Toniolo, C. (1980). *CRC Crit. Rev. Biochem.* **9**, 1–44.
Toniolo, C., Bonora, G. M., Bavoso, A., Benedetti, E., Di Blasio, B., Pavone, V. & Pedone, C. (1983). *Biopolymers*, **22**, 205–215.
Venkatachalam, C. M. (1968). *Biopolymers*, **6**, 1425–1436.

(1)                    (2)

*Acta Cryst.* (1994). C50, 565–569

# Two Cyclic Dipeptide Anticonvulsants: cyclo-Glycyl-L-phenylglycine (1) and cyclo-L-Alanyl-D-phenylglycine (2)

MARIA B. SZKARADZINSKA, MACIEJ KUBICKI†
AND PENELOPE W. CODDING

*Departments of Chemistry and of Pharmacology and Therapeutics, University of Calgary, 2500 University Dr. NW, Calgary, Alberta, Canada T2N 1N4*

## Abstract

In the title compounds, $C_{10}H_{10}N_2O_2.0.25H_2O$ (1) and $C_{11}H_{12}N_2O_2$ (2), the phenyl rings are almost perpendicular to the mean planes of the diketopiperazine rings, which assume flattened twist-boat conformations. The methyl group of the alanyl residue in (2) lies in a quasi-axial position. In both structures, hydrogen bonds connect molecules into infinite layers. In compound (1), there are two molecules per asymmetric unit and each forms an independent layer. Water molecules bind the neighboring layers of only one type into pairs. There is no interaction between symmetrically independent molecules.

## Comment

Both compounds are part of a series of cyclic dipeptides designed to act at an Na channel receptor site for anticonvulsants (Weaver, Edgecombe, Smith & Anderson, 1992). The cyclic alanyl derivative, compound (2), has significant pharmacological activity ($ED_{50}$ = 50 mg kg$^{-1}$ in mice) in the maximal electroshock (MES) test; compound (1) is pharmacologically inactive (Weaver *et al.*, 1992). The conformations and intermolecular interactions of the two compounds were determined as part of our study of Na channel anticonvulsants (Codding, Lee & Richardson, 1984; Codding *et al.*, 1990; Duke & Codding, 1992).

† Permanent address: Department of Chemistry, Adam Mickiewicz University, Grunwaldzka 660-780, Poznań, Poland.
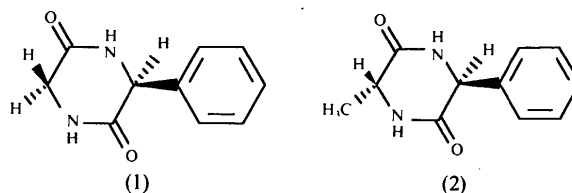
The molecular conformations are shown in Figs. 1 and 2; the diketopiperazine ring of each molecule assumes the conformation of a distorted flattened twist boat. The crystal structure of (1) contains two independent molecules per asymmetric unit (the water molecule lies in the special position with the O atom on the twofold axis). In molecule *A* of compound (1), the diketopiperazine ring is almost planar [maximum deviation from the least-squares plane is 0.028 (2) Å], while for molecule *B* of compound (1) and compound (2), the folding is more significant [maximum deviations of 0.081 (2) and 0.056 (2) Å, respectively].

As has been observed for other cyclic dipeptides (Filhol & Timmins, 1976; Benedetti, Marsh & Goodman, 1976), the strain imposed by closing two *cis* peptide bonds to form a ring introduces nonplanarity into the peptide bond [see the ω torsion angles in Table 3; torsion-angle nomenclature is given according to the IUPAC–IUB Commission on Biochemical Nomenclature (1970)]. The methyl group of the alanyl residue in (2) is in a quasi-axial position [C5—N4—C3—C31 −112.3 (4), N1—C2—C3—C31 116.4 (3)°]. In compound (2), the stereochemistry of the phenyl substituents of the phenylglycine residue places the phenyl substituent on the opposite side of the diketopiperazine ring to the methyl group of the alanyl residue [improper torsion angle C1′—C6···C3—C31 of 179.2 (2)°, see Fig. 2]. The phenyl rings are
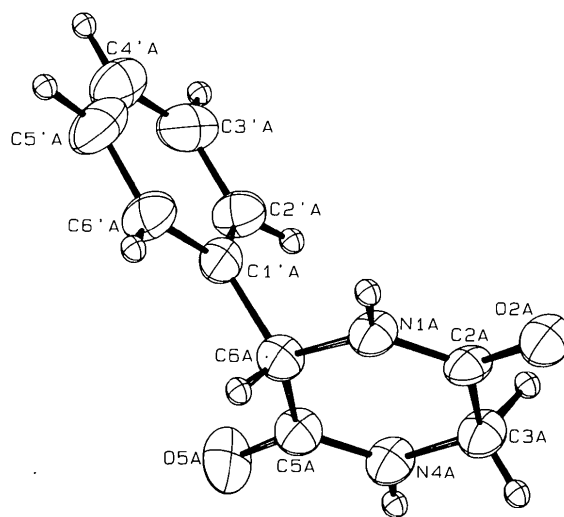


Fig. 1. A thermal-ellipsoid representation of molecule *A* of compound (1). The ellipsoids are drawn at the 50% probability level; the H atoms are drawn as spheres of arbitrary size.
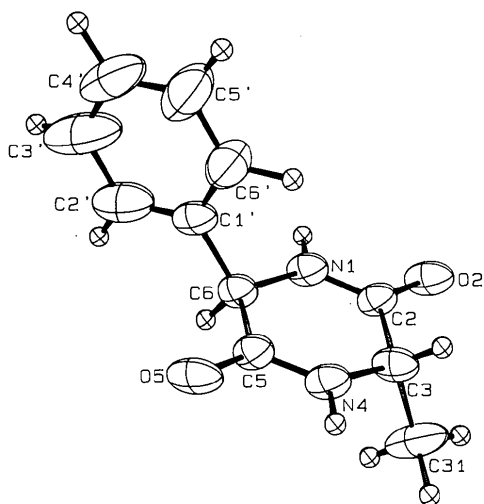
Fig. 2. A thermal-ellipsoid representation of the molecule of (2). The ellipsoids are drawn at the 50% probability level; the H atoms are drawn as spheres of arbitrary size.

nearly perpendicular to the mean planes of diketopiperazine rings; the dihedral angles between these two planes are 77.00 (10) and 70.27 (10)° for molecules $A$ and $B$, respectively, of compound (1), and 89.37 (11)° for compound (2). The combination of a nearly planar amide group attached to a phenyl ring which adopts a conformation perpendicular to the amide plane is the putative binding conformation for MES-active anticonvulsants (Codding *et al.*, 1984).

In the cyclic dipeptides both the inactive (1) and active (2) compounds adopt this conformation. Hence, the activity of compound (2) must derive from recognition of the quasi-axial methyl group *trans* to the phenyl ring across the nearly planar diketopiperazine moiety. It has been established that the stereochemistry present in compound (2) is necessary for activity (Weaver *et al.*, 1992), *i.e.* the *cis* arrangement of the phenyl substituent and the methyl group present in *cyclo*-L-alanyl-L-phenylglycine prevents activity in the MES test. In both structures, a similar pattern of hydrogen bonding is observed. For (1), the two symmetry-independent molecules are linked into separate layers along the [010] direction; molecules $B$ form dimers through hydrogen bonding to the water molecule. There is no interaction between different molecules ($A$ and $B$). All three independent molecules [$A$ and $B$ of compound (1) and the molecule of compound (2)] form a similar layer pattern through formation of chains of hydrogen-bonded rings connecting *cis* peptide groups, and chains of hydrophobic interactions. In (1), the hydrophobic region is formed by an interdigitation of phenyl rings and in (2) the hydrophobic region contains contacts between the alanyl methyl groups and the phenyl rings of a neighboring chain. The hydrogen-bonding parameters are listed in Table 4.

The observed crystal packing agrees with that predicted for diketopiperazines in the solid state (Benedetti, Cor-

radini & Pedone, 1969). Using graph notation (Etter, 1990), for both compounds (for the three molecules) there are first-order chains $C_1^1(5)C_1^1(5)$ and second-order rings $R_2^2(8)$. Molecule $B$ of compound (1) also has a second-order pattern of $R_6^4(18)$ involving the water molecule. The packing scheme for (1) is presented in Figs. 3($a$) and 3($b$), for molecules $A$ and $B$, respectively, and that for (2) is shown in Fig. 4.



($a$)



($b$)
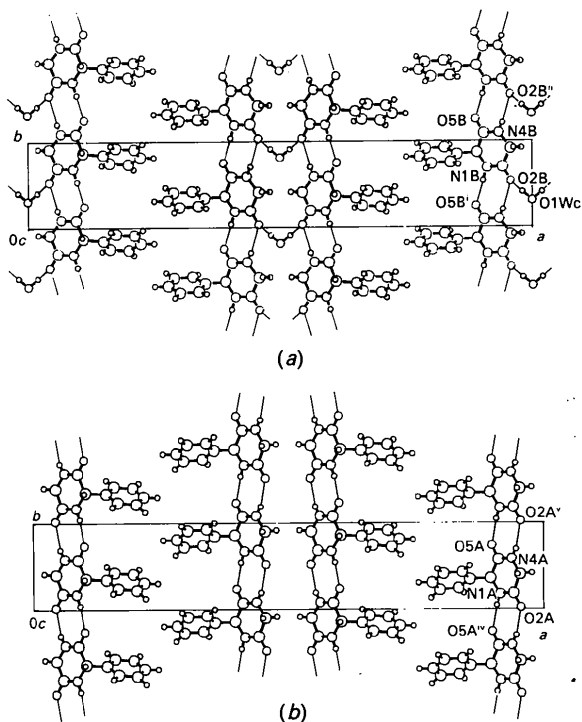
Fig. 3. The crystal packing of compound (1) as seen along the [001] direction: ($a$) the section around $z = 0.5$ (molecules $A$) and ($b$) the section around $z = 0$ (molecules $B$ and water); the symmetry codes are (i) $x$, $-1 + y$, $z$ and (ii) $x$, $1 + y$, $z$.
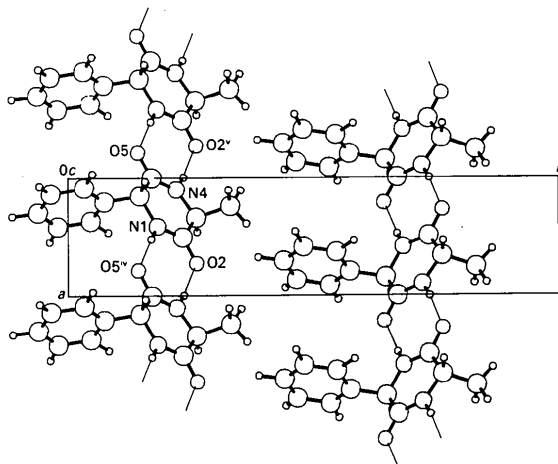


Fig. 4. The crystal packing of compound (2) as seen along the [001] direction; the symmetry codes are (iv) $1 + x$, $y$, $1 + z$ and (v) $-1 + x$, $y$, $-1 + z$.

## Experimental

### Compound (1)

*Crystal data*

$C_{10}H_{10}N_2O_2.0.25H_2O$
$M_r = 194.70$
Monoclinic
$C2$
$a = 37.462$ (2) Å
$b = 6.2017$ (3) Å
$c = 8.1843$ (4) Å
$\beta = 98.891$ (4)°
$V = 1878.6$ (2) Å$^3$
$Z = 8$
$D_x = 1.377$ Mg m$^{-3}$

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25
  reflections
$\theta = 30.29-50.07°$
$\mu = 0.824$ mm$^{-1}$
$T = 293$ (2) K
Prism
$0.54 \times 0.44 \times 0.12$ mm
Colorless

*Data collection*

CAD-4F diffractometer
$\omega/2\theta$ scans
Absorption correction:
  none
2274 measured reflections
2124 independent reflections
2057 observed reflections
  [$I > 2\sigma(I)$]

$R_{int} = 0.0242$
$\theta_{max} = 74.90°$
$h = -46 \rightarrow 46$
$k = -7 \rightarrow 0$
$l = 0 \rightarrow 10$
3 standard reflections
  frequency: 2000 min
  intensity variation: 2%

*Refinement*

Refinement on $F^2$
$R(F) = 0.0444$
$wR(F^2) = 0.1287$
$S = 1.075$
2115 reflections
337 parameters
All H-atom parameters re-
  fined except for those of
  H1$W$
Calculated weights
  $w = 1/[\sigma^2(F_o^2) + (0.0932P)^2 + 0.3109P]$
  where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.003$

$\Delta\rho_{max} = 0.254$ e Å$^{-3}$
$\Delta\rho_{min} = -0.239$ e Å$^{-3}$
Extinction correction:
  SHELXL92 (Sheldrick,
  1994)
Extinction coefficient:
  0.002 (0)
Atomic scattering factors
  from International Tables
  for Crystallography (1992,
  Vol. C, Tables 4.2.6.8 and
  6.1.1.4)
Absolute configuration:
  Flack (1983)

### Compound (2)

*Crystal data*

$C_{11}H_{12}N_2O_2$
$M_r = 204.23$
Monoclinic
$P2_1$
$a = 5.0084$ (6) Å
$b = 20.367$ (3) Å
$c = 5.2057$ (5) Å
$\beta = 105.198$ (8)°
$V = 512.44$ (11) Å$^3$
$Z = 2$
$D_x = 1.324$ Mg m$^{-3}$

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25
  reflections
$\theta = 17.9-46.8°$
$\mu = 0.761$ mm$^{-1}$
$T = 293$ (2) K
Plate
$0.40 \times 0.20 \times 0.20$ mm
Colorless

*Data collection*

CAD-4F diffractometer
$\omega/2\theta$ scans

$R_{int} = 0.0976$
$\theta_{max} = 74.83°$

Absorption correction:
  none
1211 measured reflections
1093 independent reflections
1060 observed reflections
  [$I > 2\sigma(I)$]

$h = 0 \rightarrow 6$
$k = 0 \rightarrow 25$
$l = -6 \rightarrow 6$
3 standard reflections
  frequency: 2000 min
  intensity variation: 1.5%

*Refinement*

Refinement on $F^2$
$R(F) = 0.0462$
$wR(F^2) = 0.1174$
$S = 1.106$
1092 reflections
183 parameters
All H-atom parameters
  refined
Calculated weights
  $w = 1/[\sigma^2(F_o^2) + (0.0759P)^2 + 0.0369P]$
  where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.0001$

$\Delta\rho_{max} = 0.172$ e Å$^{-3}$
$\Delta\rho_{min} = -0.228$ e Å$^{-3}$
Extinction correction:
  SHELXL92 (Sheldrick,
  1994)
Extinction coefficient:
  0.033 (5)
Atomic scattering factors
  from International Tables
  for Crystallography (1992,
  Vol. C, Tables 4.2.6.8 and
  6.1.1.4)
Absolute configuration:
  Flack (1983)

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

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

| | $x$ | $y$ | $z$ | $U_{eq}$ |
|---|---|---|---|---|
| Compound (1) | | | | |
| N1$A$ | 0.91497 (5) | 0.1743 (3) | 0.1091 (3) | 0.0406 (5) |
| C2$A$ | 0.94175 (6) | 0.1828 (4) | 0.2362 (3) | 0.0373 (5) |
| O2$A$ | 0.95594 (5) | 0.0204 (3) | 0.3064 (3) | 0.0492 (5) |
| C3$A$ | 0.95481 (7) | 0.4006 (4) | 0.3006 (4) | 0.0434 (5) |
| N4$A$ | 0.93762 (5) | 0.5832 (4) | 0.2092 (3) | 0.0416 (5) |
| C5$A$ | 0.91145 (6) | 0.5746 (4) | 0.0798 (3) | 0.0386 (5) |
| O5$A$ | 0.89902 (6) | 0.7372 (3) | 0.0068 (3) | 0.0560 (5) |
| C6$A$ | 0.89618 (6) | 0.3565 (4) | 0.0200 (3) | 0.0375 (5) |
| C1'$A$ | 0.85580 (6) | 0.3444 (4) | 0.0236 (3) | 0.0377 (5) |
| C2'$A$ | 0.84054 (7) | 0.4274 (6) | 0.1529 (3) | 0.0533 (6) |
| C3'$A$ | 0.80367 (8) | 0.4103 (7) | 0.1546 (4) | 0.0651 (8) |
| C4'$A$ | 0.78203 (8) | 0.3075 (6) | 0.0287 (5) | 0.0644 (8) |
| C5'$A$ | 0.79663 (8) | 0.2227 (7) | −0.0985 (5) | 0.0730 (9) |
| C6'$A$ | 0.83363 (7) | 0.2418 (6) | −0.1032 (4) | 0.0568 (7) |
| N1$B$ | 0.91022 (5) | 0.6867 (3) | 0.5904 (3) | 0.0395 (5) |
| C2$B$ | 0.94093 (6) | 0.6966 (4) | 0.6939 (3) | 0.0401 (5) |
| O2$B$ | 0.95710 (5) | 0.5316 (3) | 0.7521 (3) | 0.0578 (6) |
| C3$B$ | 0.95686 (7) | 0.9120 (4) | 0.7434 (4) | 0.0500 (7) |
| N4$B$ | 0.93367 (5) | 1.0922 (4) | 0.6893 (3) | 0.0414 (5) |
| C5$B$ | 0.90403 (6) | 1.0856 (4) | 0.5769 (3) | 0.0376 (5) |
| O5$B$ | 0.88768 (5) | 1.2495 (3) | 0.5247 (3) | 0.0574 (6) |
| C6$B$ | 0.89032 (6) | 0.8672 (3) | 0.5085 (3) | 0.0354 (5) |
| C1'$B$ | 0.85006 (5) | 0.8448 (4) | 0.5137 (3) | 0.0350 (4) |
| C2'$B$ | 0.82575 (6) | 0.9242 (5) | 0.3818 (3) | 0.0481 (6) |
| C3'$B$ | 0.78878 (7) | 0.9099 (6) | 0.3859 (4) | 0.0610 (7) |
| C4'$B$ | 0.77635 (7) | 0.8168 (6) | 0.5170 (5) | 0.0610 (8) |
| C5'$B$ | 0.80030 (7) | 0.7373 (6) | 0.6472 (4) | 0.0599 (7) |
| C6'$B$ | 0.83732 (7) | 0.7521 (5) | 0.6462 (3) | 0.0481 (6) |
| O1$W$ | 1/2 | 0.8121 (8) | 1 | 0.0888 (11) |
| Compound (2) | | | | |
| N1 | 0.4139 (4) | 0.18247 (11) | 0.9446 (4) | 0.0434 (5) |
| C2 | 0.5058 (5) | 0.23474 (11) | 0.8433 (5) | 0.0419 (5) |
| O2 | 0.7266 (4) | 0.26245 (10) | 0.9558 (4) | 0.0555 (5) |
| C3 | 0.3393 (5) | 0.26187 (14) | 0.5808 (5) | 0.0473 (6) |
| C31 | 0.2415 (9) | 0.3312 (2) | 0.6225 (10) | 0.0857 (14) |
| N4 | 0.1022 (4) | 0.22143 (11) | 0.4539 (4) | 0.0447 (5) |
| C5 | 0.0026 (5) | 0.17111 (12) | 0.5597 (5) | 0.0430 (5) |
| O5 | −0.2148 (4) | 0.14333 (10) | 0.4432 (4) | 0.0597 (6) |
| C6 | 0.1558 (4) | 0.14691 (12) | 0.8356 (4) | 0.0416 (5) |

| | | | |
|---|---|---|---|
| C1' | 0.2057 (5) | 0.07386 (13) | 0.8368 (5) | 0.0474 (6) |
| C2' | 0.0879 (10) | 0.0330 (2) | 0.9848 (10) | 0.0816 (12) |
| C3' | 0.1353 (15) | −0.0345 (3) | 0.9831 (16) | 0.120 (2) |
| C4' | 0.2948 (11) | −0.0606 (2) | 0.8367 (13) | 0.104 (2) |
| C5' | 0.4138 (11) | −0.0203 (2) | 0.6890 (13) | 0.099 (2) |
| C6' | 0.3684 (8) | 0.0468 (2) | 0.6896 (9) | 0.0734 (10) |

## Table 2. Selected geometric parameters (Å, °) for compounds (1) and (2)

**Compound (1)**

| | | | |
|---|---|---|---|
| N1A—C2A | 1.330 (3) | N1B—C2B | 1.321 (3) |
| N1A—C6A | 1.465 (3) | N1B—C6B | 1.450 (3) |
| C2A—O2A | 1.238 (3) | C2B—O2B | 1.246 (3) |
| C2A—C3A | 1.504 (3) | C2B—C3B | 1.493 (3) |
| C3A—N4A | 1.452 (3) | C3B—N4B | 1.443 (4) |
| N4A—C5A | 1.329 (3) | N4B—C5B | 1.328 (3) |
| C5A—O5A | 1.227 (3) | C5B—O5B | 1.229 (3) |
| C5A—C6A | 1.520 (3) | C5B—C6B | 1.524 (3) |
| C6A—C1'A | 1.519 (3) | C6B—C1'B | 1.522 (3) |
| C1'A—C2'A | 1.377 (4) | C1'B—C6'B | 1.376 (3) |
| C1'A—C6'A | 1.380 (3) | C1'B—C2'B | 1.391 (3) |
| C2'A—C3'A | 1.388 (4) | C2'B—C3'B | 1.393 (3) |
| C3'A—C4'A | 1.366 (5) | C3'B—C4'B | 1.362 (5) |
| C4'A—C5'A | 1.355 (5) | C4'B—C5'B | 1.374 (5) |
| C5'A—C6'A | 1.398 (4) | C5'B—C6'B | 1.391 (3) |

**Compound (2)**

| | | | |
|---|---|---|---|
| N1—C2 | 1.323 (3) | C5—C6 | 1.522 (3) |
| N1—C6 | 1.460 (3) | C6—C1' | 1.508 (4) |
| C2—O2 | 1.243 (3) | C1'—C2' | 1.368 (5) |
| C2—C3 | 1.507 (3) | C1'—C6' | 1.372 (5) |
| C3—N4 | 1.454 (3) | C2'—C3' | 1.397 (9) |
| C3—C31 | 1.528 (5) | C3'—C4' | 1.349 (11) |
| N4—C5 | 1.322 (4) | C4'—C5' | 1.365 (9) |
| C5—O5 | 1.236 (3) | C5'—C6' | 1.386 (5) |

**Compound (1)**

| | | | |
|---|---|---|---|
| C2A—N1A—C6A | 127.2 (2) | C2B—N1B—C6B | 126.5 (2) |
| O2A—C2A—N1A | 123.3 (2) | O2B—C2B—N1B | 122.1 (2) |
| O2A—C2A—C3A | 118.4 (2) | O2B—C2B—C3B | 118.7 (2) |
| N1A—C2A—C3A | 118.4 (2) | N1B—C2B—C3B | 119.2 (2) |
| N4A—C3A—C2A | 115.2 (2) | N4B—C3B—C2B | 114.4 (2) |
| C5A—N4A—C3A | 126.4 (2) | C5B—N4B—C3B | 126.0 (2) |
| O5A—C5A—N4A | 122.2 (2) | O5B—C5B—N4B | 122.2 (2) |
| O5A—C5A—C6A | 118.6 (2) | O5B—C5B—C6B | 119.1 (2) |
| N4A—C5A—C6A | 119.2 (2) | N4B—C5B—C6B | 118.7 (2) |
| N1A—C6A—C1'A | 110.8 (2) | N1B—C6B—C1'B | 111.0 (2) |
| N1A—C6A—C5A | 113.5 (2) | N1B—C6B—C5B | 113.4 (2) |
| C1'A—C6A—C5A | 111.4 (2) | C1'B—C6B—C5B | 110.5 (2) |
| C2'A—C1'A—C6'A | 118.5 (2) | C6'B—C1'B—C2'B | 119.6 (2) |
| C2'A—C1'A—C6A | 121.9 (2) | C6'B—C1'B—C6B | 121.7 (2) |
| C6'A—C1'A—C6A | 119.6 (2) | C2'B—C1'B—C6B | 118.6 (2) |
| C1'A—C2'A—C3'A | 120.7 (3) | C1'B—C2'B—C3'B | 119.5 (2) |
| C4'A—C3'A—C2'A | 120.2 (3) | C4'B—C3'B—C2'B | 120.5 (3) |
| C5'A—C4'A—C3'A | 119.9 (3) | C3'B—C4'B—C5'B | 120.1 (2) |
| C4'A—C5'A—C6'A | 120.5 (3) | C4'B—C5'B—C6'B | 120.3 (3) |
| C1'A—C6'A—C5'A | 120.2 (3) | C1'B—C6'B—C5'B | 120.0 (2) |

**Compound (2)**

| | | | |
|---|---|---|---|
| C2—N1—C6 | 127.5 (2) | N1—C6—C1' | 111.0 (2) |
| O2—C2—N1 | 122.5 (2) | N1—C6—C5 | 112.5 (2) |
| O2—C2—C3 | 118.3 (2) | C1'—C6—C5 | 111.4 (2) |
| N1—C2—C3 | 119.3 (2) | C2'—C1'—C6' | 118.5 (3) |
| N4—C3—C2 | 113.3 (2) | C2'—C1'—C6 | 120.4 (3) |
| N4—C3—C31 | 109.5 (2) | C6'—C1'—C6 | 121.1 (3) |
| C2—C3—C31 | 109.4 (3) | C1'—C2'—C3' | 119.7 (6) |
| C5—N4—C3 | 127.1 (2) | C4'—C3'—C2' | 121.2 (5) |
| O5—C5—N4 | 122.1 (2) | C3'—C4'—C5' | 119.5 (4) |
| O5—C5—C6 | 118.4 (2) | C4'—C5'—C6' | 119.8 (5) |
| N4—C5—C6 | 119.5 (2) | C1'—C6'—C5' | 121.3 (4) |

## Table 3. Selected torsion angles (°) for compounds (1) and (2)

| | φ | ψ | ω |
|---|---|---|---|
| (1) (molecule A) | 1.8 (3) | −3.2 (3) | 0.6 (4) |
| | 3.2 (3) | −4.5 (3) | 2.2 (4) |

| | | | |
|---|---|---|---|
| (1) (molecule B) | −14.1 (4) | 8.6 (4) | 3.8 (4) |
| | −11.2 (3) | 5.9 (3) | 6.6 (4) |
| (2) | 10.1 (4) | −6.1 (4) | −2.2 (4) |
| | 7.1 (3) | −3.3 (3) | −5.3 (4) |

## Table 4. Hydrogen-bonding geometry (Å,°) for compounds (1) and (2)

| D | A | D—H | H···A | D···A | D—H···A |
|---|---|---|---|---|---|
| **(1)** | | | | | |
| N1A | O5Aⁱ | 0.89 (4) | 1.99 (4) | 2.873 (3) | 173 (3) |
| N4A | O2Aⁱⁱ | 0.75 (5) | 2.16 (5) | 2.878 (3) | 161 (3) |
| N1B | O5Bⁱ | 1.00 (6) | 1.87 (6) | 2.866 (3) | 169 (4) |
| N4B | O2Bⁱⁱ | 0.74 (4) | 2.15 (5) | 2.884 (3) | 174 (3) |
| O1W | O2Bⁱⁱⁱ | 1.08 | 1.70 | 2.747 (3) | 163 |
| **(2)** | | | | | |
| N1 | O5ⁱᵛ | 0.92 (4) | 1.97 (4) | 2.881 (3) | 174 (3) |
| N4 | O2ᵛ | 0.87 (4) | 2.03 (4) | 2.899 (3) | 174 (3) |

Symmetry codes: (i) $x, -1 + y, z$; (ii) $x, 1 + y, z$; (iii) $-\frac{1}{2} + x, \frac{1}{2} + y, z$; (iv) $1 + x, y, 1 + z$; (v) $-1 + x, y, -1 + z$.

Data collection: *CAD-4F*. Cell refinement: *CAD-4F*. Data reduction: *XRAY* (Stewart, 1978). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*92 (Sheldrick, 1994). Molecular graphics: *ORTEP*II (Johnson, 1976); *PLUTO* (Motherwell & Clegg, 1978). Software used to prepare material for publication: *SHELXL*92.

## References

Benedetti, E., Corradini, P. & Pedone, C. (1969). *J. Phys. Chem.* **73**, 2891–2895.

Benedetti, E., Marsh, R. E. & Goodman, M. (1976). *J. Am. Chem. Soc.* **98**, 6676–6684.

Codding, P. W., Duke, N. E., Aha, J., Palmer, L. Y., McClurg, D. K. & Szkaradzinska, M. B. (1990). *Crystallographic and Modeling Methods in Molecular Design*, edited by C. E. Bugg & S. E. Ealick, pp.151–160. Berlin: Springer Verlag.

Codding, P. W., Lee, T. A. & Richardson, J. F. (1984). *J. Med. Chem.* **27**, 649–654.

Duke, N. E. C. & Codding, P. W. (1992). *J. Med. Chem.* **35**, 1806–1812.

Etter, M. (1990). *Acc. Chem. Res.* **23**, 120–126.

Filhol, A. & Timmins, P. A. (1976). *Acta Cryst.* B**32**, 3116–3118.

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

IUPAC-IUB Commission on Biochemical Nomenclature (1970). *Biochemistry*, **9**, 3471–3479.

Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Motherwell, W. D. S. & Clegg, W. (1978). *PLUTO. Program for Plotting Molecular and Crystal Structures*. Univ. of Cambridge, England.

Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.

Sheldrick, G. M. (1994). *J. Appl. Cryst.* In preparation.

Stewart, J. M. (1978). Editor. *The XRAY System of Crystallographic Programs*. Technical Report TR-446. Computer Science Center, Univ. of Maryland, College Park, Maryland, USA.

Weaver, D., Edgecombe, K. E., Smith, V. H. & Anderson, M. N. (1992). *IBM Visions, Computer Assisted Rational Drug Design Software*, pp. 533-593. IBM Corporation, USA.

*Acta Cryst.* (1994). C50, 569–574

# Stereochemistry of Transposition Reactions Involving Polycyclic Methylenecyclobutanol Derivatives

S. Ianelli and M. Nardelli*

*Istituto di Chimica Generale ed Inorganica, Università degli Studi di Parma, Centro di Studio per la Strutturistica Diffrattometrica del CNR, Viale delle Scienze 78, I-43100 Parma, Italy*

D. Belletti

*Istituto di Strutturistica Chimica, Università degli Studi di Parma, Centro di Studio per la Strutturistica Diffrattometrica del CNR, Viale delle Scienze 78, I-43100 Parma, Italy*

N. Brosse, B. Jamart-Grégoire and P. Caubère

*Laboratoire de Chimie Organique I, UA CNRS No. 457, Université de Nancy I, BP 239, 54506 Vandoeuvre-Les-Nancy CEDEX, France*

## Abstract

The configurations at the junctions of tricyclic systems obtained by transposition reactions have been defined by crystal structure analyses of the compounds *trans,syn,cis*-1-acetoxytricyclo[7.4.0.0$^{2,7}$]tridecan-8-one [C$_{15}$H$_{22}$O$_3$, (2a); IUPAC name: 8-oxotricyclo[7.4.0.0$^{2,7}$]tridecan-1-yl acetate] and *cis,anti,cis*-1-acetoxy-7-hydroxytricyclo-[7.3.0.0$^{2,7}$]dodecan-8-one, [C$_{14}$H$_{20}$O$_4$, (4); IUPAC name: 7-hydroxy-8-oxotricyclo[7.3.0.0$^{2,7}$]dodecan-1-yl acetate]. This knowledge is important in our understanding of how these reactions occur. The geometries of the molecules in the crystal, found by X-ray diffraction, are compared with those calculated for the isolated molecules by molecular-mechanics methods.

## Comment

During the study of the behaviour of the (1a) substrates with the purpose of synthesizing functionalized tricyclic compounds such as (2a) and (4), according to the following scheme, it was found necessary to unambiguously define the stereochemistry of the transposition process.
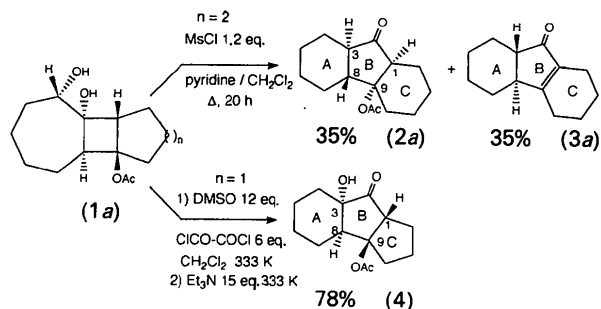


For this purpose, although some information concerning the nature of the A/B junction could be obtained from the NMR spectrum of (2a), such information could not be obtained for the B/C junction. The same is true for this ring junction in compounds (1a) and (4), and therefore a correlation between the starting materials and the transposed products could not be established. Thus, the structures of compounds (2a) and (4) were studied by X-ray diffraction and the results are illustrated in the present paper. The structure of the starting product (1a) (n = 3) has been determined previously (Ianelli, Nardelli, Belletti, Brosse, Jamart-Grégoire & Caubère, 1993).

From the results of these analyses it appears that during transposition of (1a), regardless of conditions, the B/C junction is preserved in (2a) and (4), demonstrating that no epimerization occurs during this process. In the same way the relative position of the acetate group and the proton is also retained. The interesting point is that the transposition leading to an A/B *trans* junction in (2a), gives a *cis* junction in (4).

Compound (1b), whose crystal structure has also been determined recently (Ianelli *et al.*, 1993), was submitted to transposition leading to compounds (2b) and (3a), according to the process shown below.
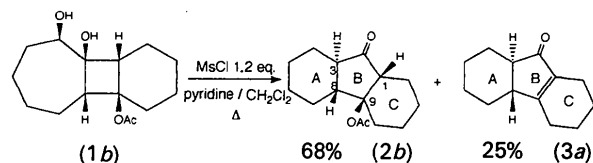


The configuration at the A/B junction of compound (3a) has been defined previously (Jamart-Grégoire, Brosse, Ianelli, Nardelli & Caubère, 1993). The NMR spectrum of (2b) gives a coupling constant for the C3 and C8 protons identical to that of compound (2a), showing that a *trans* junction also exists. These results lead to the relevant conclusion that, in this series, transposition without oxidation occurs maintaining the configurations at C atoms, while transposition with oxidation seems to lead to the most thermodynamically stable compound.