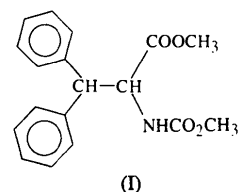Stewart, J. M., Kundell, F. A. & Baldwin, J. C. (1980). *The XRAY80 System.* Computer Science Center, University of Maryland, College Park, Maryland, USA.
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Methyl 2-Methoxycarbonylamino-3,3-diphenylpropionate, an Interesting Diphenylalanine (DIP) Derivative

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Abstract

Molecules of the interesting racemic 3,3-diphenylalanine derivative, $C_{18}H_{19}NO_4$, contain a DIP amino acid residue which adopts a semi-extended conformation. The values of φ and ψ are $-91.0\,(5)$ and $130.4\,(4)^\circ$, respectively, for the L enantiomer. The crystal structure consists of cyclic (urethane)N—H$\cdots$O=C(methyl ester) hydrogen-bonded dimers piled up in columns running parallel to the crystallographic *a* axis.

Comment

Models for bioactive conformations of peptides have been deduced from structure–activity relationships involving local or large-size constraints of the backbone orientation *via* the incorporation of *N*-methylamino acids or proline, or through cyclization. However, in order to probe the relative arrangement of the side chain of each amino acid and then generate a more precise three-dimensional envelope representing the space-filling requirements of the bioactive conformation, topographic probes which will stabilize one or two rotamers of the side chain have to be designed (Kazmierski, Yamamura & Hruby, 1991). Diphenylalanine (DIP) (Chen, Beylin, Marlatt, Leja & Guel, 1992; Josien, Martin & Chassaing, 1991) was first selected because the aromatic rings of phenylalanine often play a crucial role in peptide–receptor recognition. Recently, D-3,3-diphenylalanine (D-DIP) has proved to be a key substructural substituent in a potent peptidyl antagonist of the ET_A and ET_B endothelin receptors (Cody *et al.*, 1992). We now report the stereochemical details of the title compound, (I), an interesting DIP derivative.

(I)

The urethane linkage is found in the usual *trans* conformation [torsion angle ω_0 (C3—N—C4—O4) is 178.6 (4)°]. This, together with the *trans* arrangement of the C5—O4 bond relative to C4—N [torsion angle θ_1 (C5—O4—C4—N) is 178.0 (4)°], allows us to classify the urethane moiety as type *b* (*trans,trans*) (Benedetti *et al.*, 1980) (Fig. 1).
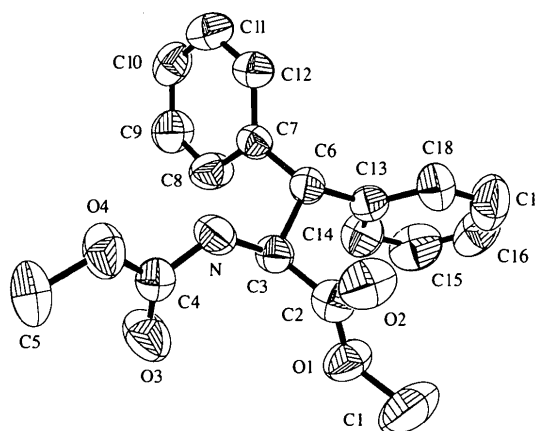

Fig. 1. The molecular structure of (I) showing 50% probability displacement ellipsoids. H atoms have been omitted for clarity.

The methyl ester group has the C1—O1—C2—C3 sequence in a *trans* disposition [176.1 (4)°] and the angle between the average planes of the urethane and methyl ester groups is 73.4 (2)°.

The DIP residue adopts a semi-extended conformation (IUPAC–IUB Commission on Biochemical Nomenclature, 1970); for the L enantiomer, the backbone torsion angles [C4—N—C3—C2 (φ) $-91.0\,(5)$ and N—C3—C2—O1 (ψ) 130.4 (4)°] fall in the *F* region of the conformational map (Zimmerman, Pottle, Nemethy & Scheraga, 1977). The two phenyl groups are *gauche* and *trans* with respect to the peptide chain, since the torsion angles around the C_α—C_β bond of the side chain [N—C3—C6—C7 (χ^{11}) and N—C3—C6—C13 (χ^{12})] are $-60.3\,(5)$ and 171.1 (4)°. The dihedral angle between the phenyl rings is 68.8 (2)°.

The crystal structure of (I) consists of cyclic hydrogen-bonded centrosymmetric dimers piled up along the crystallographic *a* axis. The urethane H atom is hydrogen bonded to the methyl ester O2 atom of the nearest symmetry-related molecule [H$\cdots$O2^i 2.28, N$\cdots$O2^i 3.109 (6) Å and N—H$\cdots$O2^i 162°; symmetry code: (i) $2-x$, $-1-y$, $-1-z$].

Experimental

The title compound, (I), was prepared from 2-cyano-3,3-di-phenylpropanoic acid in three steps [(i) partial hydrolysis of the cyano group to the amide, (ii) esterification of the carboxylic acid with diazomethane and (iii) Hoffman-type rearrangement] according to the method of Cativiela, Díaz-de-Villegas & Gálvez (1994).

Crystal data

$C_{18}H_{19}NO_4$	Mo $K\alpha$ radiation
$M_r = 313.34$	$\lambda = 0.71073$ Å
Monoclinic	Cell parameters from 28
$P2_1/n$	reflections
$a = 8.222\,(2)$ Å	$\theta = 5.22\text{--}11.55°$
$b = 12.244\,(3)$ Å	$\mu = 0.086$ mm^{-1}
$c = 17.277\,(4)$ Å	$T = 293\,(2)$ K
$\beta = 99.000\,(10)°$	Prism
$V = 1717.9\,(7)$ Å^3	$0.36 \times 0.20 \times 0.18$ mm
$Z = 4$	Colourless
$D_x = 1.212$ Mg m^{-3}	
D_m not measured	

Data collection

Siemens $P4$ diffractometer	$\theta_{max} = 25°$
$\theta/2\theta$ scans	$h = -1 \rightarrow 9$
Absorption correction:	$k = -1 \rightarrow 14$
none	$l = -20 \rightarrow 20$
4049 measured reflections	3 standard reflections
3010 independent reflections	monitored every 97
1117 observed reflections	reflections
$[I > 2\sigma(I)]$	intensity decay: none
$R_{int} = 0.0481$	

Refinement

Refinement on F^2	$(\Delta/\sigma)_{max} = 0.001$
$R(F) = 0.0742$	$\Delta\rho_{max} = 0.17$ e Å^{-3}
$wR(F^2) = 0.2042$	$\Delta\rho_{min} = -0.16$ e Å^{-3}
$S = 1.015$	Extinction correction: none
3010 reflections	Atomic scattering factors
209 parameters	from *International Tables*
Only H-atom U's refined	*for Crystallography* (1992,
$w = 1/[\sigma^2(F_o^2) + (0.0737P)^2]$	Vol. C, Tables 4.2.6.8 and
where $P = (F_o^2 + 2F_c^2)/3$	6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

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

	x	y	z	U_{eq}
O1	0.5881 (4)	−0.4238 (3)	−0.6203 (2)	0.0753 (12)
O2	0.7853 (5)	−0.5321 (3)	−0.5571 (2)	0.0820 (13)
O3	0.6739 (5)	−0.2409 (3)	−0.4431 (2)	0.0955 (15)
O4	0.8830 (5)	−0.2901 (3)	−0.3504 (2)	0.0761 (12)
N	0.8927 (5)	−0.3309 (3)	−0.4742 (2)	0.0630 (13)
C1	0.4903 (8)	−0.5201 (5)	−0.6452 (4)	0.122 (3)
C2	0.7346 (7)	−0.4431 (5)	−0.5766 (3)	0.0600 (15)
C3	0.8322 (6)	−0.3363 (4)	−0.5584 (2)	0.0513 (13)
C4	0.8046 (8)	−0.2830 (4)	−0.4245 (3)	0.0557 (13)
C5	0.8055 (8)	−0.2391 (5)	−0.2907 (3)	0.099 (2)
C6	0.9792 (6)	−0.3339 (4)	−0.6045 (3)	0.0518 (13)
C7	1.0813 (6)	−0.2299 (4)	−0.5892 (2)	0.0476 (12)
C8	1.0110 (7)	−0.1262 (5)	−0.5933 (3)	0.074 (2)
C9	1.1105 (8)	−0.0323 (5)	−0.5852 (3)	0.082 (2)
C10	1.2786 (8)	−0.0414 (5)	−0.5719 (3)	0.074 (2)
C11	1.3490 (7)	−0.1429 (5)	−0.5654 (3)	0.073 (2)
C12	1.2520 (6)	−0.2373 (4)	−0.5747 (3)	0.0579 (14)
C13	0.9235 (6)	−0.3572 (4)	−0.6912 (3)	0.0517 (13)
C14	0.8361 (7)	−0.2826 (5)	−0.7422 (3)	0.078 (2)
C15	0.7889 (8)	−0.3060 (7)	−0.8211 (4)	0.099 (2)
C16	0.8277 (9)	−0.4062 (8)	−0.8499 (4)	0.103 (3)
C17	0.9114 (10)	−0.4818 (6)	−0.8005 (4)	0.102 (2)
C18	0.9601 (7)	−0.4568 (5)	−0.7222 (3)	0.074 (2)

Table 2. *Selected geometric parameters (Å, °)*

O1—C2	1.339 (6)	N—C4	1.342 (6)
O1—C1	1.454 (6)	N—C3	1.463 (5)
O2—C2	1.196 (6)	C2—C3	1.542 (7)
O3—C4	1.190 (6)	C3—C6	1.548 (6)
O4—C4	1.344 (5)	C6—C13	1.522 (6)
O4—C5	1.437 (6)	C6—C7	1.526 (6)
C2—O1—C1	115.5 (4)	N—C4—O4	110.8 (5)
C4—O4—C5	117.1 (5)	C13—C6—C7	113.5 (4)
C4—N—C3	121.5 (4)	C13—C6—C3	111.3 (4)
O2—C2—O1	124.3 (5)	C7—C6—C3	112.3 (4)
O2—C2—C3	124.6 (5)	C12—C7—C8	118.0 (5)
O1—C2—C3	111.0 (5)	C12—C7—C6	119.3 (5)
N—C3—C2	109.1 (4)	C8—C7—C6	122.7 (4)
N—C3—C6	109.8 (4)	C18—C13—C14	117.1 (5)
C2—C3—C6	109.5 (4)	C18—C13—C6	119.7 (4)
O3—C4—N	124.9 (5)	C14—C13—C6	123.2 (5)
O3—C4—O4	124.3 (5)		
C1—O1—C2—C3	176.1 (4)	C5—O4—C4—N	178.0 (4)
C4—N—C3—C2	−91.0 (5)	N—C3—C6—C13	171.1 (4)
O1—C2—C3—N	130.4 (4)	N—C3—C6—C7	−60.3 (5)
C3—N—C4—O4	178.6 (4)		

The title structure was refined by blocked full-matrix least squares with anisotropic displacement parameters for all non-H atoms. H atoms were located in calculated positions and refined with one overall isotropic displacement parameter.

Data collection: *XSCANS* (Siemens, 1993). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1992). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *SHELXTL-Plus* (Sheldrick, 1989). Software used to prepare material for publication: *SHELXL93*. Geometric calculations: *PARST* (Nardelli, 1983).

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Absolute Configuration of Chlorojanerin,† a Chlorine-Containing Guaianolide from *Centaurea scoparia*

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Abstract

The title guaianolide, chlorojanerin [(1*R*,3*S*,4*R*,5*S*,6*S*,-7*R*,8*S*)-4-chloromethyl-3,4-dihydroxy-8-(4-hydroxymethacryloyl)-1*H*,5*H*,6*H*,7*H*-guaia-10(14),11(13)-dien-6,12-olide, $C_{19}H_{23}ClO_7$], was obtained from the ethanol extracts of the air-dried aerial flowering parts of the Egyptian plant *Centaurea scoparia* Sieb. Its absolute configuration has been elucidated by X-ray analysis, which confirms the structure as a chlorine-containing guaianolide with the 4-hydroxymethacryloyl function at the C8 position, as previously proposed on the basis of ^1H NMR and CD spectral evidence.

† IUPAC nomenclature: 9-chloromethyl-8,9-dihydroxy-3,6-bis(methylene)-2,3,3a,4,5,6,6a,7,8,9,9a,9b-dodecahydro-2-oxoazuleno[4,5-*b*]furan-4-yl 2-(hydroxymethyl)propenoate.

Comment

Chlorojanerin, (I), was isolated from the ethanol extract of *Centaurea scoparia* Sieb. It belongs to the class of rare genuine chlorine-containing sesquiterpene lactones with a guaianolide skeleton, which bears the halogen at position C15, two hydroxy groups at positions C3 and C4, and two *exo*-methylene functions at C10 and C11, together with the 4-hydroxymethacryloyl moiety at C8. Members of the chlorine-containing natural compound family were frequently isolated from marine algae and fungi, but occasionally also identified in the Asteraceae as chlorinated sesquiterpene lactones (Engvild, 1986). Recently, the complete NMR data set, as well as the relative stereochemistry of chlorojanerin, has been reported (Youssef & Frahm, 1994), but no investigation of the absolute configuration has thus far been published. Chlorojanerin was first isolated from *Centaurea janeri* (Gonzalez, Bermejo, Gabrera, Galindo & Massanet, 1977) and its structure proposed on the basis of an incomplete set of ^1H NMR data. Neither the ^{13}C NMR data nor the relative stereochemistry of chlorojanerin were contained in this paper. The absolute configuration of chlorojanerin has been elucidated by means of X-ray diffraction analysis as (1*R*,3*S*,4*R*,5*S*,6*S*,7*R*,8*S*) and is presented here for the first time.
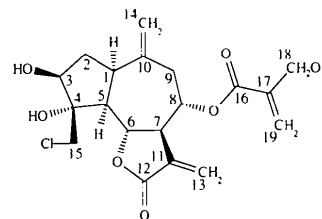
(I)

The dihedral angles H11—C1—C5—H51 (H1α/H5α) 42 (2), H51—C5—C6—H61 (H5α/H6β) −179 (2), H61—C6—C7—H71 (H6β/H7α) −140 (2) and H71—C7—C8—H81 (H7α/H8β) −173 (2)° (Table 3) give evidence of the *cis/anti/trans/trans*-junction of the five- and seven-membered rings, and the seven-membered and γ-lactone rings, as well as of the α-configuration of the ester moiety at position C8, together with the α orientation of the H atoms in positions 1, 3, 5 and 7, and the β orientation of the H atoms in positions 6 and 8 (Fig. 1). The hydroxy group in position 3 and the chloromethyl group in position 4 exist in a pseudo-equatorial, and the hydroxy group in position 4 and the ester moiety in position 8 in a pseudo-axial configuration, whereas the seven-membered ring assumes a distorted twist-chair-like conformation. The C6*S*/C7*R* *trans*-annulation of the γ-lactone ring is in agreement with the observed negative Cotton effect in the CD spectrum of chlorojanerin at 260 nm for the *n–π** transition of the α-methylene γ-lactone chromophore (Youssef & Frahm, 1996).