CONFORMATIONS OF THE 10-MEMBERED RING AND RELATIVE STABILITIES OF CONFORMERS OF (E,E)-$\Delta^{1(10),4}$-GERMACRANOLIDES

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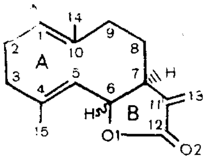
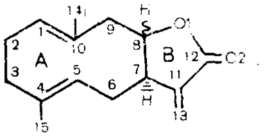
The relative stabilities of the four possible conformers in the various types of linkage of the 10-membered and lactone rings (E,E)-$\Delta^{1(10),4}$-germacranolides have been established from the results of a calculation by the method of molecular mechanics. The possibility of the realization of these conformers in linear and nonlinear (E,E)-germacranolides has been evaluated.

Germacranolides (natural sesquiterpenoids) are of particular interest among sesquiterpene lactones in view of the conformational lability of the 10-membered carbocycle. As is known from the literature [1], cyclodecane can assume a large number of conformations. However, the presence in the majority of germacranolides of two intracyclic double bonds, C1═C10 and C4═C5, of methyl groups at the C4 and C10 atoms, and, more rarely, of other substituents, and also of a γ-lactone ring condensed at the C6—C7 or C7—C8 bond considerably limits the number of possible conformations of the 10-membered rings in the germacranolides. It has been shown [2] that for (E,E)-$\Delta^{1(10),4}$-germacranolides the existence of only four conformers is possible: chair—chair of the $^{14}D_5$, $_1D^{14}$ type (a), chair—boat of the $_{15}D^5$, $^1D_{14}$ type (b), boat—boat of the $_{15}D^5$, $_1D^{14}$ type (c), and boat—boat of the $^{15}D_5$, $^1D_{14}$ type (d) (Fig. 1).

To determine the influence of the type of linkage (of the 10-membered and γ-lactone) rings on the relative stabilities of these comformers, we have made a conformational analysis by the method of molecular mechanics of the four isomers (I—IV).



I. 6β (H), 7α (H)
II. 6α (H), 7α (H)



III. 7α (H), 8β (H)
IV. 7α (H), 8α (H)

It was found that for isomer (I) the most stable conformer is type a (Ia), which is preferred over the others in terms of conformational energy (ΔE = 3.7-5.5 kcal/mole). For (II) the preferred conformer is that of type b (IIb), which is more favorable than the others by ΔE = 2.0-4.9 kcal/mole. The values of the torsional angles in ring A and of the conformational energy (E) are given in Table 1.

For isomer (III), all four types of conformers are approximately equiprobable ($\Delta E < 1.5$ kcal/mole), which presupposes an increased flexibility of the 10-membered ring in the corresponding series of compounds. For isomer (IV), the values of E for all the conformers are again close ($\Delta E < 1.0$ kcal/mole) but are 6-8 kcal/mole greater than those found for the corresponding conformers of isomer (III). This indicates a state of strain of the molecule of (IV) which is possibly one of the reasons for the absence of 7α,8α(H)-E,E-germacranolides in biological material. A greater conformational flexibility of the linear (i.e., 7,8-linked) germacranolides than the nonlinear (6,7-linked) ones is also shown by ^{13}C NMR results. Characteristic features of the NMR spectra of the nonlinear germacranolides in solution are four peaks (a single conformer predominates), while for the signals in the NMR spectra of the linear germacranolides are usually broad and overloaded [3]. The conforma-

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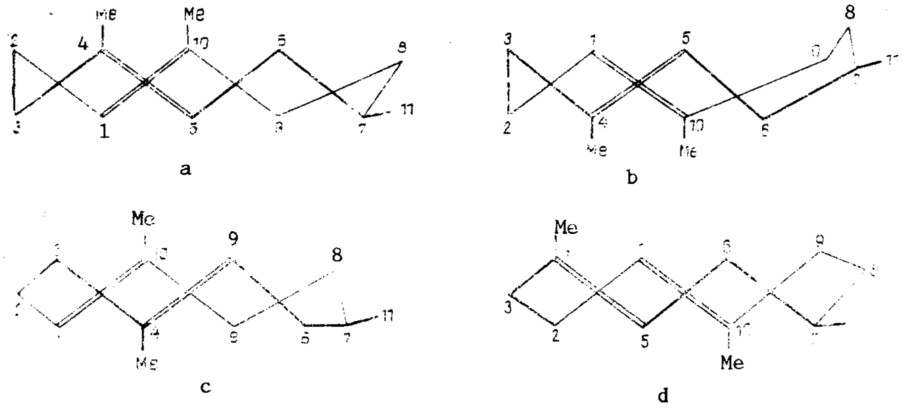


Fig. 1. Conformations of the 10-membered rings of the (E,E-germacranolides: a) chair—chair of the ${}^{15}D_5$, ${}_1D^{14}$ type; b) chair—boat of the ${}_{15}D^5$, ${}^1D_{14}$ type; c) boat—boat of the ${}_{15}D^5$, ${}_1D^{14}$ type; d) boat—boat of the ${}^{15}D_5$, ${}^1D_{14}$ type.

TABLE 1. Torsional Angles in Ring A of Various Conformers of Compound (I—IV) and Their Conformational Energies E

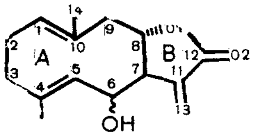
Conformation	Angle at the given bond										E, kcal/mole.
	C1—C2	C2—C3	C3—C4	C4—C5	C5—C6	C6 C7	C7—C8	C8—C9	C9—C10	C1—C10	
Ia	—99	49	—83	163	—139	87	—80	69	—115	170	21,2
IIa	—98	44	—86	176	—116	49	—74	89	—117	164	26,9
IIIa	—101	42	—87	171	—122	77	—97	84	—105	167	19,8
IVa	—97	52	—83	167	—144	66	—53	56	—119	169	26,0
Ib	112	—40	90	—161	65	73	—125	45	59	—169	26,7
IIb	95	—49	85	—170	114	22	—94	58	74	—170	22,0
IIIb	105	—43	90	—169	83	53	—118	54	64	—169	18,3
IVb	100	—46	84	—171	66	63	—37	—53	128	—161	25,4
Ic	—78	—22	91	—163	68	79	—104	59	—97	172	24,9
IIc	—74	—33	93	—167	106	36	—92	80	—101	169	24,0
IIIc	—76	—30	94	—166	85	62	—110	72	—95	170	18,3
IVc	—75	—32	88	—162	65	64	—17	—60	—13	162	26,3
Id	76	30	—92	159	—127	81	—102	55	63	—174	26,9
d	77	21	—93	172	—99	39	—92	75	59	—169	26,5
IIId	75	27	—94	167	—118	66	—108	68	62	—170	19,7
IVd	79	24	—87	162	—152	68	—5	—63	125	—167	26,3

tional flexibility of the linear germacranolides has also been confirmed by the results of x-ray structural studies. In complete agreement with the results of the conformational calculation, for all the compounds of series I investigated structurally ring A assumes a conformation of type a as, for example, in hanphyllin, salonitenolide, and sachosin [4, 5], and for the compounds of series II and conformation of type b, as in (E,E)-8-acetoxygermacra-1(10),4-dien-6,12-olide [6] and ursiniolide A [7]. Conversely, in the crystal structures of the linear trans-linked (E,E)-germacranolides all four possible conformations of ring A have been found: type a — an ivaxillin [8]; type b — in spiciformin acetate [9]; type c — in halloerol [10]; type d — in mucrin [11]. In solution, the molecules of compounds of series III may be present in the form of two and even four conformers (compare the structure of spiciformin [9] and of laurenobiolide [12].

As was to be expected, in the corresponding conformers a-d of isomers (I-III) the torsional angles in the C5—C9 section of ring A adjacent to the condensed γ-lactone ring differ most widely. Thus, while the difference in the corresponding torsional angles (Δφ) of the remaining part of the ring does not, as a rule, exceed 10°, Δφ for the C7C8C9C10 angles amounts to 13-21°, and for the C6C7C8C9 angles it ranges between 16 and 31° (Table 1). Such a difference is explained basically by the different method of linkage of the rings in the linear and nonlinear germacranolides (at the C6—C7 or the C7—C8 bond). The cis or trans linkage of the rings at the C6—C7 bond leads to larger values of Δφ for the torsional angles C4C5C6C7 (23-53°) and C5C6C7C8 (38-51°). The considerable influence of the method of linkage of the rings on the value of the torsional angles C4C5C6C7 and C5C6C7C8 is explained by the fact that on passing from trans to cis linkage there is a change in the equatorial orientation of the O1 atom of the lactone ring to the axial orientation in conformers a and d and conversely in conformers b and c, which leads to considerable deformations of the 10-membered ring. This, in particular, in our view, explains the advantageousness of a conformer of type a for (I) and of type b for (II). For the linear (E,E)-germacranolides the α-orientation of the O1 atom remains equatorial for all the conformers, which is also shown in the small differences of their conformational energies in the case of (III). For the same reason, because of the axial β-orientation of the O1 atom the values of E for the conformers of the (IV) molecule are considerably higher than for the corresponding conformers of the (III) molecule. Furthermore, it can be seen from the values of the torsional angles in the conformers of (IV) (Table 1) that the optimized conformations are close to ideal only in the case of conformer (IVa), even though for it $\Delta\varphi_{max}$ amounts to 14-44° in the C5—C10 section (as compared with an ideal chair—chair). For the other conformers the scatter of the torsional angles relative to the ideal values amounts to 49-111° (IVb), 41-93° (IVc), and 42-138° (IVd), which does actually indicate the realization for (IVb-IVd) of conformers substantially differing by the conformations of the 10-membered rings from the initial idealized forms b-d.

The most common substituent in the germacranolides is a hydroxy or ester group at C6 (in the linear compounds) or C8 (in the nonlinear compounds). In view of this, it appeared to be of interest to consider the influence of such a substituent on the relative stabilities of conformers a-d in the linear germacranolides. As follows from Fig. 1, in all the conformations of the nonlinear germacranolides, the α-orientation of the substituent is always equatorial and the β-orientation always axial and therefore the orientation cannot appreciably affect their relative stabilities. Conversely, in the linear germacranolides the α-orientation corresponds to the equatorial position in conformers a and d and the axial position in b and c (the β-orientation being the opposite, respectively). This impels us to assume an appreciable change in relative stability in the series of C6-substituted conformers of (III) as compared with the unsubstituted series in which, as was shown above, the relative energies of conformers a-d are close. Such a conclusion has also been confirmed experimentally. In laurenobiolide, which has an α-oriented C6-acetoxy group, conformers a-d are realized in a ratio of 5:4:3:1 for a, d, b, and c, respectively [12].

To calculate the relative stabilities of the conformers of the C6-substituted germacranolides we selected the model molecules 6α- and 6β-hydroxy-7α,b(H)-(E,E-)germacra-1(10),4,11(13)-trien-8,12-olides (V and VI).



V. 6α - OH VI. 6β - OH

As follows from the results obtained, for the (V) molecule the relative stability of the conformers decreases in the following sequence: d (ΔE = 0), a (ΔE = 0.6 kcal/mole), b (ΔE = 0.8 kcal/mole), and c (ΔE = 2.1 kcal/mole), which agrees qualitatively with the experimental results obtained for laurenobiolide [12]. For the (VI) molecule, according to our calculation, the stabilities of the conformers are as follows: b (ΔE = 0), a (ΔE = 0.1 kcal/mole), and a and d (ΔE = 4.8 kcal/mole). It follows from this that in solution the conformers b and c should be present in a ratio of 1:1. A comparison of the values of the torsional angles in the 10-membered rings of the (V) and (VI) molecules (Table 2) with

TABLE 2. Torsional Angles in Rings A of Various Conformers of Compounds (V) and (VI) and Their Conformational Energies E

Conformation	Angle at the given bond										E, kcal/mole
	C1—C2	C2—C3	C3—C4	C4—C5	C5—C6	C6 C7	C7—C8	C8—C9	C9—C10	C1—C10	
V a	−101	44	−86	173	126	73	−95	86	−107	166	20,7
V b	104	−41	91	−169	77	55	−119	56	63	−169	20,9
V c	−76	−30	96	−167	82	62	−110	73	−96	170	22,2
V d	75	27	−94	168	−118	65	−109	69	62	−170	20,1
VI a	−100	45	−86	172	−125	75	95	83	−107	167	22,3
VI b	106	−42	90	−169	81	54	−119	54	63	−169	17,5
VI c	−75	−30	95	−166	84	62	−110	71	−95	170	17,6
VI d	74	30	−94	167	−119	66	−108	68	61	−170	22,3

(III) shows that the influence of the hydroxy group at C6 in any orientation of it on the conformation of the ring is insignificant. Thus, in conformers (IIIb), (Vb), and (VIb) $\Delta\varphi_{max}$ = 7°, and in the others it does not exceed 4°.

The conformational calculations were made on a ES-1061 computer by means of MM2 program [13] with complete 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 literature sources [14, 15]. The initial states of the (I-VI) molecules for all four possible conformations were determined from Dreiding models.

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