STRUCTURE AND STEREOCHEMISTRY OF LAPIFERININ

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The roots of Ferula lapidosa Eug. Korov. have yielded lapiferinin, $C_{26}H_{36}O_8$, mp 157-158°C, $[\alpha]_D^{21}$ +63° (c 1.3; chloroform) – a diester of a new carotane alcohol, lapiferinol, with veratric and acetic acids. On the basis of chemical transformations and spectral characteristics, the structure of 2α-acetoxy-6β-veratroyloxy-8α,9α-epoxy-trans-carotan-4β-ol is proposed for it.

Continuing a study of the esters of Ferula lapidosa Eug. Korov. [1], from the total neutral components we have isolated a new compound with the composition $C_{26}H_{36}O_8$, M^+ 476, which we have called lapiferinin (I).

Maxima in the UV spectrum of (I) with $\lambda_{max}^{C_2H_5OH}$, cm^{-1}, 211 (log ε 4.34), 264 (log ε 4.0), and 295 (log ε 3.87) are due to the presence of substituted aromatic nucleus. The IR spectrum shows strong absorption bands with ν_{max}^{KBr}, cm^{-1}, 3550 (OH); 1730 (C=O of an ester); 1710 (C=C–C=O of an ester); and 1600 and 1520 (aromatic nucleus).

In the PMR spectrum of (I) ($CDCl_3$, δ scale, 0 – HMDS) appear the signals of the protons of an isopropyl grouping (d, 0.8 and 0.92 ppm, J = 7 Hz), of an angular methyl group (s, 1.32 ppm), of a methyl group on a carbon atom linked to oxygen (s, 1.46 ppm), of two gem-acyl protons (d, 4.81 ppm, J = 5 Hz, and sx, 5.39, J = 10, 10, and 3 Hz), and of an epoxide proton (t, 2.71, J = 7 and 7 Hz). In addition there are the signals of the protons of an acetyl group (s, 1, 1.98 ppm, 3 H) and of a residue of 3,4-dimethoxybenzoic (veratric) acid (s, 3.83 and 3.86; d, 6.78, J = 8 Hz; d, 7.39, J = 2 Hz; q, 7.52. J = 8 and 2 Hz).

The mass spectrum of lapiferinin show the peaks of ions with m/z 433 $(M - C_3H_7)^+$, 416 $(M - CH_3COOH)^+$, 373 $(M - C_3H_7 - CH_3COOH)^+$, $(373 - H_2O)^+$, 234 $(M - C_9H_{10}O_4 - CH_3COOH)^+$, 217 $(234 - 17)^+$, which confirm the presence in the molecule of (I) of isopropyl and hydroxy groups and of residues of acetic and veratric acids.

On comparing the facts given above with literature information [1-6], it may be concluded that lapiferinin is an ester of the carotane series, and this was confirmed by the formation of daucalene when (I) was dehydrogenated with palladium.

The alkaline hydrolysis of lapiferinin gave veratric acid and the sesquiterpene alcohol lapiferinol, $C_{15}H_{26}O_4$ (II). The PMR spectrum of (II) (pyridine-d_5) lacked the signals of the protons of the two acyl residues. The sextet and doublet signals of the hemiacyl protons had shifted diamagnetically to 4.41 and 3.88 ppm, simultaneously undergoing additional splitting from interaction with the protons of the geminal hydroxy groups. The latter appeared in the form of doublets at 5.67 ppm (J = 3 Hz) and 5.72 ppm (J = 6 Hz). A singlet superposed on the signal of the gem-hydroxylic proton at 3.88 ppm is due to the proton of a tertiary group. When the PMR spectrum of (II) was taken with deuterium exchange, the signals of all three hydroxy groups disappeared.

These facts, together with the elementary composition, permit the conclusion that lapiferinol is a bicyclic carotane alcohol containing an epoxide ring and two secondary and one tertiary hydroxy groups, and lapiferinin is its diester with acetic and veratric acids.

The positions of the functional groups in lapiferinol and lapiferinin were determined in the following way.

The sextet nature of the one-proton signal at 4.41 ppm in the PMR spectrum of (II) (5.39 ppm in the spectrum of (I)) shows that one hydroxy group (acyl group (I)) must be equatorially located at C_6 of the carotane skeleton of lapiferinol (lapiferinin). The same fact show that the C_5 and C_7 positions are free from substituents, by analogy with the previously described derivatives of lapidol, lapiferol, jaschkeanadiol (ferutinol), laserol, and isolaserol [1-6].

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In the PMR spectra of (I) and (II), triplets at 2.7 and 2.78 ppm (J = 7, 7 Hz) correspond to the epoxide proton and, consequently, the epoxide proton interacts with the two protons of a methylene grouping. The multiplicities of these signals and the magnitude of the vicinal coupling constant also indicate that the epoxide ring is attached to the seven-membered ring (the signal of an analogous epoxide proton present in a five-membered ring appears in the form of a broadened singlet [7]). Consequently, the only possible position of attachment of the epoxide ring is at the C_8-C_9 atoms.

Thus, the two remaining hydroxy groups can be present only in the five-membered ring, and, of them, the tertiary group must be at C_4, i.e., geminally to the isopropyl radical. This was confirmed by the presence in the mass spectra of (I) and (II) of strong peaks with m/z $(M-43)^+$ due to the detachment of the isopropyl group under the action of electron impact [2, 3].

For the other hydroxy group, the positions at C_2 and C_3 are equiprobable. However, the stability of lapiferinol to oxidation by periodic acid shows the absence of an α-diol system in its molecule, which permits an unambiguous choice in favor of C_2.

It follows from what has been said above that in lapiferinol these three hydroxy groups are present at C_2, C_4, and C_6 of the carotane skeleton and the epoxide ring involves the C_8 and C_9 atoms.

The positions of the acid residues in lapiferinin were determined on the basis of the following facts. The mild hydrolysis of (I) with an aqueous ethanolic solution of sodium carbonate formed a monoester of lapiferinol (III), $C_{17}H_{28}O_5$, in the IR spectrum of which the band with ν_{max} 1710 cm^{-1} had disappeared. Veratric acid was isolated from the acid part of the hydrolysate.

The PMR spectrum of (III) ($CDCl_3$) had retained the signal of the protons of the acetyl group (s, 1.97 ppm, H), while the sextet of the gem-acyl proton at C_6 had shifted upfield to 4.06 ppm (J= 10, 10, 3 Hz). It follows from this that in lapiferinin the veratric acid had esterified the hydroxy group at C_6 and the acetic acid residue was located at C_2.

Thus, the structure of lapiferinin is expressed by structural formula (I).

An analysis of spectral characteristics and a comparison of the latter with literature information has enabled the orientations of the functional groups and the linkage of the cyclopentane and cycloheptane rings in lapiferinol and its derivatives to be established.

As mentioned above, the signal of the proton at C_6 in the PMR spectra of (I-III) is a sextet with constants of vicinal coupling of 10, 10, and 3 Hz. The values of the constants unambiguously show the trans linkage of the cyclopentane ring with the cycloheptane ring and the α-equatorial orientation of the hydroxy group in (II) and (III) and of the acyl group in (I), as in the case of the known compounds mentioned previously [1-6].

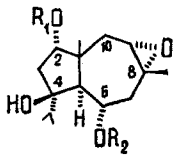
In the PMR spectrum of lapiferinin, the methyl groups of the isopropyl residue are represented in the form of doublets at 0.8 and 0.92 ppm, i.e., the difference in the chemical shifts amounts to 12 Hz. Such a difference is observed in esters of carotane alcohols and aromatic acids when the orientations of the aromatic acid residue at C_6 and of the isopropyl group at C_4 are the same and is due to the anisotropic influence of the aromatic ring on the isopropyl group spatially adjacent to it [8]. When there is a hydroxy group at C_6, the difference in the chemical shifts of these groups amounts to 3-4 Hz, as in the spectrum of the monoester (III)

$$\left(\mathrm{CH}\begin{matrix}\diagup\mathrm{CH_3}\\ \diagdown\mathrm{CH_3}\end{matrix}\ \text{d, 0.85 and 0.81 ppm,}\quad J=7\ \text{Hz,}\quad \Delta\delta=4\ \text{Hz}\right).$$

It follows from this that the isopropyl group in lapiferinol and its derivatives has the α orientation, like the hydroxyl (or acyloxy) at C_6.

The doublet structure of the signal of the proton at C_2 in the PMR spectra of lapiferinol, lapiferinin, and lapiferinol monoacetate (J= 5 Hz) shows the α-pseudoaxial orientation of the hydroxyl (acyl) group geminal to this proton [9, 10]. If the hydroxyl had the β orientation, the signal of the proton mentioned would have the form of a quartet [11].

In each of the spectra of (I-III), the epoxy proton appears in the form of a triplet (at 2.71, 2.78, and 2.73 ppm, respectively) with J = 7 Hz. A consideration of the structural formulas of the compounds on molecular models has shown that this value of the coupling constant of the epoxy proton with the vicinal protons at C_{10} corresponds to the α configuration of the epoxy ring, as in the lapiferinol derivatives studied previously [2]. Having analyzed the results obtained, for lapiferinin we propose the structure of 2α-acetoxy-6β-veratroyloxy-8α, 9α-epoxy-trans-carotan-4β-ol (I).



I. $R_1 = -C(=O)-CH_3$; $R_2 = -C(=O)-C_6H_3(OCH_3)_2$

II. $R_1 = R_2 = H$

III. $R_1 = -C(=O)-CH_3$; $R_2 = H$

EXPERIMENTAL

The conditions of recording the spectra and the isolation of the fractions of neutral components from an ethanolic extract of the roots have been described previously [1]. The esters were separated by column chromatography on silica gel with the aid of the hexane–ethyl acetate system with a rising gradient of the latter.

Isolation of Lapiferinin (I). Fractions 43-48 (hexane–ethyl acetate (2:1)) were combined, the solvent was distilled off, and the residue was crystallized from ether. This gave a crystalline substance (1 g, yield 0.26%) with the composition $C_{26}H_{36}O_8$, mp 157-158°C, $[\alpha]_D^{21}$ + 63° (c 1.3; chloroform).

The dehydrogenation of lapiferinin was carried out by heating it with 10% $Pd/CaCO_3$ at 240-250°C for 3 h [1]. This gave daucalene, the picrate of which melted at 89-90°C.

Hydrolysis of Lapiferinin. The substance (400 mg) was hydrolyzed with 2% aqueous alcoholic caustic potash solution (50 ml) with heating on the water bath for 30 min. The reaction mixture was diluted with water and treated with ethyl acetate. The ethyl acetate extracts were washed and dried and the solvent was dissolved off. This gave 125 mg of lapiferinol, $C_{15}H_{26}O_4$, mp 194-195°C (from ethyl acetate) $[\alpha]_D^{21}$ +69.3° (c 1.5; ethanol).

From the aqueous mother liquor after the extraction of the lapiferinol, we isolated an aromatic acid, $C_9H_{10}O_4$, mp 180-181°C, identical with veratric acid.

Mild Hydrolysis of Lapiferinin. A solution of 110 mg of the substance in 7 ml of ethanol was treated with 3 ml of a 5% aqueous solution of Na_2CO_3. The reaction mixture was heated on the water bath for 5 h and was then diluted with water. The reaction product was extracted with ethyl acetate. The residue obtained after the elimination of the solvent was chromatographed on a column of silica gel (40× 1), the substances being eluted with the chloroform–ethyl acetate (8:1) system. This gave 30 mg of lapiferinol monoacetate (III) with the composition $C_{17}H_{28}O_5$, mp 115-116°C (from hexane–ether), $[\alpha]_D^{20}$ −8.2° (c 0.9; chloroform). Veratric acid was isolated from the acid fraction of the hydrolysate.

SUMMARY

A new ester of the carotane series – lapiferinin – has been isolated from the roots of Ferula lapidosa Eug. Korov. A structure and relative configuration have been proposed for it on the basis of spectral characteristics and chemical transformations.

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