Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

2-[2-(Pyrrolidin-2-yl)propan-2-yl]-1*H*-pyrrole and its amide derivative 1-{2-[2-(1*H*-pyrrol-2-yl)propan-2-yl]-pyrrolidin-1-yl}ethanone

Guillaume Journot,[a] Reinhard Neier[a]* and Helen Stoeckli-Evans[b]*

[a]Institute of Chemistry, University of Neuchâtel, rue Emile-Argand 11, 2000 Neuchâtel, Switzerland, and [b]Institute of Physics, University of Neuchâtel, rue Emile-Argand 11, 2000 Neuchâtel, Switzerland
Correspondence e-mail: reinhard.neier@unine.ch, helen.stoeckli-evans@unine.ch

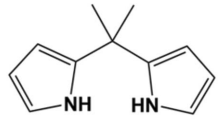
Received 8 February 2012
Accepted 20 February 2012
Online 23 February 2012

In the title compounds, $C_{11}H_{18}N_2$, (II), and $C_{13}H_{20}N_2O$, (III), the pyrrolidine rings have twist conformations. Compound (II) crystallizes with two independent molecules (*A* and *B*) in the asymmetric unit. The mean planes of the pyrrole and pyrrolidine rings are inclined to one another by 89.99 (11) and 89.35 (10)° in molecules *A* and *B*, respectively. In (III), the amide derivative of (II), the same dihedral angle is much smaller, at only 13.42 (10)°. In the crystal structure of (II), the individual molecules are linked *via* N—H···N hydrogen bonds to form inversion dimers, each with an $R_2^2(12)$ graph-set motif. In the crystal structure of (III), the molecules are linked *via* N—H···O hydrogen bonds to form inversion dimers with an $R_2^2(16)$ graph-set motif.

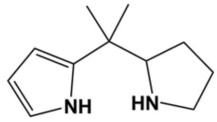
Comment

In order to study the selectivity of the hydrogenation (mono-hydrogenation *versus* total hydrogenation) and to compare the hydrogenation conditions of the dipyrromethane 2,2′-(propane-2,2-diyl)bis(1*H*-pyrrole), (I) (Journot, Neier & Stoeckli-Evans, 2010), with the hydrogenation conditions of calix[4]pyrrole (Blangy *et al.*, 2009; Journot, Letondor *et al.*, 2010), the synthesis and crystal structure of the partially reduced compound 2-[2-(pyrrolidin-2-yl)propan-2-yl]-1*H*-pyrrole, (II), were studied.

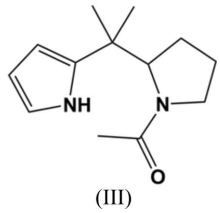
During efforts to modify partially reduced calix[4]pyrroles (Blangy *et al.*, 2009; Journot, Letondor *et al.*, 2010) by introducing amides on the pyrrolidine rings, unforeseen difficulties were encountered. Many of the known methods for creating amide bonds (Joullie & Lassen, 2010; Montalbetti & Falque, 2005; Valeur & Bradley, 2009) were unsuccessful. Screening of the classical methods for peptide synthesis (Wipf, 1995; Fletcher & Campbell, 1998; Humphrey & Chamberlin, 1997; Sonntag, 1953), and even trying novel peptide coupling reagents (Valeur & Bradley, 2009; Han & Kim, 2004), did not give satisfactory results. Based on numerous experiments with the partially reduced calix[4]pyrrole, we came to the conclusion that two major obstacles were responsible for the difficulties in achieving this seemingly simple transformation: (i) the N atoms of the pyrrolidine rings in the reduced calix[4]-pyrrole possess a considerably reduced activity, and (ii) using acyl chlorides together with organic amines leads to considerable quantities of side products, probably due to the formation of ketenes under these reaction conditions.



(I)



(II)



(III)

In an attempt to avoid the problems related to ketene formation, while keeping the high reactivity of the acyl chlorides, we finally used potassium carbonate as a base in a tetrahydrofuran–acetonitrile (2:1 *v*/*v*) solvent mixture. In order to identify the importance of the intramolecular hydrogen bond in (II), between the pyrrole NH group and the N atom of the pyrrolidine ring, we studied the transformation of (II) into its amide derivative, 1-{2-[2-(1*H*-pyrrol-2-yl)propan-2-yl]pyrrolidin-1-yl}ethanone, (III), which was prepared using this method. A similar method of amide synthesis using acyl chlorides with potassium phosphate has also been reported (Zhang *et al.*, 2009).

Compound (II) crystallizes with two independent molecules (*A* and *B*) in the asymmetric unit (Fig. 1). An *AUTO-FIT* diagram (Fig. 2; Spek, 2009) of inverted molecule *B* on mol-

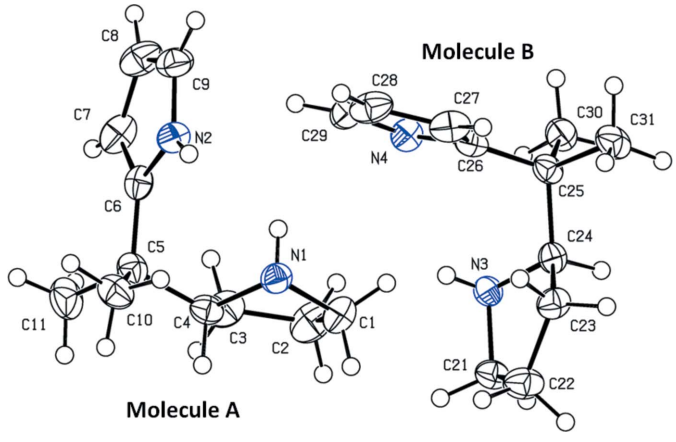


Figure 1
The structures of the two independent molecules (*A* and *B*) of (II), showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 50% probability level.

 doi:10.1107/S0108270112007603

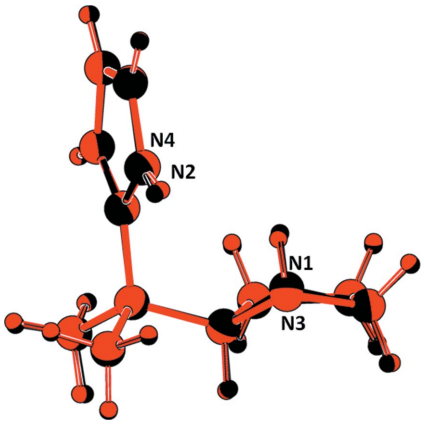


Figure 2
A view of the fit of molecule *B* (red in the electronic version of the paper) inverted on molecule *A* (black) of (II).

ecule *A* illustrates the small difference in the conformation of the two molecules. The best weighted and unit-weight r.m.s. fit parameters are only 0.032 and 0.035 Å, respectively, for the 13 non-H fitted atoms. In molecule *A*, the pyrolidine ring has a twist conformation on bond C4—N1, while in molecule *B* the twist is on the corresponding bond C24—N3. In both molecules, the mean planes of the pyrrole and pyrrolidine rings are almost perpendicular to one another; the dihedral angles are 89.99 (11) and 89.35 (10)° in molecules *A* and *B*, respectively.

In the crystal structure of (II), the individual independent molecules are linked *via* N—H···N hydrogen bonds to form inversion dimers (Table 1 and Fig. 3). These dimers can be described by an $R_2^2(12)$ graph-set motif (Bernstein *et al.*, 1995). Each dimer is composed solely of *A* or *B* molecules.

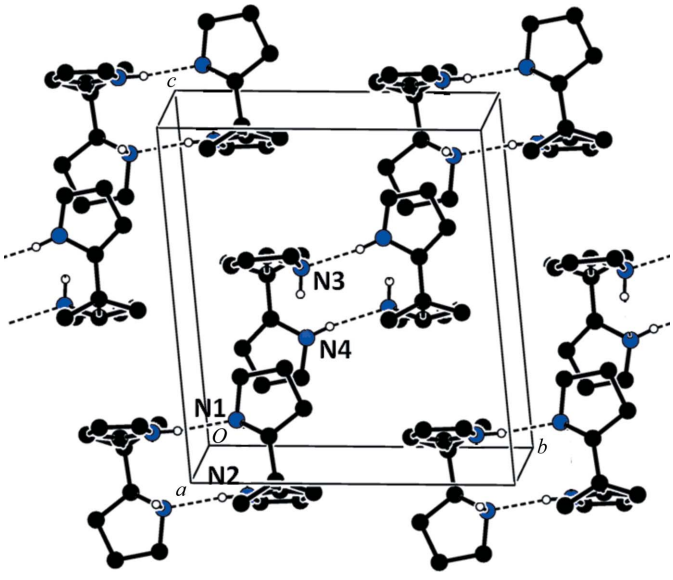


Figure 3
A view, along the *a* axis, of the crystal packing of (II), showing the formation of the N—H···N hydrogen-bonded (dashed lines) inversion dimers. C-bound H atoms have been omitted for clarity.

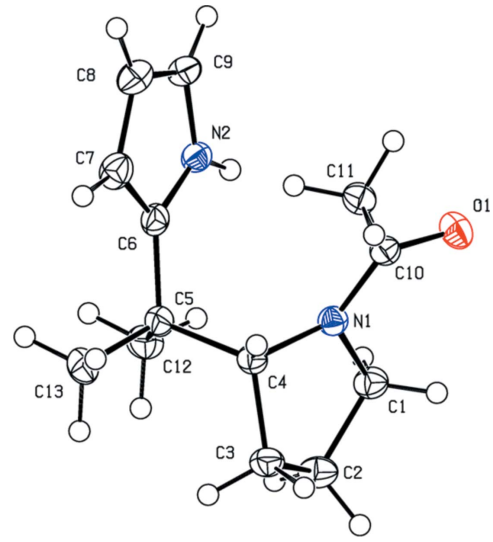


Figure 4
The molecular structure of (III), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

The crystal structure of (II) can be compared with that of the bis(1*H*-pyrrole) derivative, (I), which also crystallizes with two independent molecules per asymmetric unit (Journot, Neier & Stoeckli-Evans, 2010). There too the two pyrrole rings are almost perpendicular to one another, with dihedral angles of 87.67 (8) and 88.09 (7)° in the two independent molecules. However, the crystal packing in (I) is quite different to that of (II), with the two independent molecules being linked not by N—H···N hydrogen bonds but by N—H···π interactions.

The molecular structure of (III) is shown in Fig. 4. Here, the amide-substituted pyrrolidine ring also has a twist conformation, but this time on the C3—C4 bond. The mean plane of the pyrrole ring is inclined to the mean plane of the pyrrolidine ring by only 13.42 (10)°, compared with these planes being

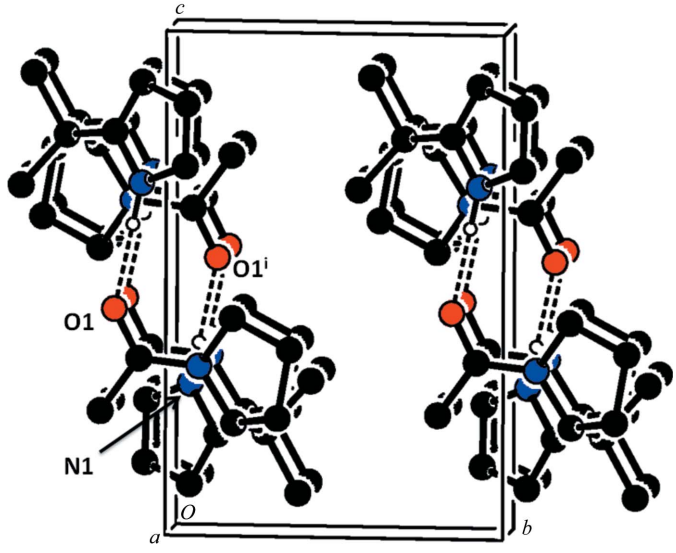


Figure 5
A view, along the *a* axis, of the crystal packing of (III), showing the formation of the N—H···O hydrogen-bonded (dashed lines) inversion dimers. C-bound H atoms have been omitted for clarity.

nearly perpendicular to one another in both independent molecules of (I) and (II).

In the crystal structure of (III), molecules are linked *via* N—H···O hydrogen bonds to form inversion dimers (Table 1 and Fig. 5), which can be described by an $R_2^2(16)$ graph-set motif.

It has therefore been shown that, under the conditions used, it was finally possible to reduce partially bis(pyrrole) (I) to (II) and to transform this partially reduced bis(pyrrole) into its amide derivative, (III). These protocols have been used subsequently to modify partially reduced calix[4]pyrroles by introducing amides on the pyrrolidine rings (Journot, 2012).

Experimental

For the synthesis of (II), 2,2′-(propane-2,2-diyl)bis(1*H*-pyrrole), (I) (Journot, Letondor *et al.*, 2010; Blangy *et al.*, 2009) (5.00 g, 29 mmol), 10% Pd/C (1.30 g), methanol (20 ml) and acetic acid (2 ml) were placed in an autoclave vessel. The reaction was kept under hydrogen (50 atm; 1 atm = 101 325 Pa) and stirred at room temperature for 20 h. The reaction mixture was then filtered through a pad of Celite and washed three times with dichloromethane. The solution was concentrated under vacuum to give a yellow slurry. The slurry was dissolved in dichloromethane and washed with 5% sodium hydroxide, and the mixture was stirred for 5 min. The organic layer was separated off and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried with sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, ethyl acetate–methanol–trifluoroacetic acid, 95:5:1 *v*/*v*/*v*) to yield colourless crystals of (II) (yield: 5.0 g, 96%; m.p. 352 K) on slow evaporation of the solvents.

For the synthesis of (III), a two-necked flask fitted with a gas inlet and containing a stirrer bar was charged with (II) (100 mg, 0.56 mmol), potassium carbonate (163 mg, 1.17 mmol) in tetrahydrofuran (5 ml), and acetonitrile (2.5 ml). The reaction vessel was flushed with argon and sealed with a septum. Dry tetrahydrofuran (9 ml) and acetonitrile (5 ml) were introduced, and acetyl chloride (83.8 µl, 1.17 mmol) in tetrahydrofuran (1 ml) was added slowly. After 15 min a precipitate appeared. The reaction mixture was stirred for a total of 2 h at room temperature, under argon. After stirring, 10% sodium carbonate was added and the reaction mixture was extracted with dichloromethane. The organic layer was washed twice successively with 10% sodium carbonate and saturated brine. The organic layer was dried with sodium sulfate and the solvents were removed under vacuum. The residue was purified by column chromatography (SiO_2, dichloromethane–methanol, 9:1 *v*/*v*). Recrystallization from a solution in ethanol yielded colourless crystals of (III) (yield: 119 mg, 96%; m.p. 437 K).

Spectroscopic data for (II) and (III) are available in the archived CIF.

Compound (II)

Crystal data

$C_{11}H_{18}N_2$
M_r = 178.27
Triclinic, $P\overline{1}$
a = 8.2140 (9) Å
b = 11.0624 (12) Å
c = 12.1981 (13) Å
α = 94.242 (13)°
β = 108.319 (13)°
γ = 102.609 (13)°
V = 1014.62 (19) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.07 mm^{-1}
T = 173 K
0.30 × 0.19 × 0.15 mm

Data collection

Stoe IPDS diffractometer
Absorption correction: multi-scan (*MULABS* in *PLATON*; Spek, 2009)
T_{min} = 0.918, T_{max} = 1.000
8026 measured reflections
3690 independent reflections
2212 reflections with $I > 2\sigma(I)$
R_{int} = 0.047

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.100
S = 0.85
3690 reflections
255 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}

Compound (III)

Crystal data

$C_{13}H_{20}N_2O$
M_r = 220.31
Triclinic, $P\overline{1}$
a = 7.0746 (6) Å
b = 8.1309 (7) Å
c = 11.1250 (9) Å
α = 89.325 (7)°
β = 88.878 (7)°
γ = 68.222 (6)°
V = 594.15 (9) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.08 mm^{-1}
T = 173 K
0.45 × 0.43 × 0.40 mm

Data collection

Stoe IPDS II diffractometer
Absorption correction: multi-scan (*MULABS* in *PLATON*; Spek, 2009)
T_{min} = 0.444, T_{max} = 1.000
11580 measured reflections
3199 independent reflections
2565 reflections with $I > 2\sigma(I)$
R_{int} = 0.093

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.062
$wR(F^2)$ = 0.152
S = 1.08
3199 reflections
152 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

In both (II) and (III), the N-bound H atoms were located in difference electron-density maps and refined freely. C-bound H atoms were included in calculated positions and treated as riding, with C—H = 1.0, 0.99, 0.98 and 0.95 Å for methine, methylene, methyl and allyl H atoms, respectively, and with $U_{iso}(H) = kU_{eq}(C)$, where k = 1.5 for methyl H atoms and 1.2 for all other H atoms.

Data collection: *EXPOSE* in *IPDS-I Software* (Stoe & Cie, 2000) for (II); *X-AREA* (Stoe & Cie, 2009) for (III). Cell refinement: *CELL*

Table 1
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2N···N1^{i}	0.905 (19)	2.04 (2)	2.9254 (18)	166.2 (17)
N4—H4N···N3^{ii}	0.873 (16)	2.092 (16)	2.9533 (19)	169.3 (16)

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

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2N···O1^{i}	0.95 (2)	1.93 (2)	2.8751 (18)	175 (2)

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

in *IPDS-I Software* for (II); *X-AREA* for (III). Data reduction: *INTEGRATE* in *IPDS-I Software* for (II); *X-RED32* (Stoe & Cie, 2009) for (III). For both compounds, program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97*, *PLATON* and *publCIF* (Westrip, 2010).

HSE thanks the staff of the XRD Application Laboratory, CSEM, Neuchâtel, for access to the X-ray diffraction equipment.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG3241). Services for accessing these data are described at the back of the journal.

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