[175.7 (4), −62.5 (5) and −69.9 (5)°], and the side chain is folded. This conformation is very similar to that of molecule *B* of L-methionine (Torii & Iitaka, 1973).

The molecular structure is stabilized by a network of N—H···O and O—H···O hydrogen bonds (Table 2).

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(3*R*,6*R*)-3,4-Dimethyl-1,4-diazabicyclo[4.4.0]decane-2,5-dione

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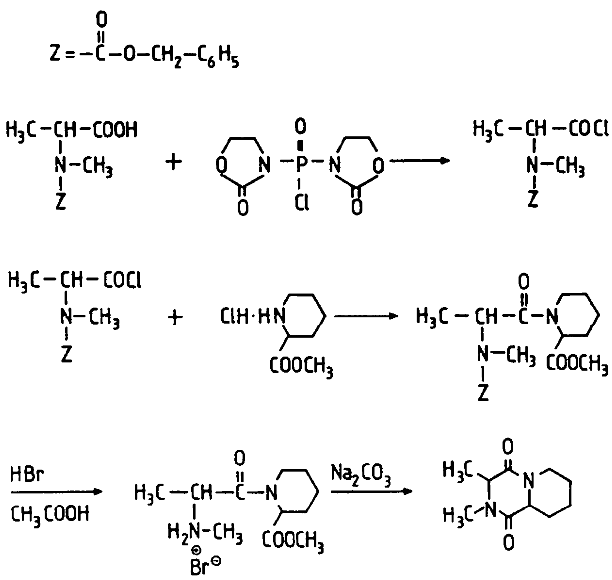
Abstract. $C_{10}H_{16}N_2O_2$, $M_r = 196.25$, orthorhombic, $P2_12_12_1$, $a = 6.593\,(3)$, $b = 6.755\,(2)$, $c = 23.653\,(4)$ Å, $V = 1053\,(1)$ Å^3, $Z = 4$, $D_x = 1.24$ Mg m^{-3}, $\lambda(\text{Mo } K\alpha) = 0.71073$ Å, $\mu = 0.08$ mm^{-1}, $F(000) = 424$, room temperature, $R = 0.031$, $wR = 0.038$ for 884 observed reflections [$I \geq 3\sigma(I)$] out of 1302 reflections measured and for 191 variables. The compound, for which the synthesis is also reported, consists of a piperidine ring in the chair form and a diketopiperazine ring in the boat form with C(3) and C(6) as bowsprits. The two rings are *cis*-fused. The methyl group at C(3) is pseudo-axially bonded, while the methyl group at N(4) is pseudo-equatorially bonded. The C═O bonds are of equal length reflecting the absence of hydrogen bonding in the structure.

Introduction. The title compound, shown in Fig. 1, contains the 2,5-diketopiperazine moiety (abbreviated DKP) and is a cyclic dipeptide composed of D-alanine and D-pipecolic acid. The compound, also known as *cis-cyclo*-[-*N*-methyl-D-Ala-D-Pec-], was synthesized in the series of reactions presented below. It belongs to a group of compounds of which some members show antiviral and antimicrobial activity (Sammes, 1975). The restrictions brought



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about by the DKP ring in combination with the rigid piperidine ring make cyclic peptides, such as the title compound, of interest in peptide conformational analysis (Ramani, Sasisekharan & Venkatesan, 1977; Anteunis, 1978; Toniolo, 1990; Ciarkowski, Gdaniec, Kolodziejczyk, Liberek, Borremans & Anteunis, 1990). Typical aspects are the shape of the DKP ring, the type of fusion of the two rings, the planarity near N atoms and the influence of hydrogen bonding on the length of the C=O bonds. The X-ray determination reported here is one of a series (Dillen & Lenstra, 1983; Lenstra, Verbruggen, Bracke, Vanhouteghem, Reyniers & Borremans, 1991; Van Poucke, Geise & Lenstra, 1983; Van Poucke & Lenstra, 1982*a*,*b*), the reports of which should be useful in the interpretation of NMR spectra and chemical activity.

Experimental. *N-(N'-Benzyloxycarbonyl-methyl-*D-*alanyl)-*D-*pipecolic acid methyl ester.* To a solution of 2.38 g (10 mmol) *N*-(benzyloxycarbonyl-methyl)-D-alanine and 1.01 g (10 mmol) triethylamine in 25 ml dichloromethane, 2.29 g (9 mmol) *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphoramide chloride was added. The mixture was stirred for 15 min at room temperature after which 1.16 g (9 mmol) of the hydrochloric acid salt of D-pipecolic acid methyl ester and 0.9 g (9 mmol) triethylamine was added. The mixture was stirred at room temperature for 20 h. The organic phase was washed with 2 × 10 ml 10% citric acid solution, 2 × 10 ml 10% $NaHCO_3$ solution, subsequently dried over $MgSO_4$ and evaporated. Yield: 2.48 g (80%), R_f = 0.87 (TLC, ethyl acetate).

*Hydrobromic acid salt of N-(N'-methyl-*D-*alanyl)-*D-*pipecolic acid methyl ester.* A solution of 1 g (3.2 mmol) of the foregoing benzyloxycarbonyl protected ester in 15 ml 40% HBr in acetic acid was stirred at room temperature for 1 h, after which the reaction mixture was evaporated. The residue was dissolved in 5 ml acetic acid and the hydrobromic acid salt of *N*-(*N'*-methyl-D-alanyl)-D-pipecolic acid methyl ester was precipitated by adding 10 ml diethyl ether. Yield: 0.9 g (90%).

(3*R*,6*R*)-3,4-*Dimethyl*-1,4-*diazabicyclo*[4.4.0]*decane*-2,5-*dione*. A solution of 0.75 g (2.30 mmol) of the foregoing HBr salt in 20 ml saturated Na_2CO_3 solution was stirred at room temperature for 2 h.

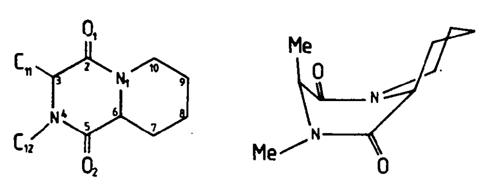

Fig. 1. Structural formula with atomic numbering scheme and conformation of the molecule.

The aqueous phase was extracted with 3 × 20 ml chloroform. After drying of the combined extracts over $MgSO_4$ and evaporation of the chloroform the reaction product was crystallized from diethyl ether. Yield: 0.35 g (60%), R_f = 0.75 (TLC, ethyl acetate).

X-ray diffraction. A suitable single crystal was obtained by slow evaporation of a chloroform solution. Crystal size 0.1 × 0.2 × 0.15 mm. Unit-cell dimensions were deduced from 25 reflections in the range $6 \leq \theta \leq 18°$. Space group was inferred from systematic extinctions. An Enraf–Nonius CAD-4 diffractometer, in $\omega/2\theta$ scan mode with scan angle $(0.8 + 0.2\tan\theta)°$, with aperture of detection unit 1.5 mm, and Mo radiation monochromated by pyrolytic graphite, was used for data collection. Three intensity control reflections monitored every 2 h showed no significant drift; three orientation control reflections monitored every 50 reflections showed no angular deviations. To a maximum Bragg angle of 27°, 1302 independent measurements were made, of which 884 were considered observed [$I \geq 3\sigma(I)$]; $0 \leq h \leq 8$, $0 \leq k \leq 8$, $0 \leq l \leq 30$. No absorption correction was applied (μ = 0.08 mm^{-1}). The structure was solved using *MULTAN* (Germain, Main & Woolfson, 1971). All H atoms were found from difference fourier calculations. Full-matrix least-squares refinements, minimizing $\sum w|\Delta F|^2$, of positional and anisotropic displacement parameters of non-H atoms and positional and isotropic displacement parameters of H atoms were performed. Reflections were weighted individually according to $\sigma(I)$ given by counting statistics. No extinction coefficient was refined. Convergence was reached at R = 0.031, wR = 0.038, S = 1.4, $(\Delta/\sigma)_{max}$ = 0.1, for 191 variables. Noise level in the final difference Fourier map was between −0.11 and 0.12 e Å^{-3}. Atomic scattering functions were obtained from *International Tables for X-ray Crystallography* (1974, Vol. IV). Enraf–Nonius *SDP* (Frenz, 1978) was employed. Refined parameters are given in Table 1,* and the atomic numbering scheme is shown in Fig. 1. According to the synthesis, the title compound has an absolute configuration (3*R*,6*R*). To facillitate the comparison with the other DKP's in the series, the geometry given in Tables 1 and 2 and Figs. 1 and 2 is in the mirror-image (3*S*,6*S*) configuration.

Discussion. Table 2 gives a comparison of bond lengths, valence angles, endocyclic torsion angles and Cremer & Pople (1975) ring parameters of the title

* Lists of structure factors, H-atom positions, anisotropic displacement parameters, bond lengths, bond angles and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55904 (16 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: MU1011]

Table 1. *Fractional coordinates and equivalent isotropic displacement parameters* (Å^2)

$$B_{eq} = (4/3)[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)].$$

	x	y	z	B_{eq}
O(1)	1.1846 (2)	0.3530 (3)	0.79058 (6)	6.10 (4)
O(2)	0.6443 (3)	0.1443 (3)	0.94694 (6)	6.37 (4)
N(1)	1.0783 (2)	0.3718 (3)	0.88097 (6)	4.57 (4)
N(4)	0.7501 (3)	0.1314 (3)	0.85689 (6)	4.28 (3)
C(2)	1.0580 (3)	0.3180 (3)	0.82694 (8)	4.29 (5)
C(3)	0.8657 (4)	0.2138 (4)	0.81000 (8)	4.30 (5)
C(5)	0.7591 (4)	0.1999 (3)	0.90970 (8)	4.22 (4)
C(6)	0.9213 (3)	0.3488 (3)	0.92375 (7)	3.91 (4)
C(7)	0.8289 (4)	0.5484 (4)	0.9379 (1)	5.05 (5)
C(8)	0.9913 (4)	0.6959 (4)	0.9550 (1)	5.78 (6)
C(9)	1.1572 (4)	0.7066 (5)	0.9113 (1)	6.48 (6)
C(10)	1.2429 (4)	0.5050 (6)	0.8986 (1)	6.52 (6)
C(11)	0.7360 (4)	0.3518 (5)	0.7746 (1)	7.23 (6)
C(12)	0.5909 (4)	−0.0098 (4)	0.8423 (1)	6.21 (6)

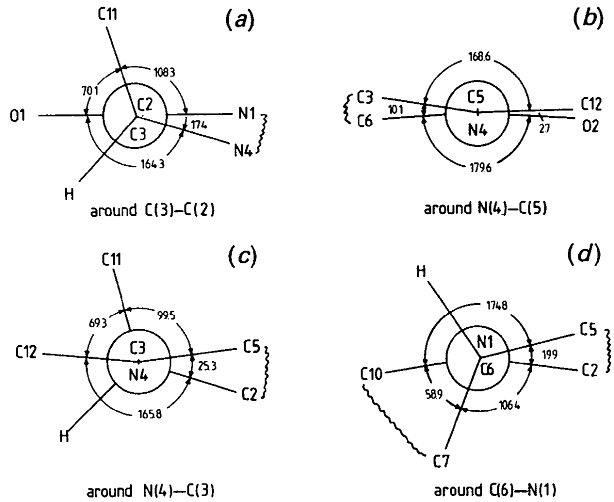

Fig. 2. Newman projections (*a*) along C(3)—C(2) showing the pseudo-axial orientation of the C(11) methyl group, (*b*) along N(4)—C(5) showing the pseudo-equatorial orientation of the C(12) methyl group, (*c*) along N(4)—C(3) also showing the pseudo-axial orientation of the C(11) methyl group and pseudo-equatorial orientation of the C(12) methyl group, and (*d*) along C(6)—N(1) showing the *cis*-like fusion of the two rings.

compound with those of the closely related (3*S*,6*S*)-3-isopropyl-1,4-diazabicyclo[4.4.0]decane-2,5-dione (*i.e. cis-cyclo*-[-L-Val-L-Pec-]) as determined by Lenstra *et al.* (1991). Some exocyclic torsion angles are shown in Fig. 2. From these data the following may be concluded. Firstly, the methyl group C(11) on C(3) is in pseudo-axial position and the methyl group C(12) on N(4) in pseudo-equatorial position. Second, the piperdine ring has the chair conformation with a puckering very close to that observed in *cis-cyclo*-[-L-Val-L-Pec-] and *trans-cyclo*-[-D-Phe-L-Pec-] (Van Poucke & Lenstra, 1982*b*). The DKP ring has a boat form with C(3) and C(6) acting as bowsprits, *i.e.* approaching the $B_{3,6}$ form in the notation of Boeyens (1978). Judging the puckering by the Q parameter [Q = 0.26 (1) Å], the ring is comparable to *trans-cyclo*-[-D-Phe-L-Pec-] [Q = 0.27 (1) Å], and more puckered than the related *cis-cyclo*-[-L-Val-L-Pec-] [Q = 0.17 (1) Å]. Third, in the title compound the fusion between the DKP ring and the piperidine ring is

Table 2. *Comparison of bond lengths* (Å), *valence angles* (°), *endocyclic torsion angles* (°) *and ring parameters* (Å, °) *of the title compound* (I) *and cis-cyclo-*[-L-*Val*-L-*Pec*-] (II)

Averaged values for the two independent molecules in the cell of *cis-cyclo*-[-L-Val-L-Pec-] are given (Lenstra *et al.*, 1991). Torsion angle e.s.d.'s are around 0.3°; the sign convention of IUPAC (1974) is used. Cremer & Pople (1975) ring parameters have e.s.d.'s according to Norrestam (1981). The sequences N(1), C(2), C(3), N(4), C(5), C(6) and N(1), C(6), C(7), C(8), C(9), C(10) were taken.

	(I)	(II)
N(1)—C(2)	1.335 (3)	1.331 (7)
C(2)—C(3)	1.504 (4)	1.506 (7)
C(3)—N(4)	1.456 (3)	1.459 (7)
N(4)—C(5)	1.333 (3)	1.327 (7)
C(5)—C(6)	1.505 (3)	1.501 (7)
C(6)—N(1)	1.456 (2)	1.454 (7)
C(3)—C(11)	1.516 (4)	1.537 (7)
N(4)—C(12)	1.459 (3)	
N(1)—C(10)	1.470 (3)	1.474 (7)
C(10)—C(9)	1.505 (5)	1.520 (5)
C(9)—C(8)	1.506 (4)	1.526 (7)
C(8)—C(7)	1.517 (4)	1.511 (7)
C(7)—C(6)	1.517 (3)	1.514 (5)
C(2)—O(1)	1.222 (2)	1.237 (6)
C(5)—O(2)	1.221 (2)	1.223 (7)
⟨C—H⟩	0.96 (4)	
N(1)—C(2)—C(3)	117.8 (2)	119.4 (4)
N(1)—C(2)—O(1)	123.5 (2)	122.4 (5)
C(3)—C(2)—O(1)	118.6 (2)	118.3 (4)
C(2)—C(3)—N(4)	114.7 (2)	113.1 (4)
C(2)—C(3)—C(11)	109.5 (2)	109.7 (4)
N(4)—C(3)—C(11)	111.1 (3)	112.8 (4)
C(3)—N(4)—C(5)	123.9 (2)	126.5 (4)
C(3)—N(4)—C(12)	116.5 (2)	-
C(5)—N(4)—C(12)	118.7 (3)	-
N(4)—C(5)—C(6)	118.1 (2)	118.7 (5)
N(4)—C(5)—O(2)	122.8 (2)	122.8 (4)
C(6)—C(5)—O(2)	119.1 (2)	118.6 (4)
C(5)—C(6)—N(1)	115.0 (2)	114.4 (4)
C(5)—C(6)—C(7)	110.9 (2)	112.7 (4)
N(1)—C(6)—C(7)	110.1 (3)	110.3 (4)
C(2)—N(1)—C(6)	124.4 (2)	125.7 (5)
C(2)—N(1)—C(10)	120.8 (2)	120.4 (5)
C(6)—N(1)—C(10)	113.2 (2)	113.8 (4)
C(6)—C(7)—C(8)	111.1 (2)	110.8 (4)
C(7)—C(8)—C(9)	111.2 (2)	110.9 (4)
C(8)—C(9)—C(10)	111.5 (3)	110.7 (4)
C(9)—C(10)—N(1)	109.5 (2)	110.0 (4)
DKP ring		
N(1)—C(2)—C(3)—N(4)	−17.4	−13.0
C(2)—C(3)—N(4)—C(5)	25.3	15.5
C(3)—N(4)—C(5)—C(6)	−10.1	−4.3
N(4)—C(5)—C(6)—N(1)	−12.3	−9.2
C(5)—C(6)—N(1)—C(2)	19.9	11.3
C(6)—N(1)—C(2)—C(3)	−4.5	0.3
Piperidine ring		
N(1)—C(6)—C(7)—C(8)	−54.4	−55.8
C(6)—C(7)—C(8)—C(9)	52.4	54.8
C(7)—C(8)—C(9)—C(10)	−53.5	−54.4
C(8)—C(9)—C(10)—N(1)	55.7	54.3
C(9)—C(10)—N(1)—C(6)	−59.4	−57.5
C(10)—N(1)—C(6)—C(7)	58.9	58.2

	DKP ring		Piperidine ring	
	(I)	(II)	(I)	(II)
q_2 (Å)	0.26 (1)	0.16 (1)	0.03 (1)	0.01 (1)
q_3 (Å)	−0.02 (1)	−0.02 (1)	−0.56 (1)	−0.56 (1)
Q (Å)	0.26 (1)	0.17 (1)	0.56 (1)	0.56 (1)
φ_2 (°)	314 (3)	304 (2)	163 (3)	294 (2)
φ_3 (°)	95 (3)	96 (2)	177 (3)	179 (2)

cis-like, because the torsion angles C(7)—C(6)—N(1)—C(10) and C(5)—C(6)—N(1)—C(2) have the same sign. Fourth, the angle between the C(3)C(2)N(1)C(6) and C(3)N(4)C(5)C(6) planes – a parameter of interest to NMR spectroscopists – amounts to 19.5 (4)°. This value is normal compared to other DKP-containing dipeptides (18–26°), but larger than that of *cis-cyclo*-[-L-Val-L-Pec-] [13.2 (5)°], showing once again the very small puckering of the DKP ring in the latter compound. Fifth, slightly pyramidal configurations are seen at the peptide atoms N(1) and N(4). This follows from the Newman projections (Fig. 2), the sum of valence angles around N(1) (358.4°) and N(4) (359.1°), as well as from the distance of N(1) to the C(2)C(6)C(10) plane [−0.106 (2) Å] and the distance of N(4) to the C(3)C(5)C(12) plane [−0.079 (2) Å]. These values put the title product at an intermediate position between the less frequently occuring planar configuration (as, *e.g.*, in *cis-cyclo*-[-L-Val-L-Pec-]) and the more frequent pyramidal configurations (*e.g.* Lenstra *et al.*, 1991). Sixth, comparing the title compound with *cis-cyclo*-[-L-Val-L-Pec-] (Table 2), most valence angles differ by less than 2° (*i.e.* less than three times the e.s.d.'s). Only around C(3) and N(4) do some larger differences occur, exactly in the region where the two compounds differ in their substitution pattern. Regarding bond lengths, none of the differences exceeds the 3σ limits. It is of interest to note that in the title compound the C(2)—O(1) distance is only 0.001 Å longer than the C(5)—O(2) distance; in *cis-cyclo*-[-L-Val-L-Pec-], however, C(2)—O(1) is 0.014 Å longer than C(5)—O(2). This might well reflect the absence of hydrogen bonds in the title compound [N(4) carries a methyl substituent] and the presence of a hydrogen bond in the other compound [N(4)—H bridging with O(2) in another molecule]. In fact, the values are in excellent agreement with the observation of Popelier, Lenstra, Van Alsenoy & Geise (1991) that a C═O bond lengthens by about 0.011 Å per hydrogen bond it accepts.

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