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X-RAY STRUCTURAL INVESTIGATION OF SESQUITERPENE ESTERS OF PLANTS OF THE GENUS Ferula.

VI. CRYSTAL AND MOLECULAR STRUCTURE OF UGAFERIN

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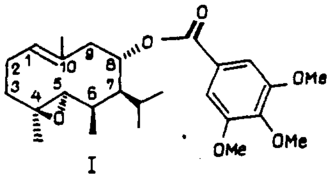
An x-ray structural investigation (diffractometer, Cu-K_α radiation, 2004 reflections, direct method, R factor 0.066) has been made of the germacrane ester ugaferin, which is 6β-hydroxy-8α-(3',4',5'-trimethoxybenzoyloxy)-4β,5α-epoxygermacr-1(10)-ene. A chair-boat conformation has been established for the ten-membered ring with a configuration of the ${}^{1}D_{14,15}D^{5}$ type.

The structure of the sesquiterpene ester ugaferin, isolated from Ferula ugamica Eug. Kor., has been established on the basis of spectral characteristics and chemical transformations [1]. However, the stereochemical aspects of this compound and, in particular, the conformation of the 10-membered ring could not be determined on the basis of PMR spectra. On the other hand, the germacrane ring of ugaferin differs from that of chimganidin by the presence of an epoxide group in the 4(5) position in place of a double bond [2]. The stereochemical closeness of the role of a double bond and of an epoxide ring have induced us to compare the conformations of the ten-membered rings in these compounds. With the aim of determining the stereochemistry of ugaferin we performed an x-ray structural investigation which has enabled its structure to be refined in the form of (I) (an OH group must be read in position 6):



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In the ugaferin molecule, shown in Fig. 1 in a projection on the (001) plane, the methyl group at C4 and the ester group — a trimethoxybenzoic acid residue at C8 — have the α-orientation. The hydroxy group at C-6 and the isopropyl group at C-7 have the β-orientation. The ester group at C-8 and the substituted benzene ring are in the same plane and are perpendicular (89°) to the mean square plane of the ten-membered ring (in chimganidin the corresponding angle is 47°). In contrast to chimganidin, this feature, probably due to a packing effect, does not permit the formation of an intramolecular H-bond between the hydroxy (OH) and carboxy (O4) groups.

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TABLE 1. Intracyclic Torsional Angles (degrees) of the Ugaferin (I) and Chimganidin (II) Molecules

Angle	I	II	Angle	I	II
C1C2C3C4	−54,1	−4,	C6C7C8C9	−133,6	−130,2
C2C3C4C5	91,7	86,1	C7C8C9C10	55,2	65,8
C3C4C5C6	−151,7	−168,	C8C9C10C1	62,2	60,0
C4C5C6C7	72,5	96,5	C9C10C1C2	−163,8	−167,0
C5C6C7C8	60,0	40,8	C10C1C	114,8	110,6

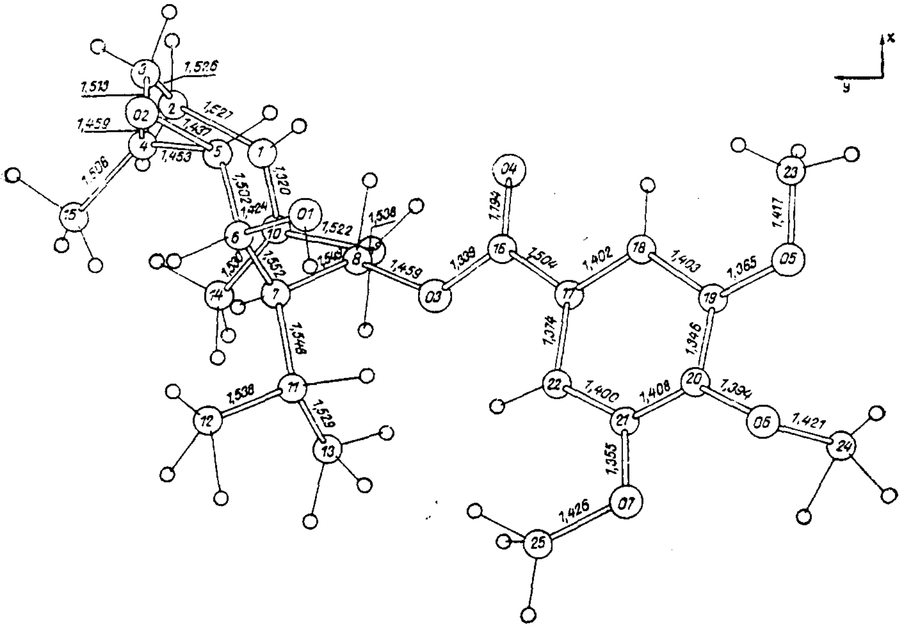

Fig. 1. Structure of the ugaferin molecule.

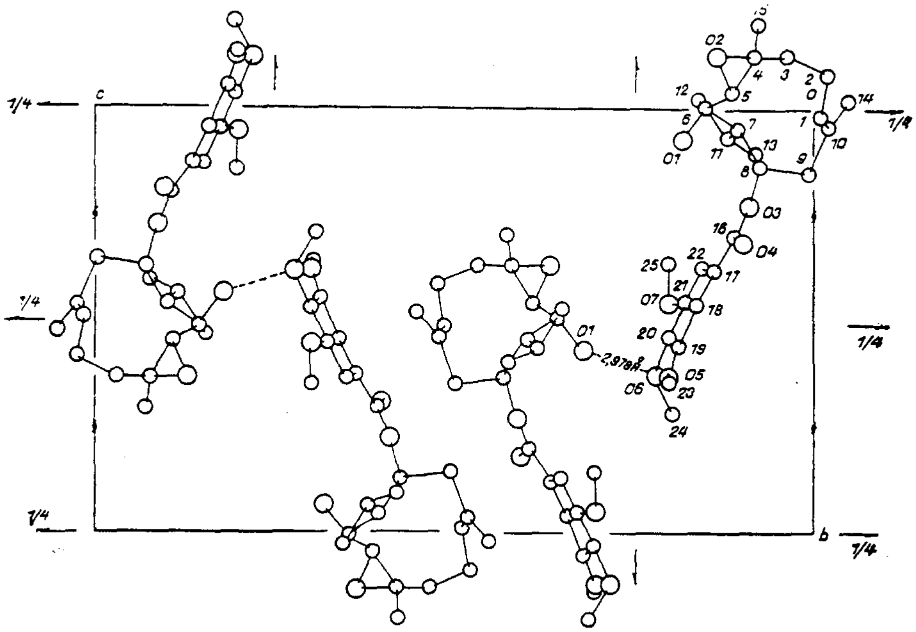

Fig. 2. Packing of the ugaferin molecules. H-bonds are shown by dashed lines.

TABLE 2. Valence Angles (deg) of the Ugaferin Molecule

Angle	φ	Angle	ψ	Angle	φ
C2C1C10	127,5	C6C7C11	112,8	C16C17C18	116,6
C1C2C3	110,1	C8C7C11	115,2	C16C17C22	121,7
C2C3C4	111,3	C7C8C9	115 5	C18C17C22	121,8
C3C4C5	117,4	C7C8O3	107,5	C17C18C19	118,2
C3C4C15	117,7	C9C8O3	108,7	C18C19C20	120,4
C5C4C15	121,4	C8C9C10	109,0	C19C20C21	121,5
C5C4O2	58,9	C1C10C9	119,6	C20C21C22	118,9
C15C4O2	112,9	C1C10C14	125,1	C20C21O7	117,1
C4C5C6	125,3	C9C10C14	115,2	C22C21O7	124,0
C4C5O2	60,4	C7C11C12	112,0	C17C22C21	119,1
C6C5O2	118,8	C7C11C13	111,7	C4O2C5	60,7
C5C6C7	112,6	C12C11C13	108,3	C8O3C16	117,7
C5C6O1	106,3	C17C16O3	110,2	C19O5C23	118,6
C7C6O1	110,5	C17C16O4	124,7	C20O6C24	115,3
C6C7C8	109,3	O3C16O4	125,0	C21O7C25	118,9

The conformation of the germacrane ring is characterized by the torsional angles given in Table 1. Their values with the participation of the endocyclic epoxy group (−151.7°) and the 1(10) double bond (−163.8°) permit ugaferin to be assigned to the trans-trans germacranolides, i.e., to the germacrolides [3]. A comparison of the torsional angles of ugaferin and chimganidin shows a great closeness of the corresponding values, although an appreciable difference (about 24°) is observed in the fragment with the participation of the epoxide group.

By projecting the molecule on to a plane perpendicular to the mean square plane of the germacrane ring it is possible to observe that the C1—C10 double bond and the C4—C5 bond of the epoxide fragment are present in a skew relationship, and the C14 and C15 methyl groups have a mutual syn-arrangement and are α-oriented. Consequently, the germacrane ring of ugaferin has a chair-boat conformation, one of the four theoretically possible for trans,-trans-germacranolides, with the ${}^{1}D_{14},{}_{15}D^{5}$ configuration [4]. This form of the ten-membered ring is also observed in chimganidin and in a number of other related germacranolides [5-7].

Thus the observed conformation of the ten-membered ring in the ugaferin molecule confirms once more a report on the predominant form of the germacrolides as a function of the orientation of the substituent at C6 [8].

No anomalies are observed in the values of the valence angles (Table 2) and interatomic distances given in Fig. 1 (the mean square deviations of the bond lengths and valence angles are not more than 0.009 Å and 0.7°).

The packing of the ugaferin molecules is shown in Fig. 2 in a projection on the b, c plane. The hydroxy group of the initial molecule and the methoxy group at C20, by a derived 2_1 axis [0, 1/4, Z], participate in intermolecular H-bonds (O1—H...O6 2.98 Å, O1HO6 159.1°), forming infinite chains of molecules along the b axis.

EXPERIMENTAL

Colorless crystals of ugaferin with a tabular form were grown from solution in chloroform and were subjected to preliminary investigation by the photographic method. The space group and the parameters of the elementary cells were established from precession x-ray diagrams. Subsequently, these parameters were refined on a Syntex-$P2_1$ diffractometer using Cu-K_α radiation: a = 8.265(2), b = 13.110(3), c = 23.116(5) Å; d_{calc} = 1.19 g/cm^3; space group $P2_12_12_1$; Z = 4.

The intensities of 2004 independent reflections with $I > 2\sigma$ were measured on the same diffractometer. The search for a model of structure was carried out by the direct method using a program of the Roentgen-75 complex [9]. The calculation was begun in the automatic regime but it was impossible to interpret the structure. After this, the search was continued with the use of the Σ_1 criterion and it was established that the reflection with the index 0.0.20 had the phase $\phi = 0°$ with a probability w = 0.791, and it was included in a new starting set of reference reflections. From them, taking the known phases of the reflections into account, 1024 variants of the phases were calculated, when variant E_3 with the R(E) factor 0.322 stood out distinctly. An E-synthesis revealed 22 nonhydrogen atoms out of the 32. We found the missing basis atoms in the following electron-density (ED) synthesis

TABLE 3. Coordinates of the Atoms ($\times 10^4$; for H, $\times 10^3$) of the Structure of Ugaferin

Atom	x	y	z	Atom	x	y	z
C1	4363 (12)	−158 (5)	126 (2)	H1	521	−66	−13
C2	5126 (12)	893 (5)	209 (3)	H2.1	632	93	48
C3	5736 (9)	1303 (4)	−370 (3)	H2.2	393	125	48
C4	4411 (7)	1300 (4)	−821 (2)	H3.1	690	100	−51
C5	4263 (6)	394 (4)	−1187 (2)	H3.2	628	189	−26
C6	2724 (5)	22 (4)	−1460 (2)	H5	501	−25	−115
C7	1542 (6)	−455 (3)	−1013 (2)	H6	208	80	−171
C8	2371 (6)	−1374 (3)	−715 (2)	H7	134	6	−70
C9	2209 (9)	−1413 (4)	−52 (2)	H8	367	−150	−82
C10	2833 (10)	−415 (4)	201 (2)	H9.1	90	−147	12
C11	−151 (5)	−676 (4)	−1272 (2)	H9.2	325	−209	−1
C12	−905 (6)	279 (4)	−1548 (2)	H11	−16	−150	−155
C13	−1321 (6)	−1081 (4)	−814 (3)	H12.1	−227	13	−174
C14	1561 (10)	241 (5)	505 (2)	H12.2	−202	75	−146
C15	3009 (8)	2022 (4)	−736 (2)	H12.3	−473	−75	316
C16	2669 (5)	−3 66 (3)	−1089 (2)	H13.1	−97	−175	−63
C17	1774 (5)	−3888 (3)	−1410 (2)	H13.2	−279	−90	−86
C18	2664 (6)	−4760 (3)	−1559 (2)	H13.3	−263	−150	−103
C19	1867 (5)	−5549 (3)	−1854 (2)	H14.1	207	100	63
C20	279 (5)	−5473 (3)	−1977 (2)	H14.2	32	25	22
C21	−612 (5)	−4590 (3)	−1839 (2)	H14.3	69	−25	85
C22	168 (5)	−3788 (3)	−1552 (2)	H15.1	355	270	−60
C23	4356 (7)	−6420 (4)	−2040 (2)	H15.2	190	175	−96
C24	−970 (9)	−7107 (4)	−1975 (3)	H15.3	239	211	−36
C25	−3018 (6)	−3612 (4)	−2002 (3)	H18	397	−476	−149
O1	3185 (4)	−715 (3)	−1882 (1)	H22	−62	−302	−150
O2	5019 (4)	1296 (2)	−1414 (1)	H23.1	480	−575	−234
O3	1667 (4)	−2391 (2)	−958 (1)	H23.2	464	−714	−219
O4	4076 (4)	−3093 (2)	−972 (2)	H23.3	465	−640	−166
O5	2642 (4)	−6417 (2)	−2025 (1)	H24.1	−177	−775	−216
O6	−537 (4)	−6219 (2)	−2292 (1)	H24.2	−20	−750	−165
O7	−2179 (4)	−4562 (2)	−2012 (1)	H24.3	−233	−675	−169
				H25.1	−428	−350	−210
				H25.2	−239	−288	−228
				H25.3	−308	−325	−149
				HO1	266	−72	−219

calculated from the whole mass of reflections. The structure was refined first by successive ED approximations (R = 0.281) and by the method of least squares (MLS) in the isotropic approximation R = (0.157) and then by full-matrix MLS with allowance for the anisotropic thermal vibrations of the nonhydrogen atoms to R = 0.104. At this stage, an ED difference synthesis was calculated and all the H atoms were localized. The final value of the R-factor after four iterations of MLS taking the H atoms into account was 0.066. The coordinates of the atoms are given in Table 3.

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