Chemistry of Natural Compounds, Vol. 41, No. 2, 2005

MOLECULAR STRUCTURE OF γ-APIENES. CRYSTAL AND MOLECULAR STRUCTURE OF FEROCIN

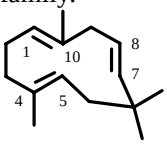
B. Tashkhodzhaev and A. I. Saidkhodzhaev

UDC 547.992:547.37+548.738

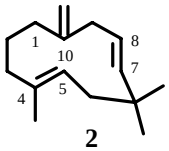
The molecular structure of the sesquiterpene humulene ester ferocin isolated from plants of the Ferula *genus was determined by x-ray structure analysis. The conformation of the 11-membered γ-humulene ring was analyzed by molecular mechanics. It was found that four energetically similar macrocycle conformations are characteristic of γ-apienes.*

Key words: *Ferula*, humulenes, γ-apienes, ferocin, x-ray structure analysis, molecular mechanics.

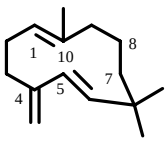
Derivatives of monocyclic sesquiterpenes, humulenes, are precursors of bicyclic sesquiterpenes that are distributed in nature. The occurrence in plants of esters of the same acid with mono- and bicyclic alcohols confirms this [1]. Three isomers of humulatriene, α-(**1**), β-(**2**), and γ-(**3**) humulenes, the C skeletons of which have an 11-membered macrocycle that differs in the location of the double bonds, and various natural derivatives of them have been isolated [2-4]. In particular, the 1(10)-*trans* and 4(5)-*cis* configurations and the lack of 7(8) double bonds are characteristic of α-apienes (**4**) isolated exclusively from plants of the Apiaceae family.



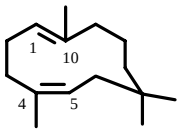
1



2

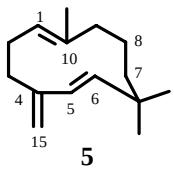


3

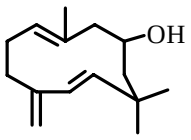


4

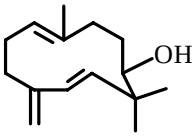
Analogously the 1(10)-*trans* configuration and 4(15),5(6)-*trans* double bonds in the humulene macrocycle are characteristic for γ-apiene (**5**) and its natural derivatives from plants of the Apiaceae family [5-8]. The chemical structures of γ-apienes were established by spectral (IR, mass, ^{1}H NMR spectroscopy) methods and certain chemical transformations. However, it is difficult to determine the dominant conformation of the 11-membered ring and the configuration of the double bonds and asymmetric centers in these compounds using spectral methods, in particular, ^{1}H NMR spectroscopy, because of the lability of the macrocycle [9].



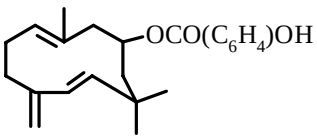
5



6



7



8

We performed an x-ray structure analysis (XSA) of the γ-apiene ferocin (**8**) in 1982 during an investigation of the conformation of the humulene macrocycle. The miniscule amount of **8** did not produce single crystals of adequate quality and size and, therefore, an XSA data set with satisfactory statistics. Sporadic attempts to solve the structure of ferocin over several years involved at one time or another the programs Rentgen-75 [10], MULTAN [11], XTL-SM [12], and AREN [13]. Attempts to solve the structure using these programs by usual approaches with a wide variation of the parameters in direct methods were not successful. However, the program SHELXS-97 was not used.

S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (99871) 120 64 75. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 125-128, March-April, 2005. Original article submitted December 13, 2004.

0009-3130/05/4102-0153

TABLE 1. Bond Lengths (r, Å) and Angles (ω, deg) in **1**

Bond	R	Angle	W
O(1)-C(16)	1.291 (19)	C(16)-O(1)-C(8)	119.0 (15)
O(1)-C(8)	1.420 (16)	C(10)-C(1)-C(2)	128.1 (19)
O(2)-C(16)	1.25 (2)	C(1)-C(2)-C(3)	108.4 (14)
O(3)-C(20)	1.332 (19)	C(4)-C(3)-C(2)	114.0 (15)
C(1)-C(10)	1.288 (19)	C(15)-C(4)-C(5)	117 (2)
C(1)-C(2)	1.490 (19)	C(15)-C(4)-C(3)	123.8 (19)
C(2)-C(3)	1.60 (2)	C(5)-C(4)-C(3)	119.0 (18)
C(3)-C(4)	1.54 (2)	C(6)-C(5)-C(4)	127.0 (15)
C(4)-C(15)	1.30 (2)	C(5)-C(6)-C(11)	125.3 (15)
C(4)-C(5)	1.51 (2)	C(11)-C(7)-C(8)	117.6 (14)
C(5)-C(6)	1.344 (17)	O(1)-C(8)-C(9)	108.6 (12)
C(6)-C(11)	1.557 (19)	O(1)-C(8)-C(7)	109.6 (14)
C(7)-C(11)	1.57 (2)	C(9)-C(8)-C(7)	113.4 (14)
C(7)-C(8)	1.558 (18)	C(8)-C(9)-C(10)	121.3 (16)
C(8)-C(9)	1.522 (19)	C(1)-C(10)-C(14)	124.3 (17)
C(9)-C(10)	1.547 (18)	C(1)-C(10)-C(9)	123.9 (19)
C(10)-C(14)	1.52 (2)	C(14)-C(10)-C(9)	111.6 (16)
C(11)-C(13)	1.48 (2)	C(13)-C(11)-C(7)	115.0 (14)
C(11)-C(12)	1.580 (19)	C(13)-C(11)-C(6)	117.8 (17)
C(16)-C(17)	1.52 (2)	C(7)-C(11)-C(6)	102.3 (13)
C(17)-C(18)	1.40 (3)	C(13)-C(11)-C(12)	115.1 (14)
C(17)-C(22)	1.40 (2)	C(7)-C(11)-C(12)	103.3 (14)
C(18)-C(19)	1.44 (2)	C(6)-C(11)-C(12)	101.2 (12)
C(19)-C(20)	1.36 (2)	O(2)-C(16)-O(1)	123.9 (19)
C(20)-C(21)	1.28 (2)	O(2)-C(16)-C(17)	122 (2)
C(21)-C(22)	1.40 (2)	O(1)-C(16)-C(17)	114 (2)
		C(18)-C(17)-C(22)	120.8 (18)
		C(18)-C(17)-C(16)	118 (2)
		C(22)-C(17)-C(16)	121 (2)
		C(17)-C(18)-C(19)	113 (2)
		C(20)-C(19)-C(18)	126 (2)
		C(21)-C(20)-O(3)	122 (2)
		C(21)-C(20)-C(19)	117.1 (18)
		O(3)-C(20)-C(19)	121 (2)
		C(20)-C(21)-C(22)	124 (2)
		C(21)-C(22)-C(17)	118.9 (19)

The empirical calculation method molecular mechanics (MM) was used to analyze conformational states of the 11-membered macrocycle in the model γ-apiene (**5**) and its natural derivatives fecerol (**6**) and fervanol (**7**).

Figure 1 shows the structure of ferocin from the XSA. It can be seen that the *p*-hydroxybenzoate is in the C8-α-position and the configuration of the endocyclic 1(10) and 5(6)-double bonds is *trans*. The almost planar (root-mean-square deviation of atoms from the plane is ±0.10 Å) *p*-hydroxybenzoate is nearly perpendicular (95.5°) to the root-mean-square plane of the macrocycle (C1-C11). However, there is a small angle (16°) between the planes of the ester (±0.03 Å) and the *p*-hydroxybenzene ring (±0.02 Å). The neighboring dienes in the macrocycle C4=C15 and C5=C6 are mutually *trans*-oriented. Therefore, the –C3–C4–C5–C6– fragment has the *cis*-configuration (torsion angle 14°). The configuration of this fragment in the γ-apiene ring corresponds to configurations observed in 4(5)-*cis* α-apienes [14]. This enables an analogy to be used in modeling the conformation of the macrocycle using MM.

The absolute configuration of isolated γ-apienes, in particular **8**, has not been established. Therefore, this conformation of the macrocycle corresponds to the relative configuration of asymmetric center C8 shown in Fig. 1.

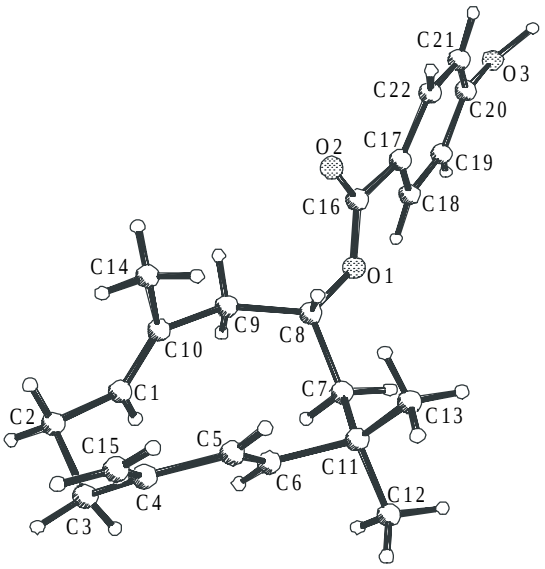


Fig. 1. Molecular structure of ferocin (**8**).

Table 1 gives the bond lengths and angles of **8** from the XSA. The uncertainty in the bond angles is 2°; in the bond lengths, 0.03 Å. Such significant uncertainties are due to the imperfection of the crystal used and the resulting limited set of experimental reflections. The agreement factor is large (see Experimental). Nevertheless, the C–C and C–O bond lengths vary over small ranges and agree within 3σ with the normal values [15].

The molecular packing of ferocin in the crystal is consistent with the presence of intermolecular H-bonds of the O–H...O type. The carbonyl oxygen (O2) of ferocin is bound through a H-bond to the hydroxyl of the benzene ring (O3–H) of another molecule translated by 2_1 symmetry (-x, 0.5 + y, 0.5 - z). The parameters of this H-bond are as follows: O2...O3, 2.81 Å; O2...H, 2.30 Å; and angle O2...H–O3, 110.4°. The H-bonds form an infinite chain along the *b* axis.

Conformational states of the 11-membered ring in γ-apienes were calculated by an empirical MM method. The flexibility of the 11-membered macrocycle in γ-humulenes is noticeably limited because of the two rather planar fragments in the 11-membered ring [–C3–C4(C15)–C5=C6–C11– and –C2–C1=C10–C9–] and their mutual repulsion. This facilitated our ability to model various conformations of the γ-apiene ring. We varied the fragment with the endo-1(10) double bond (torsion angle C8–C9–C10–C1) and the flexible part –C7–C8-(torsion angle C7–C8–C9–C10). The position of the planar fragment –C3–C4(C15)–C5=C6–C11– was fixed. It should be noted that two locations of the exo-4(15) and endo-5(6) double bonds are possible relative to the C4–C5 bond (*trans*- and *cis*-) in the last planar fragment.

The calculations showed that the conformation of the macrocycle in γ-apiene and its natural derivatives, regardless of the location of the double bonds mentioned above, has four distinct energy minima. Table 2 gives the torsion angles of the macrocycle for conformational states 1(10),4(15)-5(6)-*trans* γ-humulene (γ-apiene) from MM data. These conformational states of the 11-membered macrocycle (similar to α-apienes [14]) can also be characterized by the orientation of the C14 methyl and the location of C7 and C8 relative to the average plane of the humulene ring arbitrarily as $_{14}U^{7}_{8}$, $^{14}U^{8}_{7}$, $_{14}U^{8}_{7}$, and $^{14}U^{7}_{8}$.

Table 3 lists the energy states of the four conformers in γ-apienes for the *trans*-located exo-4(15) and endo-5(6) double bonds. These data indicate that the difference ΔE_{str} between energetically favorable $^{14}U^{8}_{7}$ and unfavorable $_{14}U^{8}_{7}$ conformations in model γ-apiene is only 1.2 kcal/mol. A clearly favorable conformation is not distinguished in the natural derivatives. Therefore, γ-apienes (in particular, **6** and **7**), depending on the presence of substituents in the 11-membered macrocycle and the medium effect (solvent or crystal field), may adopt any of the four conformations. Table 2 shows that the $^{14}U^{8}_{7}$ conformation of the macrocycle in which the C10–C14 and C4–C15 bonds are *syn* is found in crystalline ferocin. This conformation, according to MM data, is energetically the most favorable (23.9 kcal/mol).

All four conformations of the 11-membered macrocycle are energetically less favorable compared with those mentioned above in the variant where the C15=C4 and C5=C6 double bonds are mutually *cis*. Table 3 shows that the strain energy for 1(10)-*trans* and 4(15),5(6)-*cis* γ-humulene is greater on average by 4 kcal/mol compared with its *trans*-analog. This is indicative of a larger probability of finding the *trans*-configuration of the neighboring C4=C15 and C5=C6 double bonds. NMR data for fervanol esters confirm this fact [7].

TABLE 2. Torsion Angles (deg) for Conformational States of γ-Apiene from MM

Angle	Conformation				
	$_{14}U^{7}_{8}$	$^{14}U^{8}_{7}$	$_{14}U^{8}_{7}$	$^{14}U^{7}_{8}$	XSA (**1**)
1-2-3-4	57	73	55	70	71
2-3-4-5	-86	-83	-87	-85	-79
3-4-5-6	-3	-1	-2	-2	-14
4-5-6-11	175	176	175	175	179
5-6-11-7	-102	-135	-130	-96	-127
6-11-7-8	-64	68	57	-54	76
11-7-8-9	99	-93	-115	112	-105
7-8-9-10	-79	74	67	65	76
8-9-10-1	107	-115	64	-67	-104
9-10-1-2	-177	177	-177	177	177
10-1-2-3	82	-96	84	-96	-105

TABLE 3. Strain Energies (E_{str}, kcal/mol) of Four Conformational States of γ-Apienes

Compound	$_{14}U^{7}_{8}$	$^{14}U^{8}_{7}$	$_{14}U^{8}_{7}$	$^{14}U^{7}_{8}$
4(15)-5(6) *E* γ-apiene	25.1	23.9	24.9	24.4
4(15)-5(6) *Z* γ-apiene	26.6	31.6	27.5	28.5
Feserol (**6**)	28.9	24.8	25.6	27.8
Fervanol (**7**)	26.9	26.0	26.6	26.9

Energy diagrams prepared by modeling the conformational transitions of γ-apiene are consistent with an easy conformation change at room temperature. The barriers are 6-9 kcal/mol.

The content of each conformer in solution can be calculated based on the energy characteristics without taking into account the entropy factor by using the equation: $n_j/N = \{1 + \exp[(E_j - E_i)/RT]\}^{-1}$ [16]. Calculations for actual natural γ-humulenes showed that greater than half (57%) of the molecules of **7** in solution at room temperature are found in the $^{14}U^{8}_{7}$ conformation; the least, in the $_{14}U^{7}_{8}$ and $^{14}U^{7}_{8}$ (13% each); and some (16%), in the $_{14}U^{8}_{7}$ conformation. The molecule in fecerol (**6**) occurs mainly in the two conformations $^{14}U^{8}_{7}$ (79%) and $_{14}U^{8}_{7}$ (20%). The probability of occurring in the other two conformations approaches zero.

EXPERIMENTAL

Transparent crystals (mp 127-128°C) of ferocin ($C_{22}H_{28}O_3$) were grown as elongated prisms from ethanol and studied by a photomethod. The space group and unit-cell constants were measured from Weissenberg x-ray patterns. These constants were refined on a Syntex $P2_1$ four-circle diffractometer using Cu Kα-radiation (graphite monochromator, θ/2θ-scanning). The crystals were orthorhombic, a = 6.1470(10), b = 12.759(3), c = 25.313(5) Å, V = 1985.3(7) Å^3, d_{calc} = 1.139 g/cm^3, space group $P2_12_12_1$, Z = 4.

The data set of experimental reflections measured on the aforementioned diffractometer (θ < 55.1°) after initial processing consisted of 1480 structure factors, of which 466 satisfied the arbitrary condition I > 2σ(I). Absorption corrections were not applied.

The ferocin structure was solved by direct methods using the SHELXS-97 programs with an increased set of variables (TREF = 10,000). The initial E-synthesis revealed the molecular model. Further difference Fourier syntheses determined the positions of all nonhydrogen atoms. The refined structure was carried out using the SHELXL-97 program. All nonhydrogen atoms were refined by anisotropic full-matrix least-squares methods (over *F*). The H atom of the hydroxyl was found in an intermolecular H-bond in a difference electron-density synthesis.

The positions of the remaining H atoms were set geometrically and refined with fixed isotropic thermal factors $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} is the equivalent isotropic thermal factor of the corresponding C atoms. The final agreement factor $R_1 = 0.109$, $wR_2 = 0.157$ for 466 reflections with $I > 2\sigma(I)$ and $R_1 = 0.242$ and $wR_2 = 0.203$ for the whole data set (1480).

Conformational calculations by MM were performed using the MMX-86 program [17] with full geometry optimization of the molecule and using potential parameters included in this version of the program. The PC MODEL program was used to construct hypothetical and model molecules. A part of the MM calculations was carried out using this program.

The results of the XSA were deposited as a CIF file in the Cambridge Center for Data on Crystal Structures (CCDC 259985).

REFERENCES

1. A. I. Saidkhodzhaev, *Khim. Prir. Soedin.*, 437 (1979).
2. O. P. Vig, B. Ram, K. S. Atwal, and S. S. Barl, *Indian J. Chem.*, **14**, 855 (1976).
3. V. Benesova, V. Herout, and E. Sorm, *Collect. Czech. Chem. Commun.*, **26**, 1832 (1961).
4. L. A. Smedman, E. Zavarin, and C. Teranichi, *Phytochemistry*, **8**, 1457 (1969).
5. L. A. Golovina and G. K. Nikonov, *Khim. Prir. Soedin.*, 707 (1977).
6. L. A. Golovina and A. I. Saidkhodzhaev, *Khim. Prir. Soedin.*, 796 (1977).
7. M. Miski, T. J. Mabry, and O. Saya, *Phytochemistry*, **26**, 1733 (1987).
8. G. V. Sagitdinova, A. I. Saidkhodzhaev, and V. M. Malikov, *Khim. Prir. Soedin.*, 809 (1978).
9. S. Dev, J. E. Anderson, V. Cornier, N. P. Damondran, and J. D. Roberts, *J. Am. Chem. Soc.*, **90**, 1246 (1968).
10. V. I. Andrianov, Z. Sh. Safina, and B. L. Tarnopol′skii, *Zh. Strukt. Khim.*, **15**, 911 (1974).
11. G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr. Sect. A: Cryst. Phys., Diffr., Theor. Gen. Crystallogr.*, **27**, 368 (1971).
12. V. K. Pecherskii, P. Yu. Zavalii, L. K. Aksel′rud, Yu. M. Grin′, and E. M. Vladishevskii, *Vestn. L ′vov Gos. Univ., Ser. Khim.*, No. 25, 9 (1984).
13. V. I. Andrianov, *Kristallografiya*, **32**, 228 (1987).
14. B. Tashkhodzhaev and A. I. Saidkhodzhaev, *Khim. Prir. Soedin.*, 197 (1992).
15. F. N. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc. Perkin Trans. II*, S1 (1987).
16. V. G. Dashevskii, *Conformation of Organic Molecules* [in Russian], Khimiya, Moscow (1982), p. 272.
17. N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 8127 (1977).