ESTERS OF Ferula karakalensis. STRUCTURE AND STEREOCHEMISTRY OF KARAFERIN AND KARAFERININ

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Two new guaiane esters – karaferin and karaferinin – have been isolated from Ferula karakalensis, and their structures and stereochemistry have been established. It has been shown that the Ferula sesquiterpene alcohols angrendiol, ugamdiol, and karaferol are biogenetically interconnected and are products of a single chain of the biogenesis of terpenoids in plants.

Ferula karakalensis Korov. belongs to the subgenus Merwia (Fedtsch.) Korov. [1], one of the least native in E. P. Korovin's system [2]. The species of the subgenus that have been studied – F. persica, F. mogoltawica, F. szowitsiana, F. litwinowiana, and others – contain furocoumarins and various terpenoid compounds (coumarins, lactones), but no esters of terpenoid alcohols with aromatic and aliphatic acids such as have been isolated previously from many species of Ferula, particularly those belonging to the subgenus Peucedanoides Korov. [3], have yet been found in species of the subgenus Merwia.

The materials given below show that F. karakalenis is the first species of the subgenus in which compounds of this type have been detected. At the same time, the results that we have obtained do not confirm the chemical characteristics of the species, which can be drawn up from the results of phytochemical investigations published previously. There are very few such publications. M. I. Goryaev [4] has shown that F. karakalensis contains 0.09-0.3% of essential oil. The presence in this species of umbelliferone and of the terpenoid farnesiferols A and C has been demonstrated [5].

Roots of F. karakalensis for chemical investigation were gathered in the classical site of the species – on the multicolored salt-bearing formations close to the village of Karakala (Western Kopet-Dagh, Turkmanistan).

The ethanolic extraction of the comminuted plant roots yielded the total extractive substances, which were separated into phenolic and nonphenolic fractions. By separating the phenolic fraction on a column of KSK silica gel we isolated five substances of ester nature: substance (I), composition $C_{23}H_{32}O_5$, mp 140-141°C, $[\alpha]_D$ −96.9° (c 1.0; chloroform); substance (II), $C_{22}H_{30}O_4$, mp 189-191°C, $[\alpha]_D$ −91.9° (c 1.0; chloroform); substance (III), $C_{24}H_{32}O_5$, mp 179-180°C, $[\alpha]_D$ −90.9° (c 1.0; chloroform); substance (IV), $C_{22}H_{30}O_5$, mp 126-127°, $[\alpha]_D$ −78.9° (c 1.0; chloroform); and substance (V), $C_{23}H_{32}O_6$, mp 184-185°C, $[\alpha]_D$ −70° (c 1.0; chloroform).

By comparing the physicochemical constants and spectral characteristics and a direct mixed-melting point test with authentic samples, substances (I)-(III) were identified as chimganidin, ferolin, and federin, respectively [6-11]. According to their physicochemical constants, substances (IV) and (V) differed from any compounds described in the literature and are new ones.

The UV spectrum of substance (IV), which we have called karaferin, had a maximum at 260 nm (log ε 4.12), which is characteristic for a p-hydroxy-substituted benzoyl residue. The IR spectrum of the compound showed absorption bands at (cm^{-1}) 3330-3370 (hydroxy groups); 1690 (ester carbonyl group); 1670 (double bond); 1610, 1590, and 1520 (aromatic nucleus); and 1290 and 1230 (ester bond).

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The PMR spectrum of karaferin was characterized by the following signals (ppm): doublets at 0.8 and 1.0 (3H each J = 7 Hz); singlets at 1.21 and 1.58 (3H each); broadened singlet at 3.72 (1H); a sextet at 5.29 (1H, J = 10, 10, and 4 Hz); and doublets at 6.74 and 7.80 (2H each, J = 9.5 Hz). Its spectral characteristics showed that karaferin is an ester of a sesquiterpene alcohol of the guaiane type with p-hydroxybenzoic acid.

When karaferin was subjected to alkaline hydrolysis, we isolated from the neutral fraction of the hydrolysate the sesquiterpene alcohol karaferol, with the composition $C_{15}H_{26}O_3$ (VI), mp 144-145°X, $[\alpha]_D$ −84.6° (c 1.0; chloroform), and from the acid fraction p-hydroxybenzoic acid, $C_7H_6O_3$ (VII), mp 212-214°C. The IR spectrum of karaferol showed absorption bands at (cm^{-1}) 1670 (double bond) and 3340-3480 (hydroxy groups), and its PMR spectrum the signals of protons at (ppm), 0.78 and 0.95 (d, 3H each, J = 7 Hz), 1.20 (s, 3H), 1.60 (s, 3H), 3.75 (br.s, 1 H), and 4.45 (sx, 1H, J = 10, 10, and 4 Hz), which are characteristic for guaiane compounds.

The positions and orientations of the substituting groups in karaferol followed from the PMR spectra of substances (IV) and (VI): of the three hydroxy groups in karaferol, two were secondary, while the third was tertiary and was located at C_4. The absence of a signal of an olefinic proton in the PMR spectra of karaferin and karaferol showed that the double bond was present at C_1—C_{10}. This was also confirmed by the presence of the signal of a vinylmethyl group at 1.58-1.60 ppm in the PMR spectra of each of these compounds.

The secondary hydroxy groups were located at C_6 and C_8 of the guaiane skeleton, and, judging from the SSCCs of the signals of the geminal protons, had pseudoequatorial orientations. The proton at C_8, forming a four-spin system, as in the PMR spectra of ferutinol [3], was observed in the form of a well-separated sextet with SSCCs of 10, 10, and 4 Hz. It followed from this that the proton at C_8 had the β-axial orientation.

The signal of the gem-hydroxylic proton at C_6 was observed in the form of a broadened singlet. The observed value of the SSCCs between C_5—H, C_6—H, and C_7—H (~1 Hz) is found only for the α-orientations of these protons in the karaferol molecule, as was confirmed by a study of the dihedral angles between the planes of the interacting protons.

On the basis of what has been said above, for karaferol we propose the structure and relative configuration of 4β,6β,8α-trihydroxyguai-1(10)-ene.

Judging from the value of the chemical shift of the C_8—H signal in the PMR spectrum, the p-hydroxybenzoic acid residue in karaferin is located at C_8 and has the structure of 8α-O-p-hydroxybenzoyl karaferol.

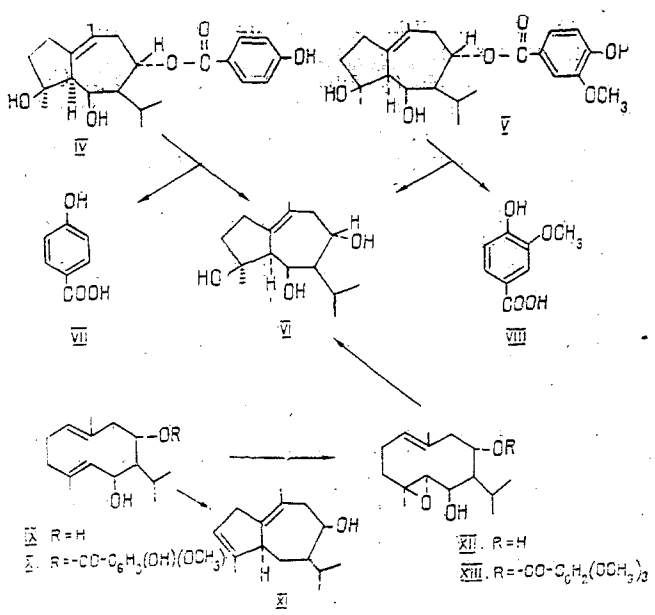
Esters of the guaiane type — microferin and microferinin — have been isolated previously from Ferula microcarpa, and their structures and stereochemistries have been shown by passage to them from the germacrane alcohol angrendiol (IX) [11]. A comparison of the proposed structures of microferol (XI) and karaferol (VI) shows that the latter is probably the product of a single chain of the biogenesis of terpenoids in plants of the genus Ferula. To confirm this hypothesis, we made the following chemical transformations.

Chimganidin (X) and ugaferin (XIII) are esters of germacrane sesquiterpene alcohols — angrendiol (IX) and ugamdiol (shiromodiol) (XII), respectively — with aromatic acids, the structures and stereochemistries of which have been shown on the basis of chemical and spectral characteristics [8, 12], while their absolute configurations have been established by x-ray structural analysis [9, 13].

To show the interrelationship of ugamdiol (XII) and angrendiol (IX), the latter was oxidized with perphthalic acid, which gave a substance with the composition $C_{15}H_{26}O_3$, mp 87-88°C, $[\alpha]_D$ +47° (c 1.0; chloroform), identical in its physicochemical constants and spectral characteristics with ugamdiol (shiromodiol).

Depending on the positions of the epoxy groups, the cyclization of epoxygermacrenes leads to the formation of eudesmane or guaiane derivatives: C_1—C_{10}-epoxygermacrenes are transformed into eudesmanes, and C_4—C_5 epoxygermacrenes into guaiane derivatives as the result of the cleavage of the epoxy ring with simultaneous trans-annular cyclization [14-16] (see scheme on following page).

The cyclization of ugamdiol — a C_4—C_5-epoxygermacrene derivative — with sulfuric acid in ethanol led to a guaiane sesquiterpene compound with the composition $C_{15}H_{26}O_3$, mp 144-145°C, identical in all respects with karaferol (VI).



Thus, we have carried out the transition between three sesquiterpene alcohols of Ferula – angrendiol, ugamdiol, and karaferol – and have shown that these substances are the products of a single chain of the biogenesis of terpenoids in plants of the Ferula genus.

Karaferinin (V) differed from karaferin only by the composition of the esterifying acid radical, which was a vanillic acid residue. Consequently, karaferinin has the structure and relative configuration of 4β,6β-dihydroxy-8α-vanilloyloxyguai-1(1))-ENE.

EXPERIMENTAL

Conditions for recording spectra have been described in [4].

Isolation and Separation of the Terpenoids. The comminuted roots of F. karakalensis (1 kg) were extracted three times with a five-fold amount of ethanol. The alcoholic extract was concentrated to 1 liter and was diluted with water in a ratio of 1:2, and the substances were extracted with ethyl acetate (3 × 1 liter). The ethyl acetate extract was treated successively with 5% sodium carbonate solution and 1% caustic potash solution. The alkaline extract was acidified with 10% sulfuric acid and the mixture was treated with ethyl acetate (3 × 1 liter). After the solvent had been distilled off, a total of 36 g of phenolic compound was obtained.

Of this material 20 g was deposited on a column (4 × 100 cm) of KSK silica gel (1:20), and the substances were eluted with hexane–ethyl acetate (initially 9:1, with increasing concentrations of ethyl acetate), 100-ml fractions being collected. Fractions IX-XIV yielded 0.7 g of federin, with the composition $C_{24}H_{32}O_5$, mp 179-180°C, $[\alpha]_D$ −90.9° (c 1; chloroform). Fractions XXI-XXX, after elimination of the eluent and crystallization from hexane–ether, yielded ferolin, $C_{22}H_{30}O_4$, mp 189-190°, $[\alpha]_D$ −91.9° (c 1.0; chloroform). Fractions XL-LI yielded chimganidin, $C_{23}H_{32}O_5$, mp 140-141°C, $[\alpha]_D$ −96.9° (c 1.0; chloroform).

Isolation of Karaferin and Karaferinin. Fractions LV-LXX were combined and rechromatographed on a column (1 × 40 cm) of KSK silica gel (1:10) with elution by hexane–ethyl acetate (4:1) and the collection of 50-ml fractions. Fractions IV-IX yield kraferin, $C_{22}H_{30}O_5$, mp 126-127°C, $[\alpha]_D$ −78.9°C (c 1.0; chloroform), and fractions XVI-XXV yielded karaferinin, $C_{23}H_{32}O_3$, mp 184-185°C, $[\alpha]_D$ −70° (c 1.0; chloroform).

Hydrolysis of Karaferin. A solution of 0.2 g of karaferin in 30 ml of 5% aqueous caustic potash was heated on the water bath for 4 h. After cooling, it was diluted with water and treated with diethyl ether. This led to the isolation of 0.13 g of karaferol, with the composition $C_{15}H_{26}O_3$, mp 144-145°C $[\alpha]_D$ −84.6° (c 1.0; chloroform). After its acidification with 10% sulfuric acid, extraction of the hydrolysate yielded p-hydroxybenzoic acid ($C_7H_6O_3$, mp 212-213°C.

Oxidation of Angrendiol. A solution of 0.15 g of angrendiol, obtained by the hydrolysis of ferolin, in 30 ml of diethyl ether was treated with an ethereal solution of perphthalic acid. The reaction mixture was left overnight, and on the following day it was treated

with a 3% solution of sodium carbonate and was then dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was passed through a column of alumina, and ugamdiol, $C_{15}H_{26}O_3$, was isolated with mp 87-88°C, $[\alpha]_D$ +47° (c 1.0; chloroform).

Cyclization of Ugamdiol to Karaferol. A solution of 0.5 g of ugamdiol in 20 ml of ethanol was treated with a 10% alcoholic solution of sulfuric acid, and the reaction mixture was left at room temperature for 30 min. Then it was diluted with water and treated with diethyl ether. The ethereal extract was washed with water, and the solvent was evaporated off. A substance with the composition $C_{15}H_{26}O_3$, mp 144-145°C, was isoalted and was found by IR spectroscopy and a mixed melting point to be identical with karaferol.

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