{ii}	0.85 (2)	2.08 (2)	2.914 (2)	167 (3)
O7—H7···O1^{iii}	0.83 (3)	1.91 (3)	2.731 (2)	172 (3)

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

For cyclo(L-Ala-L-Ser), H3, H6, H8, H10*A* and H10*B* were refined; U_{iso}(H6) = $1.2U_{eq}$(N6); H2, H5, H7*A*, H7*B*, H7*C*, H8*A* and H8*B* were refined using a riding model with U_{iso} = $1.2U_{iso}$(C).

For both compounds, data collection: *CAD*-4 *Software* (Enraf–Nonius, 1977); cell refinement: *CAD*-4 *Software*; data reduction: *MolEN* (Fair, 1990); program(s) used to solve structures: *MULTAN*80 (Main *et al.*, 1980); program(s) used to refine structures: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*93.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: SX1004). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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The Ribonucleotide Reductase R1 Inhibitor *N*-Acetyl-*N*,*O*-di(propylcarbamoyl)hydroxylamine, an Analogue of Caracemide

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Abstract

The molecular structure of the caracemide analogue *N*-acetyl-*N*,*O*-di(propylcarbamoyl)hydroxylamine (*Chemical Abstracts* nomenclature: *N*-[(propylamino)carbonyl]-*N*-{[(propylamino)carbonyl]oxy}acetamide), $C_{10}H_{19}N_3O_4$, is comparable to the structure of the parent compound *N*-acetyl-*N*,*O*-di(methylcarbamoyl)hydroxylamine. The caracemide moiety of the compound consists of two nearly planar moieties, which are almost perpendicular to each other as in the crystal structure of caracemide itself. The two propyl groups in each of the two molecules (*A* and *B*) in the asymmetric unit have different conformations. One of these groups adopts the *gauche* conformation, with torsion angles of 49.1 (6) and −61.3 (4)° for molecules *A* and *B*, respectively, while the other adopts a fully extended conformation, with respective torsion angles of 179.2 (3) and 176.5 (3)°. The main differences in bond lengths, angles and torsion angles between molecules *A* and *B* are found in one of the propyl groups.

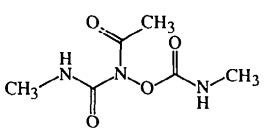
Comment

The enzyme ribonucleotide reductase (RNR) catalyzes the reduction of ribonucleotides to deoxyribonucleotides. Being an indispensable enzyme in the *de novo* synthesis of DNA precursors, RNR is a potential target for antibacterial, antiviral or antineoplastic agents. A number of RNR inhibitors have been described (Lammers & Follmann, 1983; Larsen, 1990*a*; Stubbe, 1990).

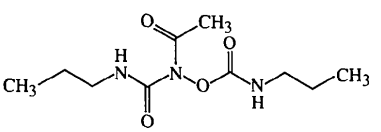
The anticancer drug caracemide [*N*-acetyl-*N*,*O*-di(methylcarbamoyl)hydroxylamine, CAR] inhibits the enzyme RNR (Moore & Loo, 1984; Newman *et al.*, 1986). CAR was originally tested on partially purified RNR of Novikoff ascites tumor cells. Using highly purified RNR of *E. coli*, it has recently been shown that CAR inhibits RNR by specific irreversible inactivation of the larger R1 subunit of the enzyme (Larsen, Cornett, Karlsson, Sahlin & Sjöberg, 1992). The substrates

of RNR protect against the inactivation of R1 by CAR in a competitive manner, and it was suggested that CAR inhibits RNR by covalent modification of a catalytically active amino acid residue, proposed to be a serine or cysteine, at the substrate binding site (Larsen *et al.*, 1992). The structure of CAR has been determined by X-ray crystallography and the molecule was found to consist of two nearly planar moieties almost perpendicular to each other (Larsen, 1990*b*).

Reifschneider (1983) prepared a number of analogues of CAR using different isocyanates and hydroxamic acids, and some of them, *e.g.* the analogue *N*-acetyl-*N*,*O*-di(propylcarbamoyl)hydroxylamine (PROCAR), were shown to be cytotoxic to HeLa cells. By testing directly on purified *E. coli* R1, PROCAR was shown to inactivate R1 under the same conditions as CAR (Larsen, Sahlin & Sjöberg, 1993). The molecular structure of PROCAR was determined in order to compare the conformation with that of CAR.



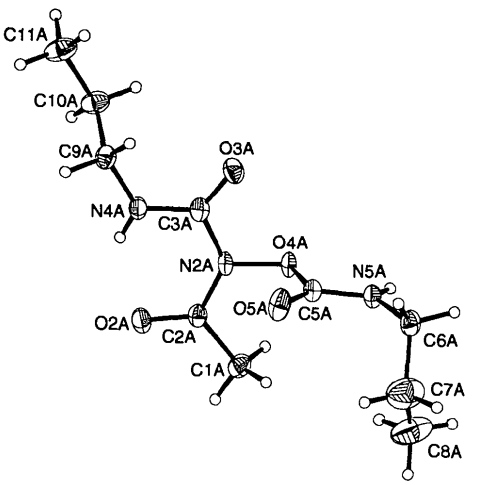
CAR



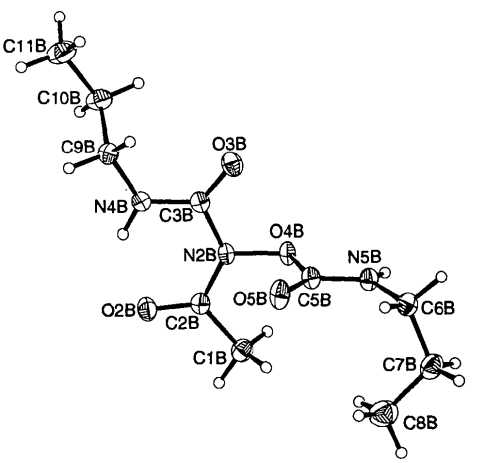
PROCAR

There are two molecules, *A* and *B*, in the asymmetric unit (Fig. 1). The two molecules are rather similar, but not identical (*cf.* Table 2). The main differences are found in the propyl group consisting of atoms C6, C7 and C8. The bonds C6—C7 and C7—C8 appear shorter in molecule *A* than in *B* and the angles C6—C7—C8 of molecules *A* and *B* differ by 6.3 (5)° (Table 2). The calculated values of the bonds and angles involving atoms C7*A* and C8*A*, however, should be taken with some reservation because of the larger displacement parameters of these atoms (Table 1, Fig. 1). The two propyl groups of each molecule are observed in different conformations. The C9—C10—C11 propyl group adopts an extended conformation in both molecules *A* and *B*, while the C6—C7—C8 propyl group adopts a folded *gauche* conformation in each molecule, but is oriented in opposite directions (Fig. 1, Table 2).

The molecular structure of PROCAR is very similar to the structure of CAR (Larsen, 1990*b*). In both molecules *A* and *B*, the conformation of N2—O4—C5=O5 is *sp* (synperiplanar), with torsion angle values of −6.3 (4) and −3.4 (4)°, respectively, as in CAR where the corresponding angle is 12.2 (2)°. The conformation of O4—N2—C3=O3 is also *sp*, whereas the



Molecule *A*



Molecule *B*

Fig. 1. The molecular structures of the two PROCAR molecules, *A* and *B*, showing the atom labelling. Displacement ellipsoids are at the 50% probability level for the non-H atoms.

conformation of O4—N2—C2=O2 is *ap* (antiperiplanar) in both molecules (see Table 2), similar to CAR. The CAR moiety of PROCAR, that is, the PROCAR structure except for the two extra C atoms of each propyl group, consists of two nearly planar moieties which are close to being perpendicular to each other (see Table 3). The same conformation was found for CAR, where the dihedral angle between the planes is 84.19 (4)°. The structures of CAR and PROCAR are almost superimposable when the extra C atoms of the propyl groups are ignored. This conformation is in all cases stabilized by an intramolecular hydrogen bond (N4—H4···O2; *cf.* Table 3).

The packing of the molecules in the unit cell is shown in Fig. 2. The hydrogen-bonding geometry (Table 3) in the crystal structure of PROCAR is very similar to

that of CAR. The intermolecular N4—H4···O2 hydrogen bond connects two adjacent centrosymmetrically related molecules and thereby forms a dimer. The same dimerization is observed in CAR, where the methyl groups point towards one another. The N5—H5···O5 hydrogen bond, which connects molecules along the *a* axis, is also a common feature in CAR and PROCAR (Table 3).

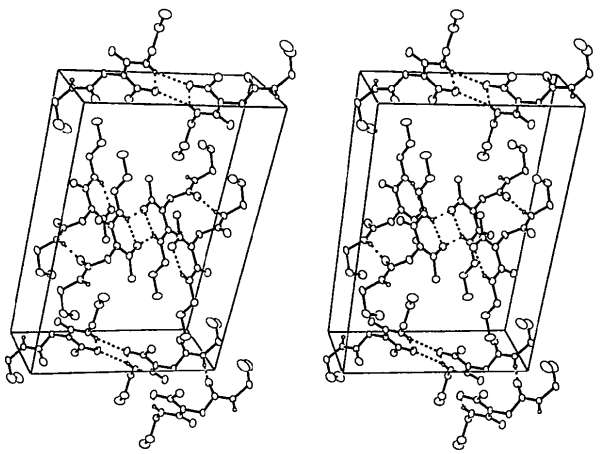


Fig. 2. A stereoscopic view of the unit cell of the PROCAR crystals showing the molecular packing. Hydrogen bonds are illustrated by dotted lines. The *b* axis is horizontal, the *c* axis is vertical and the *a* axis is out of the plane of the paper.

The molecular structures of CAR and PROCAR are found to be very similar in the crystalline state, but they are flexible molecules and may adopt other conformations upon interaction with protein R1 of *E. coli* RNR.

Experimental

The title compound was synthesized according to Reifschneider (1983) with minor modifications. A solution of 1.02 g (12 mmol) of propyl isocyanate in 5 ml of dichloromethane was added slowly to a solution of 375 mg (5 mmol) of *N*-acetylhydroxylamine in 50 ml of dichloromethane with stirring. To the reaction mixture was added 3 drops of triethylamine and the mixture was allowed to stand at room temperature for 20 h. The reaction mixture was then evaporated *in vacuo* and the white powder thereby produced was recrystallized several times from ether, whereupon single crystals were obtained [m.p. 314–317 K, literature 313–316 K (Reifschneider, 1983)]. ^{1}H NMR ($CDCl_3$, TMS): δ 0.90 (*m*, 6H, 2 × CH_3), 1.60 (*m*, 4H, 2 × CH_2), 2.25 (*s*, 3H, CH_3), 3.25 (*m*, 4H, 2 × CH_2), 5.60 (*m*, *b*, 1H, OCONH), 8.30 p.p.m. (*m*, *b*, 1H, NCONH).

Crystal data

$C_{10}H_{19}N_3O_4$
M_r = 245.28
Mo $K\alpha$ radiation
λ = 0.71073 Å
Triclinic
$P\bar{1}$
a = 4.944 (2) Å
b = 13.005 (2) Å
c = 20.234 (3) Å
α = 85.07 (1)°
β = 89.71 (2)°
γ = 79.45 (2)°
V = 1274.2 (6) Å^3
Z = 4
D_x = 1.279 Mg m^{-3}
Cell parameters from 18 reflections
θ = 16.97–20.86°
μ = 0.099 mm^{-1}
T = 122 (2) K
Pinacoidal
0.40 × 0.25 × 0.10 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
5882 measured reflections
5345 independent reflections
4600 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0336
θ_{max} = 29.96°
$h = -6 \rightarrow 6$
$k = -18 \rightarrow 18$
$l = 0 \rightarrow 28$
3 standard reflections monitored every 600 reflections
intensity decay: 0.1%

Refinement

Refinement on F^2
$R(F)$ = 0.0698
$wR(F^2)$ = 0.1755
S = 1.017
5342 reflections
325 parameters
Only coordinates of H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.0826P)^2 + 2.5401P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.130
$\Delta\rho_{max}$ = 1.917 e Å^{-3}
$\Delta\rho_{min}$ = −0.810 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

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

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

	x	y	z	U_{eq}
C1*A*	0.0337 (6)	0.6107 (2)	0.0983 (2)	0.0262 (6)
C2*A*	−0.1581 (5)	0.6127 (2)	0.0405 (1)	0.0198 (5)
O2*A*	−0.2892 (4)	0.5428 (2)	0.0345 (1)	0.0271 (4)
N2*A*	−0.1723 (5)	0.6963 (2)	−0.0064 (1)	0.0213 (5)
O4*A*	−0.0207 (4)	0.7718 (1)	0.0070 (1)	0.0215 (4)
C5*A*	−0.1761 (5)	0.8507 (2)	0.0425 (1)	0.0194 (5)
O5*A*	−0.4191 (4)	0.8542 (2)	0.0534 (1)	0.0328 (5)
N5*A*	−0.0119 (5)	0.9135 (2)	0.0602 (1)	0.0215 (5)
C6*A*	−0.1136 (6)	1.0034 (2)	0.0984 (2)	0.0260 (6)
C7*A*	−0.158 (1)	0.9721 (4)	0.1700 (2)	0.060 (1)
C8*A*	0.053 (1)	0.9015 (4)	0.2070 (2)	0.061 (1)
C3*A*	−0.3404 (5)	0.7241 (2)	−0.0660 (1)	0.0214 (5)
O3*A*	−0.3275 (4)	0.8051 (2)	−0.0993 (1)	0.0273 (4)
N4*A*	−0.4908 (5)	0.6527 (2)	−0.0797 (1)	0.0227 (5)
C9*A*	−0.6694 (6)	0.6706 (2)	−0.1381 (1)	0.0243 (6)
C10*A*	−0.5213 (6)	0.6335 (3)	−0.2000 (2)	0.0303 (6)
C11*A*	−0.7135 (7)	0.6517 (3)	−0.2602 (2)	0.0393 (8)
C1*B*	0.1462 (6)	0.3943 (2)	0.4004 (2)	0.0259 (6)
C2*B*	−0.0458 (5)	0.3895 (2)	0.4582 (1)	0.0199 (5)
O2*B*	−0.2470 (4)	0.4574 (2)	0.4650 (1)	0.0256 (4)
N2*B*	0.0213 (4)	0.3037 (2)	0.5041 (1)	0.0203 (4)
O4*B*	0.2511 (4)	0.2303 (2)	0.4900 (1)	0.0214 (4)
C5*B*	0.1810 (5)	0.1509 (2)	0.4534 (1)	0.0196 (5)
O5*B*	−0.0558 (4)	0.1482 (2)	0.4400 (1)	0.0298 (5)
N5*B*	0.4096 (5)	0.0887 (2)	0.4385 (1)	0.0213 (5)
C6*B*	0.4118 (6)	−0.0009 (2)	0.3990 (2)	0.0253 (6)

C7*B*	0.5039 (7)	0.0216 (3)	0.3279 (2)	0.0323 (7)
C8*B*	0.3163 (9)	0.1127 (3)	0.2903 (2)	0.0429 (8)
C3*B*	−0.1216 (5)	0.2740 (2)	0.5632 (1)	0.0206 (5)
O3*B*	−0.0323 (4)	0.1911 (2)	0.5948 (1)	0.0274 (4)
N4*B*	−0.3415 (5)	0.3445 (2)	0.5776 (1)	0.0221 (5)
C9*B*	−0.5095 (6)	0.3239 (2)	0.6351 (1)	0.0237 (5)
C10*B*	−0.3996 (7)	0.3551 (3)	0.6989 (2)	0.0311 (6)
C11*B*	−0.5884 (7)	0.3389 (3)	0.7573 (2)	0.0399 (8)

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

C1*A*—C2*A*	1.504 (4)	C1*B*—C2*B*	1.506 (4)
C2*A*—O2*A*	1.224 (3)	C2*B*—O2*B*	1.220 (3)
C2*A*—N2*A*	1.373 (4)	C2*B*—N2*B*	1.382 (3)
N2*A*—O4*A*	1.384 (3)	N2*B*—O4*B*	1.389 (3)
N2*A*—C3*A*	1.450 (4)	N2*B*—C3*B*	1.445 (4)
O4*A*—C5*A*	1.411 (3)	O4*B*—C5*B*	1.414 (3)
C5*A*—O5*A*	1.214 (3)	C5*B*—O5*B*	1.210 (3)
C5*A*—N5*A*	1.324 (3)	C5*B*—N5*B*	1.314 (3)
N5*A*—C6*A*	1.467 (3)	N5*B*—C6*B*	1.467 (3)
N5*A*—H5*A*	0.92 (4)	N5*B*—H5*B*	0.81 (4)
C6*A*—C7*A*	1.496 (5)	C6*B*—C7*B*	1.527 (4)
C7*A*—C8*A*	1.428 (6)	C7*B*—C8*B*	1.514 (5)
C3*A*—O3*A*	1.212 (3)	C3*B*—O3*B*	1.216 (3)
C3*A*—N4*A*	1.338 (3)	C3*B*—N4*B*	1.336 (3)
N4*A*—C9*A*	1.456 (4)	N4*B*—C9*B*	1.461 (4)
N4*A*—H4*A*	0.79 (4)	N4*B*—H4*B*	0.88 (4)
C9*A*—C10*A*	1.517 (4)	C9*B*—C10*B*	1.518 (4)
C10*A*—C11*A*	1.524 (4)	C10*B*—C11*B*	1.526 (4)
O2*A*—C2*A*—N2*A*	121.6 (3)	O2*B*—C2*B*—N2*B*	121.3 (2)
O2*A*—C2*A*—C1*A*	122.3 (3)	O2*B*—C2*B*—C1*B*	122.6 (3)
N2*A*—C2*A*—C1*A*	116.1 (2)	N2*B*—C2*B*—C1*B*	116.0 (2)
C2*A*—N2*A*—O4*A*	116.1 (2)	C2*B*—N2*B*—O4*B*	116.0 (2)
C2*A*—N2*A*—C3*A*	130.4 (2)	C2*B*—N2*B*—C3*B*	129.9 (2)
O4*A*—N2*A*—C3*A*	113.3 (2)	O4*B*—N2*B*—C3*B*	113.9 (2)
N2*A*—O4*A*—C5*A*	111.4 (2)	N2*B*—O4*B*—C5*B*	111.9 (2)
O5*A*—C5*A*—N5*A*	129.2 (3)	O5*B*—C5*B*—N5*B*	130.2 (3)
O5*A*—C5*A*—O4*A*	122.3 (2)	O5*B*—C5*B*—O4*B*	121.6 (2)
N5*A*—C5*A*—O4*A*	108.5 (2)	N5*B*—C5*B*—O4*B*	108.2 (2)
C5*A*—N5*A*—C6*A*	121.5 (2)	C5*B*—N5*B*—C6*B*	122.5 (2)
N5*A*—C6*A*—C7*A*	113.1 (3)	N5*B*—C6*B*—C7*B*	112.0 (2)
C8*A*—C7*A*—C6*A*	119.5 (4)	C8*B*—C7*B*—C6*B*	113.2 (3)
O3*A*—C3*A*—N4*A*	126.5 (3)	O3*B*—C3*B*—N4*B*	126.8 (3)
O3*A*—C3*A*—N2*A*	119.1 (2)	O3*B*—C3*B*—N2*B*	118.8 (2)
N4*A*—C3*A*—N2*A*	114.4 (2)	N4*B*—C3*B*—N2*B*	114.4 (2)
C3*A*—N4*A*—C9*A*	120.2 (2)	C3*B*—N4*B*—C9*B*	120.4 (2)
N4*A*—C9*A*—C10*A*	112.8 (2)	N4*B*—C9*B*—C10*B*	112.9 (2)
C9*A*—C10*A*—C11*A*	111.8 (3)	C9*B*—C10*B*—C11*B*	111.7 (3)
C8*A*—C7*A*—C6*A*—N5*A*	49.1 (6)	C8*B*—C7*B*—C6*B*—N5*B*	−61.3 (4)
C7*A*—C6*A*—N5*A*—C5*A*	75.1 (4)	C7*B*—C6*B*—N5*B*—C5*B*	104.1 (3)
C6*A*—N5*A*—C5*A*—O4*A*	−179.6 (2)	C6*B*—N5*B*—C5*B*—O4*B*	−178.4 (2)
N5*A*—C5*A*—O4*A*—N2*A*	173.1 (2)	N5*B*—C5*B*—O4*B*—N2*B*	176.1 (2)
C5*A*—O4*A*—N2*A*—C3*A*	85.1 (3)	C5*B*—O4*B*—N2*B*—C3*B*	85.3 (3)
O4*A*—N2*A*—C3*A*—N4*A*	−179.5 (2)	O4*B*—N2*B*—C3*B*—N4*B*	179.4 (2)
N2*A*—C3*A*—N4*A*—C9*A*	179.9 (2)	N2*B*—C3*B*—N4*B*—C9*B*	178.6 (2)
C3*A*—N4*A*—C9*A*—C10*A*	86.9 (3)	C3*B*—N4*B*—C9*B*—C10*B*	85.6 (3)
N4*A*—C9*A*—C10*A*—C11*A*	179.2 (3)	N4*B*—C9*B*—C10*B*—C11*B*	176.5 (3)
O2*A*—C2*A*—N2*A*—O4*A*	178.2 (2)	O2*B*—C2*B*—N2*B*—O4*B*	178.4 (2)
O4*A*—N2*A*—C3*A*—O3*A*	2.8 (4)	O4*B*—N2*B*—C3*B*—O3*B*	0.6 (3)
O4*A*—N2*A*—C2*A*—O2*A*	178.2 (2)	O4*B*—N2*B*—C2*B*—O2*B*	178.4 (2)
N2*A*—O4*A*—C5*A*—O5*A*	−6.3 (4)	N2*B*—O4*B*—C5*B*—O5*B*	−3.4 (4)

Table 3. *Least-squares-planes data (Å, °) and hydrogen-bonding geometry (Å, °)*

Plane	Maximum distance from plane *A*	*B*
1 (C1, C2, O2, N2, O4, C3, O3, N4, C9)	−0.034 (2)	0.039 (2)
2 (N2, O4, C5, O5, N5, C6)	−0.070 (2)	−0.046 (2)
Dihedral angle between planes 1 and 2	84.49 (7)	85.54 (7)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
CAR[a]				
N4—H4···O2	0.90 (2)	2.01 (2)	2.705 (2)	132 (2)
N4—H4···O2^{i}	0.90 (2)	2.48 (2)	3.160 (2)	132 (2)
N5—H5···O5^{ii}	0.89 (2)	2.01 (2)	2.785 (2)	145 (2)
PROCAR (Molecule *A*)				
N4*A*—H4*A*···O2*A*	0.79 (4)	2.08 (4)	2.703 (3)	137 (4)
N4*A*—H4*A*···O2*A*^{iii}	0.79 (4)	2.36 (4)	3.014 (3)	141 (3)
N5*A*—H5*A*···O5*A*^{ii}	0.92 (4)	1.99 (4)	2.897 (3)	171 (3)
PROCAR (Molecule *B*)				
N4*B*—H4*B*···O2*B*	0.88 (4)	1.99 (4)	2.688 (3)	136 (3)
N4*B*—H4*B*···O2*B*^{iv}	0.88 (4)	2.33 (4)	3.039 (3)	138 (3)
N5*B*—H5*B*···O5*B*^{ii}	0.81 (4)	2.09 (4)	2.888 (3)	168 (4)

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

Reference: (*a*) Larsen (1990*b*).

All H-atom positions were located in a difference Fourier map after refinement of positional and anisotropic displacement parameters for the non-H atoms. The H atoms were refined as riding atoms, except for the H atoms bonded to N atoms. For these H atoms the positional parameters were refined. Each H atom was assigned an isotropic displacement parameter comparable to the displacement parameter of the non-H atom to which it is bonded. Residual density was located within 1 Å of the atom C7*A*.

Data reduction: *DREADD* (Blessing, 1987, 1989). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AB1290). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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