*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)] = 0.042$
$wR(F^2) = 0.124$
$S = 1.062$
4159 reflections
326 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0631P)^2 + 0.4764P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.003$
$\Delta\rho_{max} = 0.189$ e Å$^{-3}$
$\Delta\rho_{min} = -0.173$ e Å$^{-3}$
Extinction correction: *SHELXTL* (Sheldrick, 1998)
Extinction coefficient: 0.0067 (4)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Data collections were carried out on Bruker *P*4 or Bruker CCD X-ray diffractometers. In the case of the CCD instrument, data were collected by the double-pass method. The first 50 frames of data were recollected at the end of data collection to monitor crystal decay. Corrections to the data for systematic errors were applied using *SADABS* (Blessing, 1995). H atoms were treated using appropriate riding models (*AFIX* = *m*3 in *SHELXTL*).

For (2*a*), (2*b*) and (3*d*), data collection: *XSCANS* (Siemens, 1994). For (2*c*), data collection: *SMART* (Siemens, 1997). For (2*a*), (2*b*) and (3*d*), cell refinement: *XSCANS*. For (2*c*), cell refinement: *SAINT*. For (2*a*), (2*b*) and (3*d*), data reduction: *XSCANS*. For (2*c*), data reduction: *SAINT*. For all compounds, program(s) used to solve structure: *SHELXTL* (Sheldrick, 1998); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DA1047). Services for accessing these data are described at the back of the journal.

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# Intermolecular N—H···O and C—H···O interactions form a two-dimensional network in (2*S*,4*S*,5*R*)-(−)-3,4-dimethyl-5-phenyl-2-(pyrrol-2-yl)-1,3-oxazolidine

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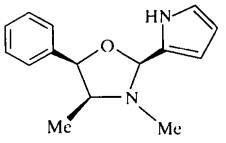
## Abstract

The title compound, $C_{15}H_{18}N_2O$, prepared from (1*R*,2*S*)-(−)-ephedrine, crystallizes in space group *P*1 with two molecules in the asymmetric unit. The oxazolidine rings of the two molecules adopt an envelope conformation, with the N atom 0.609 (6) and 0.623 (6) Å from the plane of the other four oxazolidine ring atoms. Intermolecular $N_{pyrrole}$—H···O and $C_{phenyl}$—H···O interactions generate a two-dimensional hydrogen-bonded network with N···O and C···O distances of 3.004 (4) and 3.051 (4) Å, respectively, and 3.599 (5) and 3.632 (5) Å, respectively, for the two independent hydrogen-bonding systems.

## Comment

Structural and reactivity studies of biologically active molecules are central to medicinal chemistry. Of primary importance is the synthesis of new drugs based on modified amino acids incorporating structural features which regulate normal guest–host interactions. The general principles underlying recognition processes are reasonably well understood and hydrogen-bonding in crystal structures can usually be rationalized in preferred combinations of hydrogen-bond donors and acceptors (Etter *et al.*, 1990). However, in molecules where different potential hydrogen-bond donors and acceptors are present (with cooperativity among these interactions), the ability to deduce in advance the molecular packing arrangements in the crystal structure remains an unrealised vision (Wolff, 1996).

Pyrrole derivatives have been the subject of intensive research, both in porphyrin and molecular recognition chemistry. In general, N—H donor groups can readily form hydrogen bonds with O atoms (Scherer *et al.*, 1998), N atoms (Gallagher *et al.*, 1998) and halide anions when these acceptors are available (Allen *et al.*, 1991; Beer, 1998). Reports on N—H···$\pi$ hydrogen bonds include aliphatic N—H donors to conventional aromatic acceptors, *e.g.* phenyl rings (Allen *et al.*, 1997; Starikov & Steiner, 1998). Atypical heteroaromatic N—H donors with $\pi$ acceptor systems have been described recently (Lin *et al.*, 1996; Goddard *et al.*, 1997; Bennis & Gallagher, 1998) where pyrrole groups participate both as N—H donor and $\pi_{pyrrole}$ acceptor groups. The title compound, (I), a pyrrole derivative, is of interest in hydrogen-bonding studies for an understanding of the role which pyrrole groups play in molecular recognition processes.




(I)

Compound (I) crystallizes in space group $P1$ with two independent molecules, *A* and *B*, which differ slightly in conformation but retain the same 2*S*,4*S*,5*R* configuration in the oxazolidine ring. The r.m.s. deviation for the superposition of the non-H atoms in both molecules is 0.26 Å (Spek, 1998). The absolute structure can be deduced from the known absolute configuration of the (1*R*,2*S*)-(−)-ephedrine used in the synthesis. Views of the two molecules are given in Fig. 1, with the atomic numbering schemes. Bond lengths and angles are unexceptional and in accord with anticipated values (Orpen *et al.*, 1994). The oxazolidine rings adopt an envelope conformation with N3 0.623 (6) and 0.609 (6) Å from the O1/C2/C4/C5 plane, which is at angles of 74.07 (15) and 72.43 (15)° to the phenyl and 89.52 (17) and 88.79 (17)° to the pyrrole rings, in molecules *A* and *B*, respectively. The phenyl rings are oriented at angles of 30.3 (2) and 27.1 (2)° to their respective pyrrole groups, in molecules *A* and *B*, respectively. Torsion angle differences are evident from O1—C2—C6—C7, which are −99.8 (5) and −105.0 (4)° in *A* and *B*, respectively (Table 1). The molecular geometry of (I) compares with the four independent molecules in (2*S*,4*S*,5*R*)-(−)-2-(1*H*-imidazol-2-yl)-3,4-dimethyl-5-phenyl-1,3-oxazolidine, (II) (Gallagher *et al.*, 1998), (2*S*,4*S*,5*R*)-(−)-2-(1,3-thiazol-2-yl)-3,4-dimethyl-5-phenyl-1,3-oxazolidine, (III) (Fitzsimons & Gallagher, 1999) and a *p*-bromophenyl derivative (Just *et al.*, 1983).

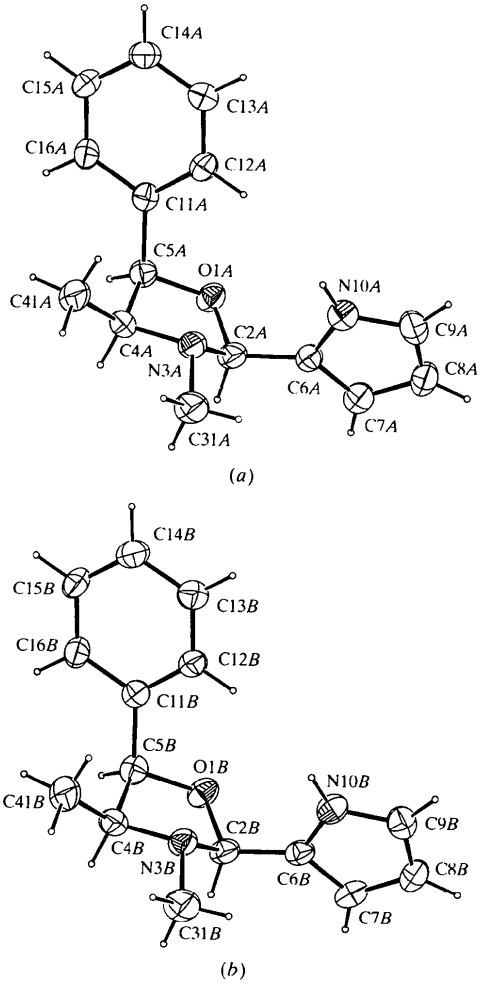



Fig. 1. View of (*a*) molecule *A* and (*b*) molecule *B* of the title compound, with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of an arbitrary radius.

There are two primary interactions present in the crystal structure of (I). Two independent intermolecular $N_{pyrrole}$—H···O hydrogen bonds form two distinct

one-dimensional chains in the *a* direction, with N···O distances of 3.051 (4) and 3.004 (4) Å along the *A* and *B* chains, respectively. Inter-chain $C_{arene}$—H···O interactions of 3.599 (5) and 3.632 (5) Å generate a two-dimensional network in the *c* direction, as depicted in Fig. 2. Further details are given in Table 2. The intermolecular H···O···H angles are 76 and 74° at O1*A* and O1*B*, respectively; the presence of weak C—H···O interactions in crystal structures has been commented on previously (Steiner, 1997). The hydrogen bonding in (I) contrasts with the imidazole derivative, (II), where N—H···N hydrogen bonds, $Csp^3$—H···$\pi_{C=C(imidazole)}$, $C_{arene}$—H···$\pi_{arene}$ and $C_{arene}$—H···O interactions generate a three-dimensional network (Gallagher *et al.*, 1998). A two-dimensional network is present in the thiazole derivative, (III), arising from C—H···N and C—H···O interactions (Fitzsimons & Gallagher, 1999). The variations in hydrogen bonding between (I) (which has an excess of donors), (II) and (III) (which has an excess of acceptors) can be rationalized in terms of the sequential replacement of potential C—H donor groups by N, and N—H acceptors by S, along the series, with (II) having the optimum number of donors and acceptors.

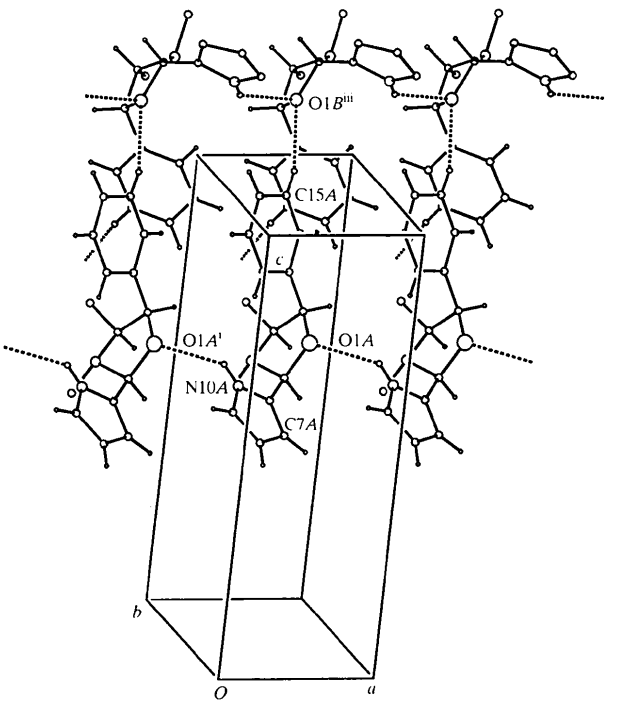



Fig. 2. A view of the intermolecular interactions in the crystal structure of (I). The methyl-H atoms and the H atoms of the pyrrole-C atoms of molecule *B* have been removed for clarity. Symmetry codes (i) and (iii) are as given in Table 2.

Analysis of pyrrole derivatives in the Cambridge Structural Database shows that the vast majority of this class of compound exhibit N—H···*X* (*X* = O, S, N or halide) hydrogen bonding (Allen *et al.*, 1991), where a suitable acceptor atom *X* is available to take part in the hydrogen bonding. In (I), an O atom facilitates N—H···O hydrogen bonding. In contrast, the presence of unusual $N_{pyrrole}$—H···$\pi_{pyrrole}$ hydrogen bonding has thus far only been noted in crystal structures where stronger acceptors are absent (Lin *et al.*, 1996; Goddard *et al.*, 1997; Bennis & Gallagher, 1998). Further comparative studies are in progress on related systems.

## Experimental

The title compound was prepared by refluxing pyrrole-2-carboxaldehyde (0.5 g, 5.25 mmol) and (1*R*,2*S*)-(−)-ephedrine (0.867 g, 5.25 mmol) in 20 ml of acetonitrile for 4 h. On cooling, the product was filtered and recrystallized from ethanol (yield 1.05 g, 83%; m.p. 398–400 K). An alternative synthesis has been reported by Davies *et al.* (1998). Spectroscopic data: IR [$\nu_{max}$(KBr), $cm^{-1}$]: 3371 (*s*, *br*), 3000 (*s*), 2789 (*s*), 1580 (*m*), 1449 (*m*), 1346 (*m*), 1220 (*m*), 1180 (*m*), 1025 (*s*), 738 (*s*); $[D]_\alpha^{20}$ = −45° (0.0238 g $cm^{-3}$, chloroform); $^1$H NMR data ($\delta$, $CDCl_3$, 400 MHz, p.p.m.): 0.77 (*d*, 3H, $CCH_3$), 2.21 (*s*, 3H, $NCH_3$), 2.95 (*m*, 1H, MeCH), 4.84 [*s*, 1H, OC(N)H], 5.11 (*d*, 1H, PhCH), 6.21 (*m*, 1H, $CH_{pyrrole}$), 6.37 (*s*, *br*, 1H, $CH_{pyrrole}$), 6.86 (*s*, *br*, 1H, $CH_{pyrrole}$), 7.26–7.38 (*m*, 5H, $C_6H_5$), 8.76 (*s*, *br*, NH).

*Crystal data*

$C_{15}H_{18}N_2O$
$M_r$ = 242.31
Triclinic
*P*1
*a* = 5.2624 (9) Å
*b* = 8.8737 (14) Å
*c* = 14.518 (3) Å
α = 82.455 (15)°
β = 85.847 (18)°
γ = 89.393 (12)°
*V* = 670.3 (2) Å$^3$
*Z* = 2
$D_x$ = 1.201 Mg $m^{-3}$
$D_m$ not measured

Mo *K*α radiation
λ = 0.7107 Å
Cell parameters from 25 reflections
θ = 7.91–18.64°
μ = 0.076 $mm^{-1}$
*T* = 290 (1) K
Block
0.35 × 0.28 × 0.25 mm
Colourless

*Data collection*

Enraf–Nonius CAD-4 diffractometer
ω scans
Absorption correction: none
3921 measured reflections
3735 independent reflections
2687 reflections with $I > 2\sigma(I)$

$R_{int}$ = 0.005
$\theta_{max}$ = 25.4°
*h* = −5 → 6
*k* = −10 → 10
*l* = −17 → 17
3 standard reflections
frequency: 120 min
intensity decay: none

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.137
*S* = 1.004
3735 reflections
330 parameters
H atoms: see below

$\Delta\rho_{max}$ = 0.19 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.22 e Å$^{-3}$
Extinction correction: *SHELXL*97 (Sheldrick, 1997*a*)
Extinction coefficient: 0.028 (6)

$w = 1/[\sigma^2(F_o^2) + (0.0891P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$

Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected torsion angles (°)*

| | | | |
|---|---|---|---|
| N3A—C2A—C6A—C7A | 142.6 (4) | N3B—C2B—C6B—C7B | 137.2 (4) |
| O1A—C2A—C6A—C7A | −99.8 (5) | O1B—C2B—C6B—C7B | −105.0 (4) |

Table 2. *Hydrogen-bonding geometry (Å, °)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N10A—H10A···O1A$^{i}$ | 0.86 | 2.36 | 3.051 (4) | 138 |
| N10B—H10B···O1B$^{ii}$ | 0.86 | 2.34 | 3.004 (4) | 134 |
| C15A—H15A···O1B$^{iii}$ | 0.93 | 2.70 | 3.599 (5) | 163 |
| C15B—H15B···O1A$^{iv}$ | 0.93 | 2.73 | 3.632 (5) | 164 |

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

H atoms were treated as riding (N—H 0.86 and C—H 0.93–0.98 Å). At an intermediate stage in the analysis, the site occupancies of the atom pairs N10*A*/C7*A* and N10*B*/C7*B* were allowed to vary in order to check for possible N/C disorder; the occupancy factors obtained did not differ significantly from unity and therefore, in the final refinement cycles, no N/C disorder was allowed for. The anomalous dispersion terms for O, N, C are small and the absolute structure was not determined by our X-ray analysis. However, it can be inferred from the known absolute configuration of the (1*R*,2*S*)-(−)-ephedrine starting material used in the synthesis and the structure of a related thiazole derivative (Fitzsimons & Gallagher, 1999).

Data collection: *CAD-4-PC Software* (Enraf–Nonius, 1992). Cell refinement: *SET*4 and *CELDIM* in *CAD-4-PC Software*. Data reduction: *DATRD*2 in *NRCVAX*96 (Gabe *et al.*, 1989). Program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997*b*). Program(s) used to refine structure: *NRCVAX*96 and *SHELXL*97 (Sheldrick, 1997*a*). Molecular graphics: *NRCVAX*96, *ORTEP*II (Johnson, 1976) and *PLATON* (Spek, 1998). Software used to prepare material for publication: *NRCVAX*96, *SHELXL*97 and *PREP*8 (Ferguson, 1998).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1298). Services for accessing these data are described at the back of the journal.

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# X-ray investigations of potential β-blockers. IV

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## Abstract

X-ray studies of 6,7-dihydroxy-1-(2-methoxypropyl)-1,2,3,4-tetrahydroisoquinolinium chloride hydrate, $C_{13}H_{20}NO_3^+ \cdot Cl^- \cdot H_2O$, show that the saturated part of the rings has a deformed half-chair conformation, with an axially attached 2-methoxypropyl group. The structure is ionic with a net of hydrogen bonds.