CONFORMATION OF THE RINGS AND RELATIVE STABILITIES OF ISOMERS OF trans, trans- AND trans,cis-EUDESM-6, 12-OLIDES

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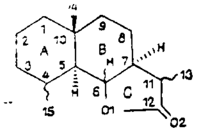
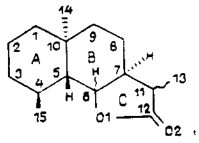
An investigation has been made by the method of molecular mechanics of a number of isomers of trans,trans- and trans,cis-eudesm-6,12-olides. Questions of the energetic advantageousness of particular isomers, the influence of the orientation of the substituents in the mechanism on their conformation, and the relative stability of the conformers with different methods of linking the rings are considered.

Sesquiterpene γ-lactones represent one of the broadest classes of natural compounds — the terpenoids. Many sesquiterpene lactones and their derivatives exhibit well-defined antifeedant, attractant, antitumoral, bactericidal, and other activities, and also growth-regulating properties [1]. In view of this, a more profound study of the spatial structures and conformations of the sesquiterpene lactones is important for solving problems of the synthesis of their biologically active analogs from industrially accessible raw material. One of the best methods for the solution of these problems is the method of molecular mechanics (MMM), which permits the modeling of the molecule of a particular compound without the performance of its synthesis and subsequent experimental study. In the present paper we give the results of a MMM calculation of 6,7-linked eudesmanolides, one of the most common types of natural sesquiterpene lactones [2].

The calculation was made for compounds with the trans,trans- and trans,cis-linkages of rings A/B and B/C with the aim of elucidating the energetic suitability of the different isomers and conformers of 6,7-linked eudesmanolides and also of establishing the influence of the orientation of substituents in the tricyclic skeleton on the conformation of its rings. Eight model compounds (I-VIII) with the β-orientation of the C14 Me group and different configurations of the chiral centers C4, C6, C11, and also four model compounds (IX-XII) with the α-orientation of the C14 Me group and the β-orientation of the C14 Me group and different configurations of the chiral centers C6 and C11, were chosen:





I. 6β (H), 13α, 15α   II. 6β (H), 13β, 15α   IX. 6β (H), 13α
III. 6β (H), 13α, 15β   IV. 6β (H), 13β, 15β   X. 6β (H), 13β
V. 6α (H), 13α, 15α   VI. 6α (H), 13β, 15α   XI. 6α (H), 13α
VII. 6α (H), 13α, 15β   VIII. 6α (H), 13β, 15β   XII. 6α (H), 13β

The choice of these compounds as models was due to the fact that they represent the basic carcass of the natural 6,7-linked eudesmanolides. Other 6,7-eudesmanolides are characterized by the presence of endocyclic double bonds and different types of substituents in the main skeleton.

The preferred conformations of rings A and B in the series of 5α,6β,7α(H)-eudesm-6,12-olides (I—IV) proved to be 3α,10β-chair ($_3C^{10}$) and 5α,8β-chair ($_5C^8$), respectively (Table 1). The conformation of ring B was more distorted ($\Delta C = 9$—10°) than that of ring

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TABLE 1. Conformations of the Rings (the asymmetry parameters ΔC* are given in parentheses) and Conformational Energies (E, kcal/mole) in Compounds (I–XII)

Compound	Conformations of the rings			E
	A	B	C	
I	$_3C^{10}$ $(\Delta C_2^{1,10} = 3°)$	$_5C^8$ $(\Delta C_2^{5,10} = 10°)$	E_7 $(\Delta C_s^7 = 3°)$	21,0
II	$_3C^{10}$ $(\Delta C_2^{1,10} = 3°)$	$_5C^8$ $(\Delta C_2^{5,10} = 10°)$	E_7 $(\Delta C_s^7 = 6°)$	22,7
III	$_3C^{10}$ $(\Delta C_2^{2,3} = 4°)$	$_5C^8$ $(\Delta C_2^{5,10} = 10°)$	E_7 $(\Delta C_s^7 = 3°)$	24,2
IV	$_3C^{10}$ $(\Delta C_2^{2,3} = 4°)$	$_5C^8$ $(\Delta C_2^{5,10} = 9°)$	E_7 $(\Delta C_s^7 = 5°)$	25,9
Va	$_3C^{10}$ $(\Delta C_2^{1,10} = 4°)$	$_5C^8$ $(\Delta C_2^{5,10} = 17°)$	E^7 $(\Delta C_s^7 = 1°)$	20,3
Vb	$_3C^{10}$ $(\Delta C_2^{1,2} = 3°)$	$B_{5,8}$ $(\Delta C_s^5 = 12°)$	E^{11} $(\Delta C_s^{11} = 1°)$	23,7
VIa	$_3C^{10}$ $(\Delta C_2^{1,10} = 4°)$	$_5C^8$ $(\Delta C_2^{5,10} = 17°)$	E^7 $(\Delta C_s^7 = 3°)$	19,9
VIb	$_3C^{10}$ $(\Delta C_2^{1,10} = 10°)$	$B_{5,8}$ $(\Delta C = 21°)$	T_{11}^7 $(\Delta C_2^{01} = 1°)$	5,1
VII	$_3C^{10}$ $(\Delta C_2^{1,10} = 6°)$	$_5C^8$ $(\Delta C_2^{5,10} = 15°)$	E^7 $(\Delta C_s^7 = 1°)$	24,5
VIII	$_3C^{10}$ $(\Delta C_2^{1,10} = 6°)$	$_5C^8$ $(\Delta C_2^{5,10} = 14°)$	E^7 $(\Delta C_s^7 = 2°)$	4,1
IX	$^3C_{10}$ $(\Delta C_2^{1,2} = 14°)$	$T_{10,7}$ $(\Delta C_2^{5,6} = 10°)$	E_7 $(\Delta C_s^7 = 1°)$	32,7
X	$^3C_{10}$ $(\Delta C_2^{1,2} = 5°)$	$T_{10,7}$ $(\Delta C_2^{5,6} = 24°)$	E_7 $(\Delta C_s^7 = 9°)$	36,2
XIc	$^3C_{10}$ $(\Delta C_2^{1,10} = 3°)$	$^5C_8$ $(\Delta C_2^{5,6} = 20°)$	E_7 $(\Delta C_s^7 = 2°)$	18,9
Xd	$^3C_{10}$ $(\Delta C_2^{1,10} = 2°)$	$T^{5,8}$ $(\Delta C_2^{5,10} = 19°)$	E^7 $(\Delta C_s^7 = 4°)$	21,5
XIIc	$^3C_{10}$ $(\Delta C_2^{2,3} = 2°)$	$^5C_8$ $(\Delta C_2^{5,10} = 24°)$	E_7 $(\Delta C_s^7 = 3°)$	21,9
XIId	$^3C_{10}$ $(\Delta C_2^{1,10} = 2°)$	$T^{5,8}$ $(\Delta C_2^{5,10} = 17°)$	T_{11}^7 $(\Delta C_2^{01} = 5°)$	21,4

*The maximum values of ΔC are given.

A (ΔC = 3-4°)*. According to the MMM calculation, the conformation of ring C is that of a 7α-envelope (E_7), but it is known from x-ray structural results that the γ-lactone ring may also assume the conformation of a 6β,7α-half-chair, as well as conformations intermediate between envelope and half-chair (see, for example, [4, 5]). In the 5α,6α,7α(H)-eudesm-6,12-olides (V-VIII), ring A retains the $_3C^{10}$ conformation, but the conformation of ring B, $_5C^8$, is considerably distorted because of the presence of the O1 atom axially oriented relative to this ring (see Table 1). Furthermore, for ring B in (V) and (VI), in addition to the 5α, 8β-chair conformation ($_5C^8$) – (Va) and (VIa)) – the 5α,8α-boat ($B_{5,8}$ – (Vb) and (VIb)) – or the close 5α,8α-twist ($T_{5,8}$) conformation becomes possible:

The conformation of ring B in the boat-like conformer (Vb) is substantially asymmetrical (ΔC_s^5 = 12°), obviously because of the spherical repulsion arising between the axially oriented C14 atom and the O1 and C11 atoms. On the whole, this conformer is less energetically suitable than the chair-shaped conformer (Va) (the difference in conformational energy $\Delta E = E_{Vb} - E_{Va}$ amounts to 3.4 kcal/mole). The conformation of ring B is still more distorted in the boat-shaped conformer (VIb), where it is intermediate between $B_{5,8}$ and $T_{5,8}$ (ΔC_s^5 = 21° and $\Delta C_2^{5,6}$ = 28°). This conformer is also less energetically suitable than the chair-shaped (VIa) (ΔE = 5.2 kcal/mole). The conformation of the lactone ring C in the molecules of (V-VIII) varies from 7β-envelope (E^7) through 7β,7α-half-chair (T_{11}^7) to 11β-envelope (E^{11}) (see Table).

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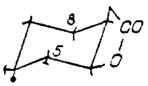
*A definition of the asymmetry parameter (ΔC) is given in [3].

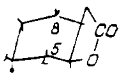
The existence of a new type of stereoisomers of AB-trans-linked eudesmanolides with the α-orientation of the 14-methyl group at the C-10 atom has been reported previously [6]. Here it was assumed that ring B in such 5β,6α,7α(H)-eudesm-6,12-olides can adopt the 5β,8α-chair ($^5C_8$), 5β,8β-boat ($B^{5,8}$) or the 5β,8β-twist ($T^{5,8}$) and 10α,7α-boat ($B_{10,7}$) or 10α,...... 7α-twist ($T_{10,7}$) conformation [6]:

c



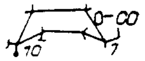
$^5C_8$

d



$B^{5,8}-T^{5,8}$

e



$B_{10,7}-T_{10,7}$

The results of the MMM calculation of compounds (XI) and (XII), belonging to this type (see Table 1), showed that the 3β,10α-chair ($^3C_{10}$) is preferable for ring A and a distorted $^5C_8$ chair (c) (ΔC = 20-24°), or, to a smaller degree, a distorted $T^{5,8}$ twist (d) (ΔC = 17–19°) for ring B. According to the calculations carried out, the $B_{10,7} - T_{10,7}$ conformation is practically impossible. The lactone ring may adopt the E^7, E_7, and T^7_{11} conformations. For the pairs of chair and boat conformers (XIc) and (XId) and (XIIc) and (XIId) of the (XI) and (XII) molecules, ΔE amounts to 2.6 and 0.5 kcal/mole with greater suitability of the chair conformation of ring B.

According to the results of calculation, for the hypothetical (not detected in nature) 5β,6β,7α(H)-eudesm-6,12-olides (IX) and (X), ring A has the chair, $^3C_{10}$, conformation and ring B the $T_{10,7}$ conformation (see Table 1); lactone ring C assumes the E_7 conformation. Particularly interesting is the fact that the conformational energies of these isomers (IX) and (X) (32.7 and 36.2 kcal/mole) are considerably higher than for the other stereoisomeric 6,7-linked eudesmanolides.

A comparison of the results of calculation for pairs of compounds with different orientations of the substituents (I) and (III), (II) and (IV), (Va), and (VII), and (VIa) and (VIII)) has shown that for the epimers with the β-orientation of the C14 methyl group at the C10 atom the α-orientation of the C15 methyl group (equatorial) is energetically more suitable; ΔE for the C15 β- and C15 α-epimers amounts to 3.2 kcal/mole in the case of the trans-linkage of rings B and C and 4.2 kcal/mole in the case of cis-linkage. This is possibly explained by the fact that with the axial orientation of the C15 methyl group steric repulsion arises between the C14 and C15 Me groups. In the case of the cis-linkage of ring B and C the nonvalent interaction of the C14 and C15 Me groups with the axially oriented O1 atom is added. A consequence of steric repulsion with the β-orientation of the C15 Me group is a greater deviation of the conformation of ring A from the ideal symmetrical chair: ΔC = 3° in (I) and (II) and 4° in (III) and (IV) (B/C-trans); ΔC = 4° in (Va) and (VIa), and ΔC = 6° in (VII) and (VIII) (B/C-cis).

The MMM calculation of the α- and β-santonins, which belong to the class of eudesmanolides under consideration, and their derivatives has shown [7] that in the case of the trans-linkage of rings B and C the 13α-isomer is more energetically suitable and in the case of the cis linkage the 13β-isomer (by 0.8 and 0.4 kcal/mole, respectively). A comparison of the corresponding model epimers ((I) and (II), and (III) and (IV) (see Table 1)) has shown that with B/C trans linkage the 13α-isomer is actually energetically more favorable by 1.7 kcal/mole (epimers with approximately the same asymmetry parameters of the rings were compared). However, in the case of the cis-linkage of rings B and C the 13β- isomers are more stable, although ΔE amounts to only 0.4 kcal/mole (for (Va) and (VIa), and for (VII) and (VIII), see Table 1). In this case, the main contribution to the value of ΔE is made by the change in the torsional component of the conformational energy along the C7–C11 and C11–C12 bonds. Such an "inversion" of ΔE on passing from the trans- to the cis-linkage of rings B and C can be explained by the assumption that in (I) and (III) the conformation along the C7–C11 bond (intermediate between antiperiplanar and +anticlinal) is more suitable by approximately 0.5 kcal/mole than in (II) and (IV) (intermediate between synperiplanar and +synclinal), while the conformation along the C11–C12 bond in (II) and (III) (torsional angle O2C12C11C13 31°) is approximately 0.8 kcal/mole more suitable than in (II) and (IV) (torsional angle O2C12C11C13 –80°) (Fig. 1).

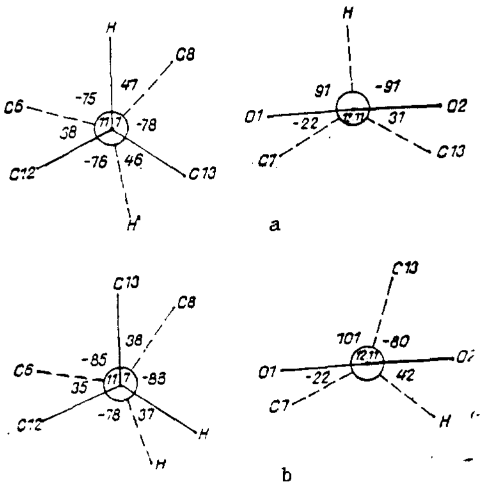


Fig. 1

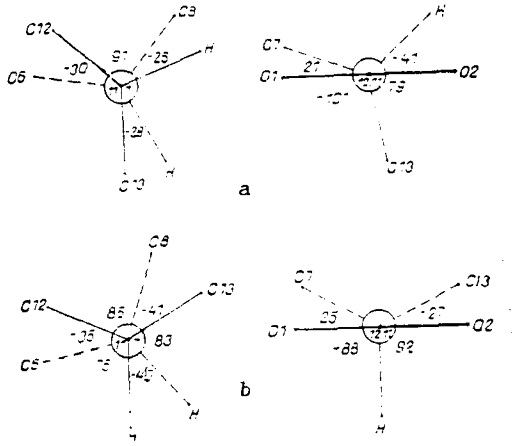


Fig. 2

Fig. 1. Newman projections along the C11—C7 and C12-C11 bonds of the molecules of (I) (a) and (II) (b).

Fig. 2. Newman projections along the C11-C7 and C12—C11 bonds of the molecules of (Va) (a) and (VI) (b).

In the case of the cis-linkage of ring B and C, the conformation along the C7—C11 bond in (VIa) and (VIII) (intermediate between synclinal and synperiplanar) is only ∿0.1 kcal/mole more suitable than in (Va) and in (VII) (intermediate between +synclinal and +anticlinal) with retention of a constant torsional component of ΔE for the C11—C12 bond (Fig. 2).

The suitability for the C11—C12 bond of that conformation in which the C13 Me group is located closer to the carbonyl than the H atom is confirmed by a MMM calculation of isobutyric acid [8], for which the conformer is 0.88 kcal/mole more stable than the alternative (in relation to the positions of H and Me). For the boat-shaped conformers (XIc) and (XIIc) with the cis-linkage of rings B and C, ΔE amounts to 3 kcal/mole. In this case, the difference in the torsional components is ∿1.5 kcal/mole and the remaining contribution is made by the distortion of the valence angles and (in XIIc)) by nonvalent interactions with the participation of the pseudoaxially oriented C13 Me group that exists in the case of the axial orientation (relative to ring B) of the C11 atom. Therefore the pseudoequatorial orientation of the C13 Me group is obviously more stable than the pseudo-axial orientation with any type of linkage with rings B and C.

The results obtained from the MMM calculations on the geometry of particular isomers and conformers are in good agreement with the experimental results obtained by the x-ray structural method (see, for example, [6, 9-11]). This shows that the most energetically suitable conformer is, with a high degree of probability, the most stable, since in the crystal, in the majority of cases, the molecules are present in the most suitable conformation when there are several possible ones.

The conformational calculations were performed on a EC-1061 computer by the MM2 program [12] using the potential parameters contained in this version and with complete optimization of the geometry of the molecules.

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X-RAY STRUCTURAL INVESTIGATION OF SESQUITERPENE ESTERS OF PLANTS OF THE GENUS Ferula.

VI. CRYSTAL AND MOLECULAR STRUCTURE OF UGAFERIN

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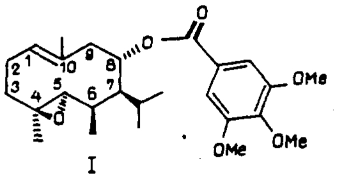
An x-ray structural investigation (diffractometer, Cu-K$_{\alpha}$ radiation, 2004 reflections, direct method, R factor 0.066) has been made of the germacrane ester ugaferin, which is 6β-hydroxy-8α-(3',4',5'-trimethoxybenzoyloxy)-4β,5α-epoxygermacr-1(10)-ene. A chair-boat conformation has been established for the ten-membered ring with a configuration of the $^{1}D_{14,15}D^{5}$ type.

The structure of the sesquiterpene ester ugaferin, isolated from Ferula ugamica Eug. Kor., has been established on the basis of spectral characteristics and chemical transformations [1]. However, the stereochemical aspects of this compound and, in particular, the conformation of the 10-membered ring could not be determined on the basis of PMR spectra. On the other hand, the germacrane ring of ugaferin differs from that of chimganidin by the presence of an epoxide group in the 4(5) position in place of a double bond [2]. The stereochemical closeness of the role of a double bond and of an epoxide ring have induced us to compare the conformations of the ten-membered rings in these compounds. With the aim of determining the stereochemistry of ugaferin we performed an x-ray structural investigation which has enabled its structure to be refined in the form of (I) (an OH group must be read in position 6):



I

In the ugaferin molecule, shown in Fig. 1 in a projection on the (001) plane, the methyl group at C4 and the ester group — a trimethoxybenzoic acid residue at C8 — have the α-orientation. The hydroxy group at C-6 and the isopropyl group at C-7 have the β-orientation. The ester group at C-8 and the substituted benzene ring are in the same plane and are perpendicular (89°) to the mean square plane of the ten-membered ring (in chimganidin the corresponding angle is 47°). In contrast to chimganidin, this feature, probably due to a packing effect, does not permit the formation of an intramolecular H-bond between the hydroxy (OH) and carboxy (O4) groups.

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