STRUCTURES OF AKIFERIDIN AND AKIFERIDININ

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UDC 547.922:547.37

Continuing a study of the esters of the roots of *Ferula akitschkensis* B. Fedtsch. ex. K.-Pol., by the chromatographic separation of the phenolic fraction of a methanolic extract we have isolated two new substances with the compositions $C_{22}H_{30}O_5$ and $C_{27}H_{36}O_7$, which we have called akiferidin (I) and akiferidinin (II), respectively.

The UV spectra of (I) and (II) have maxima at 265 and 300 nm (log ε 3.9 and 3.6) which are characteristic for a 3,4-dihydroxy-substituted benzoyl group. The IR spectra of akiferidin and akiferidinin have the absorption bands of an aromatic nucleus (1530, 1610 cm^{-1}) and of ester (1240, 1690 cm^{-1}) and hydroxy (3200-3600 cm^{-1}) groups. The mass spectrum of (II) contains the peaks of ions with m/e 454 $(M-H_2O)^+$, 429 $(M-43)^+$, 372 $(M-100)^+$, 354 $(M-18-100)^+$, 329 $(M-43-100)^+$, 275 $(M-43-154)^+$, 218 $(M-100-154)^+$, 175 $(M-100-154-43)^+$, and 154 $(M-100-218)^+$.

The characteristics of the UV, IR, and mass spectra show that akiferidin and akiferidinin are esters of sesquiterpene alcohols with aromatic acids [1-3].

The PMR spectrum of (I) has the signals of a tertiary methyl group (s, 1.05 ppm, 3 H), secondary methyl groups (d, 0.73, 0.89 ppm, J = 7.5 Hz, 3 H each), of a vinyl methyl group (s, 1.76 ppm, 3 H), of a hemiacyl proton (sextet, 5.16 ppm, J^s = 10.5, 10.5, 2.5 Hz, 1 H) and of an olefinic proton (m, 5.42 ppm, 1 H). In the weak-field region there are the signals of the protons of a dihydroxybenzoic acid residue (d, 6.70 ppm, J = 9.5 Hz, 1 H; q, 7.28 ppm, J_1 = 9.5; J_2 = 2 Hz, 1 H; d, 7.40 ppm, J = 2 Hz, 1 H).

The results of a comparison of the PMR spectra of akiferidin and ferutin and of ferutinin [2], ferutidin [3], and akiferin [4], show that (I) is an ester of ferutinol and a dihydroxybenzoic acid. In fact, when (I) was hydrolyzed the neutral fraction yielded ferutinol (III) [2], and the acid fraction an aromatic hydroxy acid with the composition $C_7H_6O_4$ (IV), mp 194-195°C. Its physical and spectral characteristics corresponded to those of 3,4-dihydroxybenzoic acid [6]. To confirm this, we acylated akiferidin with acetic anhydride in pyridine and obtained its diacetate (V). The PMR spectrum of compound (V) showed a paramagnetic shift of the signals of the aromatic protons by about 0.5 ppm. These facts unambiguously show that the aromatic acid in (I) is 3.4-dihydroxybenzoic.

On the basis of the facts presented, for akiferidin we propose the structure of 6-O-(3',4'-dihydroxybenzoyl)ferutinol (I).

The PMR spectrum of akiferidinin shows signals from a tertiary methyl group (s, 1.17 ppm, 3 H), from secondary methyl groups (d, 0.74 and 0.87 ppm, J = 7.5 Hz, 3 H each), from a vinyl methyl group (s, 1.72 ppm, 3 H), from hemiacyl protons (q, 4.49 ppm, J_1 = 10.5, J_2 = 7.5 Hz, 1 H; sextet, 5.30 ppm, J^s = 10.5, 10.5, 2.5 Hz, 1 H) and from an olefinic proton (m, 5.50 ppm, 1 H). In addition, signals were recorded from the residues of angelic acid (s, 1.89 and 1.92 ppm, 3 H each; q, 6.07 ppm, J = 7.5 Hz, 1 H), and dihydroxybenzoic acid (d, 6.88 ppm, 1 H, J = 9.5 Hz; q, 7.46 ppm, J_1 = 9.5 Hz, J_2 = 2.5 Hz, 1 H; d, 7.66 ppm, J = 2.5 H, 1 H). A comparison of the PMR spectra of akiferidin and akichenin [1] showed that they differed only by the signals of the protons of the aromatic acid. When (II) was subjected to alkaline hydrolysis, the neutral fraction yielded akichenol, $C_{15}H_{26}O_3$, with mp 154-155°C (VI) [5], and an acid fraction gave 3,4-dihydroxybenzoic acid. Angelic acid was detected chromatographically in the hydrolysis products.

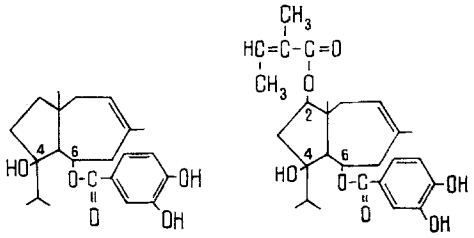
The chemical shifts and multiplicities of the hemiacyl protons in the spectra of akiferidin and akichenin [5] are the same and, therefore, in (II) the aliphatic and aromatic acids occupy the same positions as in akichenin. To confirm this, we have performed the

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 725-727, November-December, 1978. Original article submitted June 30, 1978.

0009-3130/78/1406-0617$07.50

mild hydrolysis of akiferidinin with a 1% solution of caustic potash in methanol. This gave a monoester — akichenol angelate (VII), which was identical with the monoester from akichenin [5].

In the PMR spectrum of (VII), the signals from the aromatic protons had disappeared and there was a diamagnetic shift of the sextet of the (C_6—H) signal by 1.32 ppm. Thus, akiferidin has the structure of 2-O-angeloyl-6-O-(3',4'-dihydroxybenzoyl)akichenol (II).



I

II

It must be mentioned that up to the present time esters of ferutinol and akichenol with benzoic, p-hydroxybenzoic, p-methoxybenzoic, vanillic (4-hydroxy-3-methoxybenzoic), isovanillic (3-hydroxy-4-methoxybenzoic), and veratric (3,4-dimethoxybenzoic) acids have been isolated from the genus *Ferula*. The detection of esters with 3,4-dihydroxybenzoic acid shows that these sbustances are intermediates in the biogenesis of *Ferula* esters.

EXPERIMENTAL

The UV spectra were taken on an EPS-3T spectrophotometer, the IR spectra on a UR-20 instrument (in KBr), the PMR spectra on a JNM-4H-100/100 MHz spectrometer in CCl_4 with the signal of HMDS taken as 0, and the mass spectra on an MKh-1303 spectrometer.

The purity of the substances was checked on "Silufol-R" plates in the chloroform—ethyl acetate (1:1) system. The chromogenic agent was a 1% solution of vanillin in concentrated sulfuric acid.

Isolation of Akiferidin and Akiferidinin. A 7-g sample of the phenolic fraction of the total esters remaining after the isolation of ferutin, ferutinin, akiferin, and akichenin [1] was deposited on a column of silica gel and was eluted with chloroform—ethyl acetate (7:3), 50-ml fractions being collected. Fractions 22 and 23 were combined and the solvent was distilled off. This gave akiferidinin with the composition $C_{27}H_{36}O_7$ (II), M^+ 472, mp 66-67°C (from petroleum ether—ethyl acetate), $[\alpha]_D$ +46°C (c 1.0; C_2H_5OH), R_f 0.5. Yield 0.5 g.

Fractions 45-65 yielded crystals of akiferidin, with the composition $C_{22}H_{30}O_5$ (I), mp 52-54°C (hexane—ethyl acetate), $[\alpha]_D$ +28.5° (c 1.4; $CHCl_3$) R_f 0.44. Yield 0.7 g.

Hydrolysis of Akiferidin. Compound (I) (0.15 g) was hydrolyzed in 5% aqueous caustic potash solution with heating for 2 h. The neutral fraction yielded ferutinol (III), $C_{15}H_{26}O_2$, mp 89-90°C [2]. The mother liquor was acidified and treated with ether (3 × 50 ml). After elimination of the solvent, crystals with the composition $C_7H_6O_4$ (IV) were obtained; mp 194-195°C (from diethyl ether—petroleum ether).

Acetylation of Akiferidin. Akiferidin (0.1 g) was acetylated with acetic anhydride in pyridine. The reaction product was isolated in the usual way: $C_{26}H_{34}O_7$ (V) with mp 90-91°C (from ether).

Hydrolysis of Akiferidinin. Compound (II) (0.1 g) was hydrolyzed as described above. The hydrolysis products yielded akichenol, $C_{15}H_{26}O_3$ (VI), mp 154-155°C (from ether), and 3,4-dihydroxybenzoic acid. The presence of angelic acid in the noncrystallizing part of the acid fraction was shown by paper chromatography.

Stepwise Hydrolysis of Akiferidinin. A solution of 0.5 g of the substance in 30 ml of a 1% solution of caustic potash in methanol was left at room temperature for 90 min. The reaction mixture was diluted with water and treated with ether. After elimination of the solvent the reaction product was purified on a column (0.8 × 16 cm) of silica gel with elution by hexane—ethyl acetate (5:1). Fractions 5-7 yielded a monoester with the composition $C_{20}H_{30}O_4$ (VII).

SUMMARY

The roots of *Ferula akitschkensis* have yielded two new esters — akiferidin and akiferidinin — for which the structures of 6-O-(3',4'-dihydroxybenzoyl)ferutinol and 2-O-angeloyl-6-O-(3',4'-dihydroxybenzoyl)akichenol, respectively, have been proposed.

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FEATURES OF THE MASS-SPECTROMETRIC FRAGMENTATION OF THE TEUCRINS H

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UDC 543.51+547.913

At the present time, about 16 diterpene lactones that are derivatives of clerodane and 18-norclerodane are known, these having been isolated mainly from species of *Teucrin* (family Labiatae) and being characterized by the presence of a C_{20}–C_{12}-γ-lactone group; a C_{17}-methyl group, and a furan ring at C_{12} formed by the C_{13}, C_{14}, C_{15}, and C_{16} atoms of the clerodane system [1-5]. These lactones also include the teucrins H1-H4 (I, II, III, and IV) which we have isolated from *Teucrium hyrcanicum* L. (Hyrcanian germander) [6, 7].

The lactones of this group have been little studied mass-spectrometrically. They all differ considerably in their degree of oxidation, which is responsible for the different variants of the localization of the positive charge in the molecular ions and, consequently, for the diversity of the pathways of mass-spectrometric fragmentation and for the complexity of the interpretation of the spectra.

However, a consideration of the few mass-spectrometric characteristics of the known lactones of this series given in the literature and, in particular, the analysis of the spectra of teucrins H1-H4 and the products of their transformation (V-VII) have enabled us to isolate for analytical purposes a number of common fragments and fragmentation pathways of the molecules under the action of electron impact (Schemes 1-3).

Certain authors have already reported the presence in the spectra of lactones of this group of strong peaks at m/e 95, 94, and 81 corresponding to the ions **q**, **r**, and **s** and due to the presence in the compounds studied of a β-substituted furan fragment [1-3]. The ions **q**, **r**, and **s** were also observed in the mass spectra of the teucrins and their derivatives that we studied, with relative intensities of from 12.5 to 100% and the elementary compositions C_6H_7O, C_6H_6O, and C_5H_5O (from the results of high-resolution spectroscopy).

The presence in teucrins H of a C_{20}–C_{12}-γ-lactone is obviously responsible for the ejection of β-vinylfuran from the molecular ions and the formation of the ion radical **a** $(M - 94)^+$. The formation of ion **a** is not characteristic for the diterpene furolactones marrubiin, columbin, and isocolumbin, which do not contain such a lactone system [8, 9].

The ejection of β-vinylfuran in the case of compounds (I), (IV), (V), and (VI) is also observed from the ions $M^+ - ROH$, which leads to the ions **b** $(M - ROH - 94)^+$, while for teucrin H3 (III) the elimination of β-vinylfuran takes place after the splitting out of formaldehyde and ketene, giving the ion **c** $(M - CH_2O - CH_2CO - 94)^+$.

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Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 727-736, November-December, 1978. Original article submitted May 3, 1978.

0009-3130/78/1406-0619$07.50