Acta Cryst. (1999). C**55**, 964–968

Bis-lactim ethers of cyclic dipeptides. 1. Compounds derived from *cyclo*(Gly-L-Val)

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(*Received 20 October 1998; accepted 25 January 1999*)

Abstract

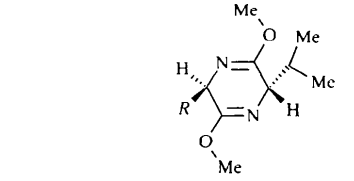
We determined the crystal structures of four bis-lactim ethers which carry an isopropyl group and a second substituent opposite to it: (2*R*,5*S*)-2-[(1*R*)-1-naphth-1-yl-2-nitroethyl]-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine, $C_{21}H_{25}N_3O_4$, (I), (2*R*,5*S*)-2-[(1*R*)-1-(3,4-dimethoxyphenyl)-2-nitroethyl]-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine, $C_{19}H_{27}N_3O_6$, (II), (1*R*,2*S*,3*R*)-1-[(2*R*,5*S*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]-2-methyl-2,3-epoxybutan-1-ol, $C_{14}H_{24}N_2O_4$, (III), and (*S*)-α-[(2*R*,5*S*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]benzyl alcohol, $C_{16}H_{22}N_2O_3$, (IV). Crystal structures of this type of dihydropyrazine have been published in a chemical but not in a structural context. Therefore, we present an overview of all known structures of this kind. The geometrical parameters of the dihydropyrazine ring are summarized and the preferred conformations of the substituents are analyzed. The characteristic features of the bis-lactim ethers are compared with those of dihydrooxazinones, a similar type of heterocycle containing one lactim ether moiety. Although the folded conformation, in which an aromatic ring shields the heterocycle, should in principle be possible for three of the four structures, it is not observed at all. However, the explanation given for the dihydrooxazinones can also be applied to bis-lactim ethers and shows that the preferred orientation of the tertiary C—H bonds determines the conformation of the substituents.

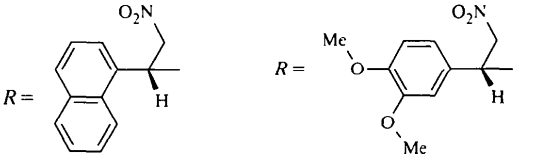
Comment

Non-proteinogenic amino acids deserve attention because of their documented or potential biological activity. Some are valuable pharmaceuticals, such as D-cycloserine (Rando, 1975), others are components of pharmaceuticals, for instance phenylglycine (Abeles, 1980). In biochemistry, they are valuable tools for investigating the mechanism of enzyme reactions (Nass *et al.*, 1971). A synthetic way to enantiomerically pure amino acids was developed by Schöllkopf (1983*a*,*b*). In this reaction sequence, bis-lactim ethers of cyclic dipeptides play an important role as intermediate products. The orientation of the substituents with respect to the dihydropyrazine ring determines the absolute configuration of the corresponding amino acids. In order to understand their reactivity and selectivity during the synthesis, it is necessary to know the conformation of these intermediates. In addition, a careful and attentive inspection of all available crystal structures containing the bis-lactim ether moiety allows the characterization of this type of heterocycle.

The so-called folded conformation, in which an aromatic residue shields the central ring, was at first found for diketopiperazines in solution (Kopple & Marr, 1967; Kopple & Ohnishi, 1969) and in the solid state (Lin & Webb, 1973), but later on also for hydantoines (Fujiwara *et al.*, 1979) and 1,4-dihydropyridines (Iwasaki *et al.*, 1987).

We have determined the crystal structures of several bis-lactim ethers in order to study their preferred conformations, especially the appearance of the folded conformation. In this paper we present the structures of four compounds derived from *cyclo*(Gly-L-Val) in which the six-membered ring carries an isopropyl group, (I)–(IV).





(I) (II)

(III) (IV)

(I) (Fig. 1) and (II) (Fig. 2) are very similar molecules which differ only in the nature of the aromatic residue (naphthyl or dimethoxyphenyl, respectively). In both structures, the latter is antiperiplanar to C2 [C2—C3—C1′—C2′ −168.4 (2), (I), and −171.4 (7)°, (II); C3—C1′—C2′—C3′ −106.2 (2), (I), and −84.3 (9)°, (II)], while the N atom of the nitro group is antiperiplanar to C3 [C3—C1′—C1″—N1″ −176.5 (2), (I), and −170.0 (6)°, (II)]. So neither of the aromatic residues adopts the position above the heterocycle, where the 2-nitroethyl group is located instead. A least-squares fit of all non-H atoms (excluding the aromatic residues) of both molecules gives a root mean square deviation of 0.22 Å. Both methoxy groups of the aromatic

side chain of (II) are in the plane of the phenyl ring [C4′—C5′—O5′—C51′ −4(1) and C7′—C6′—O6′—C61′ −11(1)°].

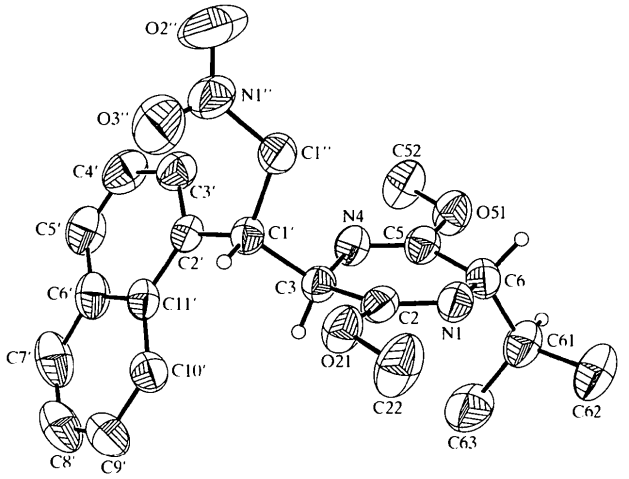


Fig. 1. Perspective view of (I) with the atom numbering and displacement ellipsoids at the 50% probability level; only tertiary H atoms are shown.

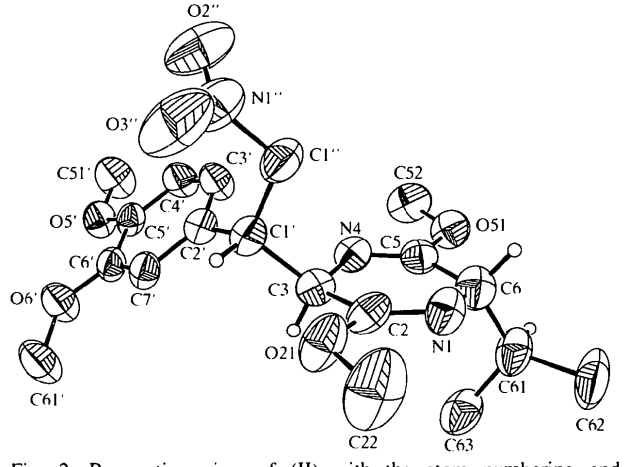


Fig. 2. Perspective view of (II) with the atom numbering and displacement ellipsoids at the 50% probability level; only tertiary H atoms are shown.

(III) (Fig. 3) and (IV) (Fig. 4) display a common structural feature: an hydroxyl group at C1′ (involved in an intermolecular hydrogen bond to an ether O atom) is located above the six-membered ring [C2—C3—C1′—O1′ 59.3(2), (III), and 62.6(2)°, (IV)]. As a result, the phenyl ring of (IV) does not shield the heterocycle.

Average values for bond lengths and angles of the bis-lactim ether moiety from the four structures in this paper and seven structures [FIGNIS (Schöllkopf, Kühnle *et al.*, 1987), FOGNUK (Schöllkopf, Grüttner *et al.*, 1987), FUPRUD (Schöllkopf *et al.*, 1986), GIDHUW (Schöllkopf, Hupfeld *et al.*, 1988), KECREP (Schöllkopf, Pettig *et al.*, 1988), TEKQUV and

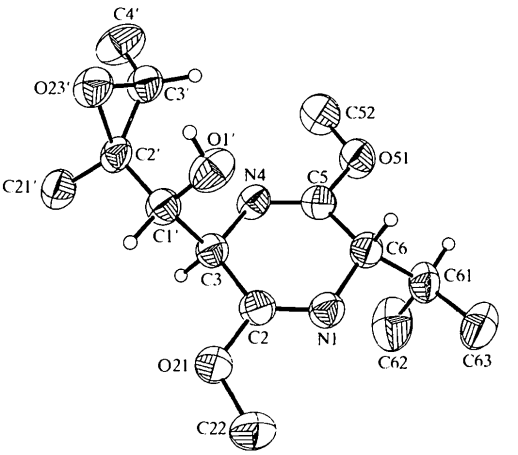


Fig. 3. Perspective view of (III) with the atom numbering and displacement ellipsoids at the 50% probability level; only tertiary and hydroxyl H atoms are shown.

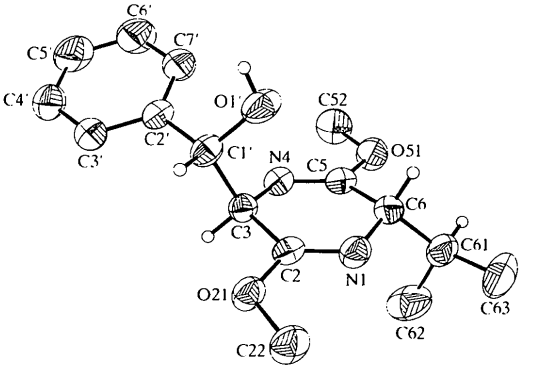


Fig. 4. Perspective view of (IV) with the atom numbering and displacement ellipsoids at the 50% probability level; only tertiary and hydroxyl H atoms are shown.

TEKRAC (Benecke & Bolte, 1996)] retrieved from the Cambridge Structural Database (version 5.15, April 1998; Allen & Kennard, 1993) show very small standard deviations (Fig. 5) and are in excellent agreement with those of the lactim ether moiety of dihydrooxazinones (Bolte, 1995). Remarkable are the rather short C=N bonds and the uneven distribution of the bond angles at the imino C atom.

All six-membered rings are planar with both methoxy groups in the plane of the dihydropyrazine ring. The isopropyl group adopts the same conformation in each of the four structures presented and in five of the structures from the CSD (TEKQUV and TEKRAC do not contain an isopropyl group). The torsion angle C5—C6—C61—H61 has a mean value of 54(1)° and the average H61···O51 distance is 2.51(7) Å. This agrees with the orientation of the isopropyl group in dihydrooxazinones [60(2)° and 2.51(4) Å]. A similar conformation is also found for the tertiary H atom at C1′ in all bis-lactim ethers (excluding FOGNUK, TEKQUV and TEKRAC, which do not contain this structural element)

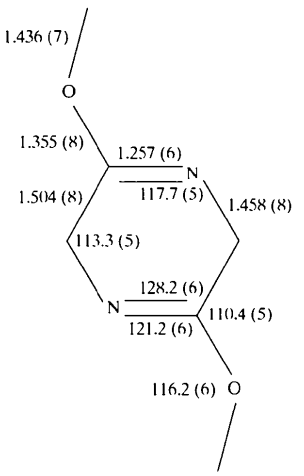


Fig. 5. Mean bond lengths (Å) and angles (°) in the bis-lactim ether moiety with standard deviations in parentheses.

and dihydrooxazinones. The mean value of the torsion angle C2—C3—C1′—H1′ is −56 (1)° and the mean H1′···O21 distance is 2.6 (4) Å for the four structures in this paper and four structures from the CSD; for dihydrooxazinones, 56 (10)° and 2.6 (1) Å were found, respectively. The orientation of the substituents at C1′ is always such that the smallest one, *i.e.* the tertiary H atom, is found in the vicinity of the methoxy O atom. Obviously, steric interactions prevent a bigger substituent occupying this position. Therefore, the folded conformation is not observed in any of the four structures. A comparison of (I) and (II) with FIGNIS clearly demonstrates that (as one would predict) the inversion of the absolute configuration at C1′ yields the folded conformation.

Experimental

All compounds were synthesized according to the method developed by Schöllkopf (1983*a*,*b*) and recrystallized from a hexane/ether solution. In cases (I), (III) and (IV), rather large crystals were used because the specimens turned out to be very brittle and cracked when we tried to cut them.

Compound (I)

Crystal data

$C_{21}H_{25}N_3O_4$
M_r = 383.44
Orthorhombic
$P2_12_12_1$
a = 7.888 (1) Å
b = 8.643 (1) Å
c = 29.832 (1) Å
V = 2033.8 (4) Å^3
Z = 4
D_x = 1.252 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54180 Å
Cell parameters from 50 reflections
θ = 30–40°
μ = 0.716 mm^{-1}
T = 293 K
Block
0.6 × 0.6 × 0.4 mm
Colourless

Data collection

Stoe Siemens four-circle diffractometer
ω–θ scans with learnt profile (Clegg, 1981)
Absorption correction: none
2831 measured reflections
2453 independent reflections
2397 reflections with $I > 2\sigma(I)$

R_{int} = 0.011
θ_{max} = 64.87°
$h = -9 \rightarrow 7$
$k = -9 \rightarrow 9$
$l = -25 \rightarrow 35$
3 standard reflections
frequency: 120 min
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.113
S = 0.968
2453 reflections
254 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0852P)^2 + 0.2997P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.148 e Å^{-3}
$\Delta\rho_{min}$ = −0.135 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0119 (8)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Compound (II)

Crystal data

$C_{19}H_{27}N_3O_6$
M_r = 393.44
Monoclinic
$P2_1$
a = 8.880 (2) Å
b = 6.748 (2) Å
c = 17.730 (4) Å
β = 100.42 (3)°
V = 1044.9 (5) Å^3
Z = 2
D_x = 1.250 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 50 reflections
θ = 10–15°
μ = 0.094 mm^{-1}
T = 293 K
Block
0.20 × 0.20 × 0.10 mm
Colourless

Data collection

Stoe Siemens four-circle diffractometer
ω–θ scans with learnt profile (Clegg, 1981)
Absorption correction: none
2278 measured reflections
2210 independent reflections
1239 reflections with $I > 2\sigma(I)$

R_{int} = 0.031
θ_{max} = 25.02°
$h = -10 \rightarrow 10$
$k = -8 \rightarrow 1$
$l = 0 \rightarrow 21$
3 standard reflections
frequency: 120 min
intensity decay: 5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.069
$wR(F^2)$ = 0.170
S = 1.126
2210 reflections
253 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0628P)^2 + 0.1709P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.192 e Å^{-3}
$\Delta\rho_{min}$ = −0.212 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Compound (III)

Crystal data

$C_{14}H_{24}N_2O_4$
M_r = 284.35
Orthorhombic
$P2_12_12_1$
a = 8.514 (1) Å
b = 9.301 (1) Å
c = 20.119 (2) Å
V = 1593.2 (3) Å^3
Z = 4
D_x = 1.185 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 50 reflections
θ = 10–15°
μ = 0.087 mm^{-1}
T = 293 K
Block
0.8 × 0.7 × 0.3 mm
Colourless

Data collection

Stoe Siemens four-circle diffractometer
ω–θ scans with learnt profile (Clegg, 1981)
Absorption correction: none
3028 measured reflections
2777 independent reflections
2512 reflections with $I > 2\sigma(I)$
R_{int} = 0.019
θ_{max} = 24.99°
h = −10 → 10
k = 0 → 11
l = 0 → 23
3 standard reflections
frequency: 120 min
intensity decay: 4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.121
S = 1.049
2777 reflections
182 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0719P)^2 + 0.2809P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.194 e Å^{-3}
$\Delta\rho_{min}$ = −0.186 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

D—H···A	D—H	H···A	D···A	D—H···A
O1′—H1′O···O21′	0.82	2.35	3.108 (2)	153.8

Symmetry code: (i) $2-x, y-\frac{1}{2}, \frac{3}{2}-z$.

Compound (IV)

Crystal data

$C_{16}H_{22}N_2O_3$
M_r = 290.36
Orthorhombic
$P2_12_12_1$
a = 8.211 (1) Å
b = 9.254 (1) Å
c = 20.861 (2) Å
V = 1585.1 (3) Å^3
Z = 4
D_x = 1.217 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 50 reflections
θ = 10–15°
μ = 0.084 mm^{-1}
T = 293 K
Block
0.7 × 0.6 × 0.5 mm
Colourless

Data collection

Stoe Siemens four-circle diffractometer
ω–θ scans with learnt profile (Clegg, 1981)
Absorption correction: none
2087 measured reflections
2087 independent reflections
1759 reflections with $I > 2\sigma(I)$
θ_{max} = 27.49°
h = 0 → 10
k = 0 → 12
l = 0 → 27
3 standard reflections
frequency: 120 min
intensity decay: 3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.121
S = 1.136
2087 reflections
191 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0570P)^2 + 0.2685P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.173 e Å^{-3}
$\Delta\rho_{min}$ = −0.209 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

D—H···A	D—H	H···A	D···A	D—H···A
O1′—H1′O···O21′	0.82	2.26	3.054 (3)	163.2

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

All H atoms were located by a difference Fourier synthesis and refined with fixed individual displacement parameters [U(H) = 1.5U_{eq}(C_{methyl}), U(H) = 1.2U_{eq}(C) or U(H) = 1.2U_{eq}(O)] using a riding model with C—H(aromatic) = 0.93, C—H(tertiary) = 0.98, C—H(secondary) = 0.97, C—H(methyl) = 0.96 or O—H = 0.82 Å, respectively. The hydroxyl bonds were also allowed to rotate about the C—O axis.

For all compounds, data collection: *D*4 (Clegg, 1981); cell refinement: *D*4; data reduction: *REDU*4 (Stoe & Cie, 1988); program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* (Sheldrick, 1991).

We thank the late Professor Dr U. Schöllkopf (University of Göttingen) for providing the samples and the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1254). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1999). C**55**, 968–973

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

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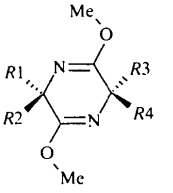
(Received 20 October 1998; accepted 3 December 1998)

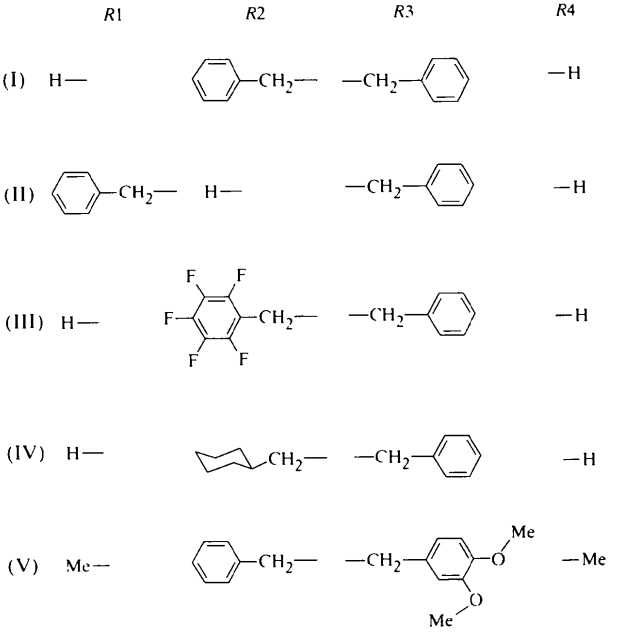
Abstract

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, $C_{20}H_{22}N_2O_2$, (I), (2*S*,5*S*)-2,5-dibenzyl-3,6-dimethoxy-2,5-dihydropyrazine, $C_{20}H_{22}N_2O_2$, (II), (2*S*,5*R*)-2-benzyl-5-(pentafluorophenylmethyl)-3,6-dimethoxy-2,5-dihydropyrazine, $C_{20}H_{17}F_5N_2O_2$, (III), (2*S*,5*R*)-2-benzyl-5-(cyclohexylmethyl)-3,6-dimethoxy-2,5-dihydropyrazine, $C_{20}H_{28}N_2O_2$, (IV), and (2*S*,5*R*)-5-benzyl-2-[(3,4-dimethoxyphenyl)methyl]-2,5-dimethyl-3,6-dimethoxy-2,5-dihydropyrazine, $C_{24}H_{30}N_2O_4$, (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 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, 1983*a*,*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.





(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