C9—C10	1.503 (4)	C27—C28	1.363 (9)
C10—N11	1.506 (3)	C28—C29	1.399 (6)
N11—C12	1.507 (3)	C30—C31	1.383 (4)
N11—O15	1.395 (3)	C30—C35	1.394 (4)
N11—C16	1.502 (4)	C31—C32	1.382 (5)
C12—C13	1.498 (4)	C32—C33	1.355 (6)
C16—C17	1.529 (4)	C33—C34	1.379 (6)
C17—C18	1.562 (4)	C34—C35	1.367 (5)

Cl1—C2—C7	120.1 (2)	C17—C18—C30	107.0 (2)
Cl1—C2—C3	118.7 (2)	C17—C18—C24	105.7 (2)
C3—C2—C7	121.2 (3)	C17—C18—C19	107.7 (2)
C2—C3—C4	118.8 (3)	C24—C18—C30	114.5 (2)
C3—C4—C5	121.8 (3)	C19—C18—C30	113.4 (2)
C4—C5—C8	121.1 (2)	C19—C18—C24	108.1 (2)
C4—C5—C6	117.8 (2)	C18—C19—N21	121.3 (3)
C6—C5—C8	121.1 (2)	C18—C19—O20	119.4 (3)
C5—C6—C7	120.8 (3)	O20—C19—N21	119.3 (3)
C2—C7—C6	119.6 (3)	C19—N21—C23	126.7 (3)
C5—C8—O14	110.9 (2)	C19—N21—C22	118.1 (3)
C5—C8—C13	112.0 (2)	C22—N21—C23	115.2 (3)
C5—C8—C9	109.5 (2)	C18—C24—C29	123.1 (3)
C13—C8—O14	105.3 (2)	C18—C24—C25	118.9 (3)
C9—C8—O14	110.8 (2)	C25—C24—C29	118.0 (3)
C9—C8—C13	108.3 (2)	C24—C25—C26	122.1 (4)
C8—C9—C10	112.4 (2)	C25—C26—C27	119.4 (5)
C9—C10—N11	111.9 (2)	C26—C27—C28	119.9 (4)
C10—N11—C16	108.2 (2)	C27—C28—C29	120.4 (4)
C10—N11—O15	109.8 (2)	C24—C29—C28	120.3 (4)
C10—N11—C12	108.7 (2)	C18—C30—C35	119.5 (3)
O15—N11—C16	109.8 (2)	C18—C30—C31	123.3 (3)
C12—N11—C16	111.3 (2)	C31—C30—C35	116.6 (3)
C12—N11—O15	109.2 (2)	C30—C31—C32	121.4 (3)
N11—C12—C13	111.6 (2)	C31—C32—C33	120.9 (3)
C8—C13—C12	112.4 (2)	C32—C33—C34	118.8 (4)
N11—C16—C17	112.6 (2)	C33—C34—C35	120.6 (3)
C16—C17—C18	115.1 (2)	C30—C35—C34	121.7 (3)

C6—C5—C8—O14	14.8 (3)	C16—C17—C18—C19	−70.8 (3)
C5—C8—C9—C10	−175.4 (2)	C16—C17—C18—C24	173.8 (2)
O14—C8—C9—C10	61.9 (3)	C16—C17—C18—C30	51.4 (3)
C9—C10—N11—O15	61.5 (2)	C17—C18—C30—C31	−113.1 (3)
C9—C10—N11—C16	−178.7 (2)	C17—C18—C24—C29	−122.5 (3)
C10—N11—C16—C17	−170.8 (2)	C17—C18—C19—N21	−176.9 (3)
N11—C16—C17—C18	−156.1 (2)		

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O14—H14···O15^{i}	0.82	1.78	2.596 (2)	174
O36—H36···O14	1.14	1.72	2.831 (2)	165
O37—H37···O38	1.16	1.81	2.959 (9)	172
O38—H38*A*···O36	0.90	2.36	2.980 (9)	126
O38—H38*B*···O20^{i}	0.91	1.98	2.852 (8)	160
O39—H39*A*···O38	1.18	1.66	2.74 (1)	150
O39—H39*B*···O15^{ii}	1.20	1.57	2.755 (7)	168

Symmetry codes: (i) $\frac{1}{2} - x, y - \frac{1}{2}, \frac{3}{2} - z$; (ii) $1 - x, y - 1, \frac{3}{2} - z$.

The structure was solved using direct methods. Isotropic refinement and subsequent electron-density synthesis revealed five extra atomic peaks, two of which were at a special position. Although two positions are at a bonding distance of *ca* 1.40 Å and could represent a methanol molecule, the electron density in this region was finally assigned to two partially occupied H_2O molecules suggested by the hydrogen-bonding scheme. Based on the measured density, which indicates 2.25 molecules of H_2O in the asymmetric unit, and on the electron density, the O36–O40 atoms were included in the full-matrix least-squares anisotropic refinement (on F^2) with fixed site-occupation factors of 0.50, 0.25, 0.50, 0.50 and 0.50, respectively. The H atoms of the loperamide *N*-oxide molecule were positioned geometrically and allowed to ride on their parent atoms. The H atoms of the H_2O molecules were located from ΔF maps, except for those of O40 which could not be found.

Data collection: *XSCANS* (Siemens, 1994). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEX*2.1 (McArdle, 1994). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

The authors thank Dr Jan Tollenaere of the Janssen Research Foundation, Beerse, Belgium, for providing a sample of loperamide *N*-oxide

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: NA1244). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1996). C**52**, 2102–2105

2-Ethyl-3-(3-pyridyl)-5(2*H*)-isoxazolone

KARLA FRYDENVANG, LOTTE BREHM, ROBERTO DI BIASE† AND ERIK FALCH

PharmaBiotec Research Center, Department of Medicinal Chemistry, Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark. E-mail: karla@medchem.dfh.dk

(*Received 15 April 1996; accepted 13 May 1996*)

Abstract

The 3-isoxazoline ring in the title compound, $C_{10}H_{10}N_2O_2$, adopts a flattened envelope conformation. The interplanar angle between the two ring systems is 31.71 (5)°, but the connecting single bond may indicate a certain degree of conjugation. The crystal packing is

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† ERASMUS student from the University of Bologna, Italy.

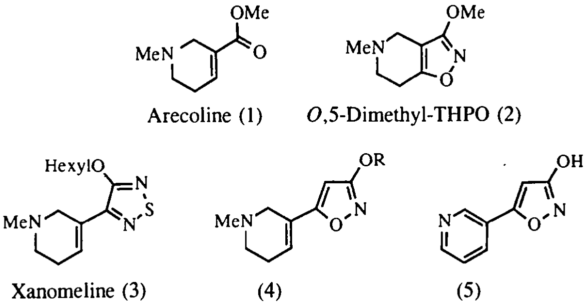
Acta Crystallographica Section C
ISSN 0108-2701 © 1996

stabilized by van der Waals interactions. Some close C—H···O contacts are observed, as well as stacking of the 3-isoxazoline ring system.

Comment

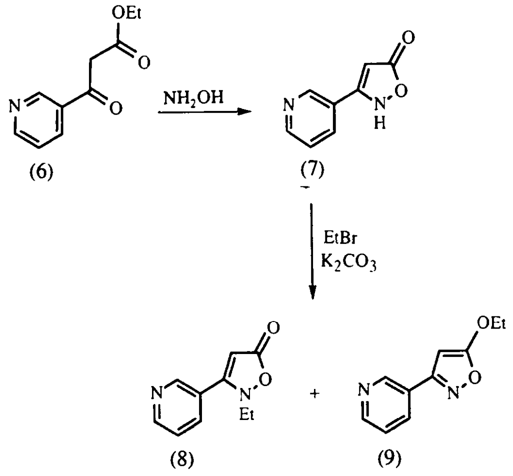
Alzheimer's disease (AD) is a progressive dementia resulting in severe memory loss and cognitive decline. The deficiencies in central cholinergic transmission (Bartus, Dean, Beer & Lippa, 1982; Sims *et al.*, 1983; Perry, 1988) observed in AD has stimulated interest in designing muscarinic acetylcholine receptor agonists.

Using arecoline [(1), Scheme I] as a lead structure, we have previously described a series of annelated bicyclic muscarinic agonists as exemplified by 3-methoxy-5-methyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine [*O*,5-dimethyl-THPO, (2)] utilizing the 3-alkoxyisoxazole as an ester bioisostere (Krogsgaard-Larsen *et al.*, 1988). More recently, the replacement of the ester functionality in arecoline (1) by five-membered-ring heterocycles has produced very potent muscarinic agonists (Sauerberg, Kindtler, Nielsen, Sheardown & Honoré, 1991; Ward *et al.*, 1992; Dunbar *et al.*, 1993), from which 3-(3-hexyloxy-1,2,5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine [xanomeline, (3)] was chosen for clinical development (Shannon *et al.*, 1994).



Scheme I

In order to further elucidate the effect of using 3-alkoxyisoxazoles as bioisosteres of ester groups, we wanted to synthesize 3-(3-alkoxyisoxazol-5-yl)-1,2,5,6-tetrahydro-1-methylpyridines, (4). The key intermediate in the syntheses of these compounds is 3-hydroxy-5-(3-pyridyl)isoxazole, (5). Attempts to synthesize compound (5) by treatment of the β-oxo ester (6) (Scheme II) with hydroxylamine, a general method (Jacobsen, Kolind-Andersen & Christensen, 1984), which normally produces a mixture of the 3-hydroxyisoxazole (5) and the isomeric isoxazolin-5-one (7), resulted in only one product. The objective of the present study was to confirm whether this sole product was compound (5) or compound (7). Because of difficulties in obtaining suitable crystals, the product was ethylated to give a chromatographically separable mixture of the *N*-ethylated (8) and *O*-ethylated (9) compounds. An X-ray analysis of the *N*-ethylated compound was carried out and the structure was determined to be the title compound, (8), thus confirming the structure of the product from the first step in the synthesis to be the isoxazolin-5-one isomer, (7). Recently, the desired isomer (5) has been synthesized by a method analogous to the published synthesis of 3-hydroxy-5-(4-pyridyl)isoxazole (Frølund *et al.*, 1995).



Scheme II

The molecular structure of (8) is shown in Fig. 1. The pyridine ring is planar and the bond lengths and angles are all within the expected ranges (Allen *et al.*, 1987). The 3-isoxazoline ring adopts a flattened N2-envelope conformation. The N2 and the exocyclic atoms O2, C6 and C12 show displacements of $\mp 0.080(2)$, $\mp 0.016(2)$, $\pm 0.004(2)$ and $\pm 0.695(3)$ Å, respectively, from the plane defined by the ring atoms O1, C3, C4 and C5. The N2 atom is pyramidal, being $\mp 0.340(1)$ Å out of the plane of its ligands, and the sum of the bond angles around it [342.9 (2)°] differs from 360°.

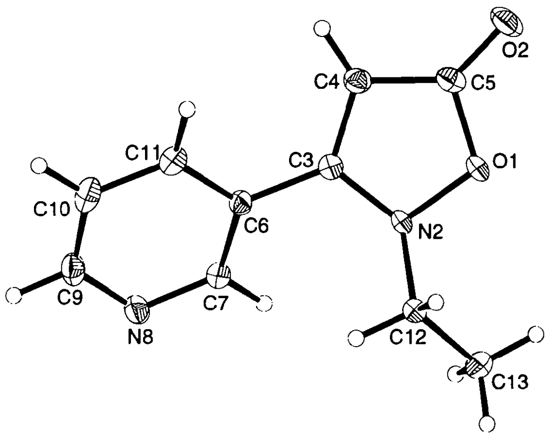


Fig. 1. A drawing (*ORTEP*II; Johnson, 1976) of the molecular structure of the title compound with the atom-labelling scheme for the non-H atoms. Displacement ellipsoids of the non-H atoms are drawn at the 50% probability level and H atoms are represented by spheres of arbitrary size.

The interplanar angle between the two rings is 31.71 (5)°. The C3—C6 bond length of 1.470 (2) Å may indicate a certain degree of conjugation between the two ring systems. The geometry of the 3-isoxazolin-5-one moiety agrees with previously determined values. The bond-length variation reflects the conjugated nature of the 3-isoxazolin-5-one moiety. A search of the Cambridge Structural Database (October 1995 release; Allen & Kennard, 1993) yielded nine structure determinations containing the 3-isoxazolin-5-one moiety (Refcodes: FOYXUM, JOBLER, JOKLOK, MPAIOA, MPIOXN, MPIOXZ10, PISXHZ, VOTXOR and YINDII). The substitution pattern of the 3-isoxazolin-5-one moiety for these structures is different and this influences the geometry of the ring system.

In the crystal packing, molecules are situated in puckered layers about the *n*-glide planes at **b** = 1/4 and 3/4 (Fig. 2). Within each layer, molecules related by a translation along the *a* axis and molecules related by an *n*-glide plane make close C—H···O contacts (Fig. 2 and Table 3; Berkovitch-Yellin & Leiserowitz, 1984; Desiraju & Kishan, 1989; Jeffrey & Saenger, 1991). The packing of the layers along the *b* axis is stabilized by a weak C—H···O contact between screw-axis-related molecules. The crystal structure is further stabilized by stacking of screw-axis-related isoxazolinone moieties [the interplanar angle is 16.68 (2)° and the average interplanar distance of 3.5 Å is equal to 1/2**b**].

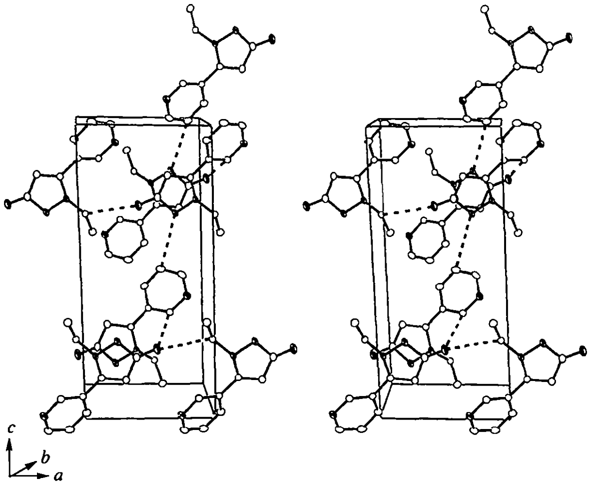


Fig. 2. Stereoscopic view (*ORTEP*II; Johnson, 1976) of the molecular packing of the unit cell viewed along the *b* axis, with horizontal *a* and vertical *c* axes. Close C—H···O contacts are illustrated with dashed lines. Displacement ellipsoids are shown at the 50% probability level and H atoms have been omitted for clarity.

Experimental

Compound (7) was synthesized as follows: a solution of hydroxylamine hydrochloride (1.39 g, 20 mmol) in NaOH (0.5 M, 20 ml) was cooled to 273 K and adjusted to pH 10 with 0.5 M NaOH. The pH of the reaction mixture was kept at 10.0±0.2 (monitored using a TTT80 combined with an ABU80 autoburette, both from Radiometer, Copenhagen), while compound (6) (Strong & McElvain, 1933) (3.86 g, 20 mmol) was added over 30 min. Stirring was continued for 30 min whereupon the mixture was poured into ice-cooled concentrated HCl (16 ml). The mixture was left at 278 K overnight after which time the precipitate was collected. The precipitate was dissolved in water (25 ml) and the pH adjusted to 4 with 1 M Na_2CO_3 in order to precipitate compound (7) (2.49 g, 77%). Recrystallization (70% aqueous EtOH) afforded pure (7); m.p. 430–431 K; ^{1}H NMR (60 MHz, DMSO-d_6) δ 8.95 (1H, *d*, *J* = 2 Hz), 8.75 (1H, *dd*, *J* = 1.5 and 5 Hz), 8.20 (1H, *dt*, *J* = 1.5 and 8 Hz), 7.60 (1H, *dd*, *J* = 5 and 8 Hz), 5.75 (*br*, *s*). Elemental analyses (C, H, N) were performed and the results were within ±0.4% of the calculated values. Compounds (8) and (9) were synthesized as follows: a mixture of (7) (811 mg, 5.00 mmol) and K_2CO_3 (1.38 g, 10 mmol) in dimethylformamide (10 ml) was stirred at 353 K for 1 h. Ethyl bromide (0.42 ml, 5.5 mmol) was added and the mixture was stirred at 323 K for 20 h. After evaporation, water (20 ml) was added to the residue and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined extracts were dried and evaporated and the residue was submitted to column chromatography [toluene/AcOEt (1:1)]. The first fractions contained compound (9) (450 mg, 47%). A sample was recrystallized (ether/light petroleum) to give (9); m.p. 351–352 K; 1H NMR (60 MHz, $CDCl_3$) δ 9.0 (1H, *m*), 8.7 (1H, *m*), 8.10 (1H, *dt*, *J* = 1.5 and 8 Hz), 7.45 (1H, *dd*, *J* = 5 and 8 Hz), 5.55 (1H, *s*), 4.40 (2H, *q*, *J* = 7 Hz), 1.45 (3H, *t*, *J* = 7 Hz). The latter fractions also contained compound (8) (240 mg, 25%). Recrystallization (AcOEt/light petroleum) gave (8); m.p. 366–368 K; ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.8 (2H, *m*), 7.85 (1H, *dt*, *J* = 1.5 and 8 Hz), 7.45 (1H, *dd*, *J* = 5 and 8 Hz), 5.45 (1H, *s*), 3.60 (2H, *q*, *J* = 7 Hz), 1.20 (3H, *t*, *J* = 7 Hz). Elemental analyses (C, H, N) were performed and the results were within ±0.4% of the calculated values.

Crystal data

$C_{10}H_{10}N_2O_2$
M_r = 190.20
Monoclinic
$P2_1/n$
a = 7.571 (1) Å
b = 7.1610 (7) Å
c = 16.535 (2) Å
β = 91.81 (1)°
V = 896.0 (2) Å^3
Z = 4
D_x = 1.410 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54184 Å
Cell parameters from 18 reflections
θ = 33.99–42.94°
μ = 0.830 mm^{-1}
T = 111 (2) K
Prism
0.25 × 0.25 × 0.10 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
4033 measured reflections
1838 independent reflections
1658 observed reflections [$I > 2\sigma(I)$]
$R_{\rm int}$ = 0.0118

$\theta_{\rm max}$ = 74.61°
$h = -9 \rightarrow 9$
$k = 0 \rightarrow 8$
$l = 0 \rightarrow 20$
3 standard reflections monitored every 300 reflections
frequency: 166 min
intensity increase: 3.8% (corrected)

Refinement

Refinement on F^2
$R(F) = 0.0371$
$wR(F^2) = 0.1065$
$S = 1.071$
1834 reflections
157 parameters
Only coordinates of H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.0557P)^2 + 0.3763P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.299$ e Å^{-3}
$\Delta\rho_{\min} = -0.300$ 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}
O1	0.2471 (1)	0.0826 (1)	0.18706 (5)	0.0183 (2)
N2	0.4084 (1)	0.0772 (2)	0.23301 (6)	0.0161 (2)
C3	0.3691 (2)	0.1160 (2)	0.31162 (7)	0.0145 (3)
C4	0.1910 (2)	0.1278 (2)	0.31949 (8)	0.0183 (3)
C5	0.1102 (2)	0.1083 (2)	0.24081 (8)	0.0185 (3)
O2	−0.0409 (1)	0.1056 (1)	0.21404 (6)	0.0266 (2)
C6	0.5094 (2)	0.1285 (2)	0.37490 (7)	0.0146 (3)
C7	0.6657 (2)	0.0264 (2)	0.37072 (7)	0.0172 (3)
N8	0.7956 (1)	0.0314 (2)	0.42752 (6)	0.0202 (2)
C9	0.7699 (2)	0.1394 (2)	0.49220 (7)	0.0211 (3)
C10	0.6173 (2)	0.2430 (2)	0.50325 (7)	0.0218 (3)
C11	0.4850 (2)	0.2384 (2)	0.44335 (7)	0.0188 (3)
C12	0.5497 (2)	0.1639 (2)	0.18728 (7)	0.0162 (3)
C13	0.6002 (2)	0.0407 (2)	0.11723 (8)	0.0221 (3)

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

O1—N2	1.418 (1)	C7—N8	1.339 (2)
N2—C3	1.371 (2)	N8—C9	1.339 (2)
C3—C4	1.362 (2)	C9—C10	1.390 (2)
C4—C5	1.427 (2)	C10—C11	1.386 (2)
O1—C5	1.399 (2)	C11—C6	1.395 (2)
O2—C5	1.214 (2)	N2—C12	1.467 (2)
C3—C6	1.470 (2)	C12—C13	1.514 (2)
C6—C7	1.395 (2)		
C5—O1—N2	107.82 (8)	C3—C6—C11	120.0 (1)
O1—N2—C3	107.05 (9)	C7—C6—C11	118.0 (1)
N2—C3—C4	110.4 (1)	C6—C7—N8	123.8 (1)
C3—C4—C5	107.7 (1)	C7—N8—C9	117.0 (1)
C4—C5—O1	106.7 (1)	N8—C9—C10	123.8 (1)
O2—C5—O1	118.4 (1)	C9—C10—C11	118.6 (1)
O2—C5—C4	134.9 (1)	C10—C11—C6	118.8 (1)
N2—C3—C6	120.9 (1)	O1—N2—C12	109.97 (9)
C4—C3—C6	128.6 (1)	C3—N2—C12	125.9 (1)
C3—C6—C7	121.9 (1)	N2—C12—C13	110.7 (1)
O1—N2—C3—C4	5.9 (1)	C5—O1—N2—C3	−5.3 (1)
N2—C3—C4—C5	−4.1 (1)	O1—N2—C12—C13	−71.4 (1)
C3—C4—C5—O1	0.7 (1)	C4—C3—C6—C11	−30.8 (2)
C4—C5—O1—N2	2.9 (1)	N2—C3—C6—C7	−29.5 (2)

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
C10—H10···O1^{i}	0.96 (2)	2.56 (2)	3.402 (2)	146 (2)
C12—H122···O2^{ii}	0.98 (2)	2.43 (2)	3.145 (1)	129 (2)
C7—H7···O2^{iii}	0.98 (2)	2.71 (2)	3.443 (2)	132 (2)

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

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989). Cell refinement: *CAD*-4 *Software*. 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).

This work was supported by grants from the Danish State Biotechnology Programme (1991/1995), the Alfred Benzon Foundation, the Lundbeck Foundation and the Danish Natural Science Research Council. The assistances of Mr F. Hansen with the X-ray data collection and of Mrs T. Lindgreen with the syntheses are gratefully acknowledged.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry, torsion angles and REFCODE references have been deposited with the IUCr (Reference: AB1380). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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