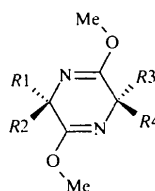


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residue shields the central ring is found in each of these structures, but modified aromatic residues, such as pentafluorophenyl or dimethoxyphenyl, and even non-aromatic residues, e.g. cyclohexyl, show the same behaviour. The structural principles derived therefrom are also applicable to diketopiperazines.

Comment

Bis-lactim ethers of cyclic dipeptides are important intermediates on a synthetic route to enantiomerically pure, non-proteinogenic amino acids (Schöllkopf, 1983a,b). In the preceding paper (Bolte *et al.*, 1999), we have studied their general structural features. Now we present the crystal structures of five compounds where the central dihydropyrazine ring carries at least one benzyl group, thus enabling the so-called folded conformation with an aromatic ring situated above the bis-lactim ether moiety.



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Bis-lactim ethers of cyclic dipeptides. 2. Benzyl-substituted compounds

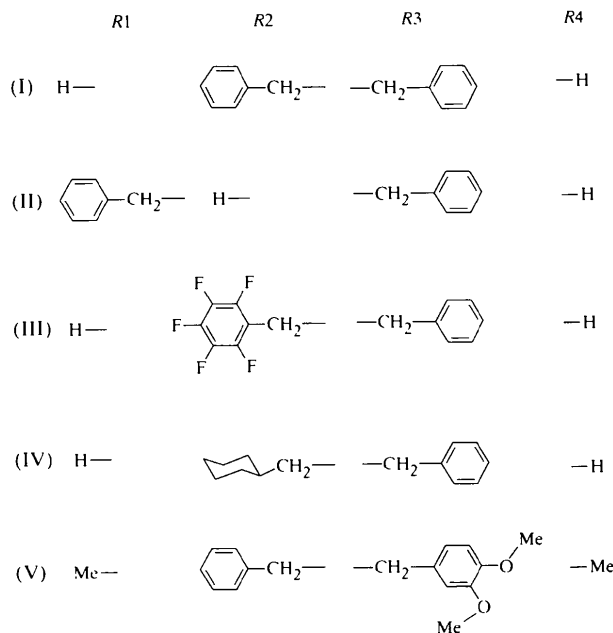
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Abstract

We determined the crystal structures of five bis-lactim ethers which carry at least one benzyl group: (2*SR*,5*RS*)-2,5-dibenzyl-3,6-dimethoxy-2,5-dihydropyrazine, C₂₀H₂₂N₂O₂, (I), (2*S*,5*S*)-2,5-dibenzyl-3,6-dimethoxy-2,5-dihydropyrazine, C₂₀H₂₂N₂O₂, (II), (2*S*,5*R*)-2-benzyl-5-(pentafluorophenylmethyl)-3,6-dimethoxy-2,5-dihydropyrazine, C₂₀H₁₇F₅N₂O₂, (III), (2*S*,5*R*)-2-benzyl-5-(cyclohexylmethyl)-3,6-dimethoxy-2,5-dihydropyrazine, C₂₀H₂₈N₂O₂, (IV), and (2*S*,5*R*)-5-benzyl-2-[(3,4-dimethoxyphenyl)methyl]-2,5-dimethyl-3,6-dimethoxy-2,5-dihydropyrazine, C₂₄H₃₀N₂O₄, (V). The geometry of the bis-lactim ether moiety agrees very well with that of the structures already published. The so-called folded conformation where an aromatic



(I) (Fig. 1) lies on a crystallographic inversion centre. Both phenyl rings shield the heterocycle, so that a sandwich-like conformation results, the angle between the heterocycle and the phenyl ring being 60.2(1)°.

(II), a diastereoisomer of (I), carries the two benzyl groups on the same side of the heterocycle (Fig. 2). Thus only one aromatic ring can adopt the folded

conformation, with an angle of $55.9(1)^\circ$ between the two rings, the other one is extended to the N atom.

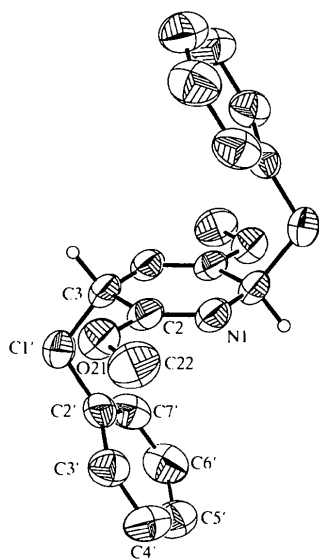


Fig. 1. Perspective view of (I) with the atom numbering and displacement ellipsoids at the 50% probability level; only tertiary H atoms are shown.

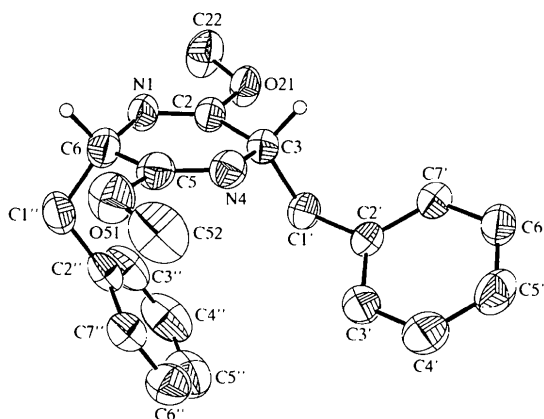


Fig. 2. Perspective view of (II) with the atom numbering and displacement ellipsoids at the 50% probability level; only tertiary H atoms are shown.

Substituting one phenyl group of (I) with a pentafluorophenyl ring leads to (III) (Fig. 3). As expected, both aromatic residues shield the heterocycle, forming an angle of $61.6(1)^\circ$ (phenyl) and $62.7(1)^\circ$ (pentafluorophenyl), respectively. In spite of the presence of five F atoms, the two structures show only minor differences.

(IV) (Fig. 4) differs from (I) in that the phenyl ring at C1' is replaced by a cyclohexyl ring, which is positioned above the heterocycle. This leads to an increase of the angle C3—C1'—C2' to $117.2(3)^\circ$ compared to C6—C1''—C2'' [$114.1(4)^\circ$]. The same phenomenon was found for dihydrooxazinones (Bolte, 1995). The phenyl

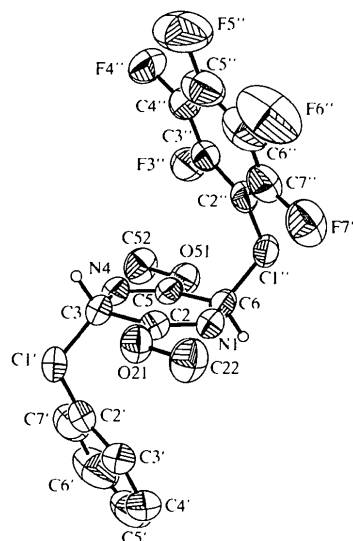


Fig. 3. Perspective view of (III) with the atom numbering and displacement ellipsoids at the 50% probability level; only tertiary H atoms are shown.

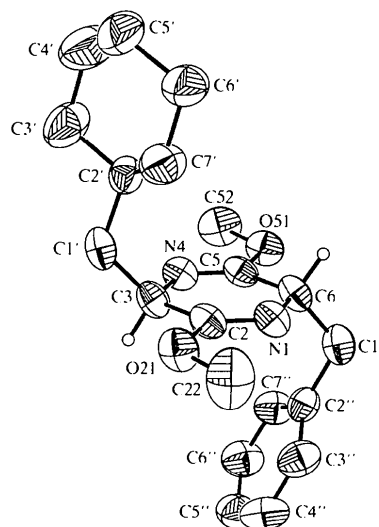


Fig. 4. Perspective view of (IV) with the atom numbering and displacement ellipsoids at the 50% probability level; only H atoms at C3 and C6 are shown.

ring again shields the heterocycle, with an angle of $61.4(1)^\circ$ between the two rings.

In (V) (Fig. 5), one phenyl ring carries two methoxy groups, which seems to have only a minor influence on the conformation of the molecule. The methyl groups at C3 and C6, however, cause a decrease of the angle between the aromatic rings and the heterocycle: $56.5(1)^\circ$ (phenyl) and $56.3(1)^\circ$ (dimethoxyphenyl), respectively.

The geometrical parameters of the bis-lactim ether moiety are in excellent agreement with those already determined (see Bolte *et al.*, 1999). The heterocycle of

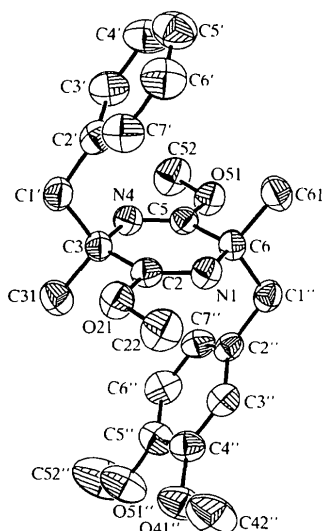


Fig. 5. Perspective view of (V) with the atom numbering and displacement ellipsoids at the 50% probability level; H atoms are omitted.

the 'double sandwich' structures is planar, while that of (II) deviates a little from planarity forming a very shallow boat. In all cases, both methoxy groups are coplanar with the dihydropyrazine ring.

In each of the five structures, the methylene C atoms C1' and C1'' carry two H atoms, one directed towards the methoxy O atom of the bis-lactim ether and the other towards the N atom, except for (II) where only one of the phenyl rings can adopt the folded conformation. Substitution of a phenyl ring with F atoms or methoxy groups does not alter the position of the aromatic ring significantly. The folded conformation seems to be favourable also for other bulky substituents, *e.g.* cyclohexyl [see (IV)]. The conformations found in the solid state coincide with those in solution, apart from (III), where NMR experiments indicate that the conformation with the pentafluorophenyl ring extended to the N atom is preferred (Maywald, 1987).

The folded conformation has also been found in diketopiperazines (Kopple & Marr, 1967; Kopple & Ohnishi, 1969; Lin & Webb, 1973). In contrast to the rigid bis-lactim ether moiety, the conformation of the diketopiperazine ring is strongly influenced by substituents; for example, two methyl groups in *cis* positions force the diketopiperazine ring into the boat conformation, while the *trans* compound shows a planar heterocycle (Sletten, 1970). A search in the Cambridge Structural Database (Version 5.15, April 1998; Allen & Kennard, 1993) revealed that aryl-CH₂-substituted diketopiperazines show a folded conformation except CITXAE10 (Mazza *et al.*, 1984) and COYJJI01 (Day *et al.*, 1985), where the heterocycle is not planar, but appears in a well pronounced boat conformation. Due to the different substituents, only two bis-lactim ethers can be compared directly with corresponding diketopiperazines: (I) with

MLDPHE10 (Benedetti *et al.*, 1976) and (II) with DUZDUX (Gdaniec & Liberek, 1986). The least-squares fits (Figs. 6 and 7) exhibit the similarities between the structures and support the conclusion that the same structural principles are applicable to both types of heterocycle. The observation that the position of the smallest residue at C1' determines whether a molecule adopts the folded conformation or not is strengthened by the only aryl-CHR-substituted diketopiperazine (DURWIW; Elix *et al.*, 1986) encountered in the CSD. As found for the bis-lactim ethers, the tertiary H atom at C1' is directed

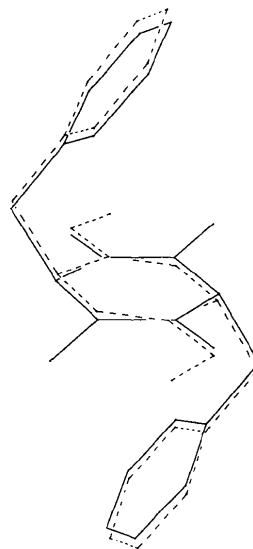


Fig. 6. Least-squares fit of (I) (dashed line) with MLDPHE10 (full line) (r.m.s. deviation of all non-H atoms except methyl-C atoms: 0.17 Å).

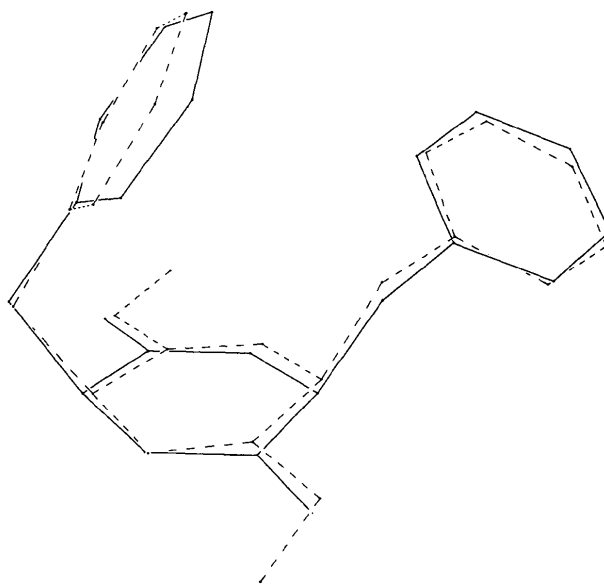


Fig. 7. Least-squares fit of (II) (dashed line) with DUZDUX (full line) (r.m.s. deviation of all non-H atoms except methyl-C atoms: 0.23 Å).

towards the (carbonyl) O atom so that the Br atom is situated above the heterocycle while the phenyl ring is extended to the NH group. Therefore the explanation for the preferred conformation of aryl-CHR-substituted bis-lactim ethers (see Bolte *et al.*, 1999) seems to be also valid for diketopiperazines. Although this is in accordance with the conformation of aryl-CH₂-substituted heterocycles, it is not clear why these compounds prefer the folded conformation relative to that with the aromatic ring extended towards the N atom.

Experimental

Compounds (I) to (IV) were recrystallized from a hexane/ether solution, (V) was recrystallized from methanol.

Compound (I)

Crystal data

C₂₀H₂₂N₂O₂
M_r = 322.40
 Monoclinic
*P*2₁/*n*
a = 5.803 (1) Å
b = 10.486 (1) Å
c = 14.762 (1) Å
 β = 90.05 (1)°
V = 898.27 (19) Å³
Z = 2
D_x = 1.192 Mg m⁻³
D_m not measured

Data collection

Stoe Siemens four-circle diffractometer
 ω - θ scans with learnt profile (Clegg, 1981)
 Absorption correction: none
 1867 measured reflections
 1588 independent reflections
 1337 reflections with $I > 2\sigma(I)$

Refinement

Refinement on *F*²
R[*F*² > 2σ(*F*²)] = 0.037
wR(*F*²) = 0.108
S = 1.041
 1588 reflections
 110 parameters
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0519P)^2 + 0.1374P]$
 where $P = (F_o^2 + 2F_c^2)/3$

Table 1. Selected geometric parameters (Å, °) for (I)

N1—C2	1.2566 (17)	C2—C3	1.5020 (19)
N1—C3'	1.4513 (18)	O21—C22	1.4378 (19)
C2—O21	1.3574 (17)		

C2—N1—C3'	118.23 (11)	C2—O21—C22	116.34 (12)
N1—C2—O21	121.06 (12)	C2—C3—N1'	113.69 (11)
N1—C2—C3	128.04 (14)	C1'—C3—N1'	109.43 (12)
O21—C2—C3	110.91 (11)		

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

Compound (II)

Crystal data

C₂₀H₂₂N₂O₂
M_r = 322.40
 Orthorhombic
*P*2₁2₁2₁
a = 10.998 (1) Å
b = 11.513 (1) Å
c = 14.464 (1) Å
V = 1831.4 (3) Å³
Z = 4
D_x = 1.169 Mg m⁻³
D_m not measured

Data collection

Stoe Siemens four-circle diffractometer
 ω - θ scans with learnt profile (Clegg, 1981)
 Absorption correction: none
 1840 measured reflections
 1840 independent reflections
 1548 reflections with $I > 2\sigma(I)$

Refinement

Refinement on *F*²
R[*F*² > 2σ(*F*²)] = 0.042
wR(*F*²) = 0.103
S = 1.080
 1840 reflections
 218 parameters
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0432P)^2 + 0.3472P]$
 where $P = (F_o^2 + 2F_c^2)/3$

Mo *K*α radiation
 λ = 0.71069 Å
 Cell parameters from 48 reflections
 θ = 10–15°
 μ = 0.076 mm⁻¹
T = 293 K
 Block
 0.6 × 0.4 × 0.4 mm
 Colourless

θ_{\max} = 24.99°
 $h = -13 \rightarrow 0$
 $k = 0 \rightarrow 13$
 $l = 0 \rightarrow 17$
 3 standard reflections
 frequency: 120 min
 intensity decay: 4%

(Δ/σ)_{max} < 0.001
 $\Delta\rho_{\max} = 0.124 \text{ e } \text{Å}^{-3}$
 $\Delta\rho_{\min} = -0.107 \text{ e } \text{Å}^{-3}$
 Extinction correction:
SHELXL97 (Sheldrick, 1997)
 Extinction coefficient:
 0.019(2)
 Scattering factors from
International Tables for Crystallography (Vol. C)

Table 2. Selected geometric parameters (Å, °) for (II)

N1—C2	1.253 (3)	N4—C5	1.248 (4)
N1—C6	1.462 (4)	C5—O51	1.364 (3)
C2—O21	1.360 (3)	O21—C22	1.429 (4)
C3—N4	1.451 (3)	O51—C52	1.439 (4)
C2—N1—C6	117.4 (2)	C5—N4—C3	117.8 (2)
N1—C2—O21	121.1 (2)	N4—C5—O51	121.6 (3)
N1—C2—C3	128.6 (3)	N4—C5—C6	128.6 (3)
O21—C2—C3	110.3 (2)	O51—C5—C6	109.8 (3)
N4—C3—C2	113.0 (2)	N1—C6—C5	112.8 (2)
N4—C3—C1'	109.4 (2)	N1—C6—C1''	109.9 (3)

Compound (III)

Crystal data

C₂₀H₁₇F₅N₂O₂
M_r = 412.36

Cu *K*α radiation
 λ = 1.54180 Å

Triclinic

P1
 $a = 5.880$ (1) Å
 $b = 7.449$ (1) Å
 $c = 11.197$ (1) Å
 $\alpha = 98.41$ (1)°
 $\beta = 90.13$ (1)°
 $\gamma = 91.97$ (1)°
 $V = 484.86$ (11) Å³
 $Z = 1$
 $D_x = 1.412$ Mg m⁻³
 D_m not measured

Data collection

Stoe Siemens four-circle diffractometer
 ω - θ scans with learnt profile (Clegg, 1981)
 Absorption correction: none
 2150 measured reflections
 1748 independent reflections (plus 402 Friedel-related reflections)

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.037$
 $wR(F^2) = 0.114$
 $S = 1.050$
 2150 reflections
 263 parameters
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0755P)^2 + 0.0428P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$

Table 3. Selected geometric parameters (Å, °) for (III)

N1—C2	1.257 (3)	N4—C5	1.261 (3)
N1—C6	1.449 (3)	C5—O51	1.348 (3)
C2—O21	1.355 (3)	O21—C22	1.432 (4)
C3—N4	1.458 (3)	O51—C52	1.431 (4)
C2—N1—C6	117.8 (2)	C5—N4—C3	118.3 (2)
N1—C2—O21	121.0 (2)	N4—C5—O51	121.3 (2)
N1—C2—C3	128.5 (2)	N4—C5—C6	127.9 (2)
O21—C2—C3	110.5 (2)	O51—C5—C6	110.9 (2)
N4—C3—C2	113.1 (2)	N1—C6—C5	114.3 (2)
N4—C3—C1'	108.7 (2)	N1—C6—C1''	109.3 (2)

Compound (IV)

Crystal data

C₂₀H₂₈N₂O₂
 $M_r = 328.44$
 Orthorhombic
 $P2_12_12_1$
 $a = 6.441$ (1) Å
 $b = 9.036$ (1) Å
 $c = 32.996$ (4) Å
 $V = 1920.4$ (4) Å³
 $Z = 4$
 $D_x = 1.136$ Mg m⁻³
 D_m not measured

Cell parameters from 52 reflections

$\theta = 30$ – 40°
 $\mu = 1.083$ mm⁻¹
 $T = 293$ K
 Block
 $0.5 \times 0.3 \times 0.3$ mm
 Colourless

2028 reflections with $I > 2\sigma(I)$
 $\theta_{\max} = 69.90^\circ$
 $h = -6 \rightarrow 1$
 $k = -9 \rightarrow 9$
 $l = -13 \rightarrow 13$
 3 standard reflections
 frequency: 120 min
 intensity decay: 5%

$\Delta\rho_{\max} = 0.124$ e Å⁻³
 $\Delta\rho_{\min} = -0.130$ e Å⁻³
 Extinction correction: SHELXL97 (Sheldrick, 1997)
 Extinction coefficient: 0.021 (2)
 Scattering factors from International Tables for Crystallography (Vol. C)
 Absolute structure: Flack (1983)
 Flack parameter = -0.1 (2)

Mo $K\alpha$ radiation
 $\lambda = 0.71069$ Å
 Cell parameters from 50 reflections
 $\theta = 10$ – 15°
 $\mu = 0.073$ mm⁻¹
 $T = 293$ K
 Block
 $0.5 \times 0.4 \times 0.3$ mm
 Colourless

Data collection

Stoe Siemens four-circle diffractometer
 ω - θ scans with learnt profile (Clegg, 1981)
 Absorption correction: none
 3808 measured reflections
 2638 independent reflections
 1606 reflections with $I > 2\sigma(I)$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.063$
 $wR(F^2) = 0.158$
 $S = 1.046$
 2638 reflections
 218 parameters
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0659P)^2 + 0.4390P]$
 where $P = (F_o^2 + 2F_c^2)/3$

$R_{\text{int}} = 0.095$
 $\theta_{\max} = 24.99^\circ$
 $h = -7 \rightarrow 3$
 $k = 0 \rightarrow 10$
 $l = 0 \rightarrow 39$
 3 standard reflections
 frequency: 120 min
 intensity decay: 5%

$(\Delta/\sigma)_{\max} = 0.001$
 $\Delta\rho_{\max} = 0.197$ e Å⁻³
 $\Delta\rho_{\min} = -0.180$ e Å⁻³
 Extinction correction: SHELXL97 (Sheldrick, 1997)
 Extinction coefficient: 0.039 (4)
 Scattering factors from International Tables for Crystallography (Vol. C)

Table 4. Selected geometric parameters (Å, °) for (IV)

N1—C2	1.258 (5)	N4—C5	1.256 (5)
N1—C6	1.454 (5)	C5—O51	1.367 (4)
C2—O21	1.358 (4)	O21—C22	1.452 (6)
C3—N4	1.462 (5)	O51—C52	1.439 (6)
C2—N1—C6	117.6 (4)	C5—N4—C3	117.9 (4)
N1—C2—O21	120.5 (4)	N4—C5—O51	120.3 (4)
N1—C2—C3	129.1 (3)	N4—C5—C6	128.8 (3)
O21—C2—C3	110.4 (4)	O51—C5—C6	111.0 (4)
N4—C3—C2	113.1 (4)	N1—C6—C5	113.5 (4)
N4—C3—C1'	109.1 (4)	N1—C6—C1''	109.2 (4)

Compound (V)

Crystal data

C₂₄H₃₀N₂O₄
 $M_r = 410.50$
 Orthorhombic
 $P2_12_12_1$
 $a = 6.860$ (1) Å
 $b = 16.461$ (1) Å
 $c = 20.386$ (2) Å
 $V = 2302.0$ (4) Å³
 $Z = 4$
 $D_x = 1.184$ Mg m⁻³
 D_m not measured

Mo $K\alpha$ radiation

$\lambda = 0.71069$ Å
 Cell parameters from 52 reflections
 $\theta = 10$ – 15°
 $\mu = 0.081$ mm⁻¹
 $T = 293$ K
 Block
 $0.6 \times 0.5 \times 0.2$ mm
 Colourless

Data collection

Stoe Siemens four-circle diffractometer
 ω - θ scans with learnt profile (Clegg, 1981)
 Absorption correction: none
 2335 measured reflections
 2335 independent reflections
 1689 reflections with $I > 2\sigma(I)$

$\theta_{\max} = 25.00^\circ$
 $h = 0 \rightarrow 8$
 $k = 0 \rightarrow 19$
 $l = 0 \rightarrow 24$
 3 standard reflections
 frequency: 120 min
 intensity decay: 2%

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.043$
 $wR(F^2) = 0.108$
 $S = 1.032$
 2335 reflections
 272 parameters
 H-atom parameters
 constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0549P)^2 + 0.1300P]$
 where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.125 \text{ e } \text{Å}^{-3}$
 $\Delta\rho_{\min} = -0.118 \text{ e } \text{Å}^{-3}$
 Extinction correction:
 SHELXL97 (Sheldrick, 1997)
 Extinction coefficient:
 0.019 (2)
 Scattering factors from
 International Tables for
 Crystallography (Vol. C)

Table 5. Selected geometric parameters (Å , $^\circ$) for (V)

N1—C2	1.257 (4)	O21—C22	1.439 (4)
N1—C6	1.463 (4)	O51—C52	1.427 (4)
C2—O21	1.367 (3)	C4''—O41''	1.370 (4)
C3—N4	1.463 (4)	C5''—O51''	1.367 (4)
N4—C5	1.258 (4)	O41''—C42''	1.430 (5)
C5—O51	1.364 (3)	O51''—C52''	1.440 (5)
C2—N1—C6	118.5 (3)	O51—C5—C6	110.2 (3)
N1—C2—O21	120.0 (3)	N1—C6—C5	112.3 (2)
N1—C2—C3	129.4 (3)	N1—C6—C61	107.3 (2)
O21—C2—C3	110.6 (3)	N1—C6—C1''	107.0 (2)
N4—C3—C2	112.0 (3)	C2—O21—C22	115.4 (2)
N4—C3—C31	107.3 (3)	C5—O51—C52	116.9 (3)
N4—C3—C1'	107.4 (2)	O41''—C4''—C3''	124.9 (3)
C5—N4—C3	118.8 (2)	O41''—C4''—C5''	115.4 (3)
N4—C5—O51	120.9 (3)	O51''—C5''—C6''	125.0 (3)
N4—C5—C6	129.0 (3)	O51''—C5''—C4''	116.1 (3)

All H atoms were located by a difference Fourier synthesis and refined with fixed individual displacement parameters [$U(\text{H}) = 1.5U_{\text{eq}}(\text{C}_{\text{methyl}})$ or $U(\text{H}) = 1.2U_{\text{eq}}(\text{C})$] using a riding model with C—H(aromatic) = 0.93, C—H(tertiary) = 0.98, C—H(secondary) = 0.97 or C—H(methyl) = 0.96 Å.

For all compounds, data collection: D4 (Clegg, 1981); cell refinement: D4; data reduction: REDU4 (Stoe & Cie, 1988); program(s) used to solve structures: SHELXS86 (Sheldrick, 1985); program(s) used to refine structures: SHELXL97 (Sheldrick, 1997); molecular graphics: XP (Sheldrick, 1991).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1255). Services for accessing these data are described at the back of the journal.

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Unexpectedly produced 2-*tert*-butyl-5-(*N,N*-dimethylcarbamoyl)pyridine† from 2-chloro-3-(*N,N*-dimethylcarbamoyl)-pyridine with a *tert*-butyl Grignard reagent

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Abstract

The title compound, $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$, was obtained by the reaction of 2-chloro-3-(*N,N*-dimethylcarbamoyl)pyridine with *tert*-butylmagnesium chloride. The structure was confirmed by NMR spectroscopy and X-ray crystallography.

Comment

Much effort has been made to understand the *AB* face selectivity in nicotinamide (NAD) coenzyme based on the orientation of the carbamoyl dipole (Donkersloot & Buck, 1981; Okamura *et al.*, 1993; Ohno *et al.*, 1994; Mikata, 1997). The carbonyl-O atom might be considered to play an important role in determining the reactive face of the coenzyme. In this communication, a precursor of NAD model compounds was synthesized with bulky substituents at the 2 position in order to orientate the carbonyl-O atom perpendicular to the pyri-

† Alternative name: *N,N*-dimethyl-5-(2-*tert*-butyl)pyridinecarboxamide.