A CHEMICAL STUDY OF THE ROOTS OF Ferula kopetdagensis

A. A. Nabiev, T. Kh. Khasanov,
and V. M. Malikov

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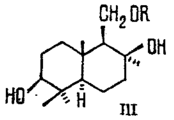
Continuing a systematic study of the terpenoid coumarins of the genus Ferula, from the roots of Ferula kopetdagensis Eug. Kor. [1] we have isolated two crystalline substances.

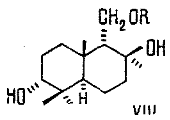
Substance (I) with the composition $C_{24}H_{32}O_5$, M^+ 400, mp 211-213°C, $[\alpha]^{22}_{D}$ +30° (c 1.0; ethanol) was identified by its IR and PMR spectrum and from the absence of a depression of the melting point with ferukrin [2, 3].

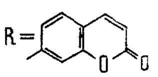
Substance (II) with the composition $C_{26}H_{34}O_6$, M^+ 442, mp 145-147°C, $[\alpha]^{22}_{D}$ +20°C (c 1.0; ethanol) is, according to its UV spectrum [λ_{max} 218, 242, 253, 325 nm (log ε 4.08, 3.52, 3.34, 4.11, respectively)] and umbelliferone derivative. The IR spectra contains absorption bands at 3550 cm^{-1} (OH group), 1732 and 1718 cm^{-1} (α-pyrone and ester C = O groups), and 1618, 1565, and 1417 cm^{-1} (aromatic nucleus).

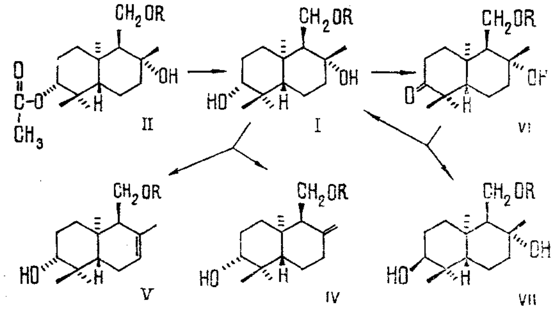
The PMR spectrum of the substance resembles that of ferukrin but differs from it by the presence of the signal of an acetyl residue at 2.00 ppm (s, 3 H) and by a paramagnetic shift of the signal of the hemihydroxylic proton (Δδ 1.25 ppm). Furthermore, a small shift in the signals of the methyl groups is shown. These facts give grounds for assuming that the coumarin investigated is natural ferukrin monoacetate. In actual fact, when the substance was saponified with caustic potash, a deacetate $C_{24}H_{32}O_5$ was obtained that was identical in its physicochemical constants, spectral characteristics, and behavior in a mixed melting point with ferukrin.

Since one and the same structure and configuration (III) has been proposed previously for ferukrin and nevskin [4] on the basis of the results of a study of PMR spectra with additions of paramagnetic shift reagents [Eu(DPM)$_3$, Eu(FOD)$_3$], it was necessary to make an additional chemical study of (I).


III


VIII





II
I
VI
V
IV
VII

The dehydration of ferukrin with sulfuric acid in acetone led to a mixture of two anhydro derivatives. By separation on a column of silica gel, substance (IV), $C_{24}H_{30}O_4$, mp 154-155°C and substance (V), $C_{24}H_{30}O_4$, mp 160-162°C were isolated.

A comparison of their IR and PMR spectra, and also a direct mixed melting point with an authentic sample showed that the anhydro derivative (IV) was identical with farnesiferol A [5-7].

The IR spectra of the anhydro derivative (V) showed absorption bands at 3530 cm^{-1} (OH group), 1707 cm^{-1} (α-pyrone C = O), and 1613, 1508, and 1470 cm^{-1} (aromatic nucleus).

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The PMR spectrum of (V), unlike that of (IV), contained no signals from the protons of an exocyclic methylene group. In place of them were the signals from a vinylmethyl group (at 1.71 ppm, s, 3 H) and from an olefinic proton (5.48 ppm, unresolved signal, $W_{1/2} = 10$ Hz). This shows that (V) is a double-bond isomer of farnesiferol A (IV).

Thus, the passage to farnesiferol A shows that ferukrin has the structure and configuration (I). The axial orientation of the tertiary hydroxy group in (I) was assigned on the basis of the production of the anhydro derivative (V) having an endocyclic double bond [8] with a high yield (64%). This is also confirmed by the results of a study of the PMR spectra of ferukrin and the presence of the paramagnetic shift reagent $Eu(DPM)_3$ [2].

When ferukrin was oxidized with chromium trioxide, a keto derivative (VI), $C_{24}H_{30}O_5$, mp 210-212°C, was obtained the subsequent reduction of which with sodium tetrahydroborate gave compound (VII), $C_{24}H_{32}O_5$, mp 134-136°C, identical according to its PMR spectrum with deacetylkellerin (VIII) [2, 3, 9]. The monoacetate of (VII) was identical with kellerin.

On the basis of the facts given above, it may be concluded that ferukrin and deacetylkellerin are epimeric compounds at C_6'.

EXPERIMENTAL

The UV spectra were taken on a Hitachi spectrophotometer (in ethanol), the IR spectra on a UR-20 instrument (tablets with KBr), the mass spectra on a MKh-1303 instrument, and the PMR spectra on a JNM-4H-100/100 MHz spectrometer in $CDCl_3$ solution with 0 – HMDS.

The purity of the substances and the course of the reactions were checked by the TLC method on Silufol (ethyl acetate–chloroform (2 : 1) system).

Isolation of the Coumarins. The comminuted air-dry roots of *Ferula kopetdagensis* (6 kg) were extracted three times with ethanol (40, 35, and 30 liters). The extract was evaporated to three liters, dilutes with water (1 : 2), and extracted with ether (5 × 800 ml). The ethereal extract was treated with 5% sodium carbonate solution, washed with water, and dried, and the solvent was distilled off. This gave 310 g of total coumarins. Of this total, 135 g was mixed with an equal amount of silica gel and placed on a column of the same adsorbent (5.5 × 150 cm; 1250 g), and was eluted with hexane–ethyl acetate with increasing concentrations of the latter: fractions 1-28 (3 : 1), 29-43 (2 : 1), 44-51 (1 : 1).

Ferukrin Acetate (II). When fractions 18-26 of the eluate were concentrated, 0.66 g (0.025% of the dry plant) of a substance $C_{26}H_{34}O_6$, M^+ 442, mp 145-147°C (hexane–ethyl acetate), $[\alpha]_D^{22}$ +20° (c 1.0; ethanol), R_f 0.64, was isolated.

PMR spectrum:

0.86, s, 6H; 1.26, s, 3H $(CH_3-\overset{|}{\underset{|}{C}}-)$; 1.33, s, 3H $(C\underline{H}_3-\overset{|}{\underset{|}{C}}-OH)$; 2.00, s, 3H (CH_3COO); 4.05, m, 2H $(R-O-C\underline{H}_2-\overset{|}{\underset{|}{C}}H)$; 4.36, m, 1H, $W_{\frac{1}{2}} = 16$ Hz $(\underline{H}-C-OCOCH_3)$; 6.17, d, 1H, $J_{3,4} = 9.5$ Hz (H_3); 7.60, d, 1H, $J_{4,3} = 9.5$ Hz (H_4); 6.71 m, 2H (H_6 and H_8); 7.33, d, 1H, $J_{5,6} = 9.0$ Hz (H_5).

Ferukrin (I). Fractions 40–48 yielded 0.68 g (0.026%) of a crystalline compound $C_{24}H_{32}O_5$, M^+ 400, mp 211-213°C (ethyl acetate–diethyl ether), $[\alpha]_D^{22}$ +30° (c 1.0; ethanol), R_f 0.39.

Saponification of Ferukrin Acetate (II). A solution of 0.1 g of (I) in 15 ml of 5% aqueous ethanolic caustic potash was boiled in the water bath for 2 h. From the hydrolysis product a substance was obtained with mp 211-213°C which was identified by a mixed melting point as ferukrin. Acetic acid was identified from its PMR spectrum and its R_f value of 0.13 in butanol saturated with 1.5 N ammonia.

Dehydration of Ferukrin (I). A solution of 0.28 g of (I) in 25 ml of acetone containing 1 ml of sulfuric acid was heated for 20 min and was then cooled and treated with ether. The ethereal extract was washed with water and dried with sodium sulfate, and the solvent was distilled off. The oily residue (0.25 g) was chromatographed on a column of silica gel (1 × 70 cm), being eluted with chloroform.

Fractions 4–13 deposited 0.16 g (64%) of crystals of a substance $C_{24}H_{30}O_4$, M^+ 382, mp 160-162°C (hexane–ethyl acetate), R_f 0.70 (V).

PMR spectrum:

0.83, 0.92, 0.97, singlets, 3 H each $(CH_3-\overset{|}{\underset{|}{C}}-)$; 1.71, s, 3H $(CH_3-C=C)$; 3.16, m, 1H $(\underline{H}-\overset{|}{\underset{|}{C}}-OH)$; 3.89, m, 2H $(R-OC\underline{H}_2-\overset{|}{C}H-)$; 5,48, v.s., 1H, $W_{\frac{1}{2}} = 10$ Hz $(H-C=C)$; 6,17, d, 1H, $J_{3,4}=9.5$ Hz (H_3); 7,56, d., 1H, $J_{4,3}=9,5$ Hz (H_4); 6,75, m, 2H (H_6 and H_8); 7,32, d 1H, $J_{5,6}=9,0$ Hz (H_5).

The last fractions, fractions 18-26, yielded 0.033 g (13.2%) of a crystalline substance $C_{24}H_{30}O_4$, M^+ 382, mp 154-155°C (hexane–ethyl acetate), R_f 0.65.

From a comparison of IR and PMR spectra and also from the results of a mixed melting point, the substance was identified as farnesiferol A.

Oxidation of Ferukrin. A solution of 0.3 g of chromium trioxide in 3 ml of water was added dropwise to a solution of 0.3 g of (I) in 30 ml of acetone. After 20 min, the mixture was diluted with water and treated with ether. The ethereal solution was washed with water and dried with sodium sulfate, and the solvent was distilled off. The ketone derivative of ferukrin (VI), $C_{24}H_{30}O_5$, M^+ 398, mp 210-212°C (diethyl ether), R_f 0.44, was isolated.

Reduction of (VI) with Sodium Tetrahydroborate. A solution of 0.25 g of (VI) in 30 ml of 85% aqueous methanol was treated with 0.35 g of sodium tetrahydroborate. After 45 min, the mixture was acidified with a 5% solution of sulfuric acid and was extracted with ether. The ethereal solution was washed with water and dried, and the solvent was distilled off. The residue was chromatographed on a column (1 × 60 cm) of silica gel and was eluted with chloroform.

Fractions 6-13 deposited crystals of a substance with the composition $C_{24}H_{32}O_5$, M^+ 400, mp 134-136°C, $[\alpha]_D^{22}$ +52°C (c 0.1; ethanol); R_f 0.52, which was identical, according to its PMR spectrum, with deacetylkellerin (VII).

The last fractions, fractions 17-26, deposited crystals of ferukrin with mp 211-213°C, R_f 0.39.

Acetylation of (VII). A solution of 0.04 g of (VII) in 2 ml of anhydrous pyridine was treated with 2 ml of acetic anhydride, and the reaction mixture was left for a day. After the usual working up, a compound $C_{26}H_{34}O_6$, M^+ 442, mp 75-77°C, R_f 0.62, was obtained, the PMR spectrum of which was identical with that of kellerin.

SUMMARY

Ferukrin and the new natural compound acetylferukrin $C_{26}H_{34}O_6$ have been isolated from the roots of *Ferula kopetdagensis*.

The absolute configuration of ferukrin has been established on the basis of the results of a study of chemical and spectral characteristics and also by means of a passage to farnesiferol A.

It has been shown that it is an epimer of deacetylkellerin at $C_{6'}$.

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