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Two stereoisomers of the rat toxicant norbormide

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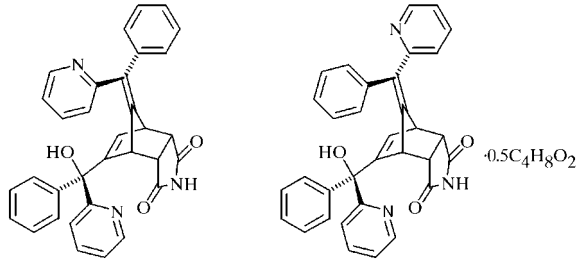
The structures of two diastereoisomers of norbormide {systematic name: 5-[hydroxy(phenyl)(2-pyridyl)methyl]-8-[phenyl(2-pyridyl)methylene]-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione}, *viz*. the unsolvated molecule, $C_{33}H_{25}N_3O_3$, and the ethyl acetate hemisolvate, $C_{33}H_{25}N_3O_3{\cdot}0.5C_4H_8O_2$, have been determined unambiguously. They differ in the relative stereochemistry about the exocyclic double bond and the relative conformations of the aryl rings. Each compound exhibits both intra- and intermolecular hydrogen bonding.

Comment

Norbormide is a compound discovered in the early 1960s that is selectively toxic to rats and relatively harmless to other rodents and mammals (Roszkowski, 1965). It exerts its lethality in the rat through mechanisms involving the control of blood pressure. Evidence suggests that norbormide acts by stimulating a number of signal transduction pathways that lead to modulation of calcium influx, presumably mediated by a cell membrane receptor(s) (Bova, Trevisi *et al.*, 2001). Physiological studies indicate that norbormide elicits divergent tissue responses, causing selective vasoconstriction of small arteries and vasodilation of large blood vessels in the rat, whilst dilating both small and large blood vessels of other species (Bova, Cima *et al.*, 2001).

We recently synthesized and purified six of the eight racemic diastereoisomers of norbormide and undertook a structure–activity relationship study of these isomers with respect to vasorelaxant and vasoconstrictor properties (Brimble *et al.*, 2004). These isomers differ according to the stereochemistry (*cis*/*trans*) of the exocyclic double bond, the orientation (*endo*/*exo*) of the maleimide ring and the stereochemistry (*erythro*/*threo*) of the tertiary alcohol. The contrasting responses of the different isomers to this toxin may be the key to understanding the secret of species specificity of drug action and provide opportunities for developing more species-selective pesticides.

Our initial work in this area (Brimble *et al.*, 2004) established that the *cis-endo-threo* isomer, (I*a*), of norbormide exhibited the most potent vasoconstrictor properties and is a lead compound for analogue development. We report here the crystal structures of the *cis-endo-threo* isomer, (I*a*), and the *trans-endo-threo* isomer, (I*b*), of norbormide in order to unambiguously confirm their structures and to facilitate molecular-modelling studies for the construction of analogues. At the outset of this work, only the crystal structure of the *N*-bromobenzyl derivative of (I*a*) was available (Abrahamsson & Nilsson, 1966) and we were keen to obtain the three-dimensional coordinates for the parent compounds.



(I*a*) (I*b*)

Fig. 1 shows a perspective view of the structure of isomer (I*a*), which crystallizes in the monoclinic space group $P2_1/n$. This structure unambiguously confirms that the most potent isomer is indeed that in which the exocyclic double bond has the 2-pyridyl substituent *cis* to the diarylmethanol substituent, which has *threo* stereochemistry, and the maleimide ring has

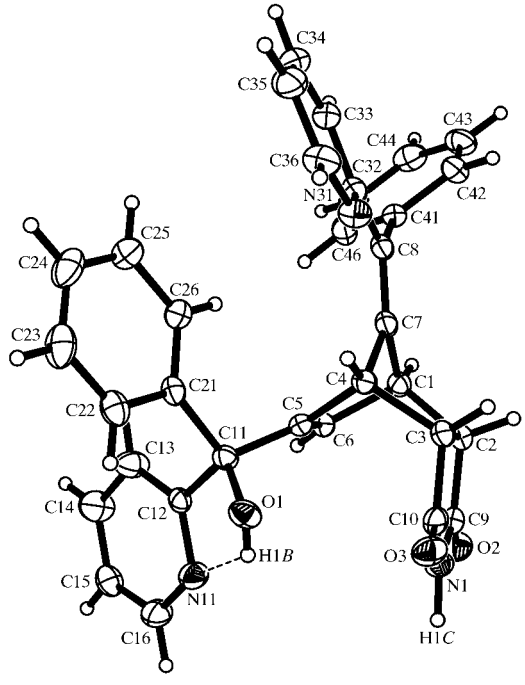


Figure 1
A perspective view of (I*a*), with the atom-numbering scheme. The wholly obscured atom C45 is not labelled. Displacement ellipsoids are drawn at the 30% probability level.

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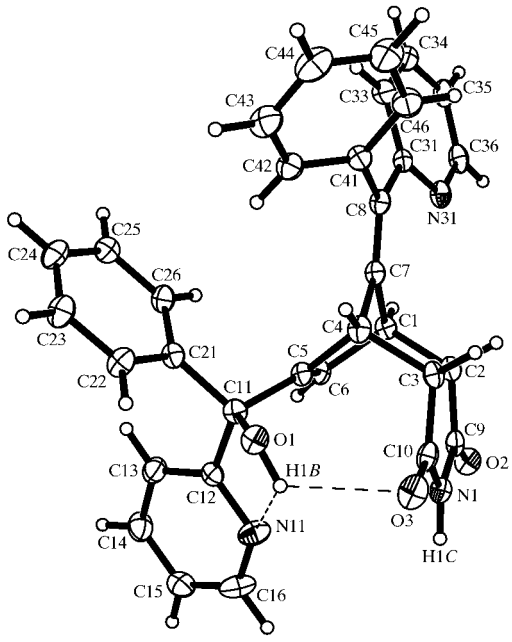

Figure 2
A perspective view and the atom-numbering scheme of (I*b*). Displacement ellipsoids are drawn at the 30% probability level. The disordered ethyl acetate solvent molecule is not shown.

an *endo* configuration. In the molecule, the hydroxy group is involved in an intramolecular hydrogen bond to the adjacent pyridine ring (Table 1). Intermolecular interactions form centrosymmetric pairs of linear hydrogen bonds [graph set notation $R_2^2(8)$] between the NH group and atom O3 of the maleimide groups (Table 1).

Fig. 2 shows the structure of isomer (I*b*), which crystallizes in the monoclinic space group *P*2/*c* along with half a molecule of ethyl acetate solvent. The solvent molecule is disordered about a twofold rotation axis. This isomer differs from (I*a*) in having the opposite stereochemistry at the exocyclic double bond, that is, the pyridine ring involving atom N31 has a *trans* relationship relative to the diarylmethanol substituent. Another difference between the two structures is that the four aryl (phenyl and 2-pyridyl) substituents have very different torsional orientations. Once again, the OH group is involved in an intramolecular hydrogen bond to atom N11. However, in this case, the hydrogen bonding is bifurcated with an additional, albeit weaker, interaction with atom O3 of the maleimide ring (Table 2). Adjacent molecules are again connected by linear intermolecular hydrogen bonds involving the maleimide groups [graph set notation $R_2^2(8)$], although, in this case, the molecules are related by a twofold axis (Table 2).

During the course of this work, we also indirectly confirmed the structure of a third isomer. Several data sets were collected using crystals of isomer (I*a*) contaminated with varying amounts of another isomer. In each case, the isomer ratio was determined independently by ^{1}H NMR and was found to vary between 2:1 and 4:1. These crystals were all isomorphous with those of pure (I*a*) (see above) and refined with disorder of the two aryl rings attached to the tertiary alcohol centre. Specifically, the rings attached to that centre had different conformations, presumably as a consequence of a different hydrogen-bonding pattern. The minor component was therefore identified as the *cis-endo-erythro* isomer.

Experimental

The title compounds were prepared and recrystallized from ethyl acetate as described previously (Brimble *et al.*, 2004; Mohrbacher *et al.*, 1966).

Compound (I*a*)

Crystal data

$C_{33}H_{25}N_3O_3$
M_r = 511.56
Monoclinic, $P2_1/n$
a = 15.433 (4) Å
b = 11.437 (3) Å
c = 17.048 (5) Å
β = 115.427 (3)°
V = 2717.6 (13) Å^3
Z = 4
D_x = 1.250 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4828 reflections
θ = 2.4–25.2°
μ = 0.08 mm^{-1}
T = 163 (2) K
Plate, colourless
0.59 × 0.48 × 0.04 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002)
T_{min} = 0.744, T_{max} = 1.000
28 763 measured reflections
4795 independent reflections
3147 reflections with $I > 2\sigma(I)$
R_{int} = 0.049
θ_{max} = 25.0°
$h = -18 \rightarrow 18$
$k = -11 \rightarrow 13$
$l = -20 \rightarrow 20$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.102
S = 1.08
4795 reflections
358 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.036P)^2 + 0.833P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °) for (I*a*).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1*B*···N11	0.79 (2)	2.12 (3)	2.645 (2)	125 (2)
N1—H1*C*···O3^{i}	0.95 (2)	2.02 (2)	2.965 (2)	174 (2)

Symmetry code: (i) $-x, 1-y, 2-z$.

Compound (I*b*)

Crystal data

$C_{33}H_{25}N_3O_3{\cdot}0.5C_4H_8O_2$
M_r = 555.61
Monoclinic, $P2/c$
a = 17.999 (3) Å
b = 12.614 (2) Å
c = 13.063 (2) Å
β = 110.834 (2)°
V = 2771.9 (8) Å^3
Z = 4
D_x = 1.331 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3124 reflections
θ = 2.3–26.0°
μ = 0.09 mm^{-1}
T = 173 (2) K
Needle, colourless
0.48 × 0.12 × 0.08 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002)
T_{min} = 0.738, T_{max} = 1.000
31 232 measured reflections
4870 independent reflections
1989 reflections with $I > 2\sigma(I)$
R_{int} = 0.159
θ_{max} = 25.0°
$h = -21 \rightarrow 21$
$k = -15 \rightarrow 15$
$l = -15 \rightarrow 11$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.062
$wR(F^2)$ = 0.125
S = 0.89
4870 reflections
396 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.050P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0046 (6)

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1*B*···N11	0.93 (3)	2.30 (3)	2.765 (4)	111 (3)
O1—H1*B*···O3	0.93 (3)	2.33 (3)	2.917 (3)	121 (3)
N1—H1*C*···O2^{ii}	0.92 (3)	1.94 (3)	2.863 (4)	175 (3)

Symmetry code: (ii) $1 - x, y, \frac{1}{2} - z$.

Crystal decay was monitored by the measurement of duplicate reflections and was found to be negligible. O- and N-bound H atoms were located from difference Fourier syntheses and their positions were refined, with an N—H bond-length restraint of 0.95 (2) Å in isomer (I*b*) and with U_{iso}(H) values of $1.5U_{eq}$(O,N). C-bound H atoms were placed in calculated positions, with C—H distances of 0.95 (aryl and alkene H atoms) or 1.00 Å (methine H atoms), and treated as riding, with U_{iso}(H) values of $1.2U_{eq}$(C) [$1.5U_{eq}$(C) for solvent methyl H atoms].

For both compounds, data collection: *SMART* (Bruker, 1997); cell refinement: *SAINT* (Bruker, 1997); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1997); software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1563). Services for accessing these data are described at the back of the journal.

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