STRUCTURE OF FEGOLIDE

M. R. Nurmukhamedova, Sh. Z. Kasymov,
N. D. Abdullaev, and G. P. Sidyakin

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A chloroform extract of the seeds of Ferula penninervis Rgl et Schmahl has yielded a new sesquiterpene lactone of the guaiane type – fegolide: $C_{20}H_{28}O_5$, mp 165-166°C $[\alpha]_D$ −150°C (c 0.17; chloroform).

We have previously shown the presence in the seeds of Ferula penninervis Rgl et Schmahl of sesquiterpene lactones and a coumarin [1, 2]. In a further study of a chloroform extract of the seeds of this plant we have isolated a new sesquiterpene lactone and have called it fegolide.

Fegolide has the composition $C_{20}H_{28}O_5$, M^+ 348. Its IR spectrum shows absorption bands of a hydroxy group (3510 cm^{-1}), of the carbonyl of a γ-lactone ring (1765 cm^{-1}), of an α,β-conjugated ester group (1720 cm^{-1}), and of double bonds (1655 cm^{-1}). The mass spectrum of fegolide contains, in addition to the molecular ion, peaks with m/z 330 $[M - H_2O]^+$, 265 $[M - 83]^+$, 248 $[M - 100]^+$, and 230 $[M - 18 - 100]^+$. These facts, and also the presence in the PMR spectrum of a broadened singlet of an olefinic proton at 5.62 ppm and of two signals of vinylmethyl groups at 2.12 and 1.87 ppm, show that the fegolide molecule includes a senecioic acid residue. This was confirmed by the results of the alkaline hydrolysis of (I), when senecioic acid was isolated as one of the reduction products.

In the PMR spectrum of (I) at 1.83, 1.42, and 1.18 ppm there are the signals of another three methyl groups belonging to main skeleton of the lactone. The singlet of the first is appreciably broadened, due to the allyl interaction of one of the methyls located on a double bond with an olefinic proton resonating at 5.43 ppm, likewise in the form of a broadened singlet. These facts show the presence in the fegolide molecule of a CH_3–C=CH grouping formed at C-3 and C-4, which permits (I) to be assigned to the sesquiterpene lactones of the guaiane type. The attachment of the lactone ring to C-6 and C-7 unambiguously follows from the multiplicity of the signal of the lactone protone (5.33 ppm, Σ^3J = 20 Hz).

The IR spectrum and the elementary composition of the substance indicated the presence in the molecule of the lactone (I) under investigation of a tertiary hydroxy group which could be located at C-10 ror C-11. It follows from an analysis of the characteristics of the NMR spectra of compounds related to fegolide that when the hydroxy group is present at C-10 the protons of the geminally arranged methyl (CH_3-14) resonate in the interval of 1.15-1.25 ppm, and when it is acetylated the signal under consideration undergoes a paramagnetic shift by 0.3-0.4 ppm. When the HO–C–CH_3 grouping is formed at C-11, the CH_3-13 protons resonate in the interval of 1.3-1.4 ppm and the size of the paramagnetic shift of this signal when the HO group is replaced by an ester group is only ~0.1-0.2 ppm [3-7]. On the basis of these facts it was possible to conclude that the above-mentioned signals at 1.18 and 1.42 ppm belonged to CH_3-14 and CH_3-13 methyl groups and therefore the hydroxy group and the senecioic acid residue were present at C-10 and C-11 of the fegolide molecule. This conclusion obtained independent confirmation in the following way. When fegolide was dehydrated a noncrystalline product $C_{20}H_{26}O_4$, M^+ 330, was isolated the IR spectrum of which lacked the band of a hydroxy group, while the bands of carbonyl groups and 1720 and 1780 cm^{-1} were retained.

The UV spectrum of the product of the dehydration of (I) was practically identical with that of fegolide, λ_{max} 218 nm (log ε 4.08). Consequently, the double bond formed on dehydration was not conjugated either with the carbonyl of the lactone function or with the initial double bond of fegolide at C-3–C-4 [3].

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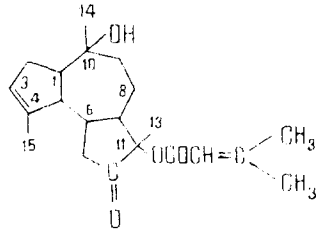
Thus, fegolide has the structure of 10-hydroxy-11-senecioyloxyguai-3-en-6,12-olide.



EXPERIMENTAL

UV spectra were recorded on a Hitachi spectrophotometer (in ethanol) IR spectra on a UR-20 instrument (tablets with KBr and films) and mass spectra on an MKh-1303 spectrometer. PMR spectra were obtained on a JNM-4H-100 spectrometer in $CDCl_3$ (δ, ppm, 0 – TMS). For TLC monitoring, Silufol plates were used in the hexane–ethyl acetate (3:1) system, the spots being revealed with a 1% solution of vanillin in concentrated H_2SO_4.

Isolation of Fegolide. The dried seeds (10 kg) collected in 1982, in the Kamchik pass at the stage of milky ripeness were extracted five times with chloroform (40 liters) by the room-temperature steeping method. The concentrated extract was dissolved in ethanol (3.2 liters) and the solution was diluted with an equal amount of water. The aqeuous ethanolic extracts, after the separation of the precipitate, were shaken with chloroform. The concentration chloroform extract (1.5 kg) was deposited on a column of silica gel. To free the substances from essential oils, the column was first eluted with petroleum ether, then with hexane–ethyl acetate (9:1), and then with solvents containing gradually increasing amounts of the latter. At a hexane–ethyl acetate ratio of 5:1, 100 mg of fegolide was isolated.

Fegolide (I), $C_{20}H_{28}O_5$, M^+ 348, mp 165-166°C, $[\alpha]_D$ –150° (c 0.17; chloroform).

UV spectrum: λ_{max} 218 nm (log ε 4.08).

IR spectrum: ν_{max}^{KBr} (cm^{-1}) 3510, 1765, 1720, 1655, 1150.

Mass spectrum: m/z, 348, 330, 265, 248, 230.

Alkaline Hydrolysis of Fegolide. A solution of 40 mg of the substance in ethanol was treated with 1.4 ml of a 4% aqueous solution of KOH and the reaction mixture was left at room temperature for 48 h. Then it was extracted with ether, after which it was acidified and was re-extracted with chloroform. The senecioic acid formed as the result of the reaction was identified by a mixed melting point with an authentic sample.

Dehydration of Fegolide. The reaction was performed at 0°C. A solution of 60 mg of fegolide in pyridine was treated with 2-3 ml of thionyl chloride. The reaction mixture was left at room temperature for 10 min and was then poured onto finely crushed ice and was extracted several times with diethyl ether. The ethereal extracts were washed once with 5% aqueous sulfuric acid and then with sodium bicarbonate. The residue was concentrated and chromatographed on silica gel with elution by hexane–ethyl acetate (3:1).

UV spectrum of the dehydration product: λ_{max} 218 nm (log ε 4.08).

IR spectrum: ν_{max}^{KBr} (cm^{-1}) 1540, 1640, 1720, 1780, 2120, 2940.

Mass spectrum: m/z 330, 312, 247, 230.

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