FELIGOSIDE and FELOSIDE — NEW PHENOL GLYCOSIDES FROM *Ferula kopetdaghensis*

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Continuing a study of *Ferula kopetdaghensis*, from the water-soluble fraction of the methanolic extract we have isolated by chromatography, in addition to kopeoside [1], another two glycosides, which we have called feligoside and feloside.

Feligoside (I), $C_{28}H_{40}O_{11}$. Its UV spectrum has a maximum at 265 nm (log ε 4.3) which shows the presence of a benzene nucleus in the molecule, and its IR spectrum shows absorption bands at 3150-3600 cm^{-1} (hydroxy groups) and 1590, 1515, and 1475 cm^{-1} (aromatic nucleus).

Substance (I) contains a free phenolic group and is a glycoside. The alkaline fusion of (I) formed pyrogallol, and on acid hydrolysis it was split into D-glucose and the aglycone (III). The yield of aglycone on hydrolysis was 65.3% and, consequently, the initial substance is a monoside. The aglycone of the glycoside gave a strong Mäule reaction [2] showing a syringyl structure. It follows from this that the aromatic nucleus of the substance contains three oxygen atoms in adjacent positions.

The NMR spectrum of the aglycone (Fig. 1) shows the signals of three aromatic protons in the form of singlets at 6.47 ppm (1 H) and 6.22 ppm (2 H), of four methoxy groups present in an aromatic nucleus — singlets at 3.80, 3.71, and 3.41, and 3.41 ppm (1:2:1), and of two phenolic hydroxyls — broadened signals at 5.40 and 5.32 ppm (1 H each), disappearing on deuterium-exchange. The presence of hydroxy groups was also confirmed by the preparation of diacetate the NMR spectrum of which showed a singlet at 2.17 ppm (6 H), while in the IR spectrum the absorption bands of hydroxyl had disappeared and bands of the carbonyl of a phenol ester had arisen. The composition of the aglycone, the nature of its UV spectrum, the nine substituents in aromatic nuclei, and the formation of pyrogallol on alkaline fusion — all these facts permit the conclusion that the aglycone has two noncondensed and nonconjugated benzene nuclei connected with six aliphatic carbon atoms.

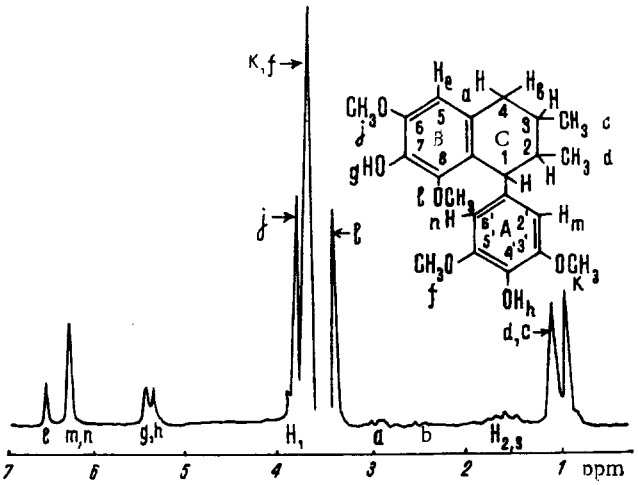

Fig. 1. NMR spectraum of the aglycone of feligoside ($CDCl_3$).

With the composition $C_{22}H_{28}O_6$ and the presence of two aromatic benzene rings with the substituents mentioned, the aliphatic part of the aglycone molecule must have a cyclic structure and, most probably, a syringocyclolignane structure.

On comparing the UV and NMR spectra of the aglycone of feligoside and the spectra of the known syringolignanes lyoniresinol [3], tomasic acid [4], and others, it can be observed that they are very similar. Consequently, these substances have identical structures of the six-membered ring. A

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doublet at 3.8 ppm, J = 6 Hz, (1 H) in the NMR spectrum is due to the H-1 benzyl proton, while the H-4A and H-4B benzyl protons form two quartets at 2.87 and 2.35 ppm, J_1 = 12.5 Hz, J_2 = 7 Hz.

A multiplet in the 1.3-1.7-ppm region (2 H) corresponds to the H-2 and H-3 methine protons, and singlets at 6.47 ppm and 6.22 ppm (2 H) to the H-5 and the H-2' and H-6' protons, respectively. In the strong-field region there is a six-proton doublet at 0.92 ppm, J = 7 Hz, corresponding to two secondary methyl groups.

On the basis of the facts given, for the aglycone of feligoside we suggest the structure shown in Fig. 1, which is confirmed by the identity of the NMR and mass spectra of the diacetate of the aglycone of feligoside with literature information for a substance of this structure obtained by synthesis [5].

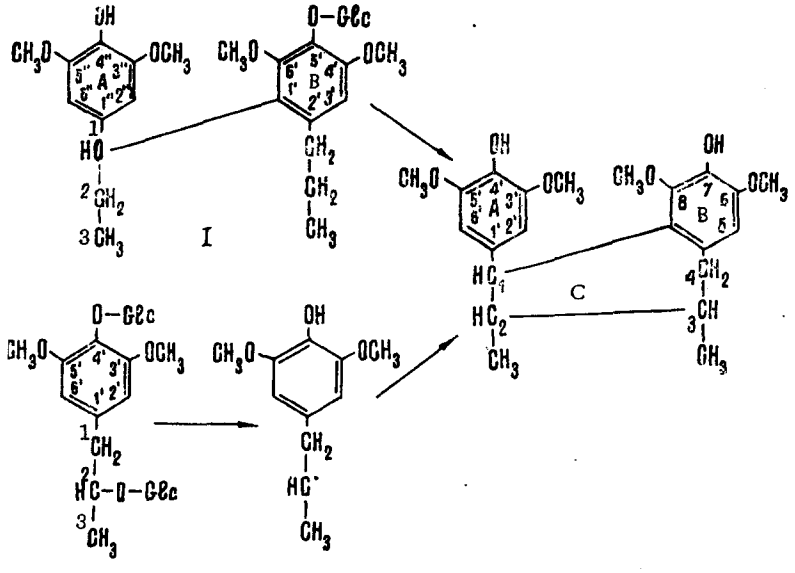
In the mass spectrum of the aglycone, in addition to the peak of the molecular ion with M^+ 388 there are peaks with m/e 234 after the elimination of ring A [5-6], with m/e 154 (fragment of ring A), with m/e 359 ($M - C_2H_5$), with m/e 205, 194, and others.

The NMR spectrum of feligoside does not differ from that of the aglycone only by the signals of the protons of the sugar residue. Thus, while in the aglycone the methyl groups are present on tertiary carbon atoms and give a six-proton doublet at 0.92 ppm, J = 7 Hz, in the glycoside they are represented by a corresponding triplet at 0.65 ppm, J = 7.5 Hz, which shows their position on a secondary carbon atom. Consequently, in the acid hydrolysis of the glycoside, together with the splitting off of the sugar the propyl chain is oxidized and a C–C bond arises between the β-carbon atoms, as a result of which the six-membered ring of a syringocyclolignane is formed, by analogy with what has been described in the literature [6].

In the NMR spectrum of feligoside there are also the signals of the protons of one molecule of glucose in the 3.1-3.9-ppm region and a doublet at 4.45 ppm, J = 7.5 Hz, belonging to the β-anomeric proton. The presence in the IR spectrum of the glycoside of absorption bands at 1085-1057 and 1035 cm^{-1} shows that the D-glucose is present in the pyranose form.

In order to establish the position of the glucose in the glycoside, we have performed its exhaustive methylation. The methylation product was subjected to acid hydrolysis. This gave an amorphous product consisting of the methylated aglycone with a free hydroxy group at the position of attachment of the glucose. In its mass spectrum, a peak with m/e 234 corresponding to the fragment formed in the elimination of ring A was retained, while the peak with m/e 154 (fragment of ring A) had increased by 14 mass units. These results show that in the glycoside the hydroxy group in ring A is free and the one in ring B is glycosidated.

On the basis of the facts given above, we propose as the most probable structure for feligoside 1-(4',6'-dimethoxy-5'-β-D-glucopyranosyloxy-2'-propylphenyl)-1-(3",5"-dimethoxy-4"-hydroxy-phenyl)propane.



Feloside (II), $C_{23}H_{36}O_{14}$. Its UV spectrum has absorption at 265 nm (log ε 4.05) in its IR spectrum there are bands at 3200-3600 cm^{-1} (hydroxy groups), 1590, 1510, and 1475 cm^{-1} (aromatic nucleus). The alkaline fusion of (II) again formed pyrogallol, and acid hydrolysis formed an aglycone with the composition $C_{22}H_{28}O_6$ with a yield of 32% and D-glucose. The yield of aglycone and the formation of an octaacetate on acetylation show that feloside contains two moles of glucose. From its melting point and IR and NMR spectra, the aglycone was identical with the aglycone obtained in the hydrolysis of feligoside. At the same time, in the mass spectrum of felosides the peak of the ion corresponding to the aglycone has 194, and not 388, mass units. This shows that in the hydrolysis of feloside the aglycone undergoes dimerization.

The NMR spectrum of feloside shows the signals of two aromatic protons — singlet at 6.55 ppm (2 H) — and of two methoxy groups on an aromatic nucleus — singlet at 3.65 ppm (6 H) — and also a doublet at 1.60 ppm, J = 5.5 Hz (3 H), due to the protons of a secondary methyl. A multiplet in the 3.20-4.15 ppm region (15 H) corresponds to the protons of two D-glucose residues and to the protons in Ar—CH_2— and —CH_2—OGlc groupings.

Doublets at 4.40 ppm, J = 0.5 Hz, and at 4.65 ppm, J = 7.5 Hz, are due to the β-anomeric protons of two glucose residues.

Thus, while the hydrolysis of feloside also forms a lignan aglycone identical with that for feligoside, this is actually an artefact, since, according to the elementary analysis of the glycoside it has the composition $C_{11}H_{16}O_4$ and, according to its spectral characteristics, contains one benzene ring.

On the basis of these facts and NMR spectroscopy, structure (II) is the most probable for feloside.

In spite of numerous attempts, we have been unable to obtain the monomeric aglycone on hydrolysis: in all cases this reaction was accompanied by the dimerization of the aglycone formed. A similar phenomenon, namely the formation of a lignan from coniferyl alcohol under the influence of acids, has been described in the literature [6]. Apparently, the hydrolysis of feloside takes place in the manner illustrated above. This is shown by the change in the UV spectrum on passing from the glycoside to the aglycone from λ_{max} 265 to 283 nm [3, 4].

To determine the positions of the sugar residues, the substance was acetylated with acetic anhydride in pyridine. This gave the octaacetate of feloside with mp 166-167°C, the NMR spectrum of which contained the signals of eight acetyl groups. On acid hydrolysis of the octaacetate, the aglycone with mp 149-150°C deposited, identical from its NMR spectrum with the aglycone of feligoside, from which it follows that feloside is a diglycoside at the phenolic and at the secondary hydroxyls. The absorption bands in the IR spectrum at 1085, 1060, and 1030 cm^{-1} give grounds for considering that both D-glucose residues are present in the pyranose form.

On the basis of what has been said above, for feloside we propose the structure of (3', 5'-dimethoxy-4'-β-D-glucopyranosyloxy-phenyl)-2-β-D-glucopyranosyloxypropane.

We are the first to have found lignane and syringyl glycosides in plants of the genus Ferula.

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrometer (KBr), the NMR spectra on a Jeol instrument at 60 MHz and on a JNM-100/100-4H instrument at 100 MHz (in deuteropyridine, trifluoroacetic acid, and deuterochloroform), the chemical shifts being given on the δ scale from the signal of HMDS taken as 0, and the mass spectra on an MKh-1303 instrument. The purity of the substances was checked by thin-layer chromatography on KSK silica gel [chloroform—ethyl acetate—methanol (15:7:3) system]. The chromatograms were revealed with a 1% solution of vanillin in concentrated sulfuric acid.

Isolation of Feligoside and Feloside. The aqueous methanolic fraction obtained in the treatment of 4.5 kg of the roots of *Ferula kopetdaghensis* after the extraction of coumarins [1] was evaporated to dryness. The dry residue was transferred to a chromatographic column (70 × 6 cm) filled with KSK silica gel (particle size 0.2 mm). On elution with chloroform, fractions 1-10 yielded umbelliferone, and on subsequent elution with propanol—chloroform (1:3), fractions 10-13 yielded 2 g (0.16%) of feligoside with mp 204-205°C, $[\alpha]_D^{20}$ —37.5° (*c* 0.5;

methanol); R_f 0.2; colorless cyrstalline substance readily soluble in hot water and in ethanol, and insoluble in ether and benzene. The substance was colored blue by ferric chloride and cherry-red by the Molisch reagent. On concentration, fractions 14-15 yielded kopeoside, and on elution with chloroform–ethanol (3:1) fraction 23-24 yielded 3.6 g (0.27%) of feloside, mp 224-225°C, R_f 0.05, $[\alpha]_D^{20} - 27.7°$ (*c* 0.99 ; water), M^+ 194, readily soluble in water, sparingly soluble in ethanol, and insoluble in ether and in chloroform.

Preparation of the Aglycone. In each case, 0.150 g of the glycoside was dissolved in 50 ml of a 0.25% solution of sulfuric acid and the solution was heated on the water bath at 70°C for 6 h. Crystals deposited with mp 149-150°C (from aqueous methanol (1:1), $[\alpha]_D^{20} -$ 13.8° (*c* 0.7; chloroform), M^+ 388, R_f 0.79. The yield of feloside was 0.098 g (65.3%), and that of feloside 0.048 g (32%).

Identification of D-glucose. The hydrolyzate after the separation of the aglycone were passed through a column (40 × 2 cm) filled with AN-2FN anion exchange resin (OH^- form). The filtrate was concentrated to small volume and chromatographed on paper in the butan-1-ol–pyridine–water (6:3:1) system. On treatment with o-toluidine, D-glucose was detected.

Preparation of the Diacetate of the Aglycone. A mixture of 0.075 g of the aglycone, 5 ml of acetic anhydride, and 2 g of fused sodium acetate was heated at 70°C for 1 h. The reaction mixture was diluted with water and treated with ether. The ethereal extract was evaporated. A colorless crystalline substance separated out with mp 146-147°C.

Feloside acetate was obtained by heating the substance with acetic anhydride in pyridine for 1 h. The solvent was driven off in vacuum and the residue was crystallized from ether. This gave a colorless crystalline substance with mp 166-167°C, R_f 0.90.

The alkaline fusions were performed by the usual methods.

SUMMARY

Two new phenol glycosides have been isolated from the roots of *Ferula kopetdaghensis*: feligoside (I) and feloside (II). On the basis of physicochemical and spectral characteristics and also of chemical transformations, the structure of 1-(4',6'-dimethoxy-5'-O-β-D-glucopyranosyloxy-2'-propylphenyl)-1-(3",5"-dimethoxy-4"-hydroxyphenyl)propane is proposed for (I) and 1-(3',5'-dimethoxy-4'-β-D-glucopyranosyloxyphenyl)-2-β-D-glucopyranosyloxypropane for (II).

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