C6αA—O6γA—C6δA	115.4 (2)
N1A—C2A—N2αA	114.0 (3)
N3A—C2A—N2αA	116.6 (3)
C2A—N2αA—C2βA	124.9 (3)
N2αA—C2βA—O2γA	124.4 (3)
N3A—C4A—N4A	115.9 (3)
C9A—C4A—N4A	126.1 (3)
C4A—N4A—C10A	120.2 (3)
C4A—N4A—C12A	124.5 (3)
C10A—N4A—C12A	115.3 (2)
N4A—C10A—C11A	113.3 (2)
N4A—C12A—C13A	111.9 (3)
C6B—S7B—C8B	90.7 (2)
S7B—C8B—C9B	112.3 (3)
C8B—C9B—C5B	110.8 (3)
C9B—C5B—C6B	113.6 (3)
C5B—C6B—S7B	112.6 (3)
C9B—C8B—N1B	126.5 (3)
C8B—N1B—C2B	112.2 (3)
N1B—C2B—N3B	129.3 (3)
C2B—N3B—C4B	117.8 (3)
N3B—C4B—C9B	118.9 (3)
C4B—C9B—C8B	115.0 (3)
S7B—C8B—N1B	121.1 (2)
C5B—C9B—C4B	134.0 (3)
C5B—C6B—C6αB	128.9 (3)
S7B—C6B—C6αB	118.4 (2)
C6B—C6αB—O6βB	122.9 (3)
C6B—C6αB—O6γB	112.4 (3)
O6βB—C6αB—O6γB	124.7 (3)
C6αB—O6γB—C6δB	116.0 (3)
N1B—C2B—N2αB	114.9 (3)
N3B—C2B—N2αB	115.9 (3)
C2B—N2αB—C2βB	126.6 (3)
N2αB—C2βB—O2γB	124.7 (4)
N3B—C4B—N4B	115.5 (3)
C9B—C4B—N4B	125.7 (3)
C4B—N4B—C10B	120.0 (3)
C4B—N4B—C12B	123.6 (3)
C10B—N4B—C12B	116.2 (2)
N4B—C10B—C11B	113.3 (3)
N4B—C12B—C13B	113.8 (3)

Data collection was performed using *CAD*-4 *Software* (Enraf–Nonius, 1989). *PROCESS* in *MolEN* (Fair, 1990) was used for data reduction. The structure was determined by direct methods using *SHELXS*86 (Sheldrick, 1985) and refined by full-matrix least-squares techniques (*SHELX*76; Sheldrick, 1976). All H atoms were located from a difference Fourier map and kept fixed (C—H = N—H = 0.97 Å). *R* values for both enantiomers were similar. The absolute structure was chosen by comparing the values of F_c/F_o for Bijvoet pairs and by considering the Flack (1983) parameters [0.10 (8) and 0.69 (9)]. All calculations were made on a MicroVAX 3400 computer. Molecular graphics were produced using *ORTEP* (Johnson, 1965).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and least-squares-planes data have been deposited with the IUCr (Reference: HR1004). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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The Cyclic Depsipeptide Backbone of the Didemnins

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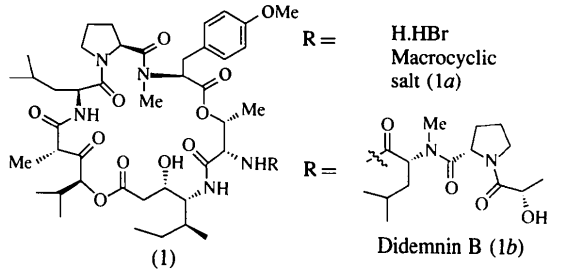
Abstract

An X-ray crystal analysis of φ-lactone *N*-{1-{*N*-{4-{[3-hydroxy-5-methyl-1-oxo-4-(*N*-L-threonylamino)heptyl]-oxy}-2,5-dimethyl-1,3-dioxohexyl}-L-leucyl}-L-prolyl}-*N*,*O*-dimethyl-L-tyrosine hydrobromide hydrate (1*a*), $C_{42}H_{66}N_5O_{11}^+.Br^-.H_2O$, was obtained in order to determine the backbone folding of the macrocycle and to compare the results obtained with those reported previously for the natural product didemnin B (1*b*). Some differences were noted in the torsion angles of the two conformers of the hydrobromide salt, denoted (1*a*) and (1*a'*). The conformation of (1*a'*) resembled the conformation of (1*b*) more closely than did that of (1*a*). Certain regions of both crystal backbones were more flexible than those in didemnin B; however, the transannular hydrogen bonds in both (1*a*) and (1*a'*) were somewhat stronger than in (1*b*).

Comment

In the course of our synthetic and structural studies of the biologically active cyclodepsipeptides, the didemnins (1), the X-ray crystal structure of the macrocyclic salt (1*a*) was determined in order to compare its molecular conformation with that of didemnin B, (1*b*). An X-ray crystal structure analysis of (1*b*) has been reported previously by Hossain *et al.* (1988).



(1) Didemnin B (1*b*)

Didemnin B is the most active of the side-chain derivatives tested for antiviral, antitumor and immunosuppressive activity (Maldonado, Lavergne & Kraiselburd, 1982; Canonico, Pannier, Huggins & Rinehart, 1982; Rinehart *et al.*, 1982; Fimiani, 1987; Montgomery, Celniker & Zukoski, 1987; Legrue, Sheu, Carson, Laidlaw & Sanduja, 1988), and it is believed that the side-chain β-turn is important in determining biological activity. As can be seen in Figs. 1 and 2, the three proposed structural features essential for bioactivity, *i.e.* the side-chain β-turn, the isostatine hydroxyl group and the tyrosine side chain (Rinehart, 1985; Hossain *et al.*, 1988; Banaigs *et al.*, 1989; Kessler, Will, Antel, Beck & Sheldrick, 1989; Shen, Zukoski & Montgomery, 1992; Kundu, Wilson & Rinehart, 1992), all lie on the periphery of the bent figure-eight macrocycle (Hossain *et al.*, 1988; Mohamadi *et al.*, 1990). The conformation of the β-turn is dictated by a hydrogen bond between the lactyl carbonyl O atom (O12) and the threonine amide group (N5) (Fig. 1). In addition, two more hydrogen bonds contribute to the globular structure of this molecule. The side chain is attached to the main macrocycle through a hydrogen bond between the leucine carbonyl O atom (O10) of the side chain and the L-leucine amide group (N3). There is also a hydrogen bond in the core of the macrocycle between the L-leucine carbonyl O atom (O3) and the amide group of the isostatine unit (N4).

Crystals of the hydrobromide salt of the macrocycle were analyzed and *ORTEP*II (Johnson, 1976) drawings of the two conformers, (1*a*) and (1*a'*), are shown in Fig. 3; the numbering scheme used is illustrated separately for clarity. Each atom of the two conformers is numbered in the same order, the only difference is that one structure is primed. There are actually two separate but similar conformers present in the unit cell (Fig. 4). The conformers differ slightly in the positions of the tyrosine side chain and isovaleryl group, and also in the fact that structure (1*a'*) has two molecules of water in the crystal. The bond distances and angles are provided in the supplementary material.

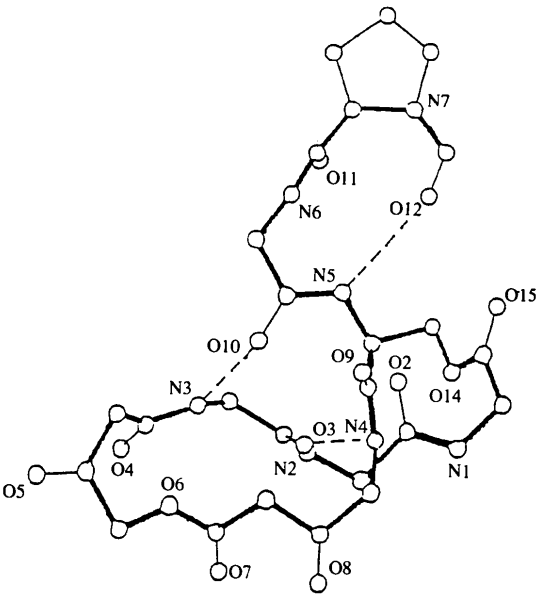


Fig. 1. View of the didemnin B, (1*b*), X-ray framework (Hossain *et al.*, 1988).

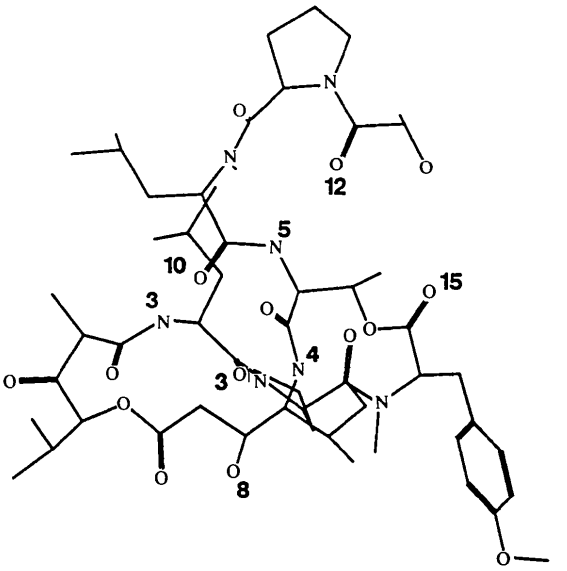


Fig. 2. Molecular-modeling structure of didemnin B, (1*b*) (Mayer & Joullié, 1995; Mohamadi *et al.*, 1990).

After a closer investigation of these conformers *via* torsion-angle comparisons (Table 2) and a molecular-modeling study (Mohamadi *et al.*, 1990), some distinct conclusions can be drawn. The molecule is oval shaped as compared with the constrained figure-eight shape of didemnin B (Fig. 3). The bromide ion is hydrogen bonded across the main macrocycle between the L-leucine amide group (N16) and the threonine amine

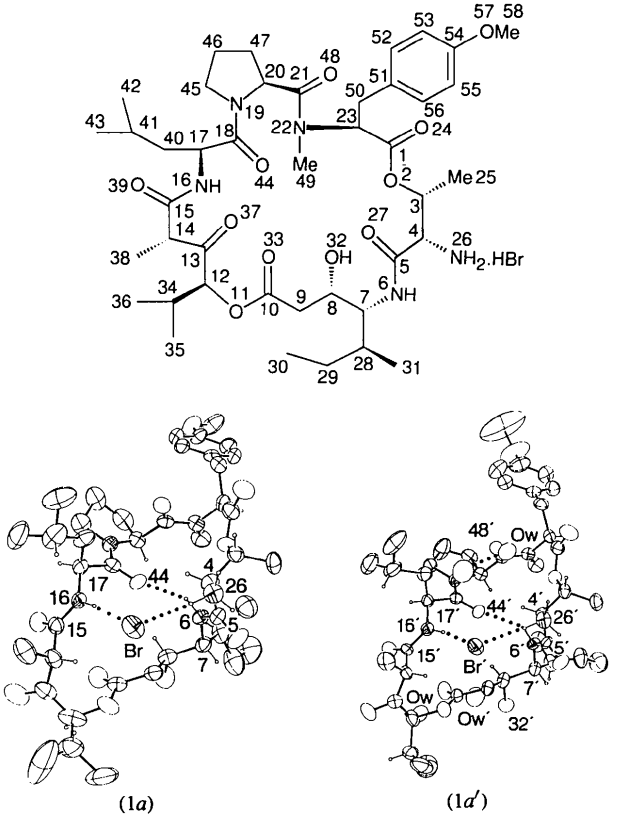


Fig. 3. *ORTEP*II drawings (Johnson, 1976) of the two conformers of the macrocyclic salt shown with 30% probability displacement ellipsoids. The numbering scheme adopted is shown above.

group (N26). A molecular-modeling study revealed that the tetrapeptide portion of the macrocyclic salt superimposed well with the analogous region of the backbone of didemnin B, while the HIP isostatine region (atoms C10 to C15) was slightly more flexible in the macrocyclic salt. The side chain of didemnin B seems to force the core of the macrocycle into a more rigid conformation. However, the transannular hydrogen bonds bridging the macrocycle between the isostatine amide (N6) and the leucine carbonyl O atom (O44) in both (1*a*) [2.834 (9) Å] and (1*a*′) [2.942 (8) Å] are somewhat stronger than the one found in didemnin B (3.020 Å; Hossain *et al.*, 1988). By examining the torsion angles, conformer (1*a*′) resembles the structure of didemnin B more closely than conformer (1*a*). In three cases (O11—C12—C13—C14, C13—C12—O11—C10 and C12—C13—C14—C15), the torsion angles of (1*a*) deviate by more than 40–50° from the torsion angles of the other two structures [(1*a*′) and (1*b*)]. This region, known as the HIP moiety, is quite distorted for conformation (1*a*) and no additional stabilization by hydrogen bonding to water molecules is present. In didemnin B, a water molecule acts as an acceptor to the isostatine hydroxyl H atom while acting as a donor to the O atoms of both the tyrosine side chain

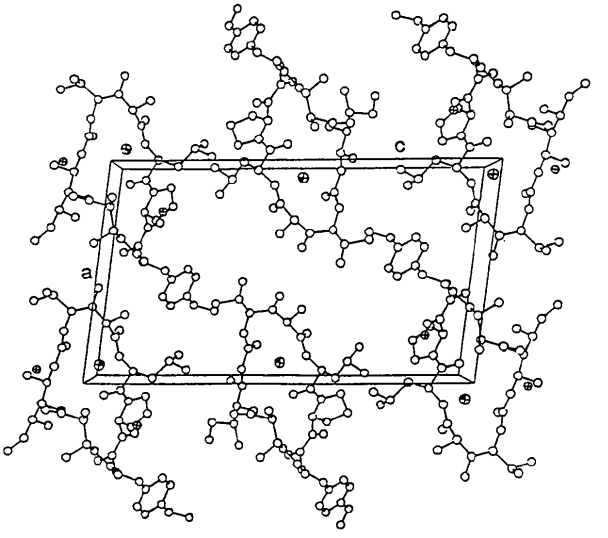


Fig. 4. Crystal packing in the unit cell viewed parallel to the *b* axis.

and the proline carbonyl group of the β-turn side chain (Hossain *et al.*, 1988). In conformer (1*a*′), additional stability is present in the lower half of the molecule. Comparison of other torsion angles shows that only one (C13—C14—C15—N16), next to the amide linkage connecting the HIP unit to L-leucine, deviates by more than 10°. In this case, the two salt conformers compare favorably, but the analogous torsion angle of didemnin B deviates by almost 20°.

The macrocycle is at present being tested for biological activity and conclusions will then be drawn regarding the structural features important for bioactivity, *i.e.* the side chain and/or backbone folding. Originally, the β-turn side chain of didemnin B was believed to be the main bioactive site, while the other two moieties, the tyrosine side chain and the isostatine hydroxyl group, served only for binding or anchoring the macrocycle to a receptor site (Hossain *et al.*, 1988).

Finally, it is interesting to note that the bromide ion is situated in the center of the macrocycle, suggesting possible ionophoric properties. As the carbonyl O atoms and hydroxyl group of the didemnin B macrocycle extend outwards rather than towards the cavity, this cyclodepsipeptide does not complex cations. Most ionophoric systems, such as valinomycin, are designed to complex cations (Voet & Voet, 1990); however, a macrocycle such as (1*a*) could possibly transport anionic species.

Experimental

For the preparation of the title compound (1*a*) (Li, Ewing, Harris & Joullié, 1990; Mayer, Ramanjulu, Vera, Pfizenmayer & Joullié, 1994), a solution of φ-lactone *N*-{1-{*N*-{4-{{3-hydroxy-5-methyl-1-oxo-4-[*N*-(*N*-*tert*-butoxycarbonyl)-L-threonylamino]heptyl}oxy}-2,5-dimethyl-1,3-dioxohexyl}-L-leucyl}-L-prolyl}-*N*,*O*-dimethyl-L-tyrosine (0.063 g,

58.7 mmol) (Li, Ewing, Harris & Joullié, 1990) in EtOAc (~ 2 ml) was cooled to 243 K. Gaseous HBr was introduced at a rate such that the temperature of the mixture was maintained between 253 and 263 K at saturation. After stirring for 1 h at this temperature the solution was stirred for a further 1 h at 273 K. The solution was then purged with N_2 for about 30 min, maintaining the temperature at 273 K. After concentrating the solution, the residue was triturated and washed by decantation with three 1 ml portions of *tert*-butyl methyl ether/hexane solution (1:4). The product was collected by filtration and dried *in vacuo* to obtain the hydrobromide salt [(1*a*), 0.0453 g, 90% yield] as a white solid. Crystals in the form of plates were grown by slow evaporation of a methanol solution: R_f 0.54 (10:90 methanol/chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86–0.97 (*m*, 15H), 1.00 (*d*, J = 6.1 Hz, 3H), 1.17–1.24 (*m*, 1H), 1.29 (*d*, J = 6.7 Hz, 3H), 1.33 (*d*, J = 4.3 Hz, 3H), 1.39–1.46 (*m*, 1H), 1.57–1.68 (*m*, 2H), 1.72–1.83 (*m*, 3H), 2.10–2.18 (*m*, 3H), 2.19–2.28 (*m*, 2H), 2.57 (*s*, 3H), 2.69–2.79 (*m*, 1H), 2.80–2.88 (*m*, 1H), 3.11 (*t*, J = 11.1 Hz, 1H), 3.34 (*d*, J = 11.1 Hz, 1H), 3.59 (*d*, J = 6.1 Hz, 1H), 3.64–3.72 (*m*, 1H), 3.79 (*s*, 3H), 3.84 (*d*, J = 8.4 Hz, 2H), 4.08–4.17 (*m*, 2H), 4.25–4.30 (*m*, 1H), 4.35 (*d*, J = 5.3 Hz, 1H), 4.64–4.71 (*m*, 2H), 5.02 (*d*, J = 3.9 Hz, 1H), 5.42–5.48 (*m*, 1H), 6.85 (*d*, J = 8.1 Hz, 2H), 7.06 (*d*, J = 7.8 Hz, 2H), 7.50–7.58 (*m*, 1H), 8.23–8.41 (*m*, 2H), 8.47–8.62 (*m*, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 14.0, 14.8, 15.1, 17.4, 18.2, 20.8, 22.6, 23.6, 24.7, 24.9, 26.9, 28.0, 31.2, 31.5, 33.9, 35.1, 39.9, 47.1, 49.5, 49.9, 54.5, 55.2, 57.3, 58.0, 66.1, 68.0, 69.2, 82.9, 114.2, 129.1, 130.2, 158.7, 165.9, 168.5, 171.0, 171.3, 172.0, 172.3, 205.3; IR ($CHCl_3$) 2350–3600 (*br*), 3330 (*m*), 3040 (*m*), 2970 (*s*), 2940 (*s*), 2880 (*m*), 2840 (*w*), 1730 (*s*), 1690 (*m*), 1660 (*s*), 1635 (*s*), 1560 (*m*), 1530 (*m*), 1510 (*m*), 1485–1495 (*m*), 1460 (*s*), 1410 (*m*), 1390 (*m*), 1370 (*m*), 1360 (*m*), 1335–1345 (*m*), 1320 (*m*), 1305 (*m*), 1275 (*m*), 1250 (*s*), 1170 (*s*), 1125 (*m*), 1105 (*m*), 1070–1090 (*m*), 1035 (*m*), 960 (*w*), 925 (*w*), 875 (*w*), 800 (*m*) cm^{-1}; HRMS *m/z* calculated for $C_{42}H_{65}N_5O_{11}$ 815.4681, found 815.4658; $[\alpha]_D^{20}$ −144° (*c* = 2.40, $CHCl_3$).

Crystal data

$C_{42}H_{66}N_5O_{11}^+.Br^-.H_2O$
M_r = 914.95
Monoclinic
$P2_1$
a = 13.663 (4) Å
b = 15.342 (3) Å
c = 23.557 (5) Å
β = 97.64 (3)°
V = 4894 (4) Å^3
Z = 4
D_x = 1.242 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 25 reflections
θ = 11.5–32.8°
μ = 1.627 mm^{-1}
T = 298 K
Plate
0.40 × 0.22 × 0.05 mm
Clear

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: none
9007 measured reflections
8610 independent reflections
5138 observed reflections [$F^2 > 3\sigma(F^2)$]
R_{int} = 0.018
θ_{max} = 65°
h = 0 → 16
k = 0 → 18
l = −27 → 27
3 standard reflections
frequency: 58.33 min
intensity decay: 18.0%

Refinement

Refinement on F
R = 0.065
wR = 0.077
S = 2.49
5138 reflections
558 parameters
H-atom parameters not refined
$w = 1/\sigma^2(F)$
$(\Delta/\sigma)_{max}$ = 0.11
$\Delta\rho_{max}$ = 0.56 e Å^{-3}
$\Delta\rho_{min}$ = −0.43 e Å^{-3}
Atomic scattering factors from *MolEN* (Fair, 1990)

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

$B_{eq} = (4/3)\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
Conformer (1*a*)				
Br	0.07942 (8)	0.0000	0.49987 (6)	8.41 (3)
C1	−0.4040 (7)	0.1380 (6)	0.4174 (4)	6.9 (3)
C3	−0.3005 (6)	0.0446 (6)	0.4795 (4)	6.0 (2)
C4	−0.1922 (7)	0.0527 (6)	0.5004 (4)	5.9 (2)
C5	−0.1716 (6)	0.1034 (7)	0.5592 (3)	5.9 (2)
C7	−0.1394 (7)	0.2497 (7)	0.6005 (4)	6.2 (2)
C8	−0.0421 (7)	0.2947 (6)	0.5925 (4)	6.3 (2)
C9	0.0403 (7)	0.2319 (7)	0.5992 (4)	6.9 (3)
C10	0.1376 (7)	0.2680 (7)	0.5879 (4)	6.4 (2)
C12	0.3072 (8)	0.2331 (8)	0.5963 (5)	9.3 (3)
C13	0.3221 (7)	0.2379 (7)	0.5358 (5)	7.7 (3)
C14	0.2638 (6)	0.1794 (7)	0.4921 (4)	6.5 (2)
C15	0.1902 (6)	0.2339 (6)	0.4494 (4)	5.7 (2)
C17	0.0353 (6)	0.2195 (7)	0.3816 (4)	6.0 (2)
C18	−0.0562 (6)	0.2562 (6)	0.4054 (4)	5.1 (2)
C20	−0.1966 (6)	0.3516 (6)	0.3894 (4)	5.8 (2)
C21	−0.2746 (6)	0.2781 (6)	0.3840 (3)	5.3 (2)
C23	−0.4379 (6)	0.2285 (6)	0.4026 (4)	5.7 (2)
C25	−0.3636 (7)	0.0079 (7)	0.5205 (4)	7.4 (3)
C28	−0.2281 (7)	0.3135 (7)	0.6024 (4)	8.6 (3)
C29	−0.2223 (9)	0.3480 (11)	0.6638 (6)	13.4 (5)
C30	−0.3085 (12)	0.4196 (14)	0.6660 (7)	16.9 (6)
C31	−0.3248 (9)	0.2642 (11)	0.5821 (6)	11.5 (4)
C34	0.3729 (8)	0.1614 (12)	0.6294 (5)	11.4 (4)
C35	0.3529 (11)	0.1500 (15)	0.6919 (5)	15.3 (6)
C36	0.4569 (13)	0.1568 (17)	0.6255 (7)	31.9 (7)
C38	0.3260 (8)	0.1293 (9)	0.4572 (6)	11.2 (4)
C40	0.0012 (8)	0.1465 (7)	0.3425 (4)	7.3 (3)
C41	0.0820 (9)	0.0913 (10)	0.3170 (5)	10.7 (4)
C42	0.0300 (11)	0.0291 (11)	0.2689 (5)	13.6 (5)
C43	0.1478 (9)	0.1498 (14)	0.2888 (5)	14.9 (6)
C45	−0.0830 (8)	0.3565 (8)	0.3190 (5)	8.5 (3)
C46	−0.1795 (9)	0.3972 (9)	0.2921 (6)	10.3 (4)
C47	−0.2232 (8)	0.4274 (7)	0.3474 (5)	8.5 (3)
C49	−0.3765 (7)	0.3742 (7)	0.4419 (4)	7.6 (3)
C50	−0.4954 (7)	0.2300 (7)	0.3403 (4)	6.5 (2)
C51	−0.5351 (6)	0.3189 (7)	0.3212 (3)	5.9 (2)
C52	−0.4943 (6)	0.3678 (7)	0.2818 (4)	6.2 (2)
C53	−0.5322 (7)	0.4460 (7)	0.2610 (3)	6.6 (2)
C54	−0.6103 (7)	0.4809 (7)	0.2788 (3)	6.5 (2)
C55	−0.6547 (7)	0.4348 (8)	0.3200 (4)	7.4 (3)
C56	−0.6150 (7)	0.3568 (8)	0.3407 (4)	6.7 (2)
C58	−0.7281 (11)	0.5935 (10)	0.2700 (5)	11.6 (4)
N6	−0.1594 (5)	0.1887 (5)	0.5526 (3)	5.3 (2)
N16	0.1056 (6)	0.1896 (5)	0.4290 (3)	5.8 (2)
N19	−0.1077 (5)	0.3166 (5)	0.3726 (3)	5.7 (2)
N22	−0.3576 (5)	0.2936 (5)	0.4121 (3)	5.6 (2)
N26	−0.1483 (6)	−0.0334 (6)	0.5127 (3)	7.1 (2)
O2	−0.3305 (4)	0.1314 (4)	0.4621 (2)	5.7 (1)
O11	0.2101 (4)	0.2093 (5)	0.6056 (3)	7.8 (2)
O24	−0.4444 (5)	0.0742 (5)	0.3948 (3)	8.4 (2)
O27	−0.1688 (6)	0.0662 (5)	0.6046 (2)	8.4 (2)
O32	−0.0213 (6)	0.3686 (5)	0.6268 (3)	10.4 (2)
O33	0.1538 (5)	0.3350 (5)	0.5666 (3)	8.8 (2)
O37	0.3856 (6)	0.2840 (7)	0.5210 (4)	12.6 (3)
O39	0.2073 (4)	0.3086 (4)	0.4329 (3)	7.1 (2)
O44	−0.0811 (4)	0.2292 (4)	0.4502 (2)	5.8 (1)

O48	−0.2685 (4)	0.2122 (4)	0.3559 (2)	6.0 (1)
O57	−0.6466 (5)	0.5553 (5)	0.2538 (3)	8.6 (2)
O*w*	−0.2168 (6)	−0.0015 (6)	0.8612 (3)	9.7 (2)
Conformer (1*a*′)				
Br′	0.07007 (7)	−0.04447 (8)	0.97901 (5)	7.03 (2)
C1′	−0.4108 (6)	0.0849 (7)	0.9200 (4)	5.7 (2)
C3′	−0.3049 (6)	−0.0061 (6)	0.9871 (4)	5.6 (2)
C4′	−0.1942 (6)	0.0019 (6)	1.0035 (3)	4.6 (2)
C5′	−0.1645 (6)	0.0351 (5)	1.0629 (3)	4.8 (2)
C7′	−0.1226 (6)	0.1662 (6)	1.1233 (4)	5.6 (2)
C8′	−0.0242 (6)	0.2180 (6)	1.1186 (3)	5.7 (2)
C9′	0.0555 (6)	0.1599 (6)	1.1023 (3)	5.4 (2)
C10′	0.1430 (6)	0.2104 (6)	1.0912 (4)	5.4 (2)
C12′	0.3161 (6)	0.1946 (7)	1.0780 (4)	6.9 (2)
C13′	0.3387 (7)	0.1586 (7)	1.0234 (4)	6.7 (2)
C14′	0.2614 (6)	0.1184 (6)	0.9798 (4)	5.7 (2)
C15′	0.1942 (5)	0.1912 (6)	0.9538 (3)	4.9 (2)
C17′	0.0311 (6)	0.2147 (6)	0.8953 (3)	5.1 (2)
C18′	−0.0621 (5)	0.2336 (5)	0.9233 (3)	4.5 (2)
C20′	−0.2136 (6)	0.3147 (5)	0.9188 (4)	4.8 (2)
C21′	−0.2849 (5)	0.2406 (5)	0.9023 (3)	4.4 (2)
C23′	−0.4469 (6)	0.1734 (6)	0.9050 (3)	5.1 (2)
C25′	−0.3624 (7)	−0.0379 (7)	1.0339 (4)	7.7 (3)
C28′	−0.2033 (7)	0.2209 (7)	1.1437 (4)	7.3 (3)
C29′	−0.2859 (8)	0.1657 (9)	1.1573 (5)	9.8 (3)
C30′	−0.3478 (10)	0.2071 (11)	1.1969 (6)	12.0 (4)
C31′	−0.2364 (8)	0.2938 (9)	1.1040 (6)	10.3 (4)
C34′	0.3934 (7)	0.1800 (8)	1.1299 (4)	7.3 (3)
C35′	0.3668 (11)	0.2262 (14)	1.1809 (6)	15.9 (6)
C36′	0.4071 (9)	0.0876 (10)	1.1434 (6)	12.7 (4)
C38′	0.3034 (7)	0.0676 (7)	0.9325 (5)	8.2 (3)
C40′	−0.0003 (6)	0.1670 (7)	0.8394 (4)	6.2 (2)
C41′	0.0821 (8)	0.1612 (9)	0.7988 (4)	8.8 (3)
C42′	0.0420 (11)	0.1034 (11)	0.7501 (5)	13.3 (4)
C43′	0.1080 (10)	0.2508 (12)	0.7773 (5)	12.6 (5)
C45′	−0.0959 (7)	0.3614 (7)	0.8557 (4)	7.0 (2)
C46′	−0.1833 (9)	0.4133 (9)	0.8452 (5)	11.8 (4)
C47′	−0.2474 (7)	0.3992 (6)	0.8869 (4)	7.0 (3)
C49′	−0.4019 (7)	0.3095 (7)	0.9622 (4)	7.0 (2)
C50′	−0.4884 (6)	0.1790 (7)	0.8406 (3)	6.2 (2)
C51′	−0.5297 (6)	0.2662 (6)	0.8225 (4)	5.9 (2)
C52′	−0.4815 (8)	0.3153 (9)	0.7811 (4)	8.3 (3)
C53′	−0.5194 (10)	0.3928 (10)	0.7585 (5)	11.3 (4)
C54′	−0.6131 (10)	0.4195 (9)	0.7767 (5)	10.4 (4)
C55′	−0.6582 (8)	0.3764 (7)	0.8184 (5)	8.4 (3)
C56′	−0.6141 (7)	0.2979 (8)	0.8411 (4)	7.5 (3)
C58′	−0.6873 (31)	0.5250 (15)	0.6968 (10)	39 (2)
N6′	−0.1565 (5)	0.1227 (4)	1.0681 (2)	4.6 (1)
N16′	0.1037 (5)	0.1629 (5)	0.9357 (3)	5.3 (2)
N19′	−0.1170 (4)	0.2984 (4)	0.9000 (3)	4.8 (2)
N22′	−0.3727 (5)	0.2413 (4)	0.9235 (3)	4.8 (2)
N26′	−0.1534 (5)	−0.0854 (5)	0.9984 (3)	6.0 (2)
O2′	−0.3402 (4)	0.0804 (4)	0.9677 (2)	5.3 (1)
O11′	0.2219 (4)	0.1561 (4)	1.0896 (3)	6.0 (1)
O24′	−0.4448 (5)	0.0190 (4)	0.8962 (3)	7.9 (2)
O27′	−0.1467 (5)	−0.0151 (4)	1.1027 (2)	7.0 (2)
O32′	0.0088 (5)	0.2541 (5)	1.1738 (2)	7.2 (2)
O33′	0.1478 (4)	0.2861 (4)	1.0835 (3)	7.4 (2)
O37′	0.4277 (5)	0.1622 (8)	1.0138 (3)	11.8 (3)
O39′	0.2239 (4)	0.2635 (4)	0.9466 (3)	6.2 (1)
O44′	−0.0838 (4)	0.1882 (4)	0.9640 (2)	5.0 (1)
O48′	−0.2648 (4)	0.1826 (4)	0.8697 (2)	5.1 (1)
O57′	−0.657 (1)	0.4923 (7)	0.7556 (4)	17.7 (4)
O*w*′	0.0318 (6)	0.4297 (6)	1.1598 (3)	10.7 (2)

Table 2. *Torsion angles in compounds* (1*a*), (1*a*′) *and* (1*b*)

	(1*a*)	(1*a*′)	(1*b*)
O2—C1—C23—N22	34.0 (11)	27.9 (9)	40.0 (5)
C23—C1—O2—C3	176.5 (7)	176.6 (7)	180.0 (3)
O2—C3—C4—C5	71.1 (8)	83.9 (8)	81.2 (4)
C4—C3—O2—C1	147.5 (7)	138.7 (7)	139.0 (4)
C3—C4—C5—N6	−91.9 (9)	−89.6 (9)	−81.1 (4)
C4—C5—N6—C7	−180.0 (10)	−176.7 (7)	−178.1 (4)
N6—C7—C8—C9	−65.7 (9)	−57.7 (9)	−58.2 (4)
C8—C7—N6—C5	122.6 (9)	118.0 (8)	113.3 (4)
C7—C8—C9—C10	175.7 (7)	173.1 (7)	163.9 (4)
C8—C9—C10—O11	168.8 (7)	165.9 (7)	166.1 (3)
C9—C10—O11—C12	178.3 (8)	179.0 (7)	177.4 (3)
O11—C12—C13—C14	−31.0 (14)	20.0 (13)	39.4 (4)
C13—C12—O11—C10	−67.0 (12)	−116.0 (8)	−141.8 (3)
C12—C13—C14—C15	113.0 (10)	70.0 (11)	60.0 (4)
C13—C14—C15—N16	−149.0 (8)	−151.9 (7)	−133.7 (4)
C14—C15—N16—C17	−168.2 (7)	−163.8 (7)	−167.4 (3)
N16—C17—C18—N19	153.8 (8)	160.9 (7)	158.0 (3)
C18—C17—N16—C15	−104.7 (9)	−121.0 (8)	−124.1 (4)
C17—C18—N19—C20	176.8 (7)	172.5 (7)	173.7 (3)
N19—C20—C21—N22	164.6 (7)	171.4 (6)	162.9 (3)
C21—C20—N19—C18	−68.3 (9)	−66.2 (9)	−75.4 (4)
C20—C21—N22—C23	173.8 (7)	175.7 (7)	177.4 (3)
C1—C23—N22—C21	56.0 (10)	60.8 (9)	51.4 (4)

The water H atoms on O*w* and O*w*′, and the hydroxy H atoms on O32 and O32′ could not be located from difference Fourier maps. All other H atoms were either calculated or located from difference maps. Calculations were performed using *MACROMODEL* (Still *et al.*, 1990) on a Silicon Graphics Iris 4D/320S computer. Minimizations were generated using *PRCD* followed by *FMNR* with *MM*2 force field to obtain r.m.s. values less than 0.050. Other computer programs used include *MolEN* (Fair, 1990).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and hydrogen-bonding parameters have been deposited with the IUCr (Reference: CR1144). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Photochromic 8-Ethoxy-2-methylspiro(*syn*-5,6-benzo-2-azabicyclo[2.2.2]oct-5-ene-3,3′-[3*H*]naphth[2,1-*b*][1,4]oxazine)

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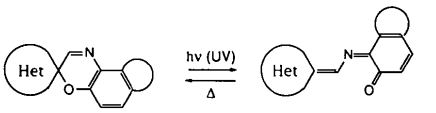
Abstract

In the photochromic title compound, $C_{25}H_{24}N_2O_2$, the C_{spiro}—O bond can be broken on photoexcitation. Conformational parameters and oxazine-ring puckering have been investigated by considering similar photochromic compounds. It is shown that when the C_{spiro}—O bond is elongated, and therefore weakened, the ring-puckering coefficient is smaller and photochromic activity increases.

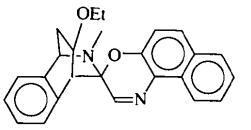
Comment

Spirooxazines are colourless photochromic compounds (Chu, 1990), which transform under UV irradiation into strongly coloured photomerocyanines. The reaction is reversible either by heat or by visible-light absorption.



spiro compound Photomerocyanine
Het = heterocycle

The rate of decolouration depends on the electronic properties or steric hindrances of either the heterocyclic part or the annulation of the benzoxazinic ring (Tardieu, Dubest, Aubard, Kellmann, Tfibel, Samat & Guglielmetti, 1992; Rickwood, Marsden, Ormsby, Staunton, Wood, Hepworth & Gabbutt, 1994). Structural features, such as the C_{spiro}—O bond distance, the distances of oxazine N and O atoms from the adjacent phenyl ring mean plane, intramolecular short contacts, and oxazine ring planarity, which are related to the difference in photochromic behaviour are discussed here. In order to obtain a better insight into the correlation between molecular substitution, conformation and photochemical reactivity, the molecular structure of the title compound, (1), has been established and compared with the conformation of some other spirooxazinic compounds. The molecular conformation and atomic labelling are shown in Fig. 1.



(1)

The title molecule contains a naphthoxazine moiety linked to a substituted benzo-2-azabicyclo[2.2.2] fragment through the spiro atom, C12, which displays regular sp^3 hybridization. The bond angles at the C12 spiro carbon have a mean value of 109.4 (8)°. Table 3 shows that the O14—C12—C13 bond angle of the spiro C atom in the oxazine ring has a mean value of 109.1 (12)° for seven spirooxazines. The conformation of the oxazine ring of the title compoud is described as a twisted boat along the C13···C25 axis.

The phenyl and naphthyl moieties are planar (r.m.s. deviations of 0.002 and 0.006 Å, respectively) and are approximately orthogonal to each other [dihedral angle 87.1 (7)°]. The benzo-2-azabicyclo[2.2.2] fragment with its cage-like structure has a small degree of freedom. It displays D_3 symmetry with a mean torsion angle of 4.2 (3)°, probably as a result of the bulky naphthoxazine moiety linking through the spiro C12 atom.