CRYSTAL AND MOLECULAR STRUCTURE OF THE SESQUITERPENE HUMULANE ALCOHOL JUNIFEROL

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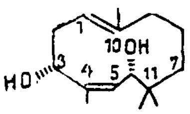
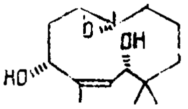
The spatial structure of the sesquiterpene humulane alcohol juniferol, which is represented in the crystal by two conformers, IA and IB, differing by the conformation of the C2...C9 section, has been established by the x-ray structural method. The strain energies of the conformers have been calculated by the method of molecular mechanics. The barrier to the interconversion of the conformers by rotation of the C2...C9 section has been calculated; it amounts to 7-8 kcal/mole. This value of the transformation barrier permits the assumption that the two conformers also exist in solution, their interconversion being hindered.

Desquiterpene esters and their alcohols with a humulane skeleton, belonging to the numerous sesquiterpenoids from natural sources, were first isolated from plants of the genus Ferula. In particular, juniferol, a sequiterpene humulane alcohol which was isolated from the roots of Ferula juniperina Eng. Kor. The structure of juniferol was investigated by spectral (IR, mass, and PMR-spectroscopic) methods and some chemical transformations, and on their basis the structure (I) was proposed [2].



I



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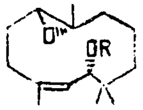

III $R = p\text{-}BrC_6H_4Cl$

The stereochemical aspects of the structure (the configurations of the asymmetric centers) of juniferol can be considered after an x-ray structural investigation of feroxol (II) [3], since this is the epoxy derivative of juniferol at the 1,10 centers. However, the question of the conformation of the 11-membered macrocycle in juniferol remained open, since it is difficult to resolve this problem unambiguously by spectroscopic methods (in particular, PMR) because of the lability of the 11-membered ring. In order to elucidate all the stereochemical aspects of the structure of juniferol and also to compare the conformations of the molecules of compound (I) and (II), an x-ray structural analysis has been made of (I).

Compound (I), like (II), crystallized with two molecules, (IA) and (IB), in the independent part of the elementary cell. In the molecules of (I), the hydroxy groups in positions 3 and 6 have the axial orientation and the unsaturated sections of the macrocycle at 1,10 and 4,5 have the trans and cis forms, respectively.* The lengths of the valence bonds and the values of the angles are given in Table 1. The errors in the determination of the valence angles are not more than 0.4°, and in the bond lengths not more than 0.007 Å. The length of

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*The numbering of the atoms that has been given is, in our view, the most desirable in the biogenetic respect — the carbon skeleton of the humulane ring is considered as the product of biochemical transformations of the germacranolides [5], although three types of numbering of the atoms in the humulane ring are found in the literature.

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TABLE 1. Valence Angles (φ, degrees) and Bond Lengths (r, Å) in the Structure of (I)

Atoms	φ_{IA}	φ_{IB}	Atoms	r_{IA}	r_{IB}
C1–C2–C3	109,8 (3)	108,6 (3)	C1–C2	1,498 (5)	1,506 (5)
C2–C3–C4	113,8 (3)	114,0 (3)	C2–C3	1,539 (4)	1,535 (4)
C2–C3–O1	111,4 (3)	107,5 (3)	C3–O1	1,438 (4)	1,446 (4)
C4–C3–O1	105,8 (3)	110,0 (2)	C3–C4	1,488 (4)	1,506 (4)
C3–C4–C5	123,8 (2)	124,0 (3)	C4–C5	1,350 (3)	1,341 (4)
C3–C4–C15	117,8 (2)	115,4 (3)	C4–C15	1,505 (5)	1,506 (5)
C5–C4–C15	118,4 (3)	120,6 (3)	C5–C6	1,501 (4)	1,499 (5)
C4–C5–C6	128,5 (3)	127,4 (3)	C6–C11	1,550 (4)	1,549 (4)
C5–C6–C11	113,7 (3)	114,5 (3)	C6–O2	1,451 (3)	1,443 (4)
C5–C6–O2	108,3 (3)	109,2 (2)	C7–C11	1,547 (4)	1,541 (5)
C11–C6–O2	108,9 (2)	112,5 (3)	C7–C8	1,518 (5)	1,551 (4)
C11–C7–C8	118,2 (3)	117,0 (4)	C8–C9	1,537 (6)	1,520 (6)
C7–C8–C9	112,8 (4)	113,1 (4)	C9–C10	1,513 (6)	1,521 (6)
C8–C9–C10	109,9 (3)	112,0 (3)	C10–C1	1,313 (6)	1,327 (5)
C9–C10–C1	121,3 (5)	119,7 (4)	C10–C14	1,495 (8)	1,490 (8)
C9–C10–C14	114,7 (4)	116,2 (4)	C11 C12	1,543 (7)	1,533 (6)
C1–C10–C14	123,8 (4)	124,0 (4)	C11–C13	1,545 (5)	1,528 (4)
C6–C11–C7	107,4 (3)	108,1 (3)			
C6–C11–C12	111,0 (3)	108,8 (3)			
C6–C11–C13	110,0 (3)	112,0 (3)			
C7–C11–C12	108,4 (3)	110,8 (3)			
C7–C11–C13	111,2 (3)	108,6 (3)			
C12–C11–C13	108,9 (3)	108,5 (3)			

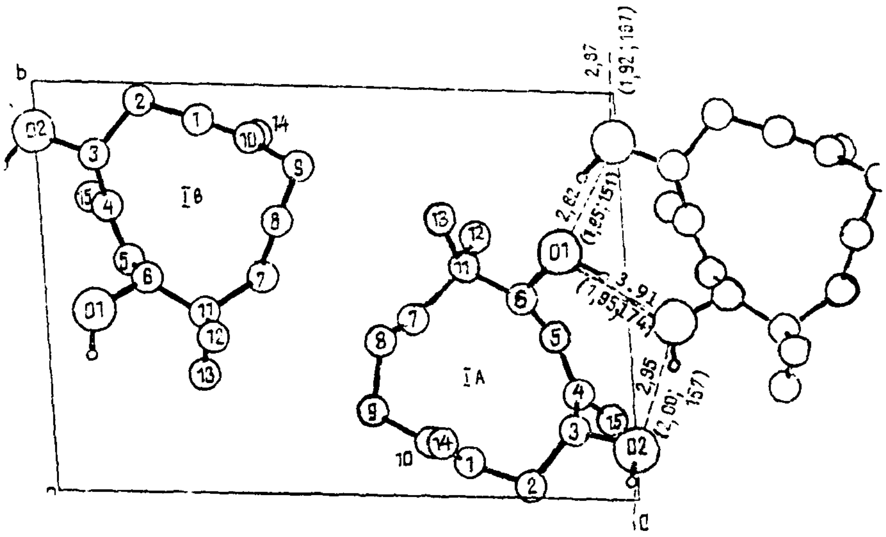

Fig. 1. Projection on ab of the structure of (I); the dashed lines are H-bonds.

the ordinary $C_{sp^3} - C_{sp^3}$ and $C_{sp^3} - S_{sp^2}$) and double carbon–carbon bonds and also of the C–O bonds vary within narrow intervals and coincide with the standard value [4] to within 3σ but it is not possible to say the same for the valence angles, since, because of steric stresses, an increase in the size of the angles at the sp²-hybridized C1, C4, and C5 atoms to 129° and also of the tetrahedral angle at C7 to 118° is observed. A similar increase in the same angles has been observed in (II), where it had values of 130 and 118°, respectively.

The geometries of the macrocycles of the two independent molecules (IA) and (1B) of juniferol are characterized by the torsion angles given in Table 1, where, for comparison, are given the average torsion angles of fexerol. In a comparison of the corresponding torsion angles in the molecules (IA) and (IB) a marked difference between the C2–C1–C10–C9, C10–C1–C2–C3, and C8–C8–C10–C1 angles can be noted, while the other are close (difference not greater than 12°). This feature can be clearly seen in Fig. 1; the isopropenyl sections (the C10–C14 bonds) in the (IA) and (IB) molecules are antiparallel. Consequently, the (IA) and (IB) molecules are conformers, which is not the case in the crystal structure of (II). Thus, it may be assumed that in a solution of (I) hindered rotation of the isopropyl group around the C9...C2 line possibly takes place. Such rotation is absent (sterically hindered) in the molecule of

TABLE 2. Torsion Angles (degrees) of the Macrocycles of Juniferol (IA and IB) and Fexorol (II, averaged over the two molecules); The Values of the Angles Calculated by MM2 are Given in Parentheses

Torsion angle around the bond	IA	IB	II
C1—C2	−79,8 (−80,6)	100,8 (103,7)	−84 (86,9)
C2—C3	−63,2 (−69,8)	−73,8 (−66,7)	−65 (−57,1)
C3—C4	108,0 (106,4)	107,2 (101,3)	118 (112,5)
C4—C5	4,3 (0,8)	1,0 (0,5)	1 (0,1)
C5—C6	−136,5 (135,6)	−140,7 (−141,9)	−127 (−130,3)
C6—C11	71,8 (71,6)	64 5 (71,8)	71 (59,3)
C11—C7	79,0 (77,7)	70,0 (71,8)	70 (77 8)
C7—C8	−139,8 (−132,5)	−145.5 (−139 4)	−154 (−146,0)
C8—C9	77,8 (75,7)	65,9 (63,1)	92 (87,0)
C9—C10	−96,9 (−96,9)	58,6 (58,1)	−81 (−89,3)
C10—C1	167,8 (173,8)	−166,8 (−175,2)	150 (161,1)

(II) because of the presence of the cumbersome epoxy group in the 1,10 position.

The molecule of (II) has almost the same conformation of the 11-membered macrocycle as the (IA) molecule (Table 2). For a comparative analysis the results of an x-ray structural investigation of the p-bromobenzoyl derivative of the humulane (III) from the plant Torilis scabra might have been included in Table 2 but, unfortunately, it is not given in the original paper [6]. In spite of this, a visual comparison of the conformations (with the aid of the MOLDRAW program) clearly showed a similarity of the conformations of the (III) and (IA) molecules. Thus, for three natural 1(10)-trans-4(5)-cis-humulanes we have two conformations of the 11-membered ring which differ only by the direction of the C10—C14 bond.

Packing of the Molecules. An analysis of the crystal structure (Fig. 1) shows the presence of intermolecular hydrogen bonds of the O—H...O type. For clarity, those H atoms that participate in these H-bonds are shown in Fig. 1 (the O...H distance and the angle at the H atom are given is parentheses). The (IA) and (IB) molecules are paired by the H-bonds O2 (IA)...H—O1(1B), O1(1A)—H...O1(1B), and O1(IA)...H—O2(1A), and these pairs form an infinite chain along a y translation axis thanks to a O2(IA)—H...O2(IB) H-bond.

The coexistence in the crystal structure of two conformers of the juniferol molecule indicates their energetic closeness. For a quantitative energetic evaluation we made a calculation of the strain energy by the method of molecular mechanics using the MM2 program [7]. In the calculations we used the parameters of the potentials of the original version of the program. As the initial approximations for minimization we took the two conformations of the (I) molecule found by x-ray structural analysis. On minimizing the strain energy, close energies of the conformers were actually obtained with a difference of 1.7 kcal/mole (for (IA), 22.4 kcal/mole, and for (IB), 20.7 kcal/mole). Then, rotating the isopropenyl group around the C2...C9 axis (carying the C10—C1—C2—C3 torsion angle in (IA) from −80 to −180° and in (IB) from 100 to 180° with a step of 20°) we determined the height of the barrier to the mutual transformation of the conformers. The curve describing the energy of the transition is shown in Fig. 2. The maximum of the strain energy (29.1 kcal/mole) is observed at a value of the torsion angle of −160°. The height of the barrier, 7-8 kcal/mole, is considerable, exceeding the energy of intermolecular interaction in the crystal [8]. Consequently, the detection of two conformers in the juniferol crystal is not a consequence of the influence of the crystal field on the conformation of the humulane ring; i.e., both conformers probably exist in solution, in a ratio of approximately 1:1.

EXPERIMENTAL

Colorless crystals of juniferol (I) were grown from solution in a mixture of methyl and ethyl alcohols. The space group and the parameters of the elementary cell were established from precession x-ray diagrams. These parameters were subsequently refined in a Nicolet R3m four-circle diffractometer using MoK_α radiation: a = 13.111; b = 9.424; c = 6.353 Å; α = 108.35, β = 102.66, γ = 90.56°; group P1; z = 2.

The group of experimental reflections measured on this diffractometer, after primary treatment, amounted to 1569 structural amplitudes. The structure was interpreted by the AREN system of programs [9] using a combination of the direct method and the method of successive

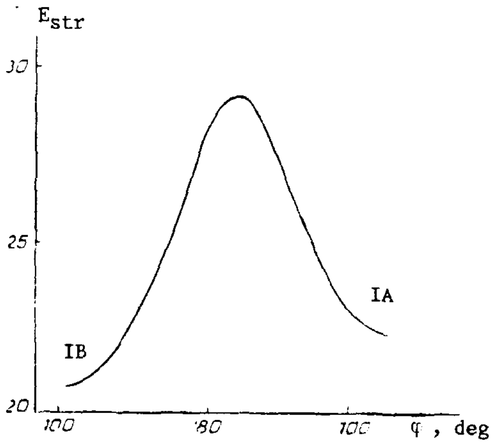

Fig. 2. Dependence of the strain energy E_{str} (kcal/mole) of the (I) molecule on the rotation of a section of the ring around the C2...C9 axis (the torsion angle C10—C1—C2—C3 has been plotted along the axis of abscissas).

TABLE 3. Coordinates ($\times 10^4$) and Thermal Parameters B_{eq} ($\mathring{A}^2$) of the Nonhydrogen Atoms in the Structure of (I)

Atom	Molecule IA				Molecule IB			
	x	y	z	B_{eq}	x	y	z	B_{eq}
C1	7095 (3)	787 (4)	6587 (7)	4,87	2809 (2)	9126 (4)	13466 (6)	4,66
C2	8168 (3)	303 (4)	7217 (8)	5,44	1807 (2)	9545 (3)	12211 (6)	4,40
C3	8562 (2)	1689 (3)	8409 (5)	3,72	977 (2)	8269 (3)	11410 (5)	3,37
C4	9682 (2)	2593 ([illegible])	8921 ([illegible])	3,44	1147 (2)	6928 (3)	9424 (5)	3,32
C5	8712 (2)	3952 (3)	7149 (5)	3,81	1484 (2)	5620 (3)	9592 (5)	3,28
C6	8187 (2)	4808 (3)	8942 (5)	3,41	1737 (2)	5163 (3)	11693 (5)	3,08
C7	6329 (2)	4312 (4)	6691 (6)	5,01	2682 (2)	5287 (4)	12134 (6)	4,43
C8	5723 (3)	3736 (4)	8079 (7)	5,49	4044 (2)	6604 (4)	14404 (7)	5,13
C9	5488 (3)	2022 (5)	7168 (9)	6,13	4490 (2)	7998 (4)	14089 (8)	5,94
C10	6460 (2)	1279 (4)	7886 (7)	5,04	3601 (2)	8088 (4)	12721 (7)	4,74
C11	7212 (2)	5587 (3)	7979 (6)	4,29	2713 (2)	4260 (3)	11896 (6)	3,63
C12	7448 (3)	6355 (4)	6279 (8)	6,09	2027 (2)	2871 (3)	9798 (6)	5,13
C13	6879 (3)	6785 (4)	9946 (8)	6,06	2820 (3)	3752 (4)	13996 (7)	4,58
C14	6670 (4)	1273 (6)	10302 (9)	7,90	3844 (3)	8738 (5)	10511 (9)	7,13
C15	9624 (3)	1930 (5)	5019 (7)	6,07	884 (3)	7182 (4)	7148 (6)	5,15
O1	8947 (1)	6048 (2)	10576 (4)	4,52	815 (1)	4393 (2)	11856 (4)	3,79
O2	9994 (1)	1270 (2)	9182 (4)	4.81	−34 (1)	8761 (2)	808 (4)	4,11

approximations [10, 11]. The search for a model was carried out in the centrosymmetric space group P1̄. The choice of 500E and the comparison of 7500 triple phase relationships (in place of 340 and 3700 in the automatic regime) permitted, after the checking of 1024 phase variants (i.e., using 10 reference reflections) the isolation of a probable fragment of the structure.

The method of successive approxiations applied to the fragment obtained did not reveal the lacking atoms and did not lead to a lowering of the R-factor (R = 42%). Passage to the space group P1 and the method of automatic refinement of the structural amplitude phases with respect to the initial fragment isolated in the centrosymmetric variant permitted the revelation of all 34 nonhydrogen atoms of the structure (R = 29%). Three successive difference Fourier syntheses in the space group P1 revealed all 52 hydrogen atoms. The final value of the R-factor after isotropic(H)-anisotropic refinement by MLS was 2.95%.

Table 3 gives the coordinates of the nonhydrogen atoms and the equivalent thermal parameters. The coordinates of the hydrogen atoms can be obtained from the authors.

The structure investigated is a case, fairly rare in crystal chemistry, of a noncentrosymmetric triclinic crystal with two independence molecules. As was found, these molecules differ in their conformations. The success in obtaining a model in the centrosymmetric variant can be explained by the fact that the structure is centrosymmetric in a xy projection (Fig. 1), and some of the atoms are also linked by a pseudocenter in space.

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CEMBRENOLIDES OF A SOFT CORAL Lobophytum sp. (COELENTERATA, OCTOCORALLIA, ALCYONACEA)

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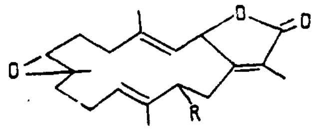
The known cembrenolide sarcophin and its new acetoxy derivative — 13-acetoxy-7,8-epoxycembra-1(15),3,11-trien-2,16-olide — have been isolated from the soft coral Lobophytum sp.. The compounds isolated are inhibitors of the activity of Na^+K^+-ATPase and are membranotropic agents. The structures of the compounds have been shown on the basis of the results of NMR spectroscopy.

Alcyonaria, or soft corals, are sources of terpenoids exhibiting various activities [1]. The presence of cembrene diterpenes is characteristic for three genera of Alcyonaria — Sarcophyton, Lobophytum, and Sinularia [1-3].

We have studied the composition of the diterpene fraction of the soft coral Lobophytum sp.. The animals were collected in the offshore waters of the republic of Madagascar during tropical expeditions of the Scientific-Research Vessel Professor Bogarov. In preliminary investigations, on aqueous alcoholic extract of the coral showed cytotoxic activity in relation to Ehrlich tumor cells. From a hexane extract of the lyophilized coral we isolated two compounds which, from the results of mass, IR, and ^1H and ^{13}C NMR spectroscopies were assigned to the cembrenolides.



I. R = H_2

II. R = H, OAc

The first compound (yield 0.01% on the weight of the freeze-dried coral) corresponded in its physicochemical characteristics to the known cembrenolide sarcophin (I) which has been isolated previously from the Red Sea coral Sarcophyton glaucum [2].

The second substance, more polar than sarcophin (yield 0.015% on the weight of the lyophilized animal) contained an acetoxy group, the presence of which was confirmed by a three-

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