F12*B*	0.0934 (3)	0.00798 (7)	0.69008 (11)	0.0602 (6)
F12*C*	−0.1703 (3)	0.06753 (9)	0.68807 (14)	0.0767 (6)
O1	0.0256 (2)	0.19728 (7)	0.50993 (9)	0.0353 (5)
C1	0.4335 (3)	0.18852 (10)	0.48464 (13)	0.0287 (6)
C2	0.3772 (3)	0.13521 (10)	0.41179 (13)	0.0330 (7)
C3	0.2606 (4)	0.16724 (12)	0.32981 (14)	0.0407 (8)
C4	0.5603 (4)	0.09549 (12)	0.3906 (2)	0.0432 (8)
C5	0.2994 (3)	0.29063 (10)	0.60364 (13)	0.0285 (6)
C6	0.2047 (3)	0.35182 (10)	0.55021 (13)	0.0318 (7)
C7	0.3388 (4)	0.41538 (12)	0.5592 (2)	0.0463 (9)
C8	−0.0059 (4)	0.36907 (12)	0.5707 (2)	0.0421 (8)
C9	0.3021 (3)	0.14426 (10)	0.64856 (13)	0.0317 (7)
C10	0.1299 (4)	0.12763 (11)	0.7001 (2)	0.0397 (8)
C11	0.2065 (5)	0.1181 (2)	0.7973 (2)	0.0571 (12)
C12	0.0060 (4)	0.06599 (13)	0.6633 (2)	0.0494 (9)

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

O1—P1	1.447 (2)	C8—F8*B*	1.317 (3)
C1—P1	1.917 (2)	C8—F8*C*	1.323 (3)
C5—P1	1.913 (2)	C9—F9*A*	1.348 (2)
C9—P1	1.914 (2)	C9—F9*B*	1.347 (2)
C1—F1*A*	1.348 (2)	C10—F10	1.370 (3)
C1—F1*B*	1.350 (2)	C11—F11*A*	1.319 (4)
C2—F2	1.370 (3)	C11—F11*B*	1.323 (3)
C3—F3*A*	1.328 (3)	C11—F11*C*	1.324 (4)
C3—F3*B*	1.318 (3)	C12—F12*A*	1.325 (3)
C3—F3*C*	1.323 (3)	C12—F12*B*	1.326 (3)
C4—F4*A*	1.317 (3)	C12—F12*C*	1.318 (4)
C4—F4*B*	1.331 (3)	C2—C1	1.557 (3)
C4—F4*C*	1.312 (3)	C3—C2	1.546 (3)
C5—F5*A*	1.347 (2)	C4—C2	1.550 (4)
C5—F5*B*	1.349 (2)	C6—C5	1.552 (3)
C6—F6	1.371 (2)	C7—C6	1.542 (3)
C7—F7*A*	1.313 (3)	C8—C6	1.556 (3)
C7—F7*B*	1.318 (3)	C10—C9	1.556 (4)
C7—F7*C*	1.320 (3)	C11—C10	1.552 (4)
C8—F8*A*	1.318 (3)	C12—C10	1.540 (3
O1—P1—C1	116.76 (9)	C8—C6—F6	106.2 (2)
O1—P1—C5	116.50 (9)	C8—C6—C5	112.5 (2)
O1—P1—C9	116.20 (9)	F6—C6—C5	107.5 (2)
C1—P1—C5	101.82 (9)	F7*A*—C7—F7*B*	109.3 (2)
C1—P1—C9	101.88 (9)	F7*A*—C7—F7*C*	108.8 (2)
C5—P1—C9	101.19 (9)	F7*A*—C7—C6	110.8 (2)
C2—C1—P1	113.18 (14)	F7*B*—C7—F7*C*	107.5 (2)
C2—C1—F1*A*	110.4 (2)	F7*B*—C7—C6	109.8 (2)
C2—C1—F1*B*	108.4 (2)	F7*C*—C7—C6	110.6 (2)
P1—C1—F1*A*	107.45 (14)	F8*A*—C8—F8*B*	108.7 (2)
P1—C1—F1*B*	110.06 (14)	F8*A*—C8—F8*C*	108.7 (2)
F1*A*—C1—F1*B*	107.2 (2)	F8*A*—C8—C6	109.5 (2)
C3—C2—C4	111.1 (2)	F8*B*—C8—F8*C*	107.9 (2)
C3—C2—F2	107.5 (2)	F8*B*—C8—C6	111.5 (2)
C3—C2—C1	112.4 (2)	F8*C*—C8—C6	110.5 (2)
C4—C2—F2	106.3 (2)	C10—C9—P1	113.45 (15)
C4—C2—C1	112.0 (2)	C10—C9—F9*A*	108.1 (2)
F2—C2—C1	107.2 (2)	C10—C9—F9*B*	110.7 (2)
F3*A*—C3—F3*B*	108.1 (2)	P1—C9—F9*A*	109.69 (14)
F3*A*—C3—F3*C*	107.9 (2)	P1—C9—F9*B*	107.67 (13)
F3*A*—C3—C2	110.8 (2)	F9*A*—C9—F9*B*	107.0 (2)
F3*B*—C3—F3*C*	108.1 (2)	C11—C10—C12	111.3 (2)
F3*B*—C3—C2	109.8 (2)	C11—C10—F10	106.3 (2)
F3*C*—C3—C2	112.0 (2)	C11—C10—C9	111.4 (2)
F4*A*—C4—F4*B*	107.3 (2)	C12—C10—F10	107.1 (2)
F4*A*—C4—F4*C*	109.7 (2)	C12—C10—C9	112.6 (2)
F4*A*—C4—C2	110.2 (2)	F10—C10—C9	107.7 (2)
F4*B*—C4—F4*C*	108.5 (2)	F11*A*—C11—F11*B*	109.2 (2)
F4*B*—C4—C2	109.8 (2)	F11*A*—C11—F11*C*	108.2 (2)
F4*C*—C4—C2	111.1 (2)	F11*A*—C11—C10	111.0 (2)
C6—C5—P1	113.63 (13)	F11*B*—C11—F11*C*	107.8 (2)
C6—C5—F5*A*	110.1 (2)	F11*B*—C11—C10	110.3 (2)
C6—C5—F5*B*	108.7 (2)	F11*C*—C11—C10	110.3 (2)
P1—C5—F5*A*	107.39 (13)	F12*A*—C12—F12*B*	107.8 (2)
P1—C5—F5*B*	109.83 (13)	F12*A*—C12—F12*C*	107.8 (2)
F5*A*—C5—F5*B*	107.0 (2)	F12*A*—C12—C10	111.6 (2)
C7—C6—C8	111.1 (2)	F12*B*—C12—F12*C*	108.3 (2)
C7—C6—F6	106.7 (2)	F12*B*—C12—C10	110.9 (2)
C7—C6—C5	112.4 (2)	F12*C*—C12—C10	110.3 (2)

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Lists of structure factors and anisotropic thermal parameters, as well as a unit-cell packing diagram have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71092 (24 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: BR1029]

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Structure and Absolute Configuration of a High Affinity 5-HT$_3$ Receptor Antagonist, (5a*S*,9a*S*)-*N*-[(3*S*)-1-Azabicyclo[2.2.2]octan-3-yl]-2-chloro-5a,6,7,8,9,9a-hexahydro-4-dibenzofurancarboxamide Hydrochloride

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Abstract

The absolute configuration was established as (*S*,*S*,*S*) by the *R*-factor test and by careful measurement of

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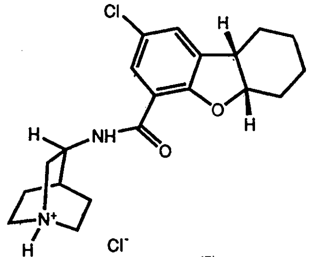
197 enantiomorph-sensitive Friedel pairs of reflections. The determination also confirms the absolute stereochemistry of (−)-3-aminoquinuclidine, a compound used in the preparation of the title material. The cyclohexane/tetrahydrofuran ring fusion is *cis*. The quinuclidine moiety has almost perfect threefold symmetry; the front and rear halves are twisted about this axis by 15°. Quinuclidine-N—H···Cl$^-$ and amide-N—H···Cl$^-$ hydrogen bonds link screw-dyad-related molecules along the *b* axis.

Comment

Nausea and vomiting frequently occur as side effects in the treatment of cancer with chemotherapy. Antagonists of the 5-HT$_3$ receptor have been shown to be effective against emesis in humans caused by chemotherapy or radiation (Carmichael, Cantwell, Edwards, Rappaport & Harris, 1988). The subject of this paper, compound (I), has been shown to be a potent 5-HT$_3$ antagonist and inhibitor of cytotoxic drug induced emesis in ferrets and dogs (Fitzpatrick, Lambert, Pendley, Martin, Bostwick, Gessner, Airey, Youssefyeh, Pendleton & Decktor, 1990; Youssefyeh, Campbell & Kuhla, 1990; Youssefyeh, Campbell, Klein, Airey, Darkes, Powers, Schnapper, Neuenschwander, Fitzpatrick, Pendley & Martin, 1992; Youssefyeh, Campbell, Airey, Klein, Schnapper, Powers, Woodward, Rodriguez, Golec, Studt, Dodson, Fitzpatrick, Pendley & Martin, 1992). The crystallographic analysis was performed to confirm the structure and determine the absolute configuration.



(I)

An *ORTEP* drawing of the molecule in the (*S*,*S*,*S*) configuration is shown in Fig. 1. The configuration was established in two ways. First, identical structure refinements of (*S*,*S*,*S*) and (*R*,*R*,*R*) models gave *wR* factors of 0.040 and 0.061, respectively, for 1668 reflections with $I > 3\sigma(I)$. The *R*-factor ratio test (Hamilton, 1964; *International Tables for X-ray Crystallography*, 1974, Vol. IV, Table 4.2) indicates that the (*S*,*S*,*S*) model is a superior fit to the data at better than the 99.9% confidence level. Second, the 197 Friedel reflection pairs predicted to be most sensitive to the absolute configuration {*i.e.* $2|F_c(R,R,R) - F_c(S,S,S)|/[F_c(R,R,R) + F_c(S,S,S)] > 0.02$} were carefully remeasured at $\pm 2\theta$. A structure-factor calculation with the (*S*,*S*,*S*) enantiomer showed that for 194 of the 197 pairs, $F_c(h,k,l)$ and $F_c(-h,-k,-l)$ had the same relative magnitudes as the corresponding experimental values $F_o(h,k,l)$ and $F_o(-h,-k,-l)$. It should be noted that this determination confirms the absolute configuration of (−)-3-aminoquinuclidine, a compound used in the preparation of (I), as (*S*).

Bond lengths and angles (Table 2) are normal. The benzene ring is planar with a 0.005 Å mean deviation from the six-atom least-squares plane. The out-of-plane deviations of the four substituents are O1 = −0.022, Cl2 = 0.071, C7 = −0.147 and C13 = 0.011 Å. The amide link between the quinuclidine and hexahydrodibenzofuran moieties has the typical *s-trans* conformation and the average deviation of the five atoms (C1, C13, C15, O2, N2) from the amide least-squares plane is 0.015 Å. There is a substantial twist between the amide and aromatic ring; the average C1—C13 torsion angle is 47.7 (3)°. The quinuclidine moiety has almost exact threefold symmetry about N1···C16, and the front and rear halves (N1, C14, C18, C19 and C16, C15, C17, C20) are twisted about this axis by approximately 15° with respect to each other. The dihydrofuran/cyclohexane ring fusion is *cis* (axial and equatorial) and the cyclohexane is only slightly distorted from a perfect chair geometry by this linkage.

A search of the Cambridge Structural Database update of June 1991, for crystal structures with the 3-aminoquinuclidine fragment located only one

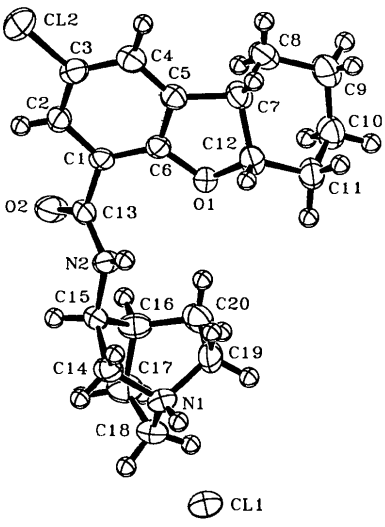


Fig. 1. *ORTEP*II drawing of (I). The C, O, N and Cl atoms are shown as 50% ellipsoids, and the H atoms are depicted as spheres with $B = 1.5$ Å^2.

entry, the anti-depressant drug quinupramine [10,11-dihydro-5-(3-quinuclidinyl)-5*H*-dibenzo[*b*,*f*]azepine (Reboul, Soyfer, Cristau, Caranoni & Pèpe, 1982)]. Similarly, a search for the hexahydrodibenzofuran moiety located 39 crystal structures, only three of which did not contain additional bridging or fused rings. Only one of the three, namely 8-chloromercuri-2-methoxy-*cis*-5a,6,7,8,9,9a-hexahydrodibenzofuran, (II) (Hosakawa, Miyagi, Murahashi, Sonoda, Matsuura, Tanimoto & Kakudo, 1978), does not possess additional substitution at either of the C atoms common to the dihydrofuran/cyclohexane fusion. The dihydrofuran/cyclohexane conformations are quite different in (I) and (II); in (I), the O1 and C5 cyclohexane substituents are axial and equatorial, respectively, whereas in (II) the corresponding atoms are best described as in equatorial and axial positions.

The structure is linked by $N^+—H\cdots Cl^-\cdots H—N$ hydrogen bonds along the screw dyad parallel to *b* (see Fig. 2). The Cl^- (x, y, z) interacts with the quinuclidinium H atoms (H1N, at x, y, z) at 2.27 (3) Å and the amide H atom (H2N) of the screw-dyad-related cation ($1-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$) at 2.43 (4) Å; the Cl^- (at $1-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$) associated with this cation is in turn linked to the amide H atom of a screw-dyad-related cation at x, $1+y$, z. Thus, ion pairs related by unit translation along *b* are bridged by an intervening screw-dyad-related ion pair. Other intermolecular distances are limited to van der Waals interactions.

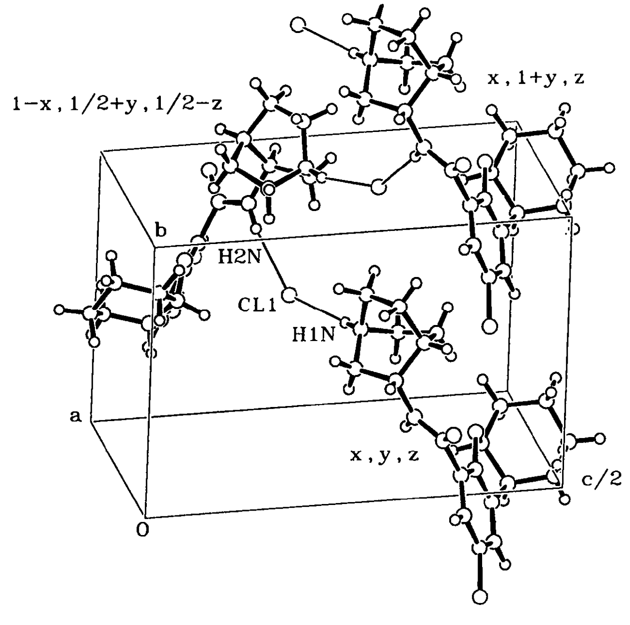


Fig. 2. *ORTEP*II ball-and-stick packing diagram for (I). The intermolecular $Cl^-\cdots H$ distances are given in the text.

Experimental

Crystal data

$C_{20}H_{26}ClN_2O_2^+.Cl^-$
$M_r = 397.34$
Orthorhombic
$P2_12_12_1$
$a = 7.4530$ (4) Å
$b = 9.5633$ (5) Å
$c = 27.831$ (3) Å
$V = 1983.7$ (4) Å^3
$Z = 4$
$D_x = 1.330$ Mg m^{-3}
Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å

Cell parameters from 25 reflections
$\theta = 7.9$–$25.4°$
$\mu = 3.08$ mm^{-1}
$T = 293$ K
Rectangular plate
0.43 × 0.26 × 0.06 mm
Colorless
Crystal source: acetonitrile solution

Data collection

Enraf-Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: *DIFABS*
$T_{min} = 1.213$, $T_{max} = 0.838$, $T_{av} = 0.982$
1797 measured reflections
1757 independent reflections
1668 observed reflections $[I > 3\sigma(I)]$

$\theta_{max} = 59.9°$
$h = 0 \rightarrow 8$
$k = -10 \rightarrow 0$
$l = 0 \rightarrow 31$
5 standard reflections
frequency: 60 min
intensity variation: −2.2 to 1.3, av. −0.5%

Refinement

Refinement on F $[1/\sigma^2(F_o)\Sigma(F_o-F_c)^2]$
Final $R = 0.030$
$wR = 0.040$
$S = 1.71$
1668 reflections
340 parameters
Coordinates of H atoms refined

$w = 1/\sigma^2(F_o)$
$\Delta\rho_{max} = 0.15$ e Å^{-3}
$\Delta\rho_{min} = -0.13$ e Å^{-3}
Extinction correction: Zachariasen
Extinction coefficient: $4.47 (6) \times 10^{-6}$

For the (*R*,*R*,*R*) configuration, final $R = 0.048$, $wR = 0.062$, $S = 2.67$, $(\Delta/\sigma)_{max} = 0.31$ and $\Delta\rho_{max} = 0.28$, $\Delta\rho_{min} = -0.30$ e Å^{-3}. For the structure-factor calculation with 394 *R*/*S*-sensitive data, $R[=\Sigma|F_o^2-F_c^2|/\Sigma(F_o^2+F_c^2)] = 0.052$ for the (*S*,*S*,*S*) configuration and 0.067 for the (*R*,*R*,*R*) configuration.

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

$$U_{eq} = \tfrac{1}{3}\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
Cl1	0.6679 (1)	0.5401 (1)	0.21041 (3)	4.01 (4)
Cl2	−0.3714 (1)	−0.2485 (1)	0.38019 (4)	4.92 (5)
O1	0.2078 (3)	0.1511 (2)	0.40830 (7)	2.88 (9)
O2	−0.2407 (3)	0.3109 (3)	0.3509 (1)	4.3 (1)
N1	0.3440 (4)	0.5113 (3)	0.2753 (1)	3.0 (1)
N2	0.0409 (4)	0.2832 (3)	0.3223 (1)	2.8 (1)
C1	−0.0830 (4)	0.1039 (3)	0.3721 (1)	2.4 (1)
C2	−0.2198 (5)	0.0048 (3)	0.3675 (1)	2.7 (1)
C3	−0.2031 (4)	−0.1248 (3)	0.3888 (1)	3.1 (1)
C4	−0.0546 (5)	−0.1609 (3)	0.4162 (1)	3.2 (1)
C5	0.0797 (4)	−0.0639 (3)	0.4214 (1)	2.8 (1)
C6	0.0644 (4)	0.0664 (3)	0.3990 (1)	2.5 (1)
C7	0.2480 (5)	−0.0613 (4)	0.4516 (1)	3.3 (1)
C8	0.2024 (6)	−0.0294 (5)	0.5039 (1)	4.4 (2)

C9	0.3599 (7)	0.0346 (5)	0.5309 (2)	5.1 (2)
C10	0.4217 (6)	0.1669 (4)	0.5066 (1)	4.1 (2)
C11	0.4841 (5)	0.1378 (5)	0.4560 (1)	3.7 (2)
C12	0.3506 (4)	0.0569 (4)	0.4258 (1)	3.2 (1)
C13	−0.1028 (4)	0.2435 (3)	0.3477 (1)	2.6 (1)
C14	0.1930 (5)	0.4209 (4)	0.2598 (1)	3.2 (2)
C15	0.0469 (4)	0.4195 (3)	0.2985 (1)	2.7 (1)
C16	0.0884 (5)	0.5388 (4)	0.3340 (1)	3.4 (1)
C17	0.1102 (6)	0.6718 (4)	0.3040 (2)	4.0 (2)
C18	0.2870 (5)	0.6613 (4)	0.2763 (1)	3.4 (2)
C19	0.4052 (5)	0.4670 (4)	0.3244 (1)	3.8 (2)
C20	0.2592 (7)	0.5070 (4)	0.3608 (1)	4.2 (2)

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

Cl2—C3	1.741 (3)	C5—C6	1.398 (4)
O1—C6	1.366 (4)	C5—C7	1.511 (5)
O1—C12	1.477 (4)	C7—C8	1.524 (5)
O2—C13	1.217 (4)	C7—C12	1.543 (5)
N1—C14	1.483 (5)	C8—C9	1.523 (6)
N1—C18	1.497 (4)	C9—C10	1.506 (6)
N1—C19	1.502 (5)	C10—C11	1.509 (5)
N2—C13	1.338 (4)	C11—C12	1.515 (5)
N2—C15	1.463 (4)	C14—C15	1.533 (5)
C1—C6	1.377 (4)	C15—C16	1.541 (5)
C1—C2	1.398 (4)	C16—C20	1.506 (6)
C1—C13	1.505 (4)	C16—C17	1.530 (5)
C2—C3	1.379 (4)	C17—C18	1.531 (6)
C3—C4	1.388 (5)	C19—C20	1.534 (6)
C4—C5	1.373 (5)		
C6—O1—C12	105.4 (2)	C9—C8—C7	112.3 (4)
C14—N1—C18	110.4 (3)	C10—C9—C8	110.6 (3)
C14—N1—C19	109.3 (3)	C9—C10—C11	110.9 (4)
C18—N1—C19	109.9 (3)	C10—C11—C12	114.2 (3)
C13—N2—C15	121.1 (3)	O1—C12—C11	110.2 (3)
C6—C1—C2	117.1 (3)	O1—C12—C7	104.1 (3)
C6—C1—C13	123.6 (3)	C11—C12—C7	116.2 (3)
C2—C1—C13	119.3 (3)	O2—C13—N2	124.3 (3)
C3—C2—C1	120.3 (3)	O2—C13—C1	121.4 (3)
C2—C3—C4	122.1 (3)	N2—C13—C1	114.3 (3)
C2—C3—Cl2	119.1 (2)	N1—C14—C15	109.8 (3)
C4—C3—Cl2	118.7 (2)	N2—C15—C14	110.4 (3)
C5—C4—C3	118.1 (3)	N2—C15—C16	112.1 (3)
C4—C5—C6	119.7 (3)	C14—C15—C16	107.6 (3)
C4—C5—C7	132.5 (3)	C20—C16—C17	110.3 (3)
C6—C5—C7	107.6 (3)	C20—C16—C15	109.7 (3)
O1—C6—C1	125.0 (3)	C17—C16—C15	106.7 (3)
O1—C6—C5	112.3 (3)	C16—C17—C18	108.2 (3)
C1—C6—C5	122.7 (3)	N1—C18—C17	108.4 (3)
C5—C7—C8	110.4 (3)	N1—C19—C20	108.3 (3)
C5—C7—C12	99.4 (2)	C16—C20—C19	108.9 (3)
C8—C7—C12	114.1 (3)		
O1—C12—C7—C5	31.9 (3)	N2—C13—C1—C2	−131.5 (3)
O1—C12—C7—C8	−85.7 (3)	N2—C13—C1—C6	48.1 (4)
O1—C12—C11—C10	78.7 (4)	O2—C13—C1—C2	47.3 (4)
C5—C7—C12—C11	153.2 (3)	O2—C13—C1—C6	−133.1 (3)
C5—C7—C8—C9	−155.6 (4)	O2—C13—N2—C15	4.5 (5)
C7—C8—C9—C10	57.8 (5)	C13—N2—C15—C14	−161.9 (3)
C7—C12—C11—C10	−39.4 (5)	C13—N2—C15—C16	78.2 (4)
C8—C7—C12—C11	35.7 (5)	N1—C14—C15—C16	13.2 (4)
C8—C9—C10—C11	−61.0 (5)	N1—C18—C17—C16	18.3 (4)
C9—C10—C11—C12	51.8 (5)	N1—C19—C20—C16	15.5 (4)

Source of (1): Dr John Airey, Rhône-Poulenc Rorer Central Research, Collegeville, PA. Data collection: Enraf-Nonius diffractometer software (version 5.0); θ-scan width of $1.5(0.75 + 0.14\tan\theta)^\circ$; scan recorded as 96 steps with two outermost 16-step blocks for background determination; scan speed 8.24-0.72° min^{-1}; scan speed 4.12-0.72° min^{-1} for remeasurement of 197 enantiomorph-sensitive data at $\pm 2\theta$. Atomic scattering factors and dispersion-correction factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV, Tables 2.2B and 2.3.1). All crystallographic calculations were performed with the *TEXSAN* program system (Molecular Structure Corporation, 1987) on Digital Equipment Corporation MicroVAX II and VAXStation II computers. The packing diagram (Fig. 2) was constructed with the *Chem-X* program (*Chem-X*, 1987) on an Evans and Sutherland PS-390 graphics system. Figs. 1 and 2 were drawn with the *ORTEP*II (Johnson, 1976) subprogram of the *TEXSAN* package; the *PLOTMD* program (Luo, Ammon & Gilliland, 1989) was used to display the drawings on a VAXStation monitor, add labels and prepare files for a Hewlett-Packard Laserjet II printer. Structure solution: *MITHRIL* (Gilmore, 1983) subprogram of *TEXSAN*. Absorption-correction software: *DIFABS* (Walker & Stuart, 1983) subprogram of *TEXSAN*.

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Lists of structure factors, structure factors for enantiomorph-sensitive Friedel pairs, anisotropic thermal parameters and H-atom coordinates and thermal parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71033 (23 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: CR1018]

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