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A second polymorph of carvedilol

H. S. Yathirajan,[a] S. Bindya,[a] T. V. Sreevidya,[b] B. Narayana[b] and Michael Bolte[c]*

[a]Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India, [b]Department of Chemistry, Mangalore University, Mangalagangotri 574 199, India, and [c]Institut für Anorganische Chemie, J. W. Goethe-Universität Frankfurt, Max-von-Laue-Strasse 7, 60438 Frankfurt/Main, Germany

Correspondence e-mail: bolte@chemie.uni-frankfurt.de

Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.002 Å
R factor = 0.040
wR factor = 0.106
Data-to-parameter ratio = 13.9

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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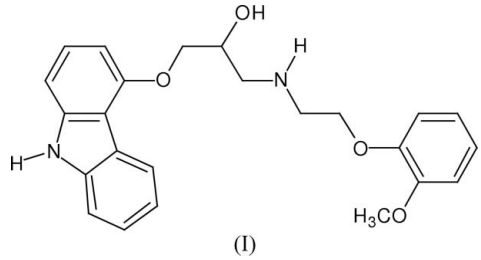
A second polymorph of the title compound [systematic name: 1-(9*H*-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol], $C_{24}H_{26}N_2O_4$, is described. The other polymorph [Chen, Zeng, Yu & Xu (1998). *Jiegou Huaxue (Chin. J. Struct. Chem.)*, **17**, 325–328] also crystallizes in the space group $P2_1/c$, but differs in two torsion angles of the chain connecting the aromatic residues. On the other hand, the hydrogen-bond patterns of the two polymorphs are rather similar.

Comment

Carvedilol, $C_{24}H_{26}N_2O_4$, is a non-selective β-adrenergic blocking agent with α1-blocking activity indicated for the treatment of congestive heart failure (CHF). It is the first β-blocker labelled in the United States especially for the treatment of heart failure of ischemic or cardiomyopathic origin with significant antioxidant activity (Ruffolo *et al.*, 1990; Feuerstein *et al.*, 1995; Zeng *et al.*, 2003).



(I)

The crystal structure of carvedilol was described in space group $P2_1/c$ (Chen *et al.*, 1998). We now report a second polymorph of carvedilol, (I) (Fig. 1), in the same space group, which differs in two key torsion angles. The bond lengths and angles for (I) can be regarded as normal (Cambridge Structural Database, Version 5.27, November 2005, updated August 2006; Mogul Version 1.1; Allen, 2002). The structure of (I) shows several significant differences from the already known (Chen *et al.*, 1998) polymorph, (II). Although both structures are monoclinic and crystallize in the same space group, the cell parameters are completely different [for (II), a = 9.094 (1) Å, b = 12.754 (1) Å, c = 18.330 (2) Å and β = 97.36 (1)°]. The molecular conformations of (I) and (II) are totally different, but a closer look reveals that only two torsion angles are in fact responsible for this difference (Table 1). Whereas the conformation about the C2—C3 bond is antiperiplanar in (I), it is synclinal in (II), and the conformation about O8—C81 is anticlinal in (I) but synclinal in (II). A least-squares fit (Fig. 2) of the matching torsion angles (*i.e.* fitting the chain from C2 to

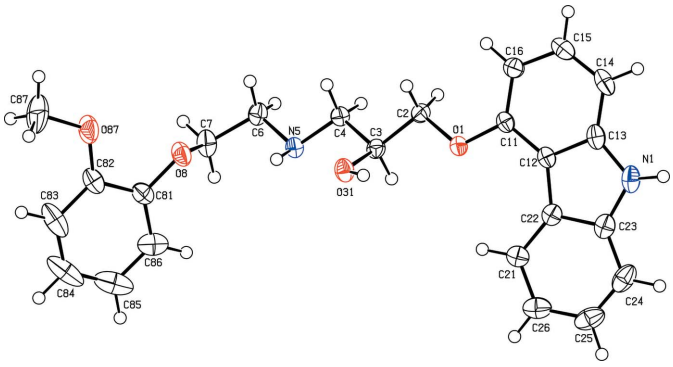


Figure 1
The molecular structure of (I), showing 50% probability displacement ellipsoids (arbitrary spheres for the H atoms).

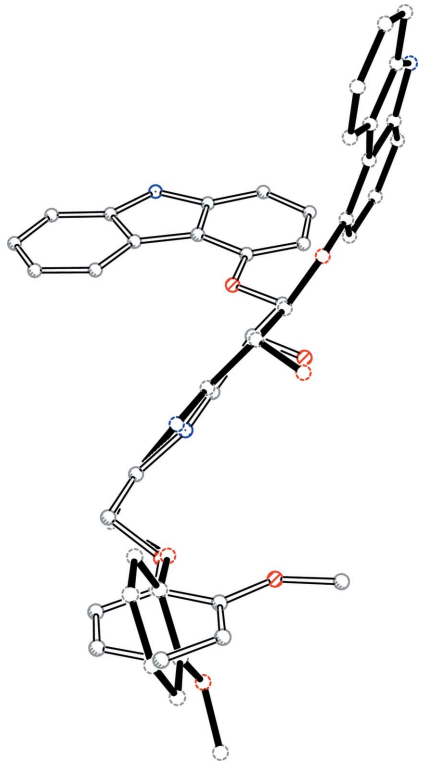


Figure 2
Least-squares overlap of the main backbones of (I) (full bonds) and (II) (open bonds).

O8; r.m.s. deviation = 0.134 Å) shows the similarities and differences of (I) and (II).

Nevertheless, the two classical hydrogen bonds in (I) are also present in (II) (Tables 2 and 3). The carbazole N atom forms an intermolecular hydrogen bond to the methoxy O atom O87 and the hydroxyl group forms an intermolecular hydrogen bond to the amino N atom. However, whereas it is a 2_1 screw axis that generates the second molecule for the N_c—H···O (c = carbazole) hydrogen bond in (I) and (II), the symmetry operation for generating the second molecule for the O—H···N hydrogen bond is a *c*-glide plane in (I), but an inversion centre in (II). The amino H atom has close contacts to the hydroxyl O atom and the ether O atom (Tables 2 and 3), but the H···O distances are rather long and the N—H···O angles are rather small.

Experimental

Carvedilol was obtained as a gift sample from Cadila Pharmaceuticals, Gujarat, India. X-ray quality crystals of (I) were obtained from toluene by slow evaporation (m.p. 385–387 K).

Crystal data

$C_{24}H_{26}N_2O_4$
M_r = 406.47
Monoclinic, $P2_1/c$
a = 15.5414 (14) Å
b = 15.2050 (12) Å
c = 9.1174 (8) Å
β = 100.730 (7)°
V = 2116.8 (3) Å^3
Z = 4
D_x = 1.275 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 173 (2) K
Block, colourless
0.36 × 0.33 × 0.32 mm

Data collection

Stoe IPDS-II two-circle diffractometer
ω scans
Absorption correction: none
12521 measured reflections
3956 independent reflections
3060 reflections with $I > 2\sigma(I)$
R_{int} = 0.034
θ_{max} = 25.7°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.106
S = 1.03
3956 reflections
285 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0583P)^2 + 0.3118P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0127 (14)

Table 1
Selected torsion angles (°) for (I) and (II).

	(I)	(II)
C12—C11—O1—C2	164.14 (11)	−175.2
C11—O1—C2—C3	−173.50 (11)	177.2
O1—C2—C3—C4	170.44 (11)	59.2
C2—C3—C4—N5	178.21 (12)	175.0
C4—N5—C6—C7	169.95 (12)	167.3
C6—C7—O8—C81	161.69 (13)	159.8
C7—O8—C81—C82	129.41 (15)	−150.7

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O31—H31···N5^{i}	0.92 (2)	2.09 (2)	2.9633 (16)	158 (2)
N1—H1···O87^{ii}	0.94 (2)	2.11 (2)	3.0336 (19)	167.4 (18)
N5—H5···O8	0.910 (19)	2.456 (18)	2.8619 (17)	107.3 (13)
N5—H5···O31	0.910 (19)	2.443 (17)	2.8198 (17)	105.0 (13)

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

Table 3
Hydrogen bond parameters for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O—H···N^{iii}	1.14	1.73	2.837	173
$N_{carbazole}$—H···O^{iv}	0.90	2.35	3.193	156
N_{amino}—H···O_{ether}	0.90	2.48	2.828	103
N_{amino}—H···$O_{hydroxyl}$	0.90	2.70	2.872	92

The geometrical values for the O—H···N bond were taken from the original publication. The other values were determined by us with H atoms placed in calculated positions. Symmetry codes: (iii) $1-x, -y, -z$; (iv) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$.

The H atoms were found in a difference map. Those bonded to C were relocated in idealized locations (C—H = 0.95–1.00 Å) and refined as riding with U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(methyl C). The positions and U_{iso} values for the H atoms bonded to N and O were freely refined.

Data collection: *X-AREA* (Stoe & Cie, 2001); cell refinement: *X-AREA*; data reduction: *X-AREA*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003) and *XP* in *SHELXTL-Plus* (Sheldrick, 1991); software used to prepare material for publication: *PLATON* and *SHELXL97*.

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