CONFORMATIONS OF THE RINGS AND RELATIVE STABILITIES OF ISOMERS OF trans,trans- AND trans,cis-EUDESMAN-8,12-OLIDES

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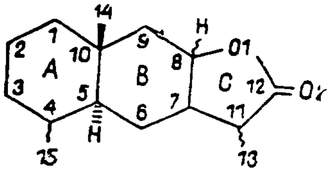
A series of isomers of trans,trans- and trans,cis-eudesman-8,12-olides has been investigated by the method of molecular mechanics (MMM). Questions of the energetic suitability of particular isomers, of the influence of the orientation of substituents attached to the basic skeleton on their conformation, and of the relative stabilities of the conformers with different methods of linking the rings are considered.

We have previously reported a study by the method of molecular mechanics (MMM) of the spatial structures and conformations of 6,7-linked eudesmanolides [1]. Continuing the study of eudesmanolides by MMM, in the present paper we give the results of a calculation for eight isomers of 7,8-linked eudesmanolides having the trans,trans- and trans,cis-linkage of the A/B and B/C rings with the aim of determining the relative energetic suitabilities of the different isomers and conformers and also of establishing the influence of the orientation of substituents attached to the tricyclic skeleton on the conformation of its rings.

For the calculation we selected eight model compounds (I-VIII) with the β-orientation of the C-14 Me group and different configurations of the chiral centers C4, C8, and C11:



I. 8β(H), 13α, 15α
III. 8β(H), 13α, 15β
V. 8α(H), 13α, 15α
VII. 8α(H), 13α, 15β

II. 8β(H), 13β 15α
IV. 8β(H), 13β 15β
VI. 8α(H), 13β 15α
VIII. 8α(H), 13β 15β

The choice of model compounds was due to the fact that they include the main carcass of the natural 7,8-linked eudesmanolides. Other 7,8-eudesmanolides differ from them by the presence of endocyclic double bonds and various substituents attached to the main skeleton.

The preferred conformations of rings A and B in the 5α,7α,8β(H)-eudesman-8,12-olides (I-IV) proved to be 3α,10β-chair ($_{3}C^{10}$) and 5α,8β-chain ($_{5}C^{8}$), respectively (Table 1). The conformations of ring A in (I) (ΔC = 4.6°) and (II) (ΔC = 5.0°) are less symmetrical than in (III) (ΔC = 2.9°) and (IV) (ΔC = 2.9°) although in (I) and (II) the C15 Me group has the equatorial orientation, while in (III) and (IV) it is axial. In a detailed consideration of the values of the intracyclic torsion angles in ring A, it is found that the smaller values of the asymmetry parameter in (III) and (IV) are due to the spatial repulsion of the Me groups attached to the C4 and C10 atoms (the C2C1C10C14 torsion angle is increased from −67° in (I) and (II) to −72° in (III) and (IV)), a consequence of which is a decrease in the sum of the intracyclic torsion angles in the ring, Σϕ, from 333° in (I) and 332° in (II) to 317° in (III) and (IV) and the equalization of the values of the torsion angles (the maximum value of Δϕ is 5° in (I) and (II) and 3° in (III) and (IV)), as in substituted cyclohexanes [2]. The axial β-orientation of the C15 Me group also leads to an increase in conformational energy (E). The difference of the conformational energies (ΔE) for the C4-epimers ((I) and (III), and (II) (IV)) amounts to 3.6 kcal/mole.

In (I)-(IV), ring B is considerably more distorted from the ideal chain conformation (ΔC = 9.6° in (I) and (II), and ΔC = 8.5° in (III) and (IV)). This is explained to a con-

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TABLE 1. Conformations of the Rings (the asymmetry parameters ΔC^* are given in parentheses) and Conformational Energies (E, kcal/mole) for the Molecules (I)-(VIII)

Compound	Conformations of rings			E
	A	B	C	
I	${}_3C^{10}(\Delta C_2^{1,10}=4,6^\circ)$	${}_5C^8(\Delta C_2^{5,6}=9,6^\circ)$	$E_7(\Delta C_8^7=3,5^\circ)$	20,6
II	${}_3C^{10}(\Delta C_2^{1,10}=5,0^\circ)$	${}_5C^8(\Delta C_2^{5,6}=9,6^\circ)$	$E_7(\Delta C_8^7=5,1^\circ)$	22,3
III	${}_3C^{10}(\Delta C_2^{1,10}=2,9^\circ)$	${}_5C^8(\Delta C_2^{5,7}=8,5^\circ)$	$E_7(\Delta C_8^7=3,5^\circ)$	24,2
IV	${}_3C^{10}(\Delta C_2^{2,3}=2,9^\circ)$	${}_5C^8(\Delta C_2^{5,7}=8,5^\circ)$	$E_7(\Delta C_8^7=5,1^\circ)$	25,9
Va	${}_3C^{10}(\Delta C^{1,10}=1,0^\circ)$	${}_5C^8(\Delta C_2^{6,7}=19,6^\circ)$	$E^7(\Delta C_8^7=1,0^\circ)$	19,9
Vb	${}_3C^{10}(\Delta C_2^{1,10}=10,0^\circ)$	$T_{5,8}(\Delta C_2^7=18,1^\circ)$	$T_7^{11}(\Delta C_2^{01}=4,7^\circ)$	22,9
VIa	${}_3C^{10}(\Delta C_2^{1,10}=1,0^\circ)$	${}_6C^4(\Delta C_2^{6,7}=17,0^\circ)$	$E^7(\Delta C_8^7=2,8^\circ)$	19,4
VIb	${}_3C^{10}(\Delta C_2^{1,10}=9,5^\circ)$	$T_{5,8}(\Delta C^7=18,8^\circ)$	$E_7(\Delta C_8^7=3,6^\circ)$	25,4
VII	${}_3C^{10}(\Delta C_2^{1,10}=6,5^\circ)$	${}_5C^8(\Delta C_2^{6,7}=20,1^\circ)$	$E^7(\Delta C_8^7=1,0^\circ)$	23,4
VIII	${}_3C^{10}(\Delta C_2^{1,10}=6,5)$	${}_5C^8(\Delta C_2^{6,7}=18,1)$	$E^7(\Delta C_8^7=2,8^\circ)$	22,9

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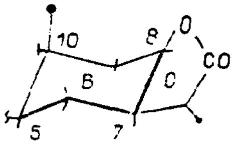
*The maximum values of the ΔC are given. A definition of the asymmetry parameter is given in [11].

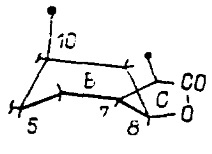
siderable degree by the presence of the lactone ring C conjugated at the C7-C8 bond in (I) and (II) (Fig. 1). In a Newman projection along the C7-C8 bond in (I) and (II) it can be seen that a decrease in the C11C7C8O1 torsion angle to 42 and 39° (the C11, C7, C8, and O1 atoms are present in the lactone ring) leads to a distortion from the antiperiplanar conformation and to a deviation of the values of the other torsion angles along the C7-C8 bond from |60|° (in particular, the C6C7C8C9 torsion angle in (I) is increased to −65°). A similar increase in the torsion angle in ring B along the bond in common with ring C is observed in the molecules of taurin (64.5°) [3], epivanin (66.3°) [4], and subcordatolide B (−65.6°) [5], which have been studied by the x-ray structural method. The intracyclic torsion angle in the lactone ring at the linkage amounts in these molecules to −37.6°, −40.3°, and 39.1°, respectively.

The conformation of the γ-lactone ring C in (II)-(IV) is a 7α-envelope (E_7) (see Table 1). The orientation of the C13 Me group considerably influences the conformation of the lactone ring. The ring is less distorted from the envelope conformation with the pseudoequatorial α-orientation of the Me group (ΔC = 3.5° in (I) and (III)) and is more distorted with the pseudoaxial β-orientation (ΔC = 5.1° in (II) and (IV)). For the epimers with respect to the C11 position, the α-orientation is more favorable than the β-orientation (ΔE = 1.7 kcal/mole), as also in the 6,7-trans-linked eudesmanolides [1].

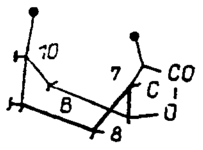
Because of the trans-linkage of rings A/B and B/C at the C1-C10 and C7-C8 bonds, the molecules of (I)-(IV) are conformationally rigid. Ring B can adopt only the chair conformation, and even strong deformation on the presence of voluminous substituents cannot force the ring out of this conformation. In the 5α,7α,8α(H)-eudesman-8,12-olides (V)-(VIII) the chair conformation for ring B is not the only possible one because of the cis-linkage of rings B and C. It follows from Dreiding models that ring B can exist in three conformations.



$_{8}C^{5}$



$B_{5,8}-T_{5,8}$



$B^{10,7}-T^{10,7}$

However, MMM calculations have shown that only the chair (${}_5C^8$) and boat-twist ($B_{5,8}$-$T_{5,8}$) conformations are realized. The ($B^{10,7}$-$T^{10,7}$) boat-twist conformation is impossible, probably because of the steric stress arising as a result of the repulsion of the axially oriented C14 Me group and the C11 atom.

The conformation of ring A in (Va) and (VIa) is a symmetrical ($\Delta C = 1.0°$) but somewhat flattened ($\Sigma\phi = 332°$) chair (see Table 1). In (VII) and (VIII), the conformation of ring A is more distorted from the ideal chair ($\Delta C = 6.5°$) because of the axial orientation of the C15 Me group, which leads to an increase in E for the molecules of these compounds by 3.5 kcal/mole in comparison with their C4-epimers. The conformation of ring B in (Va), (VIa), (VII), and (VIII) is a highly distorted chair (ΔC between 17.6 and 20.1°) (see Table 1). Such a large distortion is due to the fact that with the cis-linkage of rings B and C, the O1 atom is axially oriented with respect to ring B. The steric strain then arising between the O1 and the C14 Me group again leads to a considerable distortion of ring B. In a Newman projection along the C7-C8 bond in (Va) and (VIa) (Fig. 1, c, and d) it can be seen that the conformation deviates considerably from synclinal. The C11C7C8O1 torsion angle is less by 7-8° than in the case of the B/C-trans linkage (Fig. 1, a, b), while the C6C7C8C9 torsion angle deviates from the ideal value of −60° by 20-22°. Pronounced distortion of ring B is also observed in the molecules of the diacetate of 12β-p-bromophenylthio-11α,13-dihydropulchellin C [6], 5-hydroperoxytekelin and its pyrazoline adduct [7], and subcordatolide C [8], which have been studied by the x-ray structural method. The values of the C6C7C8C9 and C11C7C8O1 torsion angles in these molecules are, respectively, −42 and −37°, −34.3 and −29.2°, −38.1 and −34.7°, and −41.9 and −35.1°. The C11C7C8O1 torsion angle of −29.2° in the pyrazoline adduct of 5-hydroperoxytekelin is close to the ideal value (−20°) calculated by MMM for the isolated α-methylene-γ-lactone [9]. We may note that the orientation of the C13 Me group, which does not in fact affect the conformation of ring B in the C11-epimers in the case of the trans-linkage of rings B and C ((I) and (II), and (III) and (IV), has an influence on the value of the torsion angles and symmetry of ring B when it is cis-linked with ring C. A comparison of the C11-epimers ((Va) and (VIa), and (VII) and (VIII)) shows (see Table 1) that the axial α-orientation of the C13 Me group introduces a greater distortion into the conformation of ring B.

The conformation of the lactone ring C in (Va) and (VIa), (VII) and (VIII) is that of a 7β-envelope. With the pseudoequatorial β-orientation of the C13 Me group, the lactone ring is almost symmetrical ($\Delta C = 1.0°$) and with the pseudoaxial α-orientation it is somewhat distorted ($\Delta C = 2.8°$), the α-orientation being somewhat less suitable (for the C11-epimers, $\Delta E = 0.5$ kcal/mole). The difference in ΔE for the C11-epimers with the trans- and cis-linkages of rings B and C (1.7 and 0.5 kcal/mole, respectively) is connected with the same factors as in the 6,7-linked eudesmanolides [1]. The 7β-envelope conformation is not the only possible

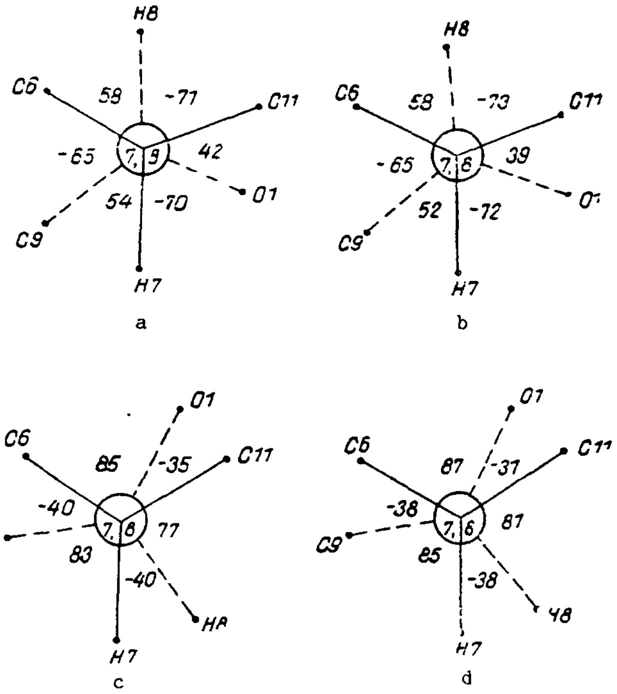


Fig. 1. Newman projection along the C-7—C-8 bonds of the molecules (I) (a), (II) (b), (Va) (c), and (VIa) (d).

one for ring C in the trans,cis-eudesman-8,12-olides. The 7β,8α-half chair conformation, which is more frequently observed when a C11═C13 exocyclic double bond conjugated with the carbonyl group of the γ-lactone is present [6, 8], is also possible.

It was shown above that in the trans,cis-eudesman-8,12-olides ring B can adopt a boat or a twist conformation. In these conformations (Vb) and (VIb); Table 1), ring A adopts a distorted chair conformation (ΔC = 10.0° for (Vb) and 9.5° for (VIb)). Ring B adopts a conformation intermediate between twist and boat (ΔC_S^7 = 18.1°, $\Delta C_2^{6,7}$ = 29.3° (Vb) and ΔC_S^7 = 18.8°, $\Delta C_2^{6,7}$ = 30.5° (VIb)), closer to a distorted twist. The conformation of the lactone ring in (Vb) is 7α,11β-half-chair (ΔC_2^{O1} = 4.7°) and in (VIa) it is intermediate between a 7α-half-chair (ΔC_S^7 = 3,6°) and a 7α,11β-half-chair (ΔC_2^{O1} = 4.7°).

The deviation of the C7 atom in the α-direction from the plane of the other atoms of ring C leads to the situation that the β-oriented C13 Me group becomes pseudoaxial, while an α-orientated group becomes pseudoequatorial, as in the case of the trans-linkage of rings B and C. It must be mentioned that the twist or boat conformation of ring B for the trans, cis-eudesman-8,12-olides has not been detected experimentally in crystal structures. A comparison of the corresponding conformers ((Va) and (Vb), and (VIa) and (VIb)) shows that the second members are less suitable by 3.0 and 6.0 kcal/mole, respectively. In actual fact, according to x-ray structural results (see above), in crystal structures of the two conformers possible for (V) and (VI) it is just the first that is realized.

The conformational calculations were performed on a ES-1061 computer according the MM2 program [10] using the parameters of the potentials contained in it and with the complete optimization of the geometry of the molecules.

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