

MOLECULAR AND CRYSTAL STRUCTURE OF THE SESQUITERPENE LACTONE KETOPELENOLIDE B

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The spatial structure of the sesquiterpene lactone ketopelenolide B has been established.

The isolation of the sesquiterpene lactone ketopelenolide B (**1**) from the epigeal part of *Ajania fruticulosa* (Ldb.) Polijak has been reported previously [1]. According to the literature, the methyl group in the lactone ring of the (**1**) molecule has the β -orientation [2] (on the basis of NOE results).

With the aim of establishing the spatial structure of (**1**), we have made an x-ray structural investigation. The structure of the stereoisomer of (**1**) at the C4 atom — ketopelenolide A (**2**) — has been established previously by the XSA method [3].

The general form of the (**1**) molecule is shown in Fig. 1. The linkage of the ten-membered and the lactone rings is *trans*- (the torsional angle H6C6C7H7 amounts to -92.7 and -93.8° in the two crystallographically independent molecules (**1a**) and (**1b**), respectively). The conformation of the lactone ring in the molecule is inverted as compared with the usual one because of the conformational mobility of the ten-membered ring (the torsional angle C5C6C7C8 has values of 154.9° and 153.9° in (**1a**) and (**1b**), respectively). In structures (**1a**) and (**1b**) ring B has the conformation of an almost ideal 7β -envelope ($\Delta C_s^7 = 1.6^\circ$ and $\Delta C_s^7 = 1.9^\circ$ in the two crystallographically independent molecules (**1a**) and (**1b**), respectively). The values of the torsional angles C2C1C10C9 and C3C4C5C6 in the ten-membered ring of (**1**) (165.2 and -56.8° in (**1a**) and 165.2 and -54.6° in (**1b**), respectively), permit this compound to be assigned to the class of E,Z-germacranolides. It follows from this and also from the values of the intracyclic torsional angles (Table 1) that the germacrane ring assumes a configuration of the boat-chair type, ${}^{14}D_1, {}_5D_{15}$. An analysis of the literature on the crystal structures of E,Z-germacranolides has shown that the ten-membered ring in ketopelenolide A (**2**) assumes a conformation of the boat-boat type ${}_{14}D^1, {}_5D_{15}$.

To determine the relative stabilities of these two conformers in the molecules of (**1**) and (**2**), we have performed a calculation by the method of molecular mechanics [4]. As a result, we have established that the difference in the values of the conformational energy (ΔE) for the conformers of the ${}^{14}D_1, {}_5D_{15}$ type and the boat-boat type ${}_{14}D^1, {}_5D_{15}$ amounts to 4.1 kcal/mole in (**1**) and 1.6 kcal/mole in (**2**), while for the (**1**) and (**2**) molecules the conformers detected in the crystal state are the more favorable. This confirms the fact that, as a rule, the most energetically favorable conformation is realized in a crystal.

A comparison of corresponding conformers of the (**1**) and (**2**) molecules shows that the boat-chair conformation of the ${}^{14}D_1, {}_5D_{15}$ type is more favorable in (**1**) and the boat-boat conformation of the ${}_{14}D^1, {}_5D_{15}$ type in (**2**), basically through the equatorial β -orientation (in **1**) and α -orientation (in **2**) of the methyl group at the C4 atom. Thus, the boat-chair conformation in (**2**) is hindered because of the steric repulsion of the *syn*-directed C15 methyl group and the O1 atom of the lactone ring. Moreover, the axial α -orientation of the Me group at the C4 atom leads to an increase in the conformational energy of this conformer of the (**2**) molecule. The difference in the conformational energies for the C4 epimers in the boat-chair conformation amounts to 3.6 kcal/mole. A somewhat smaller value of ΔE (2.1 kcal/mole) is observed for the C4-epimers in the boat-boat conformation, which is due to the mutual repulsion of the β -oriented hydrogen atoms of the ten-membered ring (at the C1, C6, and C9 atoms) and of the axial C15-methyl group.

TABLE 1. Torsional Angles (degrees) in the Rings of Molecules (1) and (2)

Angle	1a	1b	2
Ring A			
C1C2C3C4	-58.2	-61.0	-65.4
C2C3C4C5	128.6	128.8	122.5
C3C4C5C6	-56.8	-54.6	-70.0
C4C5C6C7	-73.7	-74.3	92.3
C5C6C7C8	154.9	153.9	-154.4
C6C7C8C9	-88.8	-89.3	59.9
C7C8C9C10	54.2	54.8	39.2
C8C9C10C1	-98.1	-97.0	-107.5
C9C10C1C2	165.2	165.2	157.0
C10C1C2C3	-74.5	-73.3	-79.5
Ring B			
C6C7C11C12	-35.7	-34.3	33.6
C7C11C12O1	24.6	23.7	-22.9
C11C11O1C6	-1.5	-1.7	1.0
C12O2C6C7	-22.4	-21.0	21.1
O1C6C7C11	35.4	33.9	-33.5

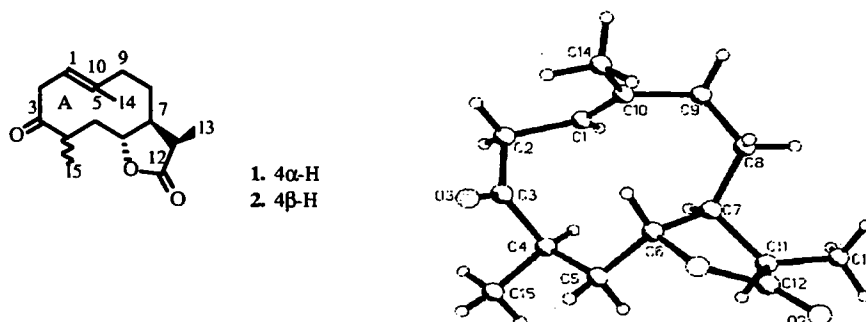


Fig. 1. Structure of the ketopelenolide B (1) molecule.

EXPERIMENTAL

Colorless acicular crystals of ketopelenolide B (1) were grown from ethyl acetate. Substance (1) was identical in its physicochemical constants and spectral characteristics (IR, mass, ^1H NMR) with the ketopelenolide B described in [2] and the product of the hydrogenation of argolide [5].

The cell parameters and the intensities of the reflections from a crystal of (1) were measured on a Siemens SMART CCD automatic four-circle diffractometer (MoK $_{\alpha}$, graphite monochromator, ω -scanning, $2\theta < 58^\circ$). The crystals of (1) were monoclinic, $a = 5.7313(8)$ Å, $b = 17.258(2)$ Å, $c = 14.074(2)$ Å, $\alpha = 90.590(3)^\circ$, $d_{\text{calc}} = 1.194$ g/cm 3 , $Z = 4(\text{C}_{15}\text{H}_{22}\text{O}_3)$, sp. gr. $P2_1$. The structure was interpreted by the direct method and was refined by the block-diagonal MLS in the anisotropic approximation for the nonhydrogen atoms. All the H-atoms were given geometrically. The final discrepancy factors were $R = 0.032$ and $R_w = 0.080$ for 5663 independent reflections with $I \geq 2\sigma$.

All the calculations were performed by means of the SHELXTL and SHELXL-95 group of programs on a Silicon Graphics work-station.

REFERENCES

1. S. M. Adekenov, A. T. Kulyyasov, V. A. Raldugin, I. Yu. Bagryanskaya, Yu. V. Gatilov, and M. M. Shakirov, *Izv. Ross. Akad. Nauk, Ser. Khim.*, No.1, 167 (1998).
2. W. Z. Wang, R. X. Tan, Y. M. Yao, Q. Wang, and H. X. Jiang, *Phytochemistry*, **37**, 1347 (1994).
3. M. K. Makhmudov, B. Tashkodzhaev, and S. Kh. Zakirov, *Khim. Prir. Soedin.*, 342 (1990).
4. N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 8127 (1977).
5. S. M. Adekenov, K. M. Aituganov, K. M. Turdybekov, S. V. Lindeman, Yu. T. Struchkov, I. Yu. Bagryanskaya, and Yu. V. Gatilov, *Khim. Prir. Soedin.*, 33 (1991).