A NEW COUMARIN, PRANFEROL, FROM THE ROOTS OF PRANGOS FERULACEA

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As reported previously [1], we have isolated several coumarin derivatives from the roots of Prangos ferulacea (L.) Lindl.: osthole, oxypeucedanin, oxypeucedanin hydrate, and isoimperatorin, and have found merancin hydrate in nature for the first time [2].

Besides the compounds mentioned, we have isolated from the roots of this plant a substance $C_{16}H_{16}O_5$. The properties of this do not correspond to any of the known coumarins. The results of an investigation of the structure of this compound, which we have called pranferol, are given in the present paper.

Pranferol (I) possesses coumarin properties. It dissolves in alkalies forming yellow solutions and precipitates unchanged when the solutions are acidified, gives a color reaction with diazonium compounds, fluoresces under UV irradiation, and gives a spot with R_f 0.80 (yellow in UV light) on paper chromatography.

UV spectrum of substance (I) (Fig. 1, curve 1): λ_{max} (in alcohol) 222, 250, 268, 308-310 mμ (log ε 4.04; 3.93; 3.88; 3.89; 3.82), which is similar to the spectra of the 5-monosubstituted furocoumarins oxypeucedanin (Fig. 1, curve 2), and oxypeucedanin hydrate [3, 4]. Bands at 250, 260, and 266-268 mμ with very similar molar absorption coefficients are characteristic for the latter. At the same time, the spectrum of (I) differs considerably from the spectra of the 8-monosubstituted furocoumarins (prangenin and imperatorin) [5] whose spectra, in the 240-270 mμ range, have one maximum at 248-250 mμ and an inflection at 260-266 mμ.

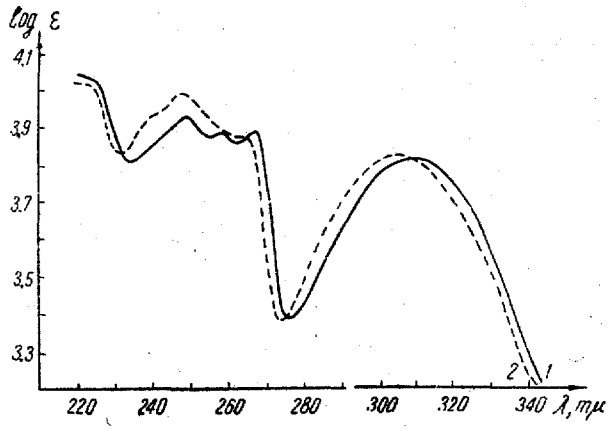


Fig. 1. UV absorption spectra of pranferol (1) and oxypeucedanin (2).

The IR spectrum of pranferol (I) taken on an IKS-14 spectrophotometer, exhibits bands at 3427 (OH), 3100, 3043 (C-H of aromatic rings), 1627, 1607, 1581 (skeletal vibrations of aromatic rings), and 865, 815, and 806 cm^{-1} (furan ring) (Fig. 2a). The IR spectrum of (I) is similar to that of oxypeucedanin (Fig. 2b) in which, as in the spectra of other 5-monosubstituted furocoumarins, in the 1600-1650 cm^{-1} region there are two strong bands at 1623 and 1602 cm^{-1} [4, 6].

In the case of the 8-monosubstituted furocoumarins (prangenin, prangenin hydrate, and imperatorin) there is only one fairly weak band at 1625-1620 cm^{-1} in this region [7].

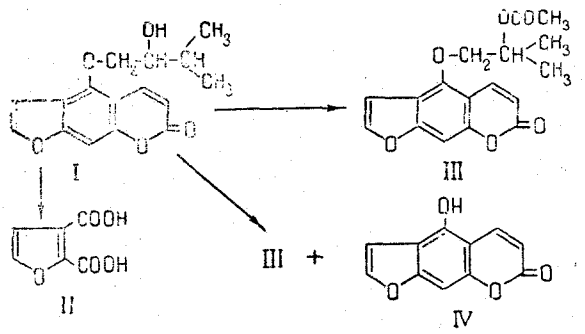
In the IR spectrum of substance (I) there are two bands in the region of the stretching vibrations of the carbonyl group, at 1727 and 1704 cm^{-1}. In chloroform, the splitting of the band disappears and only one band at 1727 cm^{-1} with an inflection at 1710 cm^{-1} remains in the spectrum. One of these bands is due to the vibrations of the carbonyl group of the α-pyrone ring but the nature of the second band remains uncertain. It may appear as a consequence of the presence in the molecule of (I) of a second carbonyl group or through the splitting of the α-pyrone carbonyl band. The causes of such splitting have been discussed in detail in the literature [8, 9]. To elucidate this question, we measured the integral intensity of the carbonyl band, which proved to be 8.00 ± 0.05 practical units in chloroform. This value is no greater than those found previously for furocoumarins [10]; consequently, it may be concluded that the molecule has only the one carbonyl group of the α-pyrone ring. (The integral intensity of the C=O band was calculated by the Wilson-Wells method. The measurements were carried out on a UR-10 spectrophotometer.) It was also impossible to confirm the presence of a second carbonyl group by chemical methods. A proof of the furocoumarin structure of (I) is the production of furan-2, 3-dicarboxylic acid (II) when (I) is oxidized with hydrogen peroxide.

The acetylation of pranferol with acetic anhydride in pyridine gave the acetyl derivative (III) with mp 111.5°-112.5° C. The band of the hydroxy group had disappeared in the spectrum of the latter, and together with the band of the C=O group of the α-pyrone ring (1724 cm^{-1}) there was the band of an ester carbonyl group (1736 cm^{-1}) (Fig. 2c).

Pranferol is fairly stable to the reaction of acids and alkalies under the conditions usually used for splitting alkoxyfurocoumarins [11]. After (I) had been treated with a mixture of acetic and sulfuric acids, the main product isolated was the acetate (III) and a small amount of a substance (IV) with a pale blue fluorescence whose IR spectrum was

identical with that of bergaptol. Bergaptol has previously been obtained by the same method from isoimperatorin. The ease of acetylation of (I) shows that the hydroxy group is primary or secondary.

The results of the study of the UV and IR spectra and the chemical investigations show that pranferol is a 5-monosubstituted furocoumarin.*



A study of the NMR spectrum of substance (I) enables the structure of pranferol as a 5-monosubstituted furocoumarin to be confirmed and the structure of the side chain to be deduced. (The NMR spectra were determined on a JNM-4H instrument, 100/100 MHz). The solvent used was deuterochloroform. The chemical shifts were calculated in parts per million with tetramethylsilane taken as 0.

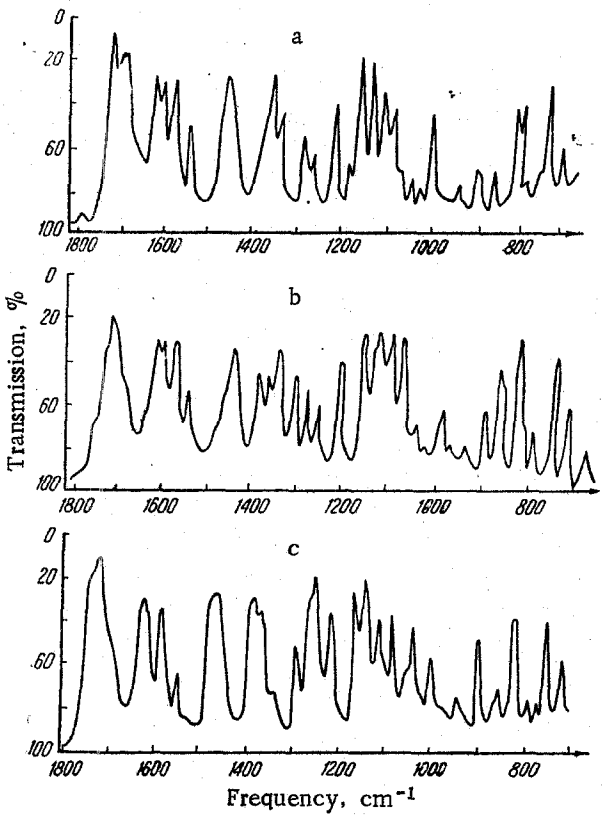
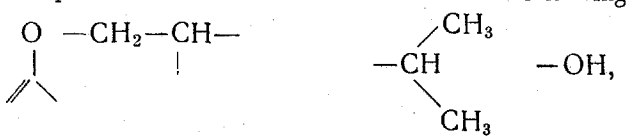


Fig. 2. IR absorption spectra (in paraffin oil, NaCl prisms) of a) pranferol, b) oxypeucedanin, and c) pranferol acetate.

The NMR spectrum of (I) (Fig. 3) has a number of peaks denoted in the figure by a, b, c, d, e, f, g, h, i. The doublets a (δ = 7.87, J = 9.5 Hz) and e (δ = 6.03, J = 9.5 Hz), as has been shown previously [12], relate to protons in positions 4 and 3. The doublets b (δ = 7.34, J = 2 Hz) and d (δ = 6.71, J = 2 Hz) correspond, respectively, to the 5' and 4' protons of the furan ring. And, finally, the singlet c (δ = 6.87) relates to the proton in position 8. These results confirm the structure of pranferol as a 5-monosubstituted furocoumarin.

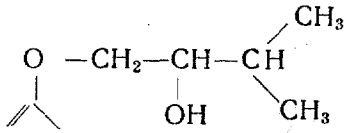
In the region of the NMR spectrum due to aliphatic protons there is a doublet f (δ = 4.23, J = 6 Hz) with an intensity of two proton units and a number of peaks g (δ = 3.70) each with an intensity of one proton unit, which may be caused [13] by a $-CH_2-CH$ group, the methine proton apparently interacting further with one proton. The position of the signals of the methylene group is characteristic for groups located adjacent to an oxygen atom which, in turn, is attached to an aromatic nucleus.

The broadened peak h (δ = 2.45) with an intensity of two proton units is probably due to the hydroxy proton and the methine proton of an isopropyl group. The signals i of two methyl groups (δ = 1.02) are separated by 7 Hz. Moreover, each of the signals is separated again into two components (distance between them 2 Hz). The 7 Hz splitting is due to the interaction of the methyls with the methine protons of the isopropyl group. The additional splitting by 2 Hz is due to the nonequivalence of the two methyl groups. The latter can arise as a result of hindered rotation of the isopropyl group around the ordinary C–C bond. Thus, an analysis of the NMR spectrum shows that the side chain has the following structural elements.



*These results were reported by G. A. Kusnetsova and A. Z. Abyshev at a symposium on the chemistry and modern methods of investigation of natural compounds, Vladivostok, September 1965.

These can be connected with one another and with the cyclic system only as follows:



A study of the NMR spectrum of pranferol monoacetate confirms the conclusions drawn. The NMR spectrum of the monoacetate has the peak of the acetyl methyl group (δ = 2.17). The signal from the methine proton adjacent to the methylene group undergoes a pronounced paramagnetic shift ($\Delta\delta$ = 1.155), as was to be expected. The additional 2 Hz splitting in the signal of the methyl group disappears and a clear doublet with J = 7 Hz remains. To prove that the splitting of the methyl signal was due to a spin-spin interaction and not to a chemical shift, the spectrum of pranferol monoacetate was taken at a frequency of 100 MHz. In this spectrum, the distance between the two components of the doublet due to the methyl groups was also 7 Hz, which showed the spin-spin nature of the splitting of the signal.

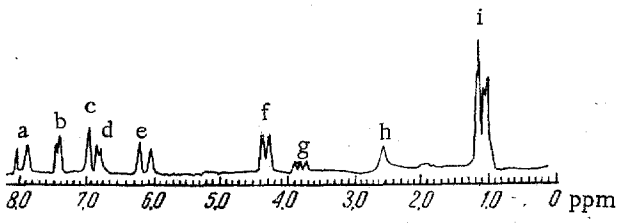


Fig. 3. NMR spectrum of pranferol.

On the basis of all that has been said above, the structure 5-(2'-hydroxy-3'-methylbutoxy)furo-2', 3':7, 6-coumarin (I) may be proposed for pranferol.

Experimental

Isolation of pranferol. A chloroform extract (225 g) of the resin from the roots (2.27 kg) was chromatographed on alumina as described previously [1, 2], and the 22nd and 23rd fractions gave, after repeated crystallization from alcohol, pranferol with mp 108.5°–111.0° C, $[\alpha]_D^{19}$ –19.38 (c 4.5; chloroform), R_f 0.80 on a paper chromatogram (yellow fluorescence in UV radiation) and R_f 0.26 in a thin layer of alumina.

Chromatography was carried out on paper impregnated with a 10% solution of formamide in methyl alcohol with benzene as the mobile phase and also in a thin layer of alumina in the solvent system ethyl acetate-benzene (1:2). The specific behaviour of pranferol on fusion must be mentioned. The substance softens at 99° C and finally the whole mass melts at 108.5°–111.0° C. The substance was chromatographically homogeneous.

Found, %: C 66.32; 66.41; H 5.66; 5.67; OH 4.97; 4.93; mol. wt. 274 (Rast). Calculated for $C_{16}H_{16}O_5$, %: C 66.66; H 5.55; OH 5.90; mol. wt. 288.

Oxidation of pranferol with hydrogen peroxide. With heating, 0.4652 g of pranferol was dissolved in methanolic alkali, and the alcohol was distilled off in vacuum. The residue was diluted with water, and 5 g of sodium hydroxide dissolved in 150 ml of water and 50 ml of 5% hydrogen peroxide solution were added. After a day, the solution was boiled to decompose the excess of hydrogen peroxide, neutralized with hydrochloric acid, and subjected to ethereal extraction. The ethereal extract yielded substance (II) with mp 220° C, identical with furan-2, 3-dicarboxylic acid.

Pranferol acetate. A mixture of 0.1141 g of pranferol, 4 ml of acetic anhydride, and 1 ml of pyridine was heated for 6 hr. Then it was cooled, diluted with water (40 ml), and extracted with ether (5 × 30 ml). The ethereal extracts were washed with water and dried with anhydrous sodium sulfate. Then the ether was distilled off and the viscous resinous mass was purified by chromatography on alumina (5 g, activity grade III).

Elution was carried out with petroleum ether. After two recrystallizations from petroleum ether, substance (III) had mp 112.5° C, R_f 0.80 (yellow under UV irradiation) in a thin layer of alumina, R_f 0.90 on a paper chromatogram.

Found, %: C 65.65; 65.61; H 5.54; 5.44. Calculated for $C_{18}H_{18}O_6$, %: C 65.45; H 5.45.

Bergaptol. A mixture of 3.028 g of pranferol, 6 ml of glacial acetic acid, and a few drops of concentrated sulfuric acid was boiled for 30 min. The hot solution was treated with 24 ml of ethyl acetate. The solution was washed with water and a 5% solution of sodium bicarbonate. The solvent was distilled off and the residue was transferred to a column of alumina. Elution was performed with petroleum ether, mixtures of petroleum ether and chloroform (2:1 and 1:1), and pure chloroform. The first fractions gave a substance (0.2 g) with mp 112.5° C which was identical with pranferol acetate. Elution with chloroform gave a small amount of a substance identical from its IR spectrum with bergaptol.

The IR spectrum of bergaptol has bands at 1698 (C=O of an α-pyrone), 1632, 1610, and 1583 cm^{-1} (aromatic rings).

Summary

A new coumarin, pranferol $C_{16}H_{16}O_5$, has been isolated from the roots of Prangos ferulacea (L.) Lindl.

The structure 5-(2'-hydroxy-3'-methylbutoxy)furo-2', 3':7, 6-coumarin has been proposed for pranferol.

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