FEXERIDIN AND FEXERININ — NEW ESTERS FROM *Ferula xeromorpha*

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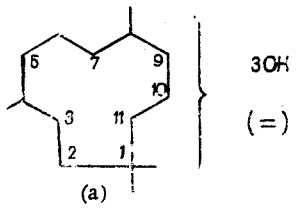
Continuing a study of the chemical composition of plants of the genus *Ferula*, from the roots of *Ferula xeromorpha* Eug. Kor. collected in the Chimkent oblast of the Kazakh SSR we have isolated another two new esters, which we have called fexeridin (I) and fexerinin (II).

Fexeridin (I), with the composition $C_{23}H_{34}O_6$, has a maximum in the UV spectrum that is characteristic for a 3,4-dihydroxy-substituted benzoyl residue, and in the IR spectrum it has absorption bands at (cm^{-1}) 1705, 1225 (ester group), 1520, 1600, 1620 (aromatic ring), and 3200-3600 cm^{-1} (hydroxy group).

On the alkaline hydrolysis of fexeridin, from the neutral fraction we isolated a sesquiterpene alcohol with the composition $C_{15}H_{28}O_3$ and mp 132-134°C — fexerol (III) — and from the acid fraction we isolated vanillic acid [1]. The mass spectrum of fexerol has the peaks of ions with m/e 236 $(M - H_2O)^+$, 221 $(M - H_2O - CH_2)^+$, 218 $(M - 2H_2O)^+$, and 200 $(M - 3H_2O)^+$.

In the PMR spectrum (Table 1) of (III) there are signals due to the presence of tertiary methyl groups and vinyl methyl groups, and also those of olefinic and gem-hydroxylic protons.

With the composition $C_{15}H_{28}O_3$, the presence of one double bond and the absence of carbonyl and ethoxy groups, the alcohol (III) must have a monocyclic structure. The absence from the mass spectra of (I) and (III) of the peaks of ions with m/e M — 43 $[(M - (CH_3)_2CH)^+]$ and a difference in the CSs of the signals of the methyl groups in the strong field in the PMR spectra of (I) and the actetates of (I) and (III) shows that the methyl groups in fexeridin are tertiary and substance (III) has the humulane skeleton (a)



(a)

The successive ejection of three molecules of water in mass spectrometry and the absence of absorption bands of carbonyl and epoxy groups in the IR spectrum of (III) shows that in (III) all three oxygen atoms are present in the form of hydroxy groups.

A comparison of the PMR spectra of juniferin (V), juniferol (IV), and juniferin acetate (VI) and of those of fexeridin (I) and fexerol (III) shows that in the molecule of the latter there is one secondary—tertiary double bond ($HC{=}C{-}\overset{|}{C}{-}$) and a methyl group geminal to a hydroxy group. One of the gem-hydroxylic protons and the olefinic proton appear in the spectra of (I) and (III) — as in the spectra of juniferin (V) and juniferol (IV) — in the form of doublets with equal SSCCs [2], which shows the position of the double bond at C_3-C_4 and of a hydroxy group at C_2. Consequently, the tertiary group is located at C_8. The C_5, C_6, C_7, C_9, C_{10}, and C_{11} positions remain for the other hydroxy groups.

If a secondary hydroxy group were present at C_7 or C_9, it would form a glycol system with the C_8-OH, which would decompose under the action of periodic acid. The stability of fexerol to periodic acid excludes this hypothesis.

As is well known, the acetylation of a hydroxy group vicinal to a gem-dimethyl group causes descreening of the protons of one of the methyl groups. As a result of this, on passing

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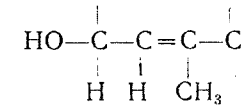
TABLE 1. Chemical Shifts (in ppm), SSCCs (in Hz), and Integral Intensities of the Signals of the Protons

Substance	C_2–H	C_3–H	C_9–CH_3 C_1–CH_3	C_5–H	C_7–H	C_1–$2CH_3$	OAC
Fexerinin (II)	5,32 J=10	5,17 J=10	1,75 s 1,68 s	4,89 q J_1=10 J_2=5	5,04 t $J_1=J_2=7,5$	0,86 s 1,04 s	—
Juniferin (V) [2]	4,18 d J=10	5,52 d J=10	1,67 s 6H	5,50 q J_1=10 J_2=5	**5,05 t** $J_1=J_2=7,5$	0,88 s 0,95 s	—
Juniferin acetate (VI) [2]	5,42	5,42	1,65 s 6H	5,85 q J_1=10 J_2=5	5,07 t $J_1=J_2=7,5$	0,78 s 0,90 s	1,88 s 2,12 s
Fexerinin acetate (VII)	5,47	5,47	1,73 s 1,76	5,65 q J_1=10 J_2=5	5,08 t $J_1=J_2=7,5$	0,82 1,04	1,95 2,26 s
Juniferol (IV) [2]	3,95 d J=10	5,35 d J=10	1,58 s 1,71 s	4,40 q J_1=10 J_2=5	4,96 t $J_1=J_2=7,5$	0,81 s 0,85 s	—
Fexerol (III)	4,29 d J=10	5,40 d J=10	1,32 s 1,82 s	4,56 q J_1=10 J_2=5	—	0,82 s 0,92 s	
Fexeridin (I)	4,50 d J=10	5,53 d J=10	1,20 s 1,78 s	5,78 br. q.	—	0,88 s 0,98 s	

Note: s) singlet; d) doublet; t) triplet; q) quartet.

from the alcohol to the acetate a change is observed in the difference between the CSs of the signals of the gem-dimethyl groups [3]. The constant value of the difference of the CSs of the gem-dimethyl groups in the spectra of fexerol and fexeridin excludes the C_{11} position for the hydroxy group.

In the PMR spectrum of (III), the gem-hydroxylic proton appears in the forms of a quartet (J_1 = 10, J_2 = 5 Hz); i.e., it is part of only a three-spin system. If the hydroxy group were present at C_6 or C_{10}, the gem-hydroxylic proton would form a multispin system and the signal would appear in the form of a multiplet, which is not in fact observed. Thus, the only possible position remaining for the hydroxy group is at C_5. This is confirmed by the following facts. The signal of the gem-hydroxylic proton in the spectrum of fexerol is found in a comparatively weak field (4.56 ppm), which is characteristic for a proton adjacent to a double bond [4].

In the study of the structure of juniferol it was shown [2] that the acetylation of the hydroxy group at C_2 leads to a paramagnetic shift of the signals of the protons at C_3 and C_5, and acetylation of the C_5–OH to a downfield shift of the C_2–H and C_3–H signals. On comparing the C_2–H and C_3–H signals in the spectra of juniferin acetate (VI), fexeridin (I) and fexerol (III), it can be seen that the relationship mentioned is also observed in fexerol derivatives. Consequently, the fexerol molecule has the  fragment; i.e., the secondary hydroxy group is located at C_5.

On the basis of what has been said above, for fexerol we propose the structure of 1,1,4,8-tetramethylcycloundec-3-ene-2,5,8-triol. The position of the acid residue at C_5 in fexeridin follows from the CS values of the gem-acyl proton in its PMR spectrum. Consequently, fexeridin is 5-vanilloylfexerol.

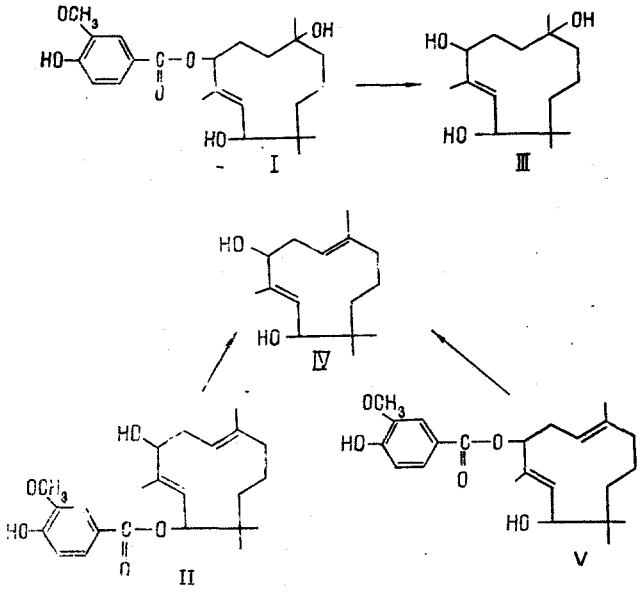
Fexerinin (II) has the composition $C_{23}H_{32}O_5$. Its UV spectrum is similar to that of fexeridin. The IR spectrum of (II) shows absorption bands at (cm^{-1}) 3200-3600 (hydroxy group), 1520, 1600, 1620 (aromatic ring), 1690, and 1230 (ester group). The alkaline hydrolysis of fexerinin yielded an alcohol with the composition $C_{15}H_{26}O_2$ which was identified by its IR and PMR spectra and a mixed-melting point as juniferol (IV) [2].

In the PMR spectrum of juniferol, the C_2–H and C_3–H protons give two doublets at 3.95 and 5.35 ppm (J = 10 Hz) which are characteristic for AX systems. As the value of the difference of the CSs of these protons approaches the value of the SSCC; i.e., on passing from

the alcohol to its esters, they form an AB system and the SSCC between the protons becomes degenerate. The internal components of the doublets are superposed upon one another and their intensity increases considerably because of the weakening of the outer components. From the acid fraction of the hydrolyzate we isolated vanillic acid [1]. Its composition and spectral characteristics indicate that fexerinin is an isomer of juniferin.

An analysis of the spectra of fexerinin shows that the C_2-H proton in the PMR spectrum of (II) is observed in a weaker field than the C_5-H proton, and the vanillic acid residue in fexerinin is located at C_2. A comparison of the spectra of fexerinin (II) and juniferol (IV) showed that the hydroxy residue in fexerinin is located at C_5, and the vanilloyl residue at C_2. On the basis of the facts given, it may be concluded that fexerinin is 2-vanilloyl-juniferol (II).

The above-mentioned transformations are shown in the following scheme:



EXPERIMENTAL

The UV spectra were taken on an Hitachi EPS-3T instrument in ethanolic solutions, the IR spectra on a UR-20 spectrophotometer (tablets with KBr), the PMR spectra on a JNM-4H-100/100 MHz spectrometer with 0 — HMDS in $CDCl_3$, and the mass spectra on an MKh-1303 mass spectrometer fitted with a glass inlet for the introduction of the substance into the ion source.

Isolation and Separation of the Esters. Isolation of Fexeridin. The dried and comminuted roots (4.5 kg) were extracted with ethanol (3 × 12 liters). The extract was concentrated, diluted with water (1:2), and extracted five times with diethyl ether. After elimination of the solvent, 160.5 g of extract was obtained, and this was treated successively with 5% sodium carbonate solution and with 0.5% caustic potash solution. The latter extracts were acidified, and the phenolic compounds were extracted with ether. After elimination of the solvent, 75 g of total material was obtained, of which 30 g was deposited on a column (6.5 × 145 cm) of KSK silica gel and was eluted with hexane—ether (9:1) with a subsequent increase in the concentration of the latter. Fractions with a volume of 200 ml were collected.

Fractions 35-51, after elimination of the eluent, yielded 1.250 g of a mixture of two substances — juniferin and fexeridin. To separate these substances they were rechromatographed on a column of KSK silica gel with elution by hexane—ethyl acetate (4:1).

Fractions 11-14 yielded fexeridin (0.2 g), with the composition $C_{23}H_{34}O_6$, mp 141-143°C, $[\alpha]_D$ +40° (c 1.09; methanol). Yield 0.023% on the weight of the dry raw material. UV spectrum: λ_{max} 267 nm (log ε 4.04); 297 nm (log ε 3.80). IR spectrum, ν_{max}: 1520, 1600, 1620, 1705, 3200-3600 cm^{-1}.

Isolation of Fexerinin. Fractions 139-144 yielded 2.12 g of fexerinin contaminated with an oil. It was purified to give 0.8 g of fexerinin in the form of an amorphous powder with the composition $C_{23}H_{32}O_5$, $[\alpha]_D$ −64° (c 1.33, methanol). Yield 0.09% on the dry raw material. UV spectrum: λ_{max} 265 nm (log ε 3.99), 297 nm (log ε 3.71). IR spectrum: ν_{max} 1520, 1600, 1620, 1690, 3200-3600 cm^{-1}.

Hydrolysis of Fexeridin. A solution of 0.1 g of the substance in 10% aqueous methanolic caustic potash was left at room temperature for a day. Then the reaction mixture was diluted with water and extracted with ether. The ethereal extracts were washed with water and dried over anhydrous sodium sulfate, and the solvent was distilled off. This gave 0.06 g of substance. Purification was carried out chromatographically on a column with elution by hexane—ethyl acetate (9:1).

From fractions 20-28 (10 ml each) was obtained an alcohol with the composition $C_{15}H_{28}O_3$, mp 132-134°C, $[\alpha]_D$ −10° (c 0.43; methanol). The mother liquor was acidified with 5% sulfuric acid and treated with ether. Elimination of the solvent gave an acid with the composition $C_8H_8O_4$, mp 205-206°C, which was identified as vanillic acid. Yield 0.03 g.

Hydrolysis of Fexerinin. Substance (II) (0.2 g) was saponified with 10% aqueous methanolic caustic potash with heating in a water bath for 6 h. The hydrolysis products were isolated by the method described above. This gave juniferol (0.13 g) with mp 135-136°C and vanillic acid (0.06 g) with mp 205-206°C.

Acetylation of Fexerinin. Compound (II) (0.15 g) was acetylated with acetic anhydride in pyridine. This gave 0.2 g of acetylation product. For purification it was deposited on a column (25 × 0.5 cm) with KSK silica gel with elution by hexane—ether (4:1). The yield of acetate was 0.087 g. Composition $C_{19}H_{30}O_4$, $[\alpha]_D$ −75° (c 1.95; methanol).

SUMMARY

The new esters fexeridin and fexerinin have been isolated from the roots of *Ferula xeromorpha* Eug. Kor. On the basis of the products of chemical transformations and spectral characteristics, it has been established that fexerinin is an ester of juniferol with vanillic acid at C_2, and fexeridin is an ester of vanillic acid and 1,1,4,8-tetramethylcycloundec-3-ene-2,5,8-triol.

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