The structures were interpreted by direct methods with the aid of the MULTAN-78 program [10] included with the XTLSM complex set up on an SM-4 computer [11]. The structures were refined first in the isotropic and then in the anisotropic approximation. Hydrogen atoms were found from the difference Fourier syntheses. To determine the multiplicities of the population of the sites by formic and acetic acid molecules in the solid substitution solution gossypol·0.82 FA·0.18AA we made use of the possibilities of the SHELXSM packet of programs [11]. The R factors amounted to 0.048 and 0.063 for the H-clathrates of gossypol with FA and with MAlc, respectively. The final coordinates and equivalent isotropic temperature factors are given in Tables 3 and 4.

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HUMULENOIDS FROM PLANTS OF THE FAMILY APIACEAE

SPATIAL STRUCTURE OF α-APIENES

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UDC 539.19:547.314

A conformational analysis has been made by the method of molecular mechanics of the α-apienes — natural sesquiterpenes isolated from plants of the Apiaceae family. The results of the mathematical method with the inclusion of those x-ray structural studies have shown that in the molecules under consideration it is possible to expect the predominant realization of four conformations of the 11-membered ring: ${}_{14}A_{8}{}^{7}$, ${}^{14}A_{7}{}^{8}$, ${}_{14}A_{7}{}^{8}$, and ${}^{14}A_{8}{}^{7}$. These four conformations of unsubstituted α-apiene and its natural derivatives have been characterized energetically, and the barriers to their interconversions have been evaluated.

Humulenoids with a 4(5)-cis double bond have been isolated from plants of the Apiaceae family and have therefore acquired the name of apienes [1] (by analogy with the heliangolides and germacranolids [2]). The conformation of the 11-membered ring in the apienes has not hitherto been studied, if we leave out of consideration individual x-ray structural communications [3-7], i.e., no attempt has been made to systematize the stereochemistry of the 11-

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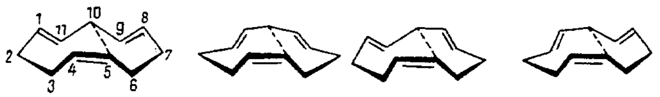
membered ring as has been done for the germacranolides [8], although there have been such attempts for the trans-humulenes [9, 10]. In the present paper we give information on the conformational systematization of the α-apienes obtained by the method of molecular mechanics (MM) and by x-ray structural analysis (from the literature).

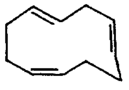
Before considering the conformations of the α-apienes, let us give the results of a calculation by the MM method of the stereochemistry of a model compound with one cis and two trans double bonds – cycloundecatriene (I). It is obvious that the theoretically enormous number of possible conformations for this molecule is limited by virtue of the fact that the actual conformation of the 11-membered ring is determined by the positions of the three plane sections containing double bonds and the ordinary bonds adjacent to them. If, moreover, we assume the actual invariability of the conformation of the C2–C7 section of the ring (as is indicated by the available x-ray structural results, see below), then three conformations of cycloundecatriene (I) and its substituted derivatives will be possible (scheme 1). If the intrinsic symmetry of the (I) molecule is disturbed (for example, on the introduction of a substituent), the third variant "splits." The transitions between the four conformations given take place through mutual rotations of the trans-double-bond sections around the C9–C10 and C10–C11 bonds.*

At first glance, the conformation of the 11-membered ring is complex; however, by drawing a line to a carbon atom of the cis double bond from the atom linking the trans double bonds it is possible to convince oneself that the conformation of this ring is determined by four possible combinations of the nominal chair (C) and boat (B) forms. The simplicity of the model compound and the existence of symmetry in it enable the nominal C and B conformations to be clearly seen, and this was one of the reasons for first performing the calculations on these models.† These possible variants of the conformation in (I) are energetically very close – the difference is not more than 0.5 kcal/mole. In the first two conformations the macrocycle has an intrinsic plane of symmetry passing through the center of the cis double bond and the atom linking the trans-double-bond sections. This can also be seen from the calculated torsional angles given in Table 1.

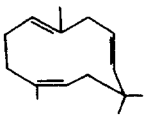


C/B C/C C/C C/B

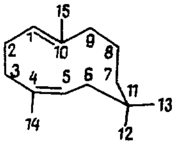
The apienes are natural derivatives of cycloundecatriene and differ from the well known α-humulenes by the cis configuration of the 4(5)-double bond. Compounds are found in which an epoxy group, stereochemically equivalent to a double bond, is present in the 1(10) position instead of a double bond.



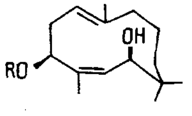
cis-Cycloundecatriene (I)



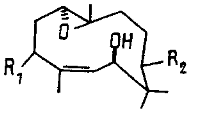
4(5)-cis-Humulene (II)



α-Apiene (III)



R = H, Juniferol (IV)
R = $COC_6H_4(OH)$, Juniferdin (V)



R_1 = OH, R_2 = H, Fexerol (VI)
R_1 = H, R_2 = OH, Caucalol (VII)

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*Note that the numbering of the cycloundecatriene ring in scheme 1 is different from that given for α-apiene (III) and used throughout the rest of the paper (including Table 1) and that the numbering of the C-14 and C-15 atoms in the formula labeled α-apiene (III) is the opposite of that used in scheme 2 and Fig. 1 and in the conformational symbols.

†In the natural sesquiterpenoid germacranolides, such nominal six-membered rings are obtained by linking the C5–C10 atoms, and in the α-apienes the C5–C9 atoms.

TABLE 1. Calculated (MM) Torsional Angles of the Four Conformations of the (I-VII) Molecules

Angle	I	II	III	IV	V	VI	VII
	Conformation $^{14}A_8^7$						
8—9—10—1	83,3	77,4	96,4	97,1	99,7	86,3	100,2
9—10=1—2	−166,4	−167,0	−174,9	−174,5	−176,2	−150,8	−159,0
10—1—2—3	87,3	94,1	89,2	79,9	81,2	85,8	83,2
1—2—3—4	61,1	64,3	62,1	61,1	58,4	58,2	49,6
2—3—4—5	−117.6	−114,3	−106,2	−106,7	−105,6	−117,7	−108,8
3—4=5—6	0	0,2	0,2	−0,3	1,1	0,5	0,0
4—5—6—11	117,7	120,0	133,8	135,0	138,5	124,7	142.0
5—6—11—7	−61,1	−65,5	−73,2	−71,6	−72,2	−64,0	−68,2
6—11—7—8	−87,4	−80,1	−77,2	−78,2	−77,2	−77,6	−72,2
11—7—8—9	166,3	167,1	132,7	133,1	127,4	150,7	126,0
7—8—9—10	−83,0	91,9	−75,8	−74,8	−74,5	−90,5	−86,0
Angle	Conformation $^{14}A_7^8$						
8—9—10—1	54,9	53,6	62,5	62,1	67,0	66,4	65,4
9—10=1—2	−167,8	−168,8	−171,1	−169,3	−173,7	−150,6	−149,2
10—1—2—3	95,4	100,9	93,0	93,6	86,7	81,2	82,2
1—2—3—4	57,3	59.9	49,5	51,1	46,1	43,1	42,4
2—3—4—5	−122,8	−118,8	−113,5	−119.6	−103,8	−118,5	−119,3
3—4=5—6	−1,7	−2,4	−2,6	−2,9	−2,2	−1,7	−1,4
4—5—6—11	105,4	106,4	128,9	121,7	143,7	130,2	129,2
5—6—11—7	−72,3	−72,0	−83,1	−76,4	−88,7	−79,3	−78,7
6—11—7—8	121,2	126,4	78,9	84,6	63,8	70,9	70,6
11—7—8—9	−171,1	−172,6	−145,6	−152,4	−129,8	−146,8	−148,9
7—8—9—10	48,3	39,5	67,1	62,7	73,3	74,7	75,5

Angle	I	II	III	IV	V
	Conformation $^{14}A_7^8$				
8—9—10—1	−82,7	−69,8	−80,9	−80,9	−81,3
9—10=1—2	166,3	166,6	170,6	169.9	171,0
10—1—2—3	−102,5	−111,2	−104,4	−103,8	−102,0
1—2—3—4	67,3	60,6	56,3	55,0	54,4
2—3—4—5	−116,9	−112,1	−104,4	−103,8	−102,0
3—4=5—6	0,0	−0,3	−1,6	−1,5	−2,5
4—5—6—11	117,3	121,4	134,4	137,4	138,3
5—6—11—7	−67,6	−64,8	−75,9	−75,4	−75,1
6—11—7—8	101,7	87,5	78,5	76,0	75,3
11—7—8—9	−166,4	−167,4	−139,8	−138,3	−136,7
7—8—9—10	83,5	95,9	91,6	92,3	92,4
Angle	Conformation $^{14}A_8^7$				
8—9—10—1	−43,3	−48,4	−57,9	−58,0	−58.8
9—10=1—2	171,1	171,6	174,7	175,3	175,1
10—1—2—3	−120,2	−113,5	−105,5	−108,8	−104,1
1—2—3—4	72,3	69,2	68,3	67,1	65,4
2—3—4—5	−105.4	−108,3	−103,0	−102,1	−100,2
3—4=5—6	1,7	2.0	0,7	0,0	0,1
4—5—6—11	122,8	124,2	138,5	140,5	143,0
5—6—11—7	−57,3	−56,3	−31,6	−61,4	−62,2
6—11—7—8	−95,4	−90,1	−72,2	−72,4	−72,1
11—7—8—9	167,3	167,8	141,2	140,7	139,4
7—8—9—10	−54,9	−61,5	−62,7	−62,4	−61,3

Analysis of the conformations of cis-4(5), trans-1(10), 7(8)-humulene (II), and of unsubstituted α-apiene (III) by the MM method showed that practically the same four conformations are realized in them as in the molecule (I) considered above (scheme 2) (see top of following page).

The spatial structures of unsubstituted α-apiene (III) in the four conformations are shown in Fig. 1. The values of the torsional angles for α-apiene and 4(5)-cis-humulene (II) in the four conformations of each are given in Table 1. It can be seen from Fig. 1 and Table 1 that, on the whole, the conformations are retained in them, although they are distorted in comparison with the model symmetrical cycloundecatriene.

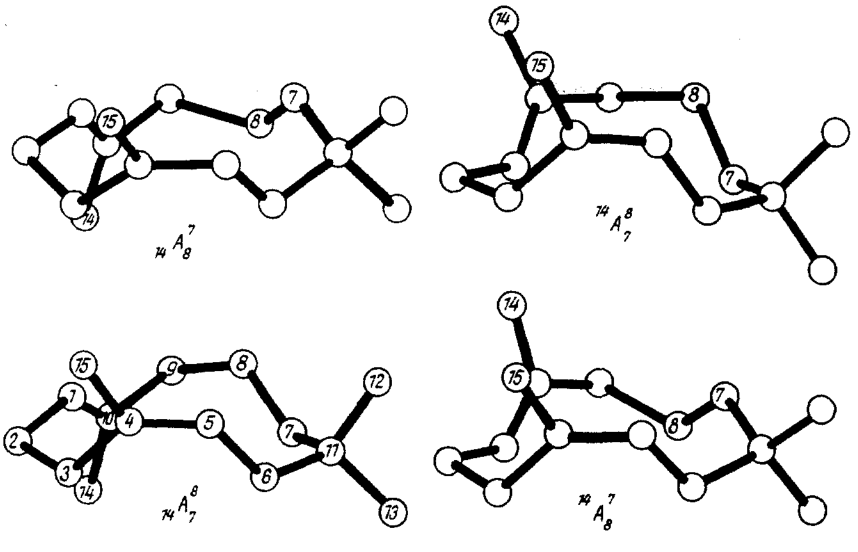

Fig. 1. Spatial structures of unsubstituted α-apiene from the results of the MM method.

TABLE 2. Strain Energies (kcal/mole) of the Four Conformations of the 11-Membered Rings in the (I-VII) Molecules

Compound	Conformation			
	$_{14}A_8^7$	$^{14}A_7^8$	$_{14}A_7^8$	$^{14}A_8^7$
I. Cycloundecatriene	20,3	19,9	20,4	20,4
II. 4(5)-cis-Humulene	23,8	23,8	23,9	23,7
III. α-Apiene	22,1	24,4	24,6	20,9
IV. Juniferol	25,3*	28,1	28,6	23,9*
V. Juniferdin	44,1*	47,3	47,3	43,2
VI. Fexerol	25,6*	—	28,3	—
VII. Caucalol	27,8	—	29,8	—

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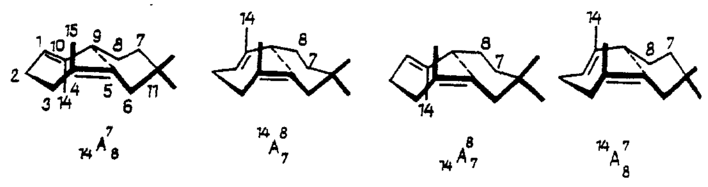
*Conformations realized in the crystalline state.



In the natural α-apiene derivatives juniferol (IV), fexerol (VI), caucalol (VII), and juniferdin (V) the general pattern of the four conformations is retained (see Table 1). It must be mentioned that in the above compounds (IV-VII), in spite of the absence of the C7—C8 double bond, the C11—C7—C8—C9 torsional angles assume values of 127-151°, i.e., closer to that characteristic for a double bond. The calculated torsional angles in the natural α-apienes (IV-VI) are comparable with the experimental values from x-ray structural analysis: in juniferol for the $_{14}A_8{}^7$ and $^{14}A_8{}^7$ conformations, and in juniferdin and fexerol for $_{14}A_8{}^7$. The discrepancies in the values of the corresponding torsional angles mostly amount to 2-3°, but reach 8° in individual cases.

The strain energies of the conformational states of the molecules (I-VII) are given in Table 2. Judging from these, for the model compound (I) and for 4(5)-cis-humulene (II) all four conformations are energetically equivalent and, therefore, they must be realized with practically equal probabilities. However, in the unsubstituted α-apiene and its natural derivatives juniferol and juniferdin the $_{14}A_8{}^7$ and $^{14}A_8{}^7$ conformations should be realized with the greatest probability, although in the juniferdin crystal only the $_{14}A_8{}^7$ conformation is

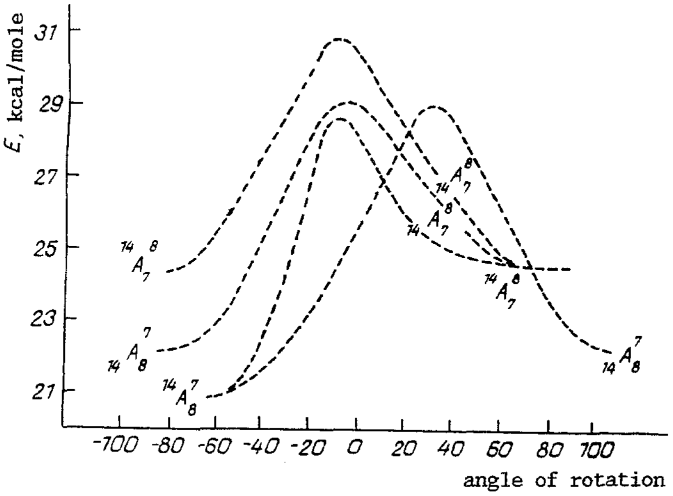


Fig. 2. Energy diagram of the conformational transitions in unsubstituted α-apiene:

Transitions	Bond about which the tors angle rotates
${}_{14}A_8^7 \leftrightarrow {}_{14}A_7^8$	—8— 9—
${}_{14}A_8^7 \leftrightarrow {}^{14}A_8^7$	—9—10—
${}^{14}A_7^8 \leftrightarrow {}_{14}A_7^8$	—9—10—
${}^{14}A_7^8 \leftrightarrow {}^{14}A_8^7$	—8— 9—

realized [6]. In fexerol and caucalol the transition to the ${}^{14}A_7{}^8$ and ${}^{14}A_8{}^7$ conformations is sterically impossible because of the presence of the epoxy group in the 1(10) position.

In nature, the conformational transitions in the 11-membered α-apiene rings take place by a complex route. However, to a first approximation, all the mutual transitions can be modeled by a change in the torsional angles around the C8—C9 and C9—C10 bonds successively. An energy diagram of the conformational transitions in unsubstituted α-apiene is shown in Fig. 2, and from this it can be seen that the transition barriers amount to 6-7 kcal/mole. This shows the ease of change of conformations of the α-apienes at room temperature [11]. For the natural α-apienes the height of the barrier does not change appreciably; thus, for example, for juniferol it amounts to 7-9 kcal/mole [5]. Calculation of the amount of each conformer on the basis of energy characteristics [11] of the natural α-apienes shows that in solution at room temperature there is 99.9% of the ${}_{14}A_8{}^7$ and ${}^{14}A_8{}^7$ conformations.

The conformational calculations were made on an IBM PC AT/286 personal computer by the PCMODEL program containing the modified program MM2 [12], using the potential parameters contained in it and with complete optimization of the geometry of the molecule.

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SYNTHESIS OF AMINO DERIVATIVES OF CARANOL BY THE ADDITION OF CYCLIC AMINES TO 3-CARENE OXIDES

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L. E. Nikitina, I. A. Litvinov, and O. N. Kataeva

UDC 547.597.1

Addition reactions of cyclic amines (morpholine, piperidine) to oxides of 3-carene in the presence of water have been studied. The reactions take place regio- and stereoselectively with the formation of amino derivatives of the carane series.

The promising nature of investigations in the field of the synthesis of amino derivatives of the terpene series is due to their valuable practical properties — they possess antiviral [1], antifeedant [2], and pesticidal [3] activities, with low toxicity for warm-blooded animals. The recent literature includes reports devoted to the development of synthetic approaches to amino derivatives of the bornane, pinane, and methane series [4, 5], while information on methods of obtaining amino derivatives with a carane structure are sparse and relate to traditional multistage syntheses [6].

In order to broaden the methods of synthesis in the field of amino derivatives of the carane series and also to obtain representatives of this group of substances with potential biological activity, we have studied the reactions of β-3,4- and α-3,4-epoxycaranes (I and II) with morpholine (III) and piperidine (IV) under catalytic conditions, since it is known that the performance of such reactions in the absence of catalysts is problematical [7].

When the reaction was performed in the presence of bases (EtONa; t-BuOK in DMSO), the initial epoxycaranes isomerized into (−)-car-4-en-3β-ol, the physicochemical constants and spectral characteristics of which agreed with those given in the literature [8]. While the use of dilute mineral acids (for example, from 1 to 0.1% H_2SO_4) favored a rapid reaction, it led to a very complex mixture of products, which was due to isomerization of the carane skeleton of the molecule [9].

The products of the addition of (III) and (IV) to the epoxycaranes (I and II) were obtained in fairly good yields on the prolonged heating of the reactants in the presence of water.

The product of the reaction of β-3,4-epoxycarane (I) with morpholine (III) consisted of an individual compound (V) the structure of which was determined from the results of IR and PMR spectroscopy and x-ray structural analysis. The PMR spectrum of compound (V) contained the signals of the protons of a cyclopropane ring (0.5-0.7 ppm), of a gem-dimethyl fragment (0.97 ppm), of a methyl group at C^3 (1.07 ppm), of a morpholine ring (2.37, 3.57 ppm), and of a hydroxy group at C^3 (3.1 ppm). The IR spectrum of the compound had the bands of the characteristic vibrations of the hydroxy group ($\nu_{(OH)}$ 3430 cm^{-1}) and also of hydrocarbon fragments, including a cyclopropane fragment ($\nu_{(CH)}$ 2995 cm^{-1}).

The structure of compound (V) in the crystalline state was studied by the method of x-ray structural analysis (Fig. 1 and Tables 1-3). It was established that the bicyclic skeleton of the (V) molecule had a conformation of the sofa type. The $C^2C^1C^6C^5C^4$ fragment was practically planar, and the hydroxy group at C^3 was oriented pseudoaxially and the morpholino

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