SPATIAL STRUCTURE OF AKIFERIN FROM Ferula akitschkensis

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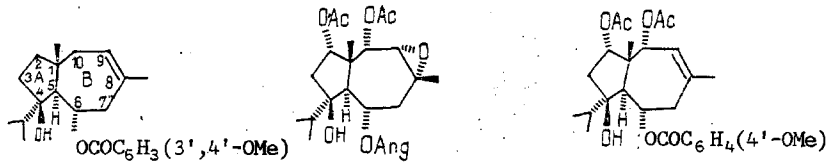
The spatial structure of the carotane ester akiferin has been established by the x-ray structural method (diffractometer, CuK_α radiation, 1109 reflections, direct method, R = 0.084). Using the method of molecular mechanics, possible conformational states of the free akiferin molecule have been calculated by rotating the para-methoxybenzoate [sic] moiety of the molecule relative to the C6–O axis.

By a study of the dependence of estrogenic activity on structure in a series of estrogenic drugs of steroid nature, it has been shown that such activity requires the presence of an aromatic nucleus and of phenolic and alcoholic hydroxy groups in the molecule. An important criterion of estrogenic activity is the distance between these hydroxy groups, and a compound possesses the maximum activity when this distance is 14.5 Å [1].

The estrogenic drugs panoferol and teféstrol, which include compounds containing the above-mentioned functional groups, have been created on the basis of carotane esters isolated from plants of genus Ferula L.

The aim of the present investigation was to establish the spatial structure of akiferin, to determine the distance between the hydroxy groups at C4 and C19,* and to check the hypothesis concerning the estrogenic activity of steroids in its application to carotane esters.

The structure of a sesquiterpene ester of the carotane series – akiferin, with the composition $C_{24}H_{34}O_5$ (I), isolated from Ferula akitschkensis, family Apiaceae has been established on the basis of chemical transformations and spectral properties [2].



I II III

The spatial structure of the akiferin molecule, determined by the x-ray structural method (Fig. 1), shows that the orientation of the substituents (C14, O1-β, O2, and C11-α) and the linkage of the rings (A/B-trans) completely confirms the stereochemistry of akiferin proposed previously on the basis of spectral results and agrees with that observed in analogues investigated structurally – (II) [3] and (IV) [4]. The conformations of the rings are characterized by the torsional angles given in Table 1. The five-membered ring A has the envelope conformation with symmetry C_S (the asymmetry magnitude ΔC_S^1 according to [5] is 0.8°). The deviation of the C1 atom from the plane of the other four amounts to –0.757 Å in the β-direction, although in the related lapidolin ring A is in an intermediate state between envelope (ΔC_S = 8.5°) and half-chair (ΔC_2 = 8.0°) conformations. The seven-numbered ring B of the (I) molecule has the chair conformation with deviations of the C5 atom and the C8 and C9 atoms in opposite directions from the plane (satisfied with an accuracy of 0.02 Å) of the other four by 0.74, –1.14, and –1.06 Å, respectively (this is also shown by the magnitude $\Delta C_S^{5-8.9}$ = 4.6°).

*Sic. There is no hydroxy group at C19 (numbering of Fig. 1) in akiferin, as is confirmed by the molecular diagrams shown: the references below to more than one hydroxyl and, in particular, to a phenolic hydroxyl in the akiferin molecule are incomprehensible – Translator.

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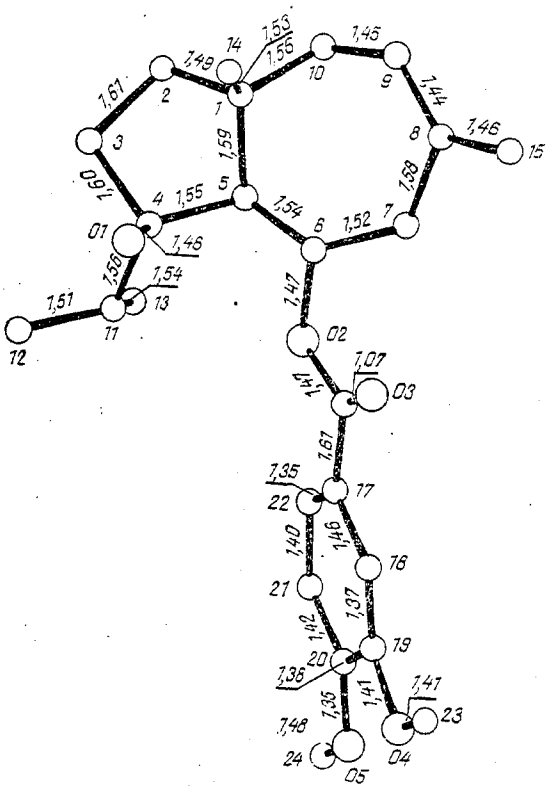

Fig. 1. Structure of the akiferin molecule.

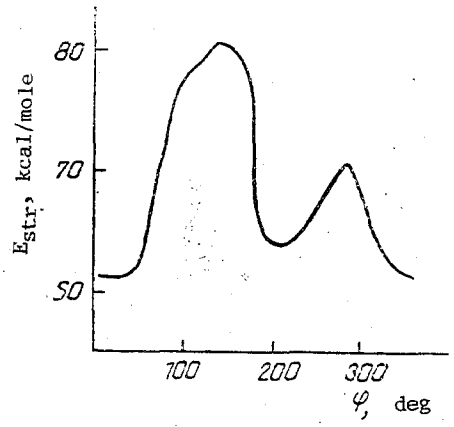

Fig. 2. Dependence of strain energy (E_{str}) of molecule I on the rotation about the C6-O2 band (on x-axis torsion angle φ = C7-C6-O2-C-16).

In the (II) and (III) molecules, also, the chair conformation of ring B is observed, with the close values for $\Delta C_S^{5-8\cdot9}$ of 6.2 and 5.6°, respectively.)

On the whole, no anomalies are observed in the values of the valence distances and angles (see Fig. 1 and Table 2), apart from the C1–C2 and C2–C3 distances of 1.49 and 1.61 Å, respectively, and the C9C8C15 angle of 128°; which deviate slightly from the magnitudes usually observed [3, 4, 6] and from the standard values [7]. The mean square errors of determination for the bond lengths and valence angles do not exceed 0.03 Å and 2°, respectively.

The geometry of the free (I) molecule was calculated by the method of molecular mechanics [8] with full optimization using the initial data from the x-ray structural investigation. We determined the possible conformational states by rotating the most mobile section – the para-methoxybenzoate [sic] moiety of the molecule – about the C6–O2 bond. Since the distance between the active fragments of the molecule is determined mainly by the position of the aromatic nucleus relative to the sesquiterpene moiety, a change in the conformation of the carotane skeleton has little effect on this distance. Figure 2 shows a graph of the dependence of the strain energy on the angle of rotation about the C6–O2 bond, from which it can be seen that, in the free state, the molecule can have, in addition to the conformer existing in the crystal (torsional angle 82°, E = 61 kcal/mole), another conformer in which the angle is −78° (E = 64 kcal/mole). In these conformers, the distance between the oxygen atoms of the hydroxy group at C4 and of the phenolic hydroxy group is 7.0 and 8.1 Å, which is little more than half that recommended for estrogen of steroid origin. If the influence of the medium on the conformation is taken into account in the calculations, the interval of variation of the distances can be expanded even more.

Thus, in estrogenic drugs created on the basis of compounds of steroid and carotane origin there is no direct correlation of activity with the distance of 14.5 Å between the "terminal" hydroxy groups. However, attention is attracted by the marked decrease in the distance between the hydroxy groups at C4 and in the aromatic ring in carotane esters as compared with that recommended for steroid estrogens.

EXPERIMENTAL

Colorless crystals of (I) in tabular form were grown from hexane–ether (1:1) solution. The space group, the parameters of the unit cell, and the intensities of the reflections from the

TABLE 1. Torsional Angles φ (degrees) in the Structure of (I)

Angle	φ	Angle	φ	Angle	φ
C1C2C3C4	—29	C8C9C10C1	70	O1C4C11C13	—178
C2C3C4C5	—2	C9C10C1C5	—85	C6O2C16O3	9
C3C4C5C1	31	C10C1C5C6	71	O2C16C17C18	—177
C4C5C1C2	—50	C4C5C6O26	64	O2C16C17C22	11
C5C1C2C3	49	C3C4C11C12	—55	C18C19O4C24	—0
C1C5C6C7	—69	C3C4C11C13	72	C24O4C19C20	—177
C5C6C7C8	80	C5C4C11C12	—176	O4C19C20O5	—1
C6C7C8C9	—63	C5C4C11C13	—49	C19C20O5C23	—176
C7C8C9C10	—4	O1C4C11C12	55	C21C20O5C23	8

TABLE 2. Valence Angles ω (degrees) in the Structure of (I)

Angle	ω	Angle	ω	Angle	ω
C5C1C2	99	C6C5C4	114	O3C16O2	129
C10C1C2	110	C7C6C5	111	C18C17C16	108
C10C1C5	108	O2C6C5	102	C22C17C16	132
C14C1C5	115	O2C6C7	103	C22C17C18	118
C14C1C10	109	C8C7C6	114	C19C18C17	118
C3C2C1	104	C9C8C7	118	C20C19C18	122
C4C3C2	100	C15C8C7	113	O4C19C18	123
C5C4C3	103	C15C8C9	128	O4C19C20	114
C11C4C3	109	C10C9C8	123	C21C20C19	117
C11C4C5	117	C9C10C1	111	O5C20C19	116
O1C4C3	102	C12C11C4	114	O5C20C21	125
O1C4C5	114	C13C11C4	111	C22C21C20	119
O1C4C11	105	C13C11C12	111	C21C22C17	122
C4C5C1	101	O2C16C17	97	C16O2C6	108
C6C5C1	114	O3C16C17	132	C23O5C20	114
				C24O4C19	117

TABLE 3. Coordinates of the Basis Atoms ($\times 10^4$) in the Structure of (I)

Atom	x	y	z	Atom	x	y	z
C1	3799(25)	9936(19)	456(4)	C15	8276(57)	12428(27)	992(8)
C2	2584(27)	8990(19)	218(4)	C16	6093(23)	8651(29)	1812(4)
C3	1235(31)	8359(20)	543(5)	C17	6406(24)	7005(18)	2015(4)
C4	2397(30)	8281(20)	936(4)	C18	6938(27)	7241(18)	2429(4)
C5	4213(23)	8765(19)	807(4)	C19	7369(24)	5996(17)	2657(4)
C6	5313(24)	9416(18)	1148(4)	C20	7352(26)	4515(17)	2507(4)
C7	7127(30)	9718(20)	1007(4)	C21	6815(26)	4304(18)	2104(4)
C8	7366(28)	11257(23)	766(6)	C22	6427(28)	5573(17)	1866(4)
C9	6474(31)	11424(25)	391(5)	C23	7830(37)	1839(27)	2593(6)
C10	5448(27)	10226(24)	210(5)	C24	7759(30)	7554(20)	3246(5)
C11	2193(30)	6679(19)	1138(5)	O1	1546(32)	9386(25)	1208(3)
C12	0388(35)	6237(25)	1233(7)	O2	5488(14)	8095(11)	1419(2)
C13	3089(35)	5416(22)	892(6)	O3	6230(26)	9796(13)	1921(4)
C14	3023(32)	11466(20)	586(5)	O4	7785(21)	6094(19)	3068(4)
				O5	7747(18)	3390(11)	2770(3)

crystal were determined on a Syntex $P2_1$ automatic four-circle diffractometer at room temperature using CuK_α radiation: a = 7.866(3), b = 8.734(3), c = 33.300(9) Å; d_{calc} = 1.172 g/cm^3; rhombic crystals; space group $P2_12_12_1$; Z = 4.

A full set of experimental reflections (1520) with $\theta < 58°$ was obtained on the above-mentioned diffractometer ($\theta/2\theta$ scanning). In the primary treatment of the group, weak reflections with $I < 2\sigma(I)$ were discarded. The calculations made use of 1109 reflections with $|F| > 4\sigma(|F|)$. The structure was determined by the direct method using the SHELXS-86 program [9] and was refined in the full matrix isotropic-anisotropic approximation using the SHELX-76 program [10] (both programs in the PC MSDOS versions). The H atoms, the initial positions of which were calculated, were refined isotropically. The final value of the discrepancy factor R = 0.084 (R_w = 0.084). The coordinates of the nonhydrogen atoms are given in Table 3.

The conformational calculations were made on a personal computer of the IBM PC AT type using the PC MODEL and MMX-86 programs [11] with complete optimization of the geometry of the molecule and the use of the potential parameters included in the given version of the program.

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SYNTHESIS OF A MONOESTER OF SUCROSE WITH trans-O-METHYLMARMESINIC ACID

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The water-soluble 6-O-monoester of sucrose with trans-O-methylmarmesinic acid has been synthesized by the transesterification of methyl trans-O-methylmarmezinate with sucrose. The structure of the compound obtained has been confirmed by UR, UV, PMR, and ^{13}C NMR spectroscopies.

Cinnamic acids play an important role in the vital activity of plants and are widespread natural compounds. In plants they are found both in the free state and in the form of esters with carbohydrates or as glycosides [1]. Many of them are biologically active substances. At the present time, the use of natural esters of cinnamic acid with carbohydrates is limited by their poor availability as a consequence of the difficulty of isolating them from plants and the complexity of their synthesis (necessity for using protective groups – acetyl, isopropylidene, etc.), and the formation of by-products when acid chlorides and anhydrides are used [2].

With the aim of developing a simpler and more accessible method of obtaining water-soluble analogues of cinnamic acids, we have studied the possibility of obtaining monoesters of trans-cinnamic acids with sucrose. This expedient, based on the opening of the lactone ring of a furocoumarin, the isomerization of the cis-cinnamic acid so formed to the trans-isomer and the subsequent esterification of a carbohydrate (in the present case, sucrose) with it, has not been described in the literature. As the starting material we used the dihydrofurocoumarin marmesin (I), obtained by the acid hydrolysis of the glycoside marmesinin [3].

It was found that the opening of the lactone ring and cis-trans isomerization takes place without the formation of by-products [4]. In the UV spectrum of product (II) the absorption band in the 335 nm region had disappeared and the band characteristic for trans-cinnamic acids in the 280 nm region was present. The PMR spectrum of compound (II) showed two doublets in the regions of 6.85 and 8.65 ppm with ^3J = 16 Hz due to trans-olefinic protons. We then subjected the trans-marmesinic acid (II) to methylation with diazomethane [5]. This led to the methylation of both the carboxylic and the phenolic hydroxy groups, with the formation of methyl trans-O-methylmarmesinate. Sucrose esters were obtained by a transesterification

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