CRYSTAL AND MOLECULAR STRUCTURE OF THE SESQUITERPENE HUMULANE ESTER JUNIFERDIN

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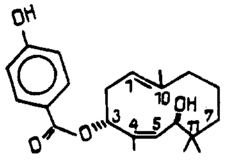
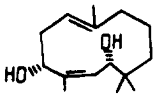
The spatial structure of the sesquiterpene humulane ester juniferdin, isolated from Ferula juniperina, has been established by the x-ray structural method. An analysis is given of the 11-membered humulane ring in comparison with the conformation observed in fexerol and juniferol.

The present paper is a continuation of a study of the spatial structures of sesquiterpene esters of the humulane series. Juniferdin (I), isolated from the plant Ferula juniperina Eug. Kor. [1], is a natural derivative (monoester at C3) of juniferol (II) [2]. Previously, in a study of the spatial structure of juniferol in the crystal, two conformers of its molecule were detected [3], although the molecule of its natural epoxy derivative (at the C1—C10 bond), fexerol (III) [4], assumes one of these conformations.



I



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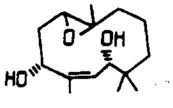

III

For this reason, it appeared of interest to study the spatial structure of juniferdin in comparison with the molecules of (II) and (III), since it is difficult to determine the conformation of the 11-membered ring of compound (I) by spectral methods, especially PMR, because of the lability of this macrolide. In order to determine the spatial structure of the (I) molecule unambiguously and also in order to compare the conformations of the three compounds mentioned (I), (II), and (III) we have made an x-ray structural study of (I).

Juniferdin crystallizes with two molecules, (IA) and (IB), in the independent part of the unit cell. The spatial structures of these molecules are shown in Fig. 1 in projection on the ab axis. It is interesting to note that there are two molecules in the independent part of the cell in the crystal structure of all three compounds of the humulane seres that we have studied: (I), (II), and (III).

The orientations of the substituents and the geometries of the double bonds in the 11-membered rings of the molecules (IA) and (IB) are analogous to those in the molecules (II) and (III): α-orientation of the substituents at C3 and C6, and trans and cis conformations of the C1—C10 and C4—C5 double bonds, respectively.

Bond lengths and valence angles are given in Table 1. The error in the determination of the valence angles amounts to 3°, and that in the bond lengths to 0.03 Å. Such considerable errors are connected with an imperfection of the single crystal used and, as a consequence, the limited set of experimental reflections and the high value of the discrepancy index (see Experimental). In spite of this, the C—C and C—O bond lengths vary within narrow intervals and agree with the standard values [5] to within 3σ. The same cannot be said in relation to the valence angles. In a study of the structure of the (II) and (III) molecules an increase in the angles at the sp^2-hybridized C1, C4, and C5 atoms to 130° and in that at the tetrahedral C7 to 118° was observed. Thus, a tendency to an increase in these angles is obvious even though, because of the large error, it is pointless to compare their numerical values.

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

Bond	r_{IA}	r_{IB}	Angle	ω_{IA}	ω_{IB}	Angle	ω_{IA}	ω_{IB}
C1—C2	1,47(2)	1,47(2)	C10C1C2	127(2)	124(3)	C6C11C12	112(3)	112(3)
C1—C10	1,32(2)	1,36(2)	C1C2C3	110(2)	110(2)	C6C11C13	111(3)	111(3)
C2—C3	1,54(2)	1,52(2)	C2C3C4	110(2)	115(2)	C7C11C12	106(2)	113(3)
C3—C4	1,45(2)	1,47(2)	C2C3O2	107(2)	108(2)	C7C11C13	111(3)	104(2)
C3—O2	1,45(2)	1,49(2)	C4C3O2	164(3)	105(2)	C12C11C12	108(3)	111(3)
C4—C5	1,37(2)	1,36(2)	C5C4C15	118(3)	120(2)	C3O2C16	119(2)	119(2)
C4—C15	1,57(2)	1,53(3)	C3C4C5	122(3)	124(3)	O2C16O3	124(3)	122(3)
C5—C6	1,45(2)	1,51(2)	C3C4C15	120(3)	115(2)	O2C16C17	110(3)	115(3)
C6—C11	1,55(2)	1,56(2)	C4C5C6	130(3)	130(3)	O3C16C17	126(3)	123(3)
C6—O1	1,48(2)	1,44(2)	C5C6C11	117(3)	116(2)	C16C17C18	124(3)	121(3)
C7—C8	1,61(3)	1,59(2)	C5C6O1	109(2)	109(2)	C16C17C22	119(3)	122(2)
C7—C11	1,48(3)	1,60(3)	C11C6O1	107(2)	109(2)	C18C17C22	117(3)	117(2)
C8—C9	1,45(3)	1,52(3)	C11C7C8	123(3)	115(2)	C17C18C19	122(3)	124(3)
C9—C10	1,54(3)	1,48(2)	C7C8C9	111(3)	121(4)	C18C19C20	115(3)	114(3)
C10—C14	1,56(3)	1,46(3)	C8C9C10	107(2)	199(2)	C19C20C21	125(3)	125(3)
C11—C12	1,55(2)	1,52(3)	C9C10C1	122(3)	121(3)	C19C20O4	118(3)	114(2)
C11—C13	1,50(2)	1,60(2)	C9C10C14	114(3)	119(3)	C21C20O4	117(3)	121(3)
C16—O2	1,34(2)	1,37(2)	C1C10C14	124(3)	121(3)	C20C21C22	116(4)	119(3)
C16—O3	1,20(2)	1,27(2)	C6C11C7	109(2)	107(2)	C21C22C17	124(3)	121(2)
C16—C17	1,52(2)	1,41(2)						
C17—C18	1,40(2)	1,40(2)						
C17—C22	1,39(2)	1,41(2)						
C18—C19	1,38(2)	1,42(2)						
C19—C20	1,37(2)	1,40(2)						
C20—C21	1,41(3)	1,31(2)						
C20—O4	1,41(2)	1,37(2)						
C21—C22	1,32(3)	1,39(2)						

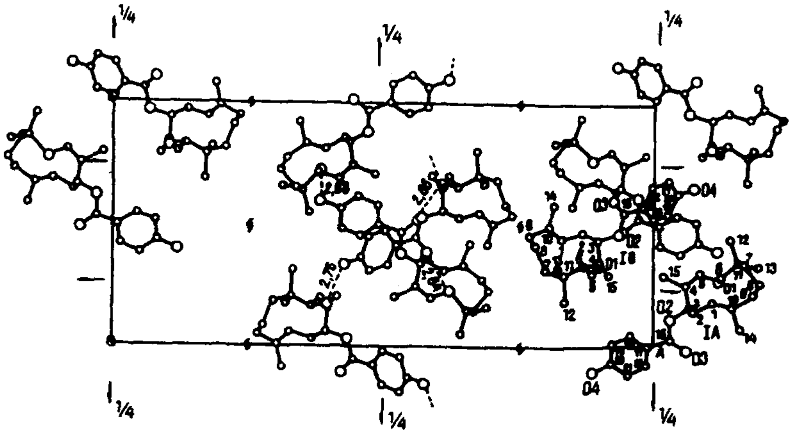

Fig. 1. Packing of juniferdin molecules.

In the para-hydroxybenzoic acid moieties of the two molecules (IA) and (IB) the angles between the planes of the hydroxy group and the benzene ring differ considerably (17° in (IA) and 7° in (IB)). However, in each case the para-hydroxybenzoic acid group as a whole is perpendicular to the mean square plane of the humulane ring.

The conformations of the macrocycles of the (IA) and (IB) molecules are characterized by the torsional angles given in Table 2. A comparison of the corresponding torsional angles in (IA) and (IB) shows, in spite of the considerable differences in the values of some of them (up to 14°), an identity of the macrocycles on the whole. The values or the corresponding angles of (II) and (III) given in Table 2 permit the conformations of the three related molecules to be compared. As can be seen from the Table the values averaged for the two molecules of (I) agree to an accuracy of 3° with the values for one of the conformers of the juniferol molecule, (IIA), and are also close to the corresponding values for the fexerol molecule (III); i.e., the conformations of the 11-membered humulane rings in these molecules are monotypical, and only in (IIB) is there a different conformation. Thus, two conformations of the macrocycle that differ from one another by the anti- and syn- directions of C10—C14 and C4—C15 bonds are characteristic for the known trans-1(10),cis-4-dienic humulanes.

TABLE 2. Torsional Angles Ψ (degrees) of the Macrocycles of the (IA), (IB), (II), and (III) Molecules

Torsional angle around the bond	Ψ_{IA}	Ψ_{IB}	Ψ_{I}^{*}	Ψ_{IIA}	Ψ_{IIB}	Ψ_{III}^{*}
C1—C2	—70	—82	—76	—79,8	100,8	—84
C2—C3	—65	—65	—65	—63,2	—73,8	—65
C3—C4	113	108	110	108,0	107,2	118
C4—C5	—4	12	4	4,3	1,0	1
C5—C6	—134	—137	—136	—135,5	—140,7	—127
C6—C11	72	65	69	71,8	64,5	71
C11—C7	74	79	77	79,0	70,0	70
C7—C8	—131	—145	—138	—139,8	—145,5	—154
C8—C9	73	84	79	77,8	65,9	92
C9—C10	—103	—99	—93	—96,9	58,6	—81
C10—C1	172	164	168	167,8	—166,8	150

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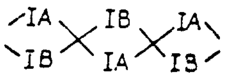
*The values of Ψ_I and Ψ_{II} have been averaged for the two molecules.

TABLE 3. Coordinates (×10^4) of the Nonhydrogen Atoms of Structure (I)

Atom	Molecule I			Molecule		
	x	*y*	*z*	*x*	*y*	*z*
C1	1084(4)	1869(10)	—3596(19)	—1740(4)	4454(11)	1736(18)
C2	0728(4)	1417(10)	—3087(18)	—1354(4)	4704(12)	0922(20)
C3	0661(4)	1573(9)	—1368(22)	—1075(3)	4405(9)	2166(20)
C4	0563(3)	2499(10)	—1092(21)	—1045(3)	3442(8)	2367(14)
C5	0835(4)	3025(8)	—0297(21)	—1183(3)	3026(8)	3488(18)
C6	1215(4)	2829(10)	0316(21)	—1338(3)	3372(9)	4986(20)
C7	1651(4)	3487(12)	—1602(30)	—2052(4)	3172(10)	4375(22)
C8	1910(4)	2698(15)	—2307(35)	—2229(3)	4137(9)	4527(21)
C9	1792(5)	2245(11)	—3568(21)	—2332(4)	4517(13)	2971(26)
C10	1445(5)	1654(12)	—3248(21)	—1981(4)	4922(10)	2301(18)
C11	1538(4)	3524(10)	0032(20)	—1719(3)	2935(9)	5580(20)
C12	1394(5)	4479(9)	0324(31)	—1813(4)	3225(12)	7178(28)
C13	1882(5)	3369(14)	1048(26)	—1691(5)	1884(10)	5485(25)
C14	1563(5)	0771(11)	—2449(28)	—1882(5)	5831(10)	2709(26)
C15	0189(4)	2979(11)	—1621(24)	—0875(5)	2940(13)	1009(27)
C16	0308(4)	0285(10)	—0531(21)	—0572(4)	5553(11)	1923(19)
C17	—0096(3)	—0124(8)	—0152(15)	—0208(3)	5784(8)	1316(19)
C18	—0436(5)	0422(10)	—0314(23)	—0045(3)	6525(9)	1531(18)
C19	—0787(4)	0135(12)	—0170(27)	0283(4)	6883(10)	0713(24)
C20	—0805(4)	—0687(10)	0580(21)	0433(3)	6334(10)	—0336(19)
C21	—0491(4)	—1185(10)	0984(22)	0390(4)	5479(9)	—0639(23)
C22	—0135(4)	—0830(11)	0605(25)	—0015(4)	5216(10)	0314(18)
O1	1184(2)	2707(7)	1990(13)	—1042(2)	3268(6)	6140(17)
O2	0299(2)	1142(5)	—0982(14)	—0577(2)	4689(6)	1707(14)
O3	0595(2)	—0165(6)	—0665(15)	—0781(3)	6183(7)	2687(13)
O4	—1177(3)	—1016(8)	0922(15)	0740(3)	6584(7)	—1227(14)

Analysis of the packing of the molecule in structure (I) showed the existence of OH...O hydrogen bonds of two types. The H-bonds of the first type are formed between the OH groups of molecules of the same kind: O4H...O1H (—x, y + 1/2, —z + 1/2) at an O...O distance of 2.66 Å for pairs of (IA) molecules and 2.76 Å for pairs of (IB) molecules. The H-bonds form double helices of molecules around 2_1 screw axes (1/2, y, 1/4).



Between the individual helices of the doubles helices are formed H-bonds of the second type between a hydroxy group of a molecule in one helix and a carbonyl group in the other: O1H(IA)...O3(IB) and O1H(IB)...O3(IA) at O...O distances of 2.84 and 2.86 Å, respectively.

EXPERIMENTAL

Transparent crystals of (I) in the form of elongated prisms were grown from ethyl alcohol and were subjected to preliminary study by the photo method. The space group and the unit cell parameters were determined from Weissenberg x-ray photographs. Subsequently, these parameters were refined on a Syntex $P2_1$ four-circle diffractometer using CuK_α radiation ($\theta/2\theta$ scanning): $a = 34.450(9)$; $b = 15.158(4)$; $c = 8.724(3)$ Å; $d_{calc} = 1.050$ g/cm^3; space group $P2_12_12_1$; $Z = 8$, two independent molecules. The intensities of 2143 reflections with $I > 1\sigma$ were measured on the above-mentioned diffractometer up to $\theta < 58°$.

To solve the structure we used in stages the Rentgen-75 [6], MULTAN [7], and XTL-SM [8] programs, and also AREN [9]. Attempts to solve the structure with the aid of the first three programs by the usual approaches with a wide variation of the parameters in the direct method did not lead to success. Therefore, to select a more reliable set of phases in the multivariant method in the AREN system of programs [9] we employed the NQEST estimate, using the ratios between the phases of four reflections — so-called negative quartets [10]:

$$\mathrm{NQEST} = \Sigma B \cos\,(\varphi_h + \varphi_k + \varphi_l + \varphi_m)/\Sigma B,$$

where $B = 2/N|E_hE_kE_\ell E_m|$ and N is the number of independent atoms in the unit cell.

The NQEST values were calculated from 200 negative quartets. The multivariant method with the choice of the best phase variants according to the NQEST estimate picked out as the first variant a set of phases with NQEST = −0.095. The automatic method of successive approximations [11, 12], after five iterations, revealed all 52 nonhydrogen atoms of the structure; it was found that the initial E-synthesis contained only 15 correct peaks.

All the calculations were made by the AREN system of programs [9], and the structure was refined by the method of least squares (MLS), first in the isotropic and then in the anisotropic approximation with allowance for extinction according to Zachariasen. The final value of the R-factor was 0.111 from 1911 reflections included in the MLS. The positions of the hydrogen atoms were found geometrically and were not refined. The coordinates of the nonhydrogen atoms are given in Table 3.

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