THE STRUCTURES OF TENUFERIN, TENUFERININ, AND TENUFERIDIN

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Continuing a study of the esters of the roots of Ferula tenuisecta Eug. Kor. collected in the Tashkent oblast (upper reaches of the R. Angren), we have isolated three esters of phenolcarboxylic acid (I-III) and a sesquiterpene alcohol. Substance (I) has the composition $C_{23}H_{32}O_6$ (M^+ 404); UV spectrum, λ_{max}: 263, 298 nm (log ε 4.07, 3.81). Substance (II) has the composition $C_{23}H_{32}O_6$ (M^+ 404); UV spectrum: λ_{max}: 263, 298 nm (log ε 4.02, 3.69). Substance (III) has the composition $C_{22}H_{30}O_5$ (M^+ 374); UV spectrum, λ_{max}: 263 nm (log ε 4.15).

The maxima observed in the UV spectra of (I-III), of which the long-wave maxima underwent bathochromic shifts when the spectra were taken with the addition of alkali, are due to the presence of 3,4-dihydroxy- and 4-monohydroxy-substituted benzoyl groups, respectively.

The IR spectra of (I-III) contain, in addition to the absorption bands of an aromatic nucleus (1520, 1580, 1620 cm^{-1}), maxima at 1690-1710 cm^{-1} due to the carbonyl of an ester group.

A comparison of the physicochemical constants and spectra (UV, IR, PMR) characteristics with those of known esters showed that all three substances are new and for them we propose the names tenuferin (I), tenuferinin (II), and tenuferidin (III).

When tenuferin, tenuferinin, and tenuferidin were hydrolyzed, the neutral fraction of the hydrolyzate yielded a sesquiterpene alcohol with the composition $C_{15}H_{26}O_3$ (IV), and the acid fraction in the case of (I) yielded isovanillic acid ($C_8H_8O_4$, mp 249-250°C) (V); (II) yielded vanillic acid ($C_8H_8O_4$, mp 205-206°C) (VI); and (III) yielded p-hydroxybenzoic acid ($C_7H_6O_3$, mp 210-212°C) (VIII). The phenolcarboxylic acids were identified by comparing their IR spectra and determining the melting points of mixtures with authentic samples, which we obtained by the hydrolysis of ferutin, ferutinin [1], and teferin [2].

Thus, (I-III) are esters of the acids mentioned and the same sesquiterpene alcohol (IV). The study of the structures of tenuferin, tenuferinin, and tenuferidin reduced to determining the structure of (IV) and establishing the position of the acyl residues in (I-III).

The IR spectrum of (IV) showed absorption bands at (cm^{-1}) 3200-3600 (hydroxy group) and 882, 1060, 1280 (oxide ring). [3].

The acetylation of (IV) with acetic anhydride in pyridine led to a monoacetate of (IV), (VIII), the IR spectrum of which included, together with the absorption band of an ester group (1250, 1735 cm^{-1}), the absorption band of a hydroxy group (3400-3600 cm^{-1}). In the PMR spectrum of (VIII) the signal of the proton attached to the carbon atom bearing the acetyl group had shifted downfield by 1.15 ppm as compared with the initial substance (IV) and a three-proton singlet of an acetyl group had appeared at 1.98 ppm. The presence in the PMR spectrum of (IV) of the signal of a hemihydroxylic proton and the detection in the IR spectrum of the acetate of (IV), (VIII), of the absorption band of a hydroxy group showed that of the three oxygen atoms in the molecule of the sesquiterpene alcohol, two are present in the form of hydroxy groups having secondary and tertiary natures, respectively.

The PMR spectrum of the diol (IV) shows, in addition to other signals, a triplet at 2.6 ppm (1 H, $J_1 = J_2 = 6.5$ Hz), which is probably due to a proton attached to an oxide ring. To confirm this hypothesis we treated tenuferidin with oxalic acid. A substance was obtained with the composition $C_{22}H_{32}O_6$ (IX), the PMR spectrum of which showed the disappearance of the signal of the epoxide proton – triplet at 2.85 ppm – and the appearance of the signal of a hemihydroxylic proton at 3.79 ppm (broadened signal, $1/2\Sigma = 9$ Hz). The acetylation of (IX) with acetic anhydride in pyridine led to the diacetate of (IX) with the composition $C_{26}H_{36}O_8$ (X). The PMR spec-

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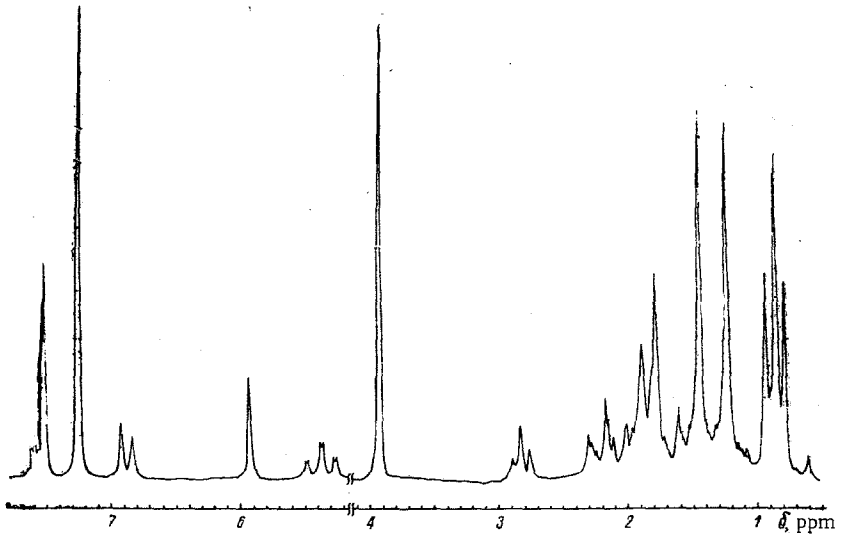
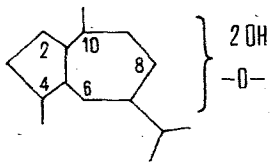


Fig. 1. PMR spectrum of tenuferin.

trum of the latter contained the signals of the protons of the two acetyl groups at 2.0 and 2.26 ppm and those of two hemiacyl protons (4.85 and 5.72 ppm).

With the composition $C_{15}H_{26}O_3$, the absence from the PMR spectrum of the signals of olefinic and vinylmethyl protons, and the presence of an epoxide ring, the diol (IV) probably has a bicyclic carbon skeleton. In actual fact, when the diol (VI) was dehydrogenated with selenium we obtained a blue oil the picrate of which melted at 110-112°C, which corresponds to the picrate of guaiazulene (XI) [4].

In the PMR spectrum of the diol, the protons of the methyl groups gave signals at 0.73 and 0.88 ppm (d, 3 H each, J = 5 Hz) and 1.08 and 1.33 ppm (s, 3 H each). In view of the formation of guiazulene (XI) on dehydrogenation and the multiplicity and chemical shifts of the signals of the methyl groups in the PMR spectrum of (IV), the following developed formula may be proposed for the latter:

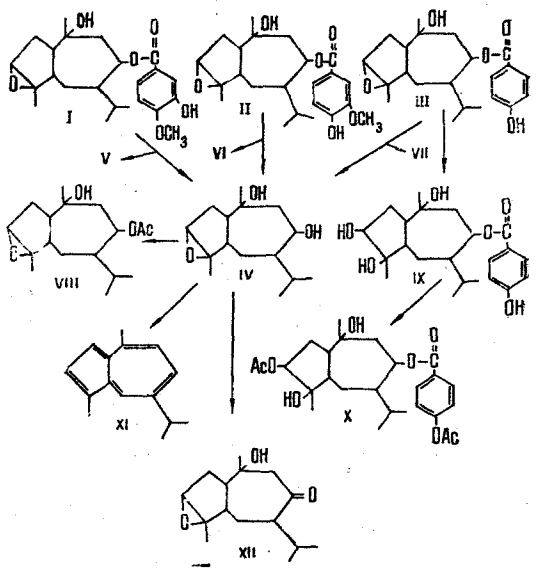


The positions of the functional groups were shown on the basis of the following facts.

In the PMR spectra of tenuferin, tenuferinin, and tenuferidin, the hemiacyl proton appears in the form of a sextet ($J_1 = J_2 = 10$ Hz, $J_3 = 2.5$ Hz). A similar splitting has been observed in the PMR spectra of ferutin, ferutinin [1], teferin [2], ferutidin [5], and teferidin [6]. This shows that in each of compounds (I-III) the hemiacyl proton forms a four-spin system, i.e., it interacts with three neighboring protons. Such a phenomenon can exist only when the secondary hydroxy group is present at C_2 or C_8. To choose between these positions, we oxidized (IV) with chromium trioxide; this gave a ketone $C_{15}H_{24}O_3$ (XII) the IR spectrum of which had an adsorption band at 1700 cm^{-1}, which is characteristic for a carbonyl group in a seven-membered ring [3]. Thus, the secondary hydroxy group is located at C_8.

The positions of the tertiary hydroxy group and of the epoxide ring follow from the positions and nature of the signals of the methyl groups and of the epoxide protons in the PMR spectra of (I-IV) and (XII). As mentioned above, in the PMR spectrum of (IV) the signals from the tertiary methyl groups are located at 1.08 and 1.33 ppm, which is characteristic for methyls on a carbon atom connected with an oxygen function [7]. Consequently, the tertiary hyroxy group is located at C_4 or C_{10} and the oxide ring at C_3-C_4 or C_9-C_{10}. Since in the PMR spectra of tenuferin (I), tenuferinin (II), tenuferidin (III), the diol (IV), and the ketone (XII), the epoxide proton appears in the form of a triplet, the tertiary hydroxy group is located at C_{10} and the oxide ring at C_3-C_4. On the basis of what has been said above the structure of 8,10-dihydroxy-3,4-epoxyguaiane (IV) is proposed for the diol. Consequently, tenuferin, tenuferinin, and tenuferidin have structures (I-III), respectively.

The transformations mentioned above can be represented in the following form:



EXPERIMENTAL

The UV spectra were taken on a Hitachi EPS-3T spectrophotometer (in ethanol), the IR spectra on a UR-10 instrument (tablets with KBr), the mass spectra on an MKh-1303 mass spectrometer, and the PMR spectra on a JNM-4H-100 MHz spectrometer in $CDCl_3$ solution. The R_f values were obtained on "Silufol-R" plates in the chloroform–ethyl acetate (4 : 1) system with a 1% solution of vanillin in concentrated sulfuric acid as the chromogenic agent.

Isolation of Tenuferin, Tenuferinin, and Tenuferidin. The combined esters from the finely cut roots of F. tenuisecta that remained after the isolation of ferutin, ferutinin, and teferin [1, 2, 4] (15 g) were transferred to a column (3 × 90 cm) of KSK silica gel and were eluted with chloroform, 50-ml fractions being collected. Fractions XX-XXVII were combined and the substance that they contained was crystallized from ether. This gave tenuferin, with the composition $C_{23}H_{32}O_6$, mp 176-178°C, $[\alpha]_D$ +134.6°C (c 0.49; methanol). Fractions XXIX-XXXIV yielded tenuferinin, $C_{23}H_{32}O_6$, mp 102-103°C, from ether $[\alpha]_D$ +106.8 (c, 0.6; methanol). When the column was eluted with chloroform–ethyl acetate (30 : 1) fractions XXXIX-XLVI yielded tenuferidin, with the composition $C_{22}H_{30}O_5$, mp 164-165°C (from ether), $[\alpha]_D$ +75.0° (c, 1.2; chloroform).

Saponification of Tenuferin, Tenuferinin, and Tenuferidin. A solution of 0.1 g of tenuferin in 30 ml of 5% aqueous methanolic caustic potash was heated on the water bath for 2 h. Then the reaction mixture was diluted with water and the neutral fraction was extracted with ether. The ethereal extract was washed with water and dried over sodium sulfate, and the solvent was distilled off. A substance with the composition $C_{15}H_{26}O_3$ (IV), mp 113-114°C, $[\alpha]_D$ +42.1° (c, 1.2; $CHCl_3$), R_f 0.19, was isolated. The aqueous methanolic solution after the isolation of the diol was acidified with 5% sulfuric acid and treated with ether. When the solvent was driven off, crystals deposited with the composition $C_8H_8O_4$, mp 249-250°C, identified as isovanillic acid.

When tenuferinin and tenuferidin were hydrolyzed, the neutral fractions of the hydrolyzate yielded (IV) and the acid fractions yielded vanillic acid ($C_8H_8O_4$, mp 205-206°C) (VI) and p-hydroxybenzoic acid ($C_7H_6O_3$, mp 210-212°C) (VII), respectively.

Acetylation of the Diol. A solution of 0.1 g of (IV) in 3 ml of pyridine was treated with 2 ml of acetic anhydride and the mixture was heated at 80°C for 4 h. The acetyl derivative was isolated by the usual method. $C_{17}H_{28}O_4$ (VIII), mp 127-128°C (from ether), R_f 0.28.

IR spectrum, ν_{max}, cm^{-1}: 1735, 3300-3600.

Opening of the Epoxide Ring of (III). A solution of 0.3 g of tenuferidin in 2 ml of ethanol was treated with 20 ml of a 1% aqueous solution of oxalic acid. The mixture was heated at 80°C for 2 h. Then it was diluted with water and was treated with ether. The ethereal extract was washed with 5% sodium carbonate solution and with water.

After elimination of the solvent, 0.285 g of a mixture of substances with R_f 0.1, 0.2, and 0.3 (chloroform–ethyl acetate (1:1) system) was obtained. The reaction product was deposited on a column (1 × 30 cm) of KSK silica gel and was eluted with chloroform–ethyl acetate (1:1), 15-ml fractions being collected. Fractions 22-29 yielded a substance with the composition $C_{22}H_{32}O_6$ (IX), R_f 0.1 (same system).

PMR spectrum: broadened singlet at 3.79 ppm.

Acetylation of Substance (IX). Substance (IX) (0.1 g) was acetylated with acetic anhydride in pyridine at 80°C. The acetyl derivative was isolated in the usual way. $C_{26}H_{36}O_8$ (X), R_f 0.22.

PMR spectrum: singlets at 2.0 and 2.26 ppm (3 H each).

Dehydrogenation of (IV). A mixture of 0.25 g of the diol and 0.3 g of selenium was heated at 180-220°C for 30 min. The hydrocarbon formed was passed through a column of alumina, with elution by hexane. After the solvent had been driven off, the picrate of a hydrocarbon with mp 110-112°C was obtained, which corresponds to the picrate of guaiazulene (XI).

Oxidation of (IV). A solution of 0.1 g of the diol in 15 ml of acetone was treated with a solution of 0.1 g of chromium trioxide in 80% aqueous acetone. The mixture was left overnight and was then diluted with water and treated with ether. The ethereal extract was washed with water and the solvent was distilled off. $C_{15}H_{24}O_3$ (XII) (M^+ 252).

IR spectrum, ν_{max}, cm^{-1}: 1700, 3200-3600.

Acetylation of Tenuferidin. Tenuferidin (0.1 g) was acetylated with acetic anhydride in pyridine. This gave (XIII) with the composition $C_{24}H_{32}O_6$, mp 188-190°C.

PMR spectrum: singlet at 2.2 ppm (CH_3COO-).

SUMMARY

Three new substances – tenuferin, tenuferinin, and tenuferidin – have been isolated from the roots of Ferula tenuisecta Eug. Kor. It has been shown that they are esters of an undescribed sesquiterpene alcohol – 8,10-dihydroxy-3,4-epoxyguaiane – and isovanillic, vanillic, and p-hydroxybenzoic acids, respectively.

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