NATURAL (-)-7-METHOXY-8-(β,γ-DIHYDROXYISOPENTYL)-COUMARIN

G. A. Kuznetsova and A. Z. Abyshev

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We have isolated from the roots of Prangos ferulaceae (L.) Lindl. a number of coumarin compounds [1], identified as osthole, oxypeucedanin, isoimperatorin, and the hydrate of oxypeucedanin, and also a coumarin base (substance A) with mp 128° $[\alpha]_D^{20}$ −53.03° (c 8.34; alcohol), composition $C_{15}H_{18}O_5$. This substance is unlike any of the known coumarin derivatives, but, as the results of the investigation described below show, it is in fact the hydrate of the natural coumarin meransin [2-4].

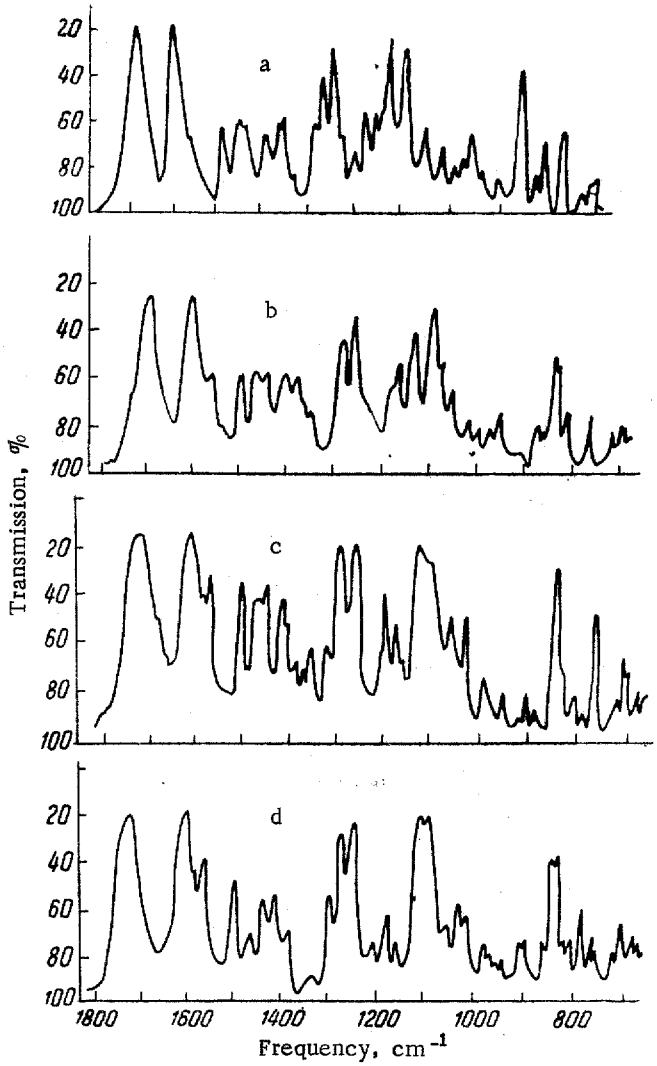


Fig. 1. Infrared absorption spectra of natural meransin hydrate (a); synthetic meransin hydrate (b); an isomer of meransin (isomeransin) (c); osthole oxide (d).

Coumarin A contains one methoxy and two hydroxy groups. The reaction with ferric chloride is negative, which excludes the presence of phenolic hydroxy groups in this compound. The IR spectrum of compound A has absorption bands characteristic for OH groups (3512, 3401 cm^{-1}). The presence of the latter can also explain the low value of the absorption band characteristic for a carbonyl group of a δ-lactone (1679 cm^{-1}) (Fig. 1, a).

The acetylation of substance A gave a monoacetyl derivative $C_{17}H_{20}O_6$.

The IR spectrum of the acetate had a broad absorption band at 1717-1744 cm^{-1} due to the superposition of the frequencies of the vibration of a carbonyl group in an ester linkage and of a δ-lactone.

The UV spectrum of substance A (Fig. 2, curve 1) is very similar to that of osthole (Fig. 2, curve 2), differing mainly in the magnitude of the absorption coefficient.

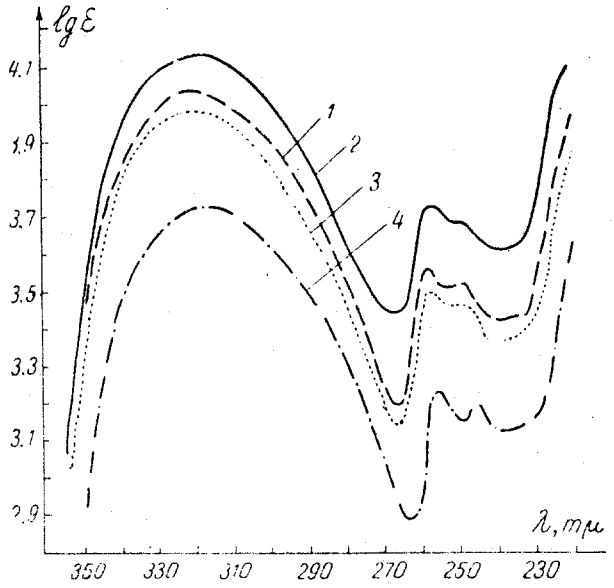
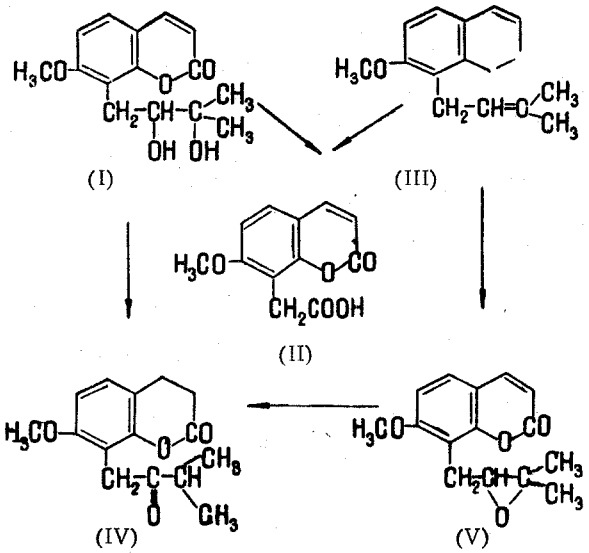


Fig. 2. Ultra-violet absorption spectra of the natural meransin hydrate (a); of synthetic meransin hydrate (3); and of osthole oxide (4).

From the products of the oxidation of the coumarin A with chromic acid in glacial acetic acid, we isolated a compound (II) with mp 245-246°. A mixture of the crystals formed with 7-methoxycoumarin-8-yl-acetic acid, i.e., ostholic acid, obtained by the oxidation of osthole (III) in the same way, gave no depression of the melting point. This permitted the assumption that substance A has structure (I), 7-methoxy-7-(β, γ-dihydroxyisopentyl)-coumarin, corresponding to the monoacetyl derivative formed.

Confirmation of this structure is given by the preparation of the dehydration product of substance A, $C_{15}H_{16}O_4$ (IV). In this process, besides the elimination of a molecule of water, isomerization with the formation of a ketone group very probably takes place. The compound $C_{15}H_{16}O_4$ does in fact correspond to the known product of the isomerization of the natural coumarin meransin (auraptene) – isomeransin (isoauraptene) [2].

According to literature data [2], the hydrate of meransin (auraptene) $C_{15}H_{18}O_5$ obtained by the hydration of meransin (auraptene) (V), $C_{15}H_{16}O_4$, has mp 128-129°, $[\alpha]_D^{15}$ −43.8° (in alcohol). The acetyl derivative has not been obtained previously.



The structure of substance A was confirmed by synthesis. The oxidation of osthole with benzoyl hydroperoxide (by Prilezhaev's method) [5] gave us osthole oxide (V), 7-methoxy-8-(β,γ-oxyisopentyl)-coumarin with mp 105-105.5°.

The composition of osthole oxide ($C_{15}H_{16}O_4$) corresponds to natural meransin (auraptene). The UV spectrum of the osthole oxide that we had obtained (Fig. 2, curve 4) was very similar to the spectra of natural meransin hydrate (Fig. 2, curve 1) and osthole (Fig. 2, curve 2).

The hydration of osthole oxide with 1% oxalic acid gave an optically inactive hydrate $C_{15}H_{18}O_5$ with mp 118-119° of the same composition as meransin hydrate. The hydrate of osthole oxide has not previously been isolated in the crystalline state [3].

The UV and IR spectra of the natural and synthetic hydrates of meransin are extremely similar (Fig. 2, curves 1 and 3; Fig. 1, a and b, respectively). Mixtures of the two substances gave no depression of the melting point.

The structure of natural meransin hydrate (substance A) was definitely confirmed by the preparation from synthetic osthole oxide and from substance A of one and the same isomer of meransin (IV) with mp 65-66°. The UV and IR spectra of the two isomers coincided completely and a mixture gave no depression of the melting point. On a thin-layer chromatogram, a single spot with R_f 0.70 was obtained.

Experimental

Isolation of substance A with mp 128°. A chloroform extract of the roots (225 g of resin from 2.27 kg of roots) was transferred to a column of alumina (1.5 kg, activity grade III). Elution was carried out with a mixture of chloroform and petroleum ether (1 : 4 for fractions 1-19 and 1 : 2 for fractions 20-23), and with chloroform (for fractions 24-32). The volume of each fraction was 750 ml. After distillation of the solvent from the chloroform fractions 24-32, substance A was precipitated with mp 128° (from benzene, $[\alpha]_D^{20}$ −53.03° (c 8.34; alcohol).

The qualitative composition of the fractions and the homogeneity of the substances isolated were checked by thin-layer and paper chromatography. The paper chromatogram was obtained by the descending method on type "B" chromatographic paper of the Leningrad "Goznak" mill. The paper was impregnated with a 10% solution of formamide in methyl alcohol, and the mobile phase was benzene. The chromatograms were examined under UV light.

On the paper chromatogram, substance A gave a spot with R_f 0.28 with a purple fluorescence in UV light, and on the thin-layer chromatogram with alumina (mobile phase a mixture of isobutyl acetate and benzene, 1 : 2), R_f 0.05 (same fluorescence). UV spectrum: λ_{max} 248 (log ε 3.53), 258 (log ε 3.57), 320-322 mμ (log ε 4.04). IR spectrum: 1697 (δ-lactone), 1619, 1573 (aromatic ring), 3401, 3512 cm^{-1} (OH group).

Found, %: C 64.55; H 6.64; OH 11.10; OCH_3 10.90; mol. wt. 293 (by titration). Calculated for $C_{15}H_{18}O_5$, %: C 64.74; H 6.47; OH 12.23; OCH_3 11.15; mol. wt. 278.

Acetylation of meransin hydrate (substance A). A mixture of 0.28 g of substance A, 5 ml of acetic anhydride and 0.5 g of freshly-fused sodium acetate was heated for 5 hr. By the usual method, after recrystallization from ether, the reaction products yielded a monacetyl derivative (0.11 g) with mp 130-131°, giving a spot with R_f 0.25 on the thin-layer chromatogram (pale blue fluorescence in UV light).

Found, %: C 63.59; H 6.04. Calculated for $C_{15}H_{17}O_5$ (CH_3CO), %: 63.75; H 6.20.

Production of isomeransin. A mixture of 0.5 g of substance A, 2 ml of glacial acetic acid, and a few drops of concentrated sulfuric acid was heated for 1 hr on a water bath, after which the mixture was poured into ice-water and treated in the usual way. This gave 0.23 g of a substance with mp 66° (from petroleum ether). The same compound is formed by heating substance A with 20% sulfuric acid. On paper chromatography, it gave a spot with R_f 0.22 (pale blue fluorescence on UV irradiation) and on a thin-layer chromatogram a spot with R_f 0.70. The paper chromatogram was obtained by the descending method with ethylene glycol as the stationary phase and petroleum ether as the mobile phase [6]. UV spectrum: λ_{max} 246-248 (log ε 3.37), 256 (log ε 3.40), 320-322 mμ (log ε 3.90). IR spectrum: 1739-1721 (CO of a δ-lactone and a saturated aliphatic ketone), 1609, 1567 cm^{-1} (aromatic ring).

Found, %: C 69.52; H 6.36. Calculated for $C_{15}H_{16}O_4$, %: C 69.23; H 6.15.

Oxidation of meransin hydrate (substance A). A solution of 0.4 g of substance A in 10 ml of glacial acetic acid was treated with 0.5 g of chromic anhydride in 10 ml of 50% glacial acetic acid and was left to stand for 3 days. The reaction products yielded a substance (0.2 g) with mp 245-246° (from ethanol). A mixture of this substance with 7-methoxycoumarin-8-yl-acetic acid (ostholic acid) obtained similarly from natural osthole gave no depression of the melting point.

Production of osthole oxide. With cooling and stirring, 30 ml of a chloroform solution of benzoyl hydroperoxide (1.44 g) was added to a solution of 1.2443 g of osthole, mp 82.5°, in 10 ml of chloroform, and the mixture was left

for 5 days at room temperature. Then it was diluted with a large volume of ether (300 ml) and extracted with 10% potassium carbonate solution. The ether-chloroform solution was concentrated in vacuum. The concentrated solution deposited crystals (0.6 g) with mp 105-105.5° (ethanol), R_f 0.71 [pale blue fluorescence on UV irradiation on a thin-layer chromatogram on alumina in the ethyl acetate-benzene (1 : 4) system]. UV spectrum: λ_{max} 246 (log ε 3.19), 256 (log ε 3.22), 320 mμ (log ε 3.72). IR spectrum: 1729 (δ-lactone), 1607, 1566 cm^{-1} (aromatic ring).

Found, %: C 69.15, 69.13; H 6.23, 6.15. Calculated for $C_{15}H_{16}O_4$, %: C 69.23; H 6.15.

Hydrate of osthole oxide. A solution of 0.25 g of oxalic acid in 17 ml of water was brought to the boil and 0.54 g of osthole oxide was added. Then the mixture was heated for 45 min, after which it was cooled and extracted with ether (200 ml). The ethereal solution was washed twice with water (15 ml portions) and dried with anhydrous sodium sulfate and the solvent was distilled off. The viscous residue (0.35 g) was chromatographed on alumina (5 g). It was eluted with petroleum ether and a mixture of petroleum ether and chloroform (4 : 1). The elution with the mixture of petroleum ether and chloroform gave a substance with mp 118-119° (from benzene). A mixture of this substance with a sample of natural meransin hydrate gave no depression of the melting point. UV spectrum: λ_{max} 248 (log ε 3.46), 258 (3.51), 320-322 mμ (3.98). IR spectrum: 1702 (δ-lactone) 1609, 1560, (aromatic ring), 3405, 3472 cm^{-1} (OH group).

Found, %: C 64.86; H 6.66. Calculated for $C_{15}H_{18}O_5$, %: C 64.74; H 6.47.

Isomerization of osthole oxide. A solution of 0.24 g of osthole oxide in 2 ml of acetic acid was treated with 20 ml of 20% sulfuric acid. The reaction mixture was heated for 4 hr and, after cooling, was extracted with ether (100 ml). The ethereal solution was washed and was dried with anhydrous sodium sulfate. The resinous residue left after the ether had been distilled off (0.10 g) was chromatographed on alumina (3.0 g, activity grade II). Elution was carried out with petroleum ether and a mixture of petroleum ether and chloroform (4 : 1). The elution with the mixture of solvents gave a substance with mp 64-65.5° (from petroleum ether), R_f 0.70, [on a thin layer of alumina in the ethyl acetate-benzene (1 : 4) system, pale blue fluorescence]. A mixture of this substance with the isomer of meransin gave no depression of the melting point.

UV spectrum: λ_{max} 246 (log ε 3.21), 256 (3.25), 320-322 mμ (log ε 3.75). IR spectrum: 1736-1720 (CO of a δ-lactone and a saturated aliphatic ketone), 1609, 1567 cm^{-1} (aromatic ring).

The UV spectra were obtained on a SF-4 spectrophotometer in 96% ethyl alcohol. The IR spectra were taken on a IKS-14 spectrophotometer in liquid paraffin. NaCl (1800-700 cm^{-1}) and LiF (3100-3600 cm^{-1}) prisms.

Summary

The roots of Prangos ferulaceae (L.) Lindl. have yielded (-)-7-methoxy-8-(β,γ-dihydroxyisopentyl)-coumarin, composition $C_{15}H_{18}O_5$, with mp 128°. $[\alpha]_D^{20}$ −53.03°, identical with a synthetic hydrate of meransin and found by us in nature for the first time. Various coumarin derivatives are present in the roots of Prangos ferulaceae (L.): osthole, oxypeucedanin, oxypeucedanin hydrate, and isoimperatorin.

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Komarov Botanical Institute
AS USSR