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POSSIBLE CONFORMATIONS OF THE SEVEN-MEMBERED RINGS AND RELATIVE STABILITIES OF 1β,5α,6β,7α(H)- AND 1α,5α,6β,7α(H)-GUAI-11(13)-EN-6,12-OLIDES

K. M. Turdybekov, S. V. Lindeman,
T. V. Timofeeva and Yu. T. Struchkov

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A calculation has been made by the method of molecular mechanics, using the MM2 program, of a number of stereomeres of 1β,5α,6β,7α(H)- and 1α,5α,6β,7α(H)-guai-11(13)-en-6,12-olides. The possibilities of the adoption by the seven-membered ring of particular conformations according to the type of its linkage with the 5-membered carbocycle have been considered. Questions of the influence of the orientation of the Me groups on the degree of distortion of the conformation of the seven-membered ring from the ideal and the relative stabilities of the various conformers are discussed.

We have previously reported on the analysis by the method of molecular mechanics (MMM) of the spatial structures and conformations of 6,7- and 7.8-linked eudesmanolides [1, 2]. Continuing conformational studies of sesquiterpene lactones, in the present paper we give the results of a MMM calculation for some trans,trans- and cis,trans-linked nonlinear guaianolides with the aim of elucidating the possibility of the realization of particular conformations of their seven-membered carbocycles and relative stabilities of these conformers for different (α or β) orientations of the methyl groups at the C4 and C10 atoms.

For calculation we selected eight model compounds (I-VIII) with different configurations of the chiral centers – the C1, C4, and C10 atoms – and the trans-linkage of rings B and C.

The choice of just these compounds as models was due to the fact that nonlinear guaianolides with such types of skeletons are found most frequently in nature [3, 4].

A preliminary consideration of the conformations of the molecules (I-VIII) using Dreiding molecular models showed that the seven-membered ring B in the molecules (I-IV), having the trans-linkage of rings A/B can assume four chair (C) conformations: 7α,1,10β-C (a), 9,10α,6β-C (b), 5α,8,9β-C (c), and 7,8α-1β-C (d). In the molecules (V-VIII), having the cis-linkage of rings A/B, ring B can assume three chair conformations: 1,5α,8β-C (e), 5α,8,9β-C (f), and 7,8α,1β-C (g) and three boat (B) conformations: 1,7,8α-B (h), 6,9,10β-B (i), and 5,6,9β-B (j).

After optimization of the geometry of the four initial idealized conformers a-d of molecules (I-IV) (Table 1) it was found that only three conformers of (I) were stable: conformer a is only slightly distorted relative to the ideal transition into form IA; $\left(\Delta C_s^7 = \right.$ and

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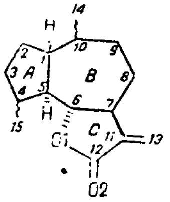
$\Sigma_2/(\Sigma_s+\Sigma_2)=0,7\big)$ conformer b passes into the intermediate conformation IB between 5α,8,9β-C and 6,7α,1,5β-twist-chair (TC) $\big(\Delta C_s^5=17,8°$, $\Delta C_2^{5,6}=18,8°$ and $\Sigma_2/(\Sigma_s+\Sigma_2)=0,4\big)$, and conformers c and d pass into the form 1,10α,5,6β-TC (IC) $\big(\Delta C_2^{1,5}=10,5°, \Sigma_2/(\Sigma_s+\Sigma_2)=0,2\big)$. The values of the torsional angles in ring B of these conformers obtained after optimization are given in Table 2. The most stable of all the conformers of compound (I) is IC; IB is somewhat less stable (ΔE = 1.1 kcal/mole), while IA is considerably less stable (ΔE = 4.1 kcal/mole).



I: 1 α (H), 14β, 15α
II: 1 α (H), 14β, 15β
III: 1 α (H), 14α, 15α
IV: 1α (H), 14α, 15β

V: 1β (H), 14β, 15α
IV: 1β (H), 14β, 15β
VII: 1β (H), 14α, 15α
VIII: 1β (H), 14α, 15β

For compound (II), two conformers are realized: in the first (IIA), just as in (I) the a conformation of ring B is retained $\big(\Delta C_s^7=5,0°, \Sigma_2/(\Sigma_s+\Sigma_2)=0,9\big)$, and in the second 1,10α,5,6β-TC (IIB) is realized $\big(\Delta C_2^{1,5}=9,9°, \Sigma_2/(\Sigma_s+\Sigma_2)=0,2\big)$, in which, on potimization, the initial conformers b-d fused together. The stable 6,7α,1,5β-TC conformation was not detected for (II), which is apparently explained by the β-orientation of the Me group at C4. Such an orientation leads to the appearance on nonvalent repulsion betweeen the Me group and the O1 atom of the lactone ring, which causes twisting round the C5—C6 bond (the C4C5C6O1 torsional angle is 49° in (IIb) and 56° in (IB)) and, as a consequence, an instability of the 6,7α,1,5β-TC conformation. We may note that for (II), as also for (I), conformer (IIA) is 5.1 kcal/mole less stable than (IIB).

The stability of the less favorable conformer, 7α,1,10β-C, for (I) and (II) with the axial orientation of the C14 Me group is explained by the fact that the passage of ring B into the apparently more suitable 5,6α,7,8β-TC conformation leads to an increase in steric repulsion between H1 and one of the H atoms at C8, while the transition to 8,9α,6,7β-TC prevents the appearance of the axial orientation of the Me group which, with the trans-linkage of rings A and B, does not permit the C6C5C1C10 torsional angle to be decreased.

In the isomers (III) and (IV), the C14 Me group has the equatorial α-orientation, ring B passes from conformation a into one intermediate between the initial 7α,1,10β-C and 8,9α,6,7β-TC (IIIa) and (IVa)) $\Delta C_2^{7,8}$ = 24.0 and 19.2°, ΔC_s^7 = 17.5 and 18.2°, respectively, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.4 (Table 2). Conformers b, c, and d pass into a more energetically favorable conformation — 6,7α,1,5β-TC. However, in the case of the initial conformer b such a conformation of ring B after optimization is somewhat distorted in the 9,10α,6β-C direction ((IIIB) and (IVB) ($\Delta C_2^{5,6}$ = 6.2 and 7.0° respectively, $\Sigma_2/\Sigma_s + \Sigma_2)$ = 0.2. Then no steric repulsion arises between the Me group at C4 and O1 in conformer (IVB) since the conformation of ring A is a 4-envelope (ΔC_s^1 = 6.3°) with the axial orientation of the C15 Me group.

From the two initial conformers (c) and (d) after optimization a different conformation of ring B is realized which deviates somewhat in the 5α,8,9β-C direction ((IIIC) and (IVC)) ($\Delta C_2^{5,6}$ = 5.0 and 5.4° respectively, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.1 and 0.2, while ring A adopts the 2α, 1β-half-chair conformation ($\Delta C_2^{1,2}$= 5.6 and 4.1° respectively. We may note that the values of ΔE for the three conformers in (III) and (IV) are small, amounting to 0.9 and 0.9 kcal/mole, respectively (Tble 2). The realization in the molecule of (III), having the α-orientation of the Me group at C4 of what would appear to be the more suitable 1,10α,5,6β-TC conformation of ring B, as in the case of (I), does not take place, apparently because of the steric repulsion arising between the Me group at C10, oriented axially, and the H7 atom.

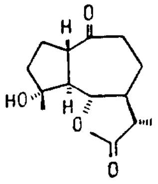
A comparison of the results of the MMM calculation of the conformations of molecules (I-IV) with 4α-hydroxy-10-oxo-1β,5α,6β,7α(H)-guai-6,10-olide (IX) [5], 5α-hydroxy-1β,4α, 6β,11β(H)-guai-2,10(15)-dien-6,12-olide (X) [6], and 3,10α-dichloro-1,4β-dihydroxyar-glabin (XI) [7], which have been investigated experimentally by the x-ray structural method showed that the conformation of ring B in these compounds — 6,7α,1,5β-TC — corresponds to one of those calculated for the model isomers (I), (III), and (IV).

TABLE 1. Torsional Angles in Ring B of the Initial Idealized Conformers of Compounds (I-IV) (a-d) and (V-VIII) (e-j)

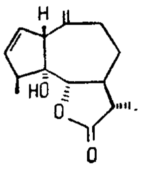
Conformation	Angles at the bonds						
	C1—C5	C5—C6	C6—C7	C7—C8	C8—C9	C9—C10	C1—C10
7α,1,10β-*C* (a)	74	−95	79	−77	88	−65	−8
9,10α,6β-*C* (b)	91	−69	80	−98	62	11	−82
5α,8,9β-*C* (c)	85	−65	98	−88	4	77	−108
7,8α,1β-*C* (d)	−94	84	−10	−76	104	−76	71
1,5α,8β-*C* (e)	−3	−85	112	−84	49	−124	107
5α,8,9β-*C* (f)	39	−45	95	−79	−6	91	−88
5,8α,1β-*C* (g)	38	−78	92	−19	−71	102	−52
1,7,8α-*B* (h)	−40	−47	84	−1	−91	63	35
6,9,10β-*B* (i)	−41	−58	62	36	−92	6	84
5,6,9β-*B* (j)	−79	−12	90	−31	−73	76	28

TABLE 2. Torsional Angles in Ring B of Various Conformers of Compounds (I-IV) and Their Conformational Energy E Obtained as the Result of Optimization

Conformation	Angles at the bonds							E, kcal/mole
	C1—C5	C5—C6	C6—C7	C7—C8	C8—C9	C9—C10	C1—C10	
7α,1,10β-*C* (IA)	68	−88	76	−70	81	−58	−8	31,3
6,7α,1,5β-*TC* (IB)	72	−65	86	−80	21	50	−85	28,3
1,10α,5,6β-*TC* (IC)	62	−75	93	−46	−31	83	−77	27,2
7α,1,10β-*C* (IIA)	62	−86	76	−69	81	−62	0	33,4
1,10α5,6β-*TC* (IIB)	59	−73	92	−47	−32	84	−75	28,3
8,9α,6,7β-*TC* (IIIA)	55	−93	78	−62	78	−76	17	31,7
6,7α,1,5β-*TC* (IIIB)	76	−64	81	−86	39	31	−81	31,1
6,7α,1,5β-*TC* (IIIC)	75	−64	83	−84	34	35	−81	31,0
8,9α 6,7β-*TC* (IVA)	51	−89	77	−64	78	−77	20	33,5
6,7α,1,5β-*TC* (IVB)	77	−65	81	−86	39	30	−79	32,6
6,7α,1,5β-*TC* (IVC)	73	−61	81	−86	35	35	−81	32,6



IX



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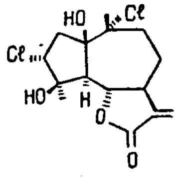


XI

For compounds (V-VIII), the optimization of the geometry of the initial conformers e-j (the torsional angles in ring B are given in Tble 1) leads to the realization for ring B of two TC conformations and one twist-boat (TB) conformation. The conformation of ring B passes from e to 7,8α,1,10β-TC (VA-VIIIA), from f and g into 1,10α,5,6β-TC (VB-VIIIB), and from all boat-shaped conformations (h, i, and j) into 7,8α,5,6β-TB (VC-VIIIC), the different orientations of the Me groups in the isomers (V-VIII) leading to different distortions of the ring conformation from the ideal TC and TB. Thus, a comparison of the torsional angles in ring B of the corresponding conformers (CA-VIIIA) (Table 3) of compounds (V-VIII) showed that while in the case of the equatorial α-orientation of the C14 Me group the ring is slightly distorted in the direction of the 1,5α,8β-C conformation from the ideal 7,8α,9,10β-*TC* ($\Sigma_2/(\Sigma_s+\Sigma_2)=0{,}2$, $\Delta C_2^{8,9}=11{,}4$ and 9.2 in (VIIA) and (VIIIA), respectively), in the case of its axial orientation the distortion of the symmetry of the ring increases considerably ($\Sigma_2/(\Sigma_s+\Sigma_2)$ = 0.3 and 0.4, $\Delta C_2^{8,9}$ = 17.1 and 17.9°, ΔC_s^1 = 21.4 and 20.7° in (VA) and (VIA), respectively.

The influence of an axial orientation of the C14 Me group on the conformation of ring B is shwon in a considerable difference of the corresponding angles of the C10 epimers ((VA) and (VIIA), and (VIA) and (VIIIA)), the mean value of the difference in the corresponding torsional angles ($\Delta\varphi$) amounting to 5-6°, while the influence of the orientation of the C15 group is only slight ($\Delta\varphi<1°$) . However, on the other hand, the observed tendency of ring B to pass into the formally less suitable chair conformation can be explained only by the influence of the mutual repulsion of the C14 Me group and the H4 atom ($\Sigma_2/(\Sigma_s+\Sigma_2)$ = 0.3) in (VA) and of the C14 and C15 Me groups in (VIA) ($\Sigma_2/(\Sigma_s+\Sigma_2)$ = 0.4).

TABLE 3. Torsional Angles in Rings B of Various Conformers of Compounds (V-VIII) and Their Conformational Energies E Obtained as the Result of Optimization

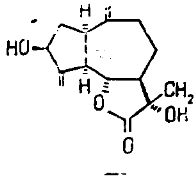
Conformation	Angles at the bonds							E, kcal/mole
	C1–C5	C5–C6	C6–C7	C7–C8	C8–C9	C9–C10	C1–C10	
7,8α, 9,10β-*TC* (VA)	−25	−49	92	−75	59	−71	75	28,4
1,10α, 5,6β-*TC* (VB)	40	−67	97	−45	−39	86	−61	29,1
7,8α, 5,6β-*TB* (VC)	−44	−41	88	−22	56	35	45	34,8
7,8α, 9,10β-*TC* (VIA)	−24	−49	92	−76	60	−72	74	31,4
1,10α, 5,6β-*TC* (VIB)	42	−67	97	−45	−33	85	−62	29,1
7,8α, 5,6β-*TB* (VIC)	−40	−43	89	−22	−55	37	41	37,3
7,8α, 9,10β-*TC* (VIIA)	−32	−49	95	−71	53	−73	85	27,8
1,10α, 5,6β-*TC* (VIIB)	36	−68	94	−38	−44	81	−51	29,4
7,8α, 5,6β-*TB* (VIIC)	−49	−27	89	34	−53	50	31	31,9
7,8α, 9,10β-*TC* (VIIIA)	−34	−47	95	−71	53	−73	85	28,9
1,10α, 5,6β-*TC* (VIIIB)	42	−70	94	−38	−42	81	−56	31,4
7,8α, 5,6β-*TB* (VIIIC)	−45	−32	90	−32	−53	48	32	34,1

A comparison of the corresponding torsional angles of conformers (VB-VIIIB) (conformation of ring B being 1,10α,5,6β-TC) showed that in this case, as well, the influence of the orientation of the Me group at C10 on the conformation of ring B is considerable: the values of for (VB) and (VII) and for (VIB) and (VIIIB) amount to 4-5° (Table 3). However, in contrast to (VA) and (VIA), in conformers (VIIB) and (VIIIB) the axial α-orientation of the C14 Me group does not cause appreciable deviation of ring B from the ideal TC conformation ($\Sigma_2/(\Sigma_S + \Sigma_2) = 0.2$, $\Delta C_2^{1,5}$ = 12.8 and 11.3° for (VIIB) and (VIIIB), respectively), since in these conformers there is no steric strain between the Me groups at C4 and C10, as in (VB) and (VIB), where, when the C14 Me group has the β-orientation, the conformation of ring B is almost ideal TC ($\Sigma_2/(\Sigma_S + \Sigma_2) = 0.1$, $\Delta C_2^{1,5}$ = 8.0 and 8.5° for (VB) and (VIB), respectively).

A comparsion of the conformational energies (E) of the two TC conformers of each of compounds (V-VIII) showed that for (VII) and (VIII), having the α-orientation of the C14 Me group, conformers (VIIA) and (VIIIA) are more favorable than (VIIB) and (VIIIB) by 1.6 and 2.5 kcal/mole). For (VA), because of the axial orientation of the C14 Me group, this conformer is more stable than (VB) by only 0.7 kcal/mole, while for (VIA) the axial syn orientation of the C14 and C15 Me groups makes this conformer 2.3 kcal/mole less stable than (VIB). For the boat-shaped conformers (VC-VIIIC) the considerable difference in the values of E between the most stable TC conformer and the less TB conformer makes it possible to assume a low probability of the realization of the latter (for (V-VIII) ΔE = 6.4, 5.9, 4.1, and 5.2 kcal/mole, respectively; see Table 3).

The conformation of ring B in (VC-VIIIC) likewise depends considerably on the orientation of the C14 Me group ($\Delta\varphi = 9°$ for (VC) and (VIIC), $\Delta\varphi = 7°$ for (VIC) and (VIIIC)). Then, when the C14 Me group has the α-orientation, ring B assumes the 7,8α,5,6β-TC conformation slightly distorted in the 5,6,9β-B direction $\Delta C_2^{6,7}$ = 11.9 and 10.3° and $\Sigma_2/(\Sigma_S + \Sigma_2) = 0.3$ and 0.2 for (VIC) and (VIIIC), respectively).

A comparison of the results of the analysis by MMM of the conformations of the seven-memered ring in compounds (V-VIII) with those found experimetnally by the x-ray structural method showed that in the crysals, as a rule, ring D assumes the 7,8α,9,10β-TC conformation, as, for example, in solstitialin (XII) [8] or 1,10α,5,6β-TC as in centaurepsin (XIII) [9], confirming the results of our calculations. It must be mentioned that in the structure of the fluoroguaianolide (XIV) [10] the 1,5α,8β-C conformation of ring B has been detected, which is possibly explained by the presence in the crystal of intermolecular hydrogen bonds that can stabilize this conformation.



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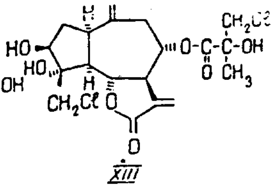

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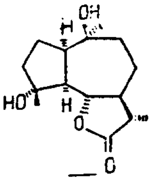

XIV

The conformational calculations were made on a ES-1061 computer by the MM2 program [11] with full optimization of the geometry of the molecules and the use of the parameters of the potentials present in this version of the program with the exception of the parameters for the O1—C12—C11 valence angle and the C6—O1—C12—C11, C7—C11—C12—O1, C13—C11—C12—O1 and C13—C11—C12—O2 torsional angles, which were taken from other literature sources [12, 13].

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TERPENOIDS OF Artemisia splendens

S. V. Serkerov and A. N. Aleskerova

UDC 633.81:633.88

d-Camphor, ℓ-borneol, stearic acid, β-sitosterol, austricin, and a new sesquiterpene lactone which has been called splendolide have been isolated from the epigeal part of <u>Artemisia splendens</u> Willd. The structure of splendolide has been established as 1β-hydroxy-6βH,7αH-eudesma-4,11(13)-dien-6,12-olide.

There is no information in the literature on the chemical composition of Asia Minor wormwood <u>Artemisia splendens</u> Willd. By column chromatography on silica gel of the total extractive substances obtained from the epigeal part of Asia Minor wormwood (gathered in the Nakhechevan ASSR, Shakhbuz region, environs of the village of Bichenek) we have isolated six substances (I-VI).

Substance (I) – $C_{10}H_{16}O$, mp 178-179°C (sublimation). The IR spectrum of (I) showed the absorption band of a carbonyl group in the region of characteristic frequencies (1755 cm^{-1}). The PMR spectrum had the signals of quaternary methyl groups at 0.80, 0.89, and 0.94 ppm. No signals belonging to any protons were observed in the 3.00-10.00 ppm region.

Substance (II) – $C_{10}H_{18}O$, mp 201-202°C (sublimation). The IR spectrum of (II) had the bands of an OH group (3350 cm^{-1}). The hydroxy group was undoubtedly secondary, since the PMR spectrum contained a one-proton doublet at 4.00 ppm (J = 10 Hz) with greatly broadened ($W_{\frac{1}{2}}$ = 6 Hz) components. A singlet (9 H) belonged to three quaternary methyl groups. There were no signals in the 4.20-10.00 ppm region of the spectrum. The oxidation of (II) with chromium trioxide led to substance (I), which was identified from its IR spectrum in the absence of a depression of the melting point in a mixed sample.

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