THE STRUCTURE OF GUMMOSIN

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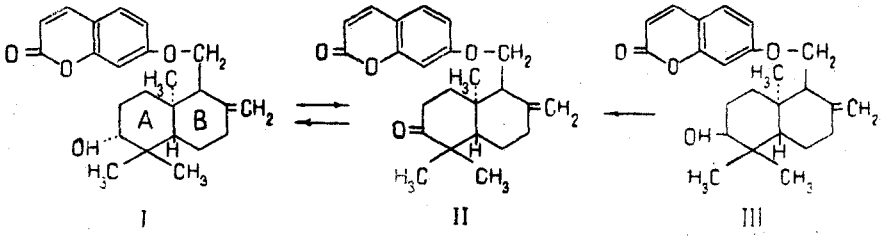
In an investigation of an acetone extract of the dry roots of Ferula gummosa Boiss. and F. pseudoreoselinum (Rgl. et Schmalh.) K-Pol, we found that the neutral part of this extract contains a substance sparingly soluble in ether with the composition $C_{24}H_{30}O_4$, mp 176–177°C, $[\alpha]_D$ −54°C (chloroform), which we have called gummosin [1]. A substance with the properties of gummosin was apparently isolated by Casparis and Baumann from the resin of F. assafoetida L. [2] and by Kunz and Wöldicke from galbanum resin [3].

It is known that gummosin is a derivative of umbelliferone and the hydrogenation of one double bond, probably of the CH_2= type, forms dihydrogummosin $C_{24}H_{32}O_4$. The main maxima of the IR spectrum (Fig. 1) and the UV spectrum (λmax at 322 mμ, log ε 4.2, shoulders at λ_{max} 298 and 240 mμ) confirm that gummosin belongs to the coumarin series. In an acid medium, this substance readily forms umbelliferone and a mixture of liquid products. The dehydrogenation of gummosin with selenium for 20–30 min gives umbelliferone and 1, 2, 5, 6-tetramethylnaphthalene, which shows the structural similarity of gummosin and galbanic acid [1] or farnesiferol A [4]. We established the presence of one double bond of the CH_2= type in the substance under consideration by ozonolysis, formaldehyde being readily produced. The aceylation of gummosin in pyridine formed a monoacetate $C_{26}H_{32}O_5$, giving the starting material on saponification. The formation of a monoacetate shows that gummosin has one OH group capable of being acetylated. Its presence in gummosin is also confirmed by the band at 3500 cm^{-1} in its IR spectrum. By oxidizing gummosin with chromic anhydride in acetone or acetic acid solution, we obtained a substance with the composition $C_{24}H_{28}O_4$, the properties and IR and UV spectra of which did not differ from those of a substance $C_{24}H_{28}O_4$ found by Caglioti, Naef, Arigoni, and Jeger [4] in the oxidation of farnesiferol A. When the substance $C_{24}H_{28}O_4$ obtained from gummosin was reduced with sodium borohydride, we obtained a product $C_{24}H_{30}O_4$ identical with farnesiferol A. This showed that the structure of gummosin differs from that of farnesiferol A only in the spatial arrangement of the secondary hydroxy group. Jeger et al. have established structure (I) for farnesiferol A, this being characterized by the presence of the secondary OH group in the α position (equatorial hydroxy group) and a stereochemical linkage of rings A and B the opposite of that for the pentacyclic triterpenes.



The presence of an equatorial hydroxy group in farnesiferol A was shown experimentally by the back-formation of farnesiferol A from the keto compound $C_{24}H_{28}O_4$. The latter must evidently have the structure (II).

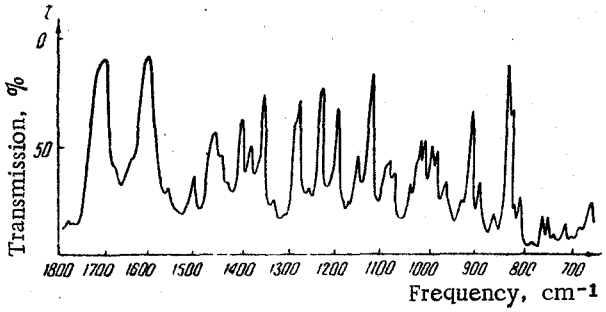


Fig. 1. IR spectrum of gummosin with mp 176–177°C.

The impossibility of re-forming gummosin from its keto derivative (III) on reduction with $NaBH_4$ permits the assumption that in gummosin the OH group is in the β-position, i.e. it is axial and, therefore, gummosin apparently has the structure (III).

The PMR spectrum of gummosin was taken and interpreted by M. Perel'son of the Scientific Research Institute for Medicinal and Aromatic Plants, Moscow [in deuterochloroform on a JNM-1-60 instrument at a frequency of 60 Hz; the scale is given in parts per million (ppm) relative to tetramethylsilane (Fig. 2)]. It confirms the structure assigned to gummosin. The signal at 0.97 ppm corresponds to a gem-dimethyl group and that at 0.9 ppm to a CH_3 group. The numerals 3, 4, 5, 6, 8, in the figure denote the numbers of the protons of the coumarin nucleus corresponding to the appearance of the signals concerned.

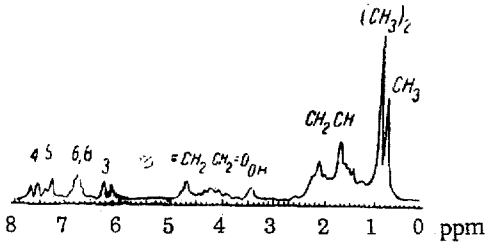


Fig. 2. PMR spectrum of gummosin.

The noncoincidence of the properties of some derivatives obtained from gummosin and from farnesiferol A must be due to the presence of the axial hydroxy group in gummosin. Thus, the acetate of gummosin mentioned above melts at 128.5–130°C, while the acetate of farnesiferol A has mp 142–144°C. The diol $C_{15}H_{28}O_2$ that we obtained by the exhaustive hydrogenation of gummosin melts at 140–141°C, while the diol $C_{15}H_{28}O_2$ formed by the exhaustive hydrogenation of farnesiferol A melts, according to the literature [4], at 183–185°C. Obviously, all other derivatives of gummosin retaining the original axial secondary OH group will differ in melting point and other properties from the corresponding derivatives of farnesiferol A.

However, we may mention that an acetone extract of F. samarkandica Eug. Kor. contains a substance $C_{24}H_{30}O_4$ with mp 180–181°C, the UV and IR spectra of which are identical with those of gummosin. On oxidation, like gummosin, this substance forms a compound $C_{24}H_{28}O_4$ with mp 132°C. The substance with mp 180–181°C from F. samarkandica is obviously identical with gummosin, but we were unable to raise the melting point of gummosin from F. gummosa from 176–177°C to 180–181°C by recrystallization or chromatography.

Experimental

Isolation of gummosin. A. The neutral fraction of the resin from the roots of F. gummosa or F. samarkandica was dissolved in ether and the solution was cooled for a long period (−10°C). A crystalline precipitate deposited which was washed with ether and recrystallized from alcohol. The melting point of the gummosin from F. gummosa was 176–177°C and that from F. samarkandica was 180–181°C. Yield 5–10%.

B. The neutral fraction of the resin from the roots of F. pseudoreoselinum was saponified for 2 hr with a 5% alcoholic solution of caustic potash, and the mixture was then diluted with water and the alcohol was evaporated off. After extraction with ether, the alkaline solution was acidified with dilute sulfuric acid, and the precipitate was filtered off, washed with water, dried, and dissolved in ether. On standing, the ethereal solution deposited gummosin with mp 176–177°C (from alcohol). Yield 3–5%.

C. The neutral fraction of the resin from F. pseudoreoselinum was dissolved in chloroform and chromatographed on alumina (activity grade III). The first portions of eluate contained pure gummosin $[\alpha]_D$ −54° (c 10; chloroform), IR spectrum: 3500, 1715, 1682, 1651, 1616, 1560, 1500, 1400, 1387, 1356, 1330, 908, 893, 836, 829 cm^{-1}.

The substance was sparingly soluble in alcohol and ether.

Hydrolysis of gummosin. 1 g of gummosin was dissolved with heating in 10 ml of acetic acid. The solution was cooled, without crystallization of the substance being permitted, and diluted sulfuric acid (5 ml of concentrated acid + +2 ml of water) was added dropwise. After 15 min, the colored mass was diluted with 100 ml of water and the solution was extracted with ether. The ethereal extract was shaken with 5% caustic potash solution. The precipitate which deposited when the alkaline solution was acidified was recrystallized from boiling water. This gave needles with mp 233–234.5°C (the substance gave no depression of the melting point in admixture with umbelliferone). Yield 0.3 g.

Ozonization of gummosin. 2% ozone was passed through a solution of 2 g of gummosin in 50 ml of chloroform until a 5% solution of potassium iodide gave an intense coloration. The chloroform was distilled off. The yellow oil was boiled under reflux with 100 ml of water for 1 hr. 5 ml of liquid was distilled off, and when this was heated with a solution of dimedone it yielded acicular crystals with mp 185–187°C (from alcohol) corresponding to the melting point of the dimedone derivative of formaldehyde.

Dehydrogenation of gummosin. A mixture of 0.5 g of gummosin and 0.5 g of selenium was heated to 250–300°C for 2 hr and was then cooled and extracted with ether. The ethereal solution was shaken several times with 2% caustic potash. The alkaline solution was acidified. This gave a substance with mp 231–232°C (giving no depression of the melting point in admixture with authentic umbelliferone). The ether was evaporated; the yellow residue was dissolved in petroleum ether and filtered through a column of alumina (activity grade II). The eluate was colorless. The petroleum ether was distilled off and the residue was recrystallized from alcohol, mp 112–112.5°C. By the usual method, the substance readily formed a picrate with mp 154–155°C (from alcohol), which corresponds to the melting point of the picrate of 1, 2, 5, 6-tetramethylnaphthalene. By filtering an ethereal solution of the picrate through a column of alumina (activity grade II) we obtained crystals of 1, 2, 5, 6-tetramethylnaphthalene with mp 114–115°C (from alcohol) giving no depression of the melting point in admixture with authentic 1, 2, 5, 6-tetramethylnaphthalene.

Acetylation of gummosin. A solution of 0.5 g of gummosin in 4 ml of pyridine and 4 ml of acetic anhydride was heated in a water bath for 1 hr. The solution was evaporated under vacuum and the residue (an oil which partially crystallized) was crystallized from a mixture of ether and petroleum ether, mp 128.5–130°C, $[\alpha]_D$ −30° (c 1; alcohol).

The IR spectrum of the acetate had the following maxima 1728, 1644, 1614, 1560, 1509, 1390, 1369, 1345, 896, 839 cm^{-1} etc. There was no OH group. UV spectrum: λ_{max} at 324 mμ (log ε 4.13) and shoulders at 298 and 249 mμ (log ε 3.9, 3.28, respectively).

Found, %: C 73.57; H 7.61. Calculated for $C_{26}H_{32}O_5$, %: C 73.56; H 7.60. Saponification of the acetate reformed the initial gummosin with mp 176–177°C.

Oxidation of gummosin. At room temperature, a solution of chromic anhydride (1 g) in 1 ml of water diluted with 10 ml of acetone was added to a solution of 1 g of gummosin in 25 ml of water and extracted with ether. The ethereal solution was evaporated and the residue was recrystallized from aqueous alcohol, mp 132–133°C. The oxidation of gummosin (1 g) in solution in 15 ml of acetic acid with chromic anhydride (1 g) in 2 ml of 50% acetic acid also gave a substance with mp 132–133°C, $[\alpha]_D$ −45.6° (c 2.5; dioxane); the IR spectrum of the substance had a strong bands at 1732, 1693, 1608, 1505, 1460, 1380, 850, 830, 820 cm^{-1}, and the UV spectrum had maxima at λ_{max} 323, 252 mμ (log ε 4.12, 2.93, respectively) and a shoulder at λ_{max} 296 mμ.

Found, %: C 75.74, 75.58; H 7.36, 7.44. Calculated for $C_{24}H_{28}O_4$, %: C 75.79; H 7.37.

Farnesiferol A. A solution of 1 g of the substance with mp 132–133°C in 20 ml of 92% ethanol was mixed with 0.5 g of $NaBH_4$. The mixture was kept at room temperature for 2 hr. With cooling, 15 ml of 2% sulfuric acid was gradually added and the mixture was extracted with ether. The residue after the distillation of the ether was recrystallized from 70% alcohol. This gave a substance with mp 154–155°C; yield 0.6 g. The farnesiferol A dissolved considerably more readily in alcohol and ether than gummosin. $[\alpha]_D$ −60°C (c 1; alcohol). The IR spectrum had bands at 3500 cm^{-1} (OH group), 1724, 1647, 1610, 1554, 1500 cm^{-1}. The UV spectrum had λ_{max} at 323, 252 mμ (log ε 4.23, 3.13, respectively) and shoulders at λ_{max} 296 and 242 mμ.

Found, %: C 75.38; H 7.73. Calculated for $C_{24}H_{30}O_4$, %: C 75.53; H 7.69.

Hydrogenation of gummosin. A solution of 3 g of gummosin in 50 ml of acetic acid was treated with 0.8 g of PtO_2 and hydrogenated at 40–50° C. The consumption of hydrogen was 1163 ml (approximately corresponding to five double bonds). The clear colorless solution was decanted off the settled catalyst into a separating funnel and diluted with water, and the liquid, which had become turbid, was extracted with ether several times. The ethereal solution was washed with water and sodium carbonate solution. The ether was distilled off. The residue (2.9 g) was dissolved in 30 ml of alcohol and heated in a water bath for 1 hr with 1.2 g of caustic potash, after which it was cooled, diluted with water, and extracted with ether. The ethereal solution was dried with sodium sulfate. The ether was distilled off. The residue (0.8 g) was dissolved in a small amount of acetone. On standing, colorless crystals deposited with mp 140–141°C (0.2 g), $[\alpha]_D$ +30° (c 1; alcohol). IR spectrum: 3500, 3330, 3225 cm^{-1} (OH group); there were no maxima in the region of the CO group or double bonds. The UV spectrum showed no absorption.

Found, %: C 75.3, 75.22; H 11.92, 11.90. Calculated for $C_{15}H_{28}O_2$, %: C 74.95; H 11.74.

The microanalyses were carried out by E. A. Sokolova. The UV and IR spectra were obtained by T. V. Bukreeva and T. N. Timofeeva.

The roots of F. samarkandica Eug. Kor. (from the south-western slopes of Malyi Chimgan, Tashkent Ala-Tau) and of F. pseudoreoselinum Rgl. et Schmalh. (from the gorge of the R. Ugam) were collected by L. P. Markova, and the roots of F. gummosa Boiss. (from the Ashkhabad region) by V. V. Nikitin.

Summary

From the neutral fraction of an acetone extract of the roots of plants of the genus Ferula, F. gummosa Boiss., F. pseudoreoselinum Rgl. et Schmalh. (K-Pol.) and F. Samarkandica Eug. Kor., we have isolated a coumarin gummosin with the composition $C_{24}H_{30}O_4$, mp 176–177°C, $[\alpha]_D$ −54°C. The structure of gummosin corresponds to formula (III).

With respect to structure, gummosin is a spatial isomer of farnesiferol A; it differs from the latter by the fact that the secondary OH group in gummosin is axial.

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