Photochemical Transformation of Hanphilline and Crystal Structure of 1(10)*Z*,4*Z*-Hanphilline

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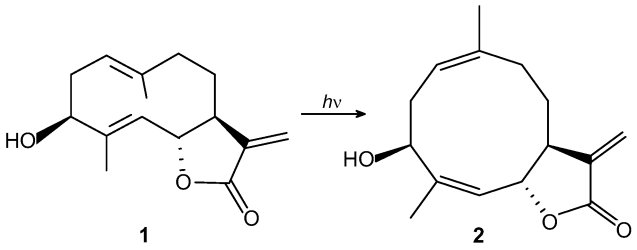
The *E,E*-germacranolide hanphilline has been photochemically transformed into its *Z,Z*-isomer; an X-ray structural study has shown that the ten-membered ring in this compound adopts the previously unknown $_{15}D_{5},_{1}D_{14}$ boat-boat conformation.

It is known that Δ1(10),4-germacranolides exist in nature as four geometrical isomers: *E,E*, *Z,E*, *E,Z* and *Z,Z*.[1] The subgroup of *Z,Z*-germacranolides is the least numerous. Therefore, the stereochemistry of these compounds is practically unknown. We decided to prepare the new *Z,Z*-isomers photochemically from the known *E,E*-germacranolides because of the absence of data on interconversions of isomeric germacranolides and in order to obtain new data about the structures of *Z,Z*-germacranolides.

The crystalline substance **2** was obtained by irradiation of a hanphilline[2] **1**† solution using a mercury high-pressure lamp:



1 **2**

According to spectral data,‡ molecule **2** is very similar in structure to the initial compound **1**; for a determination of the full three-dimensional structure of **2** we carried out an X-ray investigation.§

Fig. 1 shows that the conformation around the C(1)=C(10) and C(4)=C(5) double bonds is *cis* [torsion angles C(2)C(1)C(10)C(9) equal to 2° and 1° and C(3)C(4)C(5)C(6) equal to –1 and –3° in two crystallographically independent molecules **2a** and **2b**, respectively]. The ten-membered and lactone cycles are *trans*-fused [torsion angles H(6)C(6)C(7)H(7) equal to –102° (**2a**) and –97° (**2b**)]. The hydroxy group linked to C(3) has a β-orientation. Thus, compound **1** is a stereoisomer of hanphilline and represents 3β-hydroxy-6β,7αH-*Z,Z*-germacr-1(10),4,11(13)-triene-6,12-olide.

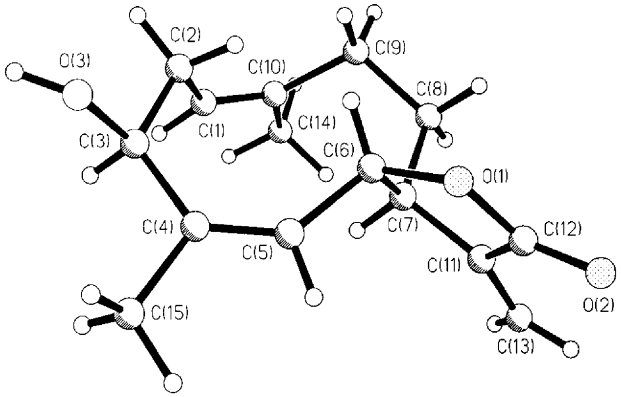


Fig. 1 Crystal structure of **2**.

The conformation of the lactone ring in **2** is intermediate between 6α,7β-half-chair and 7β-envelope. Methyl groups linked to C(4) and C(10) have α-*syn*-orientation in the ten-membered 1,5-diene ring and the pseudotorsion angle C(10)C(1)C(4)C(5) is equal to 8° in both **2a** and **2b**. On this basis the conformation of the ten-membered ring may be described as a $_{15}D_{5},_{1}D_{14}$ boat-boat (torsion angles are given in Table 1).

A search of the Cambridge Structural Database (release 1991) revealed the structures of four *Z,Z*-germacranolides, *i.e.* longicornine A,[4] melrosine A,[5] onopordopicrine and eupatoriopicrine,[6] which have been investigated by an X-ray diffraction method earlier. However, for the latter two compounds atomic coordinates are not published. Analysis of the structure of longicornine A and melrosine A shows that the ten-membered diene ring in these molecules has a

Table 1 Torsion angles (deg.) in the ten-membered ring of molecule **2**.

Angle	**2a**	**2b**
C(10)C(1)C(2)C(3)	–129(1)	–128(1)
C(1)C(2)C(3)C(4)	75(1)	60(1)
C(2)C(3)C(4)C(5)	13(1)	26(1)
C(3)C(4)C(5)C(6)	–1(1)	–3(1)
C(4)C(5)C(6)C(7)	–96(1)	–106(1)
C(5)C(6)C(7)C(8)	145(1)	147(1)
C(6)C(7)C(8)C(9)	–61(1)	–62(1)
C(7)C(8)C(9)C(10)	–49(1)	–44(1)
C(8)C(9)C(10)C(1)	104(1)	108(1)
C(9)C(10)C(1)C(2)	2(1)	1(1)

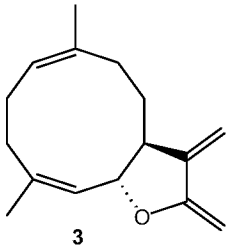
† Experimental procedure for **2**: a solution of **1** (300 mg, 1.2 mmol) in acetone (50 ml) was irradiated using a mercury high-pressure lamp at 20 °C for 20 h. Solvent was evaporated and 310 mg of residue was obtained. The residue was chromatographed on a column with 9 g of silica gel. A crystalline substance **2**, 45 mg (15%), m.p. 110–112 °C, was isolated after elution by a mixture of hexane–ethyl acetate (2:3).

‡ Spectral data for **2**: $[\alpha]_D^{18}$ –61°(*c* 0.01; $CHCl_3$); IR (ν/cm^{-1}): 3520 (OH), 1660 (C=O), 1610 (C=C); ^{1}H NMR ($CHCl_3$, δ_{TMS}): 1.70 (s, 3H, 14-3H); 1.72 (d, 3H, 15-3H, $J_{15\text{-}3H,5}$ 1.5 Hz); 4.28 (q, 1H, 6-H, $J_{6,5}$ 8.0, $J_{6,7}$ 7.0 Hz); 5.10 (m, 1H, 3-H); 5.15 (br.dd, 1H, 5-H, $J_{5,6}$ 8, $J_{5,15\text{-}3H}$ 1.5 Hz); 5.60 (br.dd, 1H, 1-H, $J_{1,2\text{-}Ha}$ 3, $J_{1,2\text{-}Hb}$ 9.5 Hz); 5.52 (d, 1H, $J_{13\text{-}Ha,7}$ 2.0 Hz) and 6.21 (d, 1H, $J_{13\text{-}Hb,7}$ 2.5 Hz).

§ Crystal data for **2**: $C_{15}H_{20}O_3$, orthorhombic, space group $P2_12_12_1$, a = 8.190(2), b = 12.920(3), c = 26.994(5) A, D_c = 1.155 g cm^{-3}, Z = 8, F(000) = 1072. 2810 independent reflections were measured with a Siemens P3/PC automated diffractometer (graphite monochromatized Mo-Kα radiation, θ/2θ-scan, 2θ≤ 50°). The structure was determined by direct methods and refined by full-matrix least-squares in anisotropic approximation for non-hydrogen atoms on 1999 reflections with $F^2 \geq 3\sigma$. Coordinates of all H atoms were calculated and fixed with the exception of hydroxy group hydrogen localized in the difference Fourier synthesis and refined in isotropic approximation. The final R-factor is 0.076 (R_W = 0.078). All calculations were performed using the PC Version of the Siemens SHELXTL programme package using an IBM PC computer. Atomic coordinates, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Centre (see Notice to Authors, *Mendeleev Commun.*, 1994, issue 1).

chair-chair $_{15}D_5,^1D^{14}$ conformation. Thus, in molecule **2** the new conformation of the ten-membered ring in *Z,Z*-germacrenolides, the $_{15}D_5,_1D_{14}$ boat-boat, was first proved experimentally.

We carried out molecular mechanics[¶] calculations on the relative stability of both conformers of the molecule **3** to prove the preference of one of these two conformations in non-linear *Z,Z*-germacranolides:



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It was found that the difference in conformational energy between these two conformers is insignificant. The conformer of the ten-membered diene ring in the $_{15}D_5,^1D^{14}$ chair-chair conformation is only 0.8 kJ mol^{-1} more stable than that with the $_{15}D_5,_1D_{14}$ boat-boat type conformation, which therefore has a considerable probability of existing.

[¶] Molecular mechanics calculations on the relative stability of both conformers of the molecule **3** were performed by the program MM2[7] adapted for an IBM PC/AT computer.

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